PONTIFICIAE ACADEMIAE SCIENTIARVM ACTA 25

Edited by JOACHIM VON BRAUN
MARCELO SÁNCHEZ SORONDO

TRANSFORMATIVE ROLES OF SCIENCE IN SOCIETY: FROM EMERGING BASIC SCIENCE TOWARD SOLUTIONS FOR PEOPLE'S WELLBEING

Plenary Session
12-14 November 2018
Casina Pio IV
Vatican City

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Transformative Roles of Science in Society: From Emerging Basic Science Toward Solutions for People's Wellbeing

Pontificiae Academiae Scientiarvm Acta 25

The Proceedings of the Plenary Session on

Transformative Roles of Science in Society: From Emerging Basic Science Toward Solutions for People's Wellbeing

12-14 November 2018

Edited by
Joachim von Braun
Marcelo Sánchez Sorondo

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"Today, both the evolution of society and scientific changes are taking place ever more rapidly, each following the other. It is important that the Pontifical Academy of Sciences consider how these interconnected changes require a wise and responsible commitment on the part of the entire scientific community. The splendid ivory tower security of early modern times has given way, in many, to a salutary unrest, for which today's scientists are more easily open to religious values and can glimpse, beyond the achievements of science, the richness of the spiritual world of peoples and the light of divine transcendence. The scientific community is a part of society, and must not be considered separate and independent; indeed, it is called to serve the human family and its integral development".

Pope Francis,
Address to the Pontifical Academy of Sciences,
12 November 2018


L. BARAÑ
R. VICUÑA
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S. MONCADA


W.J. SINGER


AMBASSADOR

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Address of His Holiness Pope Francis to Participants in the Plenary Session of the Pontifical Academy of Sciences

Consistory Hall
Monday, 12 November 2018

Distinguished Ladies and Gentlemen,

I am pleased to meet the full complement of the Pontifical Academy of Sciences. I offer cordial welcome to the new Members and I am grateful to the former President, Professor Werner Arber for his gracious words of introduction, while I pray that Professor Joachim von Braun may be restored to full health. I also thank the distinguished speakers for the valued contribution that they have made to this meeting.

The scientific world, which in the past tended to assert its independence and self-sufficiency, and to show a certain distrust vis-à-vis spiritual and religious values, seems today instead to be increasingly aware of the ever more complex reality of the world and of the human being. We see signs of a certain lack of security and some fear before the possible evolution of a science and technology that, if left to their own devices, could turn their back on the good of individuals and of peoples. True, science and technology influence society, yet the world's peoples with their values and their customs in turn influence science. Often the direction and emphasis given to certain developments of scientific research are influenced by commonly shared opinions and by the desire for happiness deeply rooted in human nature. Nonetheless, greater attention should be paid to the values and fundamental goods that are at the basis of the relationship between peoples, society and science. This relationship demands a rethinking aimed at promoting the integral advancement of each human being and of the common good. Open dialogue and attentive discernment are indispensable, especially as science becomes more complex and the horizons that it opens up bring decisive challenges for the future of humanity. For today, both the evolution of society and scientific changes are taking place ever more rapidly, each following the other. It is important that the Pontifical Academy of Sciences consider how these interconnected changes require a wise and responsible commitment on the part of the entire scientific community. The splendid ivory tower security of early modern times has given way, in many, to a salutary unrest, for which today's scientists are more easily open to religious values and can glimpse, beyond the achievements of science, the richness of the spiritual world of peoples and the light of divine transcendence. The scientific community is a part of society, and must not be considered separate and independent; indeed, it is called to serve the human family and its integral development.

The possible fruits of this mission of service are countless: here I would like to mention only a few. First, there is the immense and ongoing crisis of climate change and the nuclear menace. Following in the footsteps of my predecessors, I reaffirm the fundamental importance of commitment to a world without nuclear arms (cf. Message to the United Nations Conference to Negotiate a Legally Binding Instrument to Prohibit Nuclear Weapons, Leading Towards their Total Elimination, 23 March 2017), and I ask – as did Saint Paul VI and Saint John Paul II – that scientists actively cooperate to convince government leaders of the ethical unacceptability of such weaponry, because of the irreparable harm that it causes to humanity and to the planet. Consequently, I too reaffirm the need for a disarmament which today seems a subject less and less raised at the tables around which great decisions are made. May I be able to thank God, as did Saint John Paul II in his Testament, that in my Pontificate the world was spared the immense tragedy of an atomic war.

Global changes are increasingly influenced by human actions. Hence there is also a need for adequate responses aimed at protecting the health of the planet and its inhabitants, a health put at risk by all those human activities that employ fossil fuels and deforest the planet (cf. *Laudato Si'*, 23). Just as the scientific community has made progress in identifying these risks, it is now called to propose workable solutions and to convince societies and their leaders to pursue them.

In this regard, I am aware that in your sessions you have identified the insights that emerge from basic science and have worked to link them with strategic visions aimed at studying the problems in depth. It is your calling to come up with innovative developments in all the principal disciplines of basic science and to acknowledge the boundaries between the various scientific sectors, particularly in physics, astronomy, biology, genetics and chemistry. This is part of the service that you render to humanity.

I welcome the fact that the Academy also concentrates on the new knowledge necessary to confront the scourges of contemporary society. The world's peoples rightly ask to take part in forming their own societies.

The universal rights we proclaim must become reality for all, and science can contribute decisively to this process and to breaking down the barriers that stand in its way. I thank the Academy of Sciences for its valued cooperation in combating the crime against humanity that is human trafficking for the sake of forced labor, prostitution and organ trafficking. I stand at your side in this battle for humanity.

There is a long way to go towards a development that is both integral and sustainable. The elimination of hunger and thirst, high levels of mortality and poverty, especially among the eight hundred million needy and excluded of our earth, will not be achieved without a change in our way of living. In the encyclical *Laudato Si'*, I presented some key proposals for attaining this goal. Nonetheless I believe I can say that there is a lack of will and political determination to halt the arms race and to put an end to wars, in order to pass urgently to sources of renewable energy, programmes aimed at ensuring water, food and health for all, and investing for the common good the enormous capital that remains inactive in fiscal paradises.

The Church does not expect science merely to follow principles of ethics, which are a priceless patrimony of the human race. It expects a positive service that we can call with Saint Paul VI the "charity of knowledge". You, dear scientists and friends of science, have been entrusted with the keys of knowledge. I would like to stand before you as the advocate of the peoples that receive only rarely and from afar the benefits of vast human knowledge and its achievements, especially in the areas of nutrition, health, education, connectivity, well-being and peace. Allow me to say to you in their name: may your research benefit all, so that the peoples of the earth will be fed, given to drink, healed and educated; may political life and economy of peoples receive from you indications on how to advance with greater certainty towards the common good, for the benefit especially of the poor and those in need, and towards respect for our planet. This is the immense panorama that opens up before men and women of science when they take stock of the expectations of peoples: expectations animated by trusting hope, but also by anxiety and unrest.

I bless all of you from the heart, I bless your work and I bless your initiatives. I thank you heartily for all that you do. I accompany you with my prayers and I ask you please, do not forget to pray for me. Thank you.

Introduction and Overview

JOACHIM VON BRAUN

Introduction

In the 2018 Plenary we attempted to identify emerging insights from basic science, and – where appropriate – connect new insights with visions for problem-solving research and related strategies. The 2018 PAS Plenary was guided by the ideas that

– Basic sciences remain fundamental for generating a valid and evidence-based model of the world,
– Sciences become ever more interconnected across disciplines, including the humanities,
– Scientists and science policy makers need to continuously engage with society to foster trust in science.

"Trust" and "Science" are in an ambivalent relationship: trustworthy review mechanisms are an essential element of science; review is part of checks and balances within science; no invention is trusted right away; skepticism and falsification must be part of science.

Science communication is an obligation of the science community. Complex issues need to be explained to the public, because citizens need to understand inventions, innovations and their consequences. Otherwise, fears can arise and populists can misuse science insights and undermine trust in science and freedom of science. Our Academy is particularly sensitive to any such tendencies, and therefore entered in dialogues with science policy makers, as well as religious leaders at the Plenary Session 2018.

This Plenary had the following objectives:

1. To identify evidence-based and sustainable problem-solving strategies and related research for people's wellbeing, poverty reduction, health, and humanity's current problems of environmental destructions and conflicts.
2. To identify groundbreaking developments in the main disciplines of basic science.
3. To identify and share approaches on how to maintain and strengthen societies' trust in science.

We live in times, in which people's livelihoods and world views are hugely influenced by science, innovation, and technological changes. The potentials of science for the betterment of livelihoods are large. If trust in science systems declines, it may jeopardize this transformative power of science. Reduced support of science by society would reduce innovation and undermine the capacity by social and natural sciences to address challenges such as environmental destruction, climate change, inequality, hunger, and poverty. At the Plenary, opportunities to enhance trust in science were identified, including science education, science communication, and citizen science, i.e. participation and inclusion of citizens in the science processes. We also embraced the theme, how to foster fruitful relations between sciences and religions.

Overview

We structured the Plenary Conference in three blocks: a first block aimed to cover scientific assessment of a set *of large global humanities issues*, including population, health, climate change, ecology, and the underlying causes of problems related to these domains. A second block addressed *frontiers in science disciplines*, i.e. physics, chemistry, biology, and a third block dealt with transformative *roles of science in society* and the fruitful inclusion of science in society.

1. Scientific assessment of a set of large global humanities issues

In this segment, Academicians and guests covered world population change and future population dynamics, climate and energy, basic issues of (un-)sustainability, climate, health, genomics, antibiotics, ecology and bio-systems and the oceans. The complementary nature of scientific experimentation and thought experiments was presented, too. By selecting this set of issues, the Academy expressed its concern about challenges faced by humanity. At the same time, the Academy highlighted science opportunities for solutions to problems in these domains. Typically, these solutions are based on interdisciplinary research and involve non-science actors, citizens, governments, and corporate sectors. At the same time, it was evident that many of the solutions of societal challenges result in part from breakthroughs in basic sciences that show impact for society in the long run. New basic science insights achieved in the past often became "applied" and problem solving science later.

2. Frontiers in science disciplines

The science community of PAS members and guest speakers highlighted science frontiers in key disciplines. Firstly, such frontier insights were presented independently from linking them to applications or solution orientation; later and during discussions, new insights were related to innovations for wellbeing of people and the planet. Exciting new research insights were reported in *physics* (e.g. constants of nature and their applications for measurement; quantum technology; origins of life), *in astronomy* (e.g. the space renaissance; uses of small satellites; exoplanets), in *biology, genetics, and chemistry* (e.g. stem cells and tissue regeneration; the role of microscopy; gene biology and evolution; amino acid polymers for drug development; cancer immunotherapy; protein degradation; CRISPR-Cas). Related to several of these new insights it became evident that the pathways from so-called basic science toward innovations for problem solving have become short, and the distinction between the categories of basic and applied science may lose relevance.

3. Transformative roles of science in societies and way forward

The third block of presentations and discussions attempted to arrive at syntheses from the previous two blocks with a focus on transformative roles of science in societies, and especially distilling implications for science policy making. The discourse included engagement of Academicians with science policymakers and Christian religious leaders. Causes of lack of trust in *scientists* and/or in *science systems* were discussed. Some questioned, whether there is actually evidence of such loss of trust in science.

Pressures to do translational science and to justify basic science with short-term utilitarian rather than epistemic arguments were noted, however. The moral and ethical aspects and needs for sharing of science across countries and globally was stressed, as were moral dimensions of science policy choices.

The key role of science for shaping opportunities of people and planet will only be maintained if education for science is taken seriously. The large potentials of fruitful relations between science communities and religious communities to improve the wellbeing of people were highlighted. This relationship will foster the transformative roles of science in society only if both, the science communities and the religious communities, consider themselves as citizens and not as separate communities in society.

The insights from the Plenary Conference are compiled in the *Conference Statement* in the next section. I am grateful to the Academicians and all guest speakers for their contributions to the conference and to this volume.

We are particularly grateful to His Holiness, Pope Francis, for his address to the Pontifical Academy of Sciences on this occasion. In his address, he called upon us that

> *…greater attention should be paid to the values and fundamental goods that are at the basis of the relationship between peoples, society and science. This*

> *relationship demands a rethinking aimed at promoting the integral advancement of each human being and of the common good.*

And Pope Francis gave voice to the poor and disadvantaged by stating in front of us,

> *I would like to stand before you as the advocate of the peoples that receive only rarely and from afar the benefits of vast human knowledge and its achievements, especially in the areas of nutrition, health, education, connectivity, well-being and peace. Allow me to say to you in their name: may your research benefit all, so that the peoples of the earth will be fed, given to drink, healed and educated; may political life and economy of peoples receive from you indications on how to advance with greater certainty towards the common good, for the benefit especially of the poor and those in need, and towards respect for our planet.*

Final Conference Statement

His Holiness Pope Francis has made clear in his Encyclical *Laudato Si'* in 2015 and other comments that the world is facing unprecedented challenges, which threaten the future of civilization. These challenges have been identified and discussed in numerous previous meetings of the Pontifical Academy of Sciences. We refer to the respective statements by the Pontifical Academy, as they remain highly relevant.[1]

This statement by the Pontifical Academy of Sciences is based on its Plenary Session of 2018 and takes note of some trends in society and science and shares scientific insights on key risks of humanity and science opportunities to address them. Frontiers in main scientific disciplines are highlighted and potential action items emerging from science policy consultations are derived. The purpose of this statement is to stimulate thought and action for more fruitful exchange among science and society. In that context, we also embraced the theme of how to foster fruitful relations between the natural sciences, the empirical branches of the social sciences, and religion.

I) On science and society

People's wellbeing is the goal of the world's longstanding commitment to sustainable development. Achieving it requires coordinated progress on all of the UN's recently adopted Sustainable Development Goals. Advances in science are essential to achieving such progress.

Both societal change and scientific changes occur more and more rapidly, and the two are interlinked. PAS notes that these interlinked changes require responsible engagement by science communities. Science is an integral part of human culture and scientists must not view themselves as a separate community in society.

Global change is increasingly impacted by human actions but appropriate and comprehensive responses to the Anthropocene's risks for human

[1] Selected Recent Statements by the Pontifical Academy of Sciences: *Biological Extinction – How to Save the Natural World on Which We Depend*, PAS-PASS Workshop 2017; *Health of People and Planet: Our Responsibility*, PAS-PASS Conference 2017, with a focus on climate change; *Science and Sustainability. Impacts of Scientific Knowledge and Technology on Human Society and Environment*, 2016; *Sustainable Humanity, Sustainable Nature: Our Responsibility*, 2014

wellbeing and planetary health are currently insufficient. Science has progressed with identifying these risks but needs to focus more intensively on working with society and politics to identify and implement solutions that are equitable and just and that acknowledge the inherent complexities of the tightly coupled inanimate and animate systems of our planet.

While acknowledging the limitations of science to predict its own dynamics, let alone the even more complex societal changes, foresight into risks and opportunities in the long-term future is needed. Intensified interaction between science and society and trust in science are needed in order to identify large global risks and opportunities and the roles of science and technologies in addressing them rationally, with wisdom and collectively.

Science must constantly earn the trust of society. Advances in science and changes in society constantly challenge the relationship between science and society. Especially in a time when 'post-truth' sentiments are voiced regularly, the importance and relevance of evidence-based insights and solutions must be effectively demonstrated, not just asserted. A loss of trust in science would result in multiple consequences for society, including reduced opportunity for scientific knowledge to inform societal decisions and fewer opportunities for science to have a transformative impact on innovation and technology. Our Academy is particularly sensitive to any such tendencies and therefore seeks ongoing effective dialogue and interaction with science policy leaders and citizens. Transparency and humility are imperative in such exchanges. We seek to strengthen both the ability of science to deliver transformative knowledge as well as the mechanisms to enable society to benefit from new and existing scientific knowledge.

We note that freedom of thought is fundamental for societal wellbeing - including minorities - and freedom of sciences is fundamental for science to identify new truths and facilitate progress with responsibility. PAS is an independent body within the Holy See and appreciates freedom of research. PAS has as its goal the promotion of the progress of the sciences, the study of related epistemological questions, the investigation of ethical implications of scientific discoveries and their application as well as the broad dissemination of scientific knowledge for the betterment of human wellbeing.

The discourse between science and society will be endangered, if equality of rights is not assured, including equal rights of women and men, rights of the poor and most vulnerable, and children's rights. Science must get involved in this discourse, foster understanding of the barriers and drive changes needed to overcome human trafficking, modern slavery and abuse.

Progress in achieving the Sustainable Development Goals (SDGs) has been sporadic. Many of the targets, including overcoming hunger and high mortality, will not be achieved without major changes in the course of action taken and the integration across the seventeen SDGs. Pope Francis' Encyclical *Laudato Si'* has made key proposals for accelerating progress. Science is directly relevant to that progress. Scientists need to play a more active role in engaging with society and offering information, assistance and potential solutions at global, national, and local levels. Inclusion of youth is key for the success of these efforts.

II) Selected insights from sciences frontiers to address humanities' challenges

In the 2018 PAS Plenary Session, we identified emerging insights from both basic science and use-inspired or translational science. We aimed to identify:

- Groundbreaking developments in the main disciplines of basic science.
- Evidence-based problem-solving strategies and related research for people's wellbeing, poverty reduction, and humanity's current problems of environmental destructions and conflicts.
- Approaches on how to maintain and foster societies' trust in science.

From the PAS Plenary themes, several frontiers in science disciplines may be highlighted.

Astronomy, Space: Thanks to improved instruments, in space and on the ground, cosmologists can trace the history of our expanding universe back to the first nanosecond. This progress brings into focus a new set of questions: What generated the observed 'mix' of atoms, dark matter, dark energy, and radiation? Was 'our' big bang the only one? And the realization that there are likely to be billions of Earth-sized 'habitable' planets orbiting stars within our galaxy, has initiated a vibrant new research effort, linking astronomy more closely with biology and environmental science. Due to these novel insights, questions on the origin of life seem to have become more approachable.

Physics: Physics continues to expand its reach across scales and contributes tools to many other areas of science, from astrophysics to biochemistry and medicine. At the most fundamental level, physics tries to model the basic constituents of matter and their interactions. Experiments at high particle energies or with extreme precision are probing conceivable limits of the standard model. Precise measurements of fundamental constants are making it possible to redefine the basic units of measurements so that human-made artifacts can be entirely avoided. The laws of quantum physics have led to a far-reaching understanding of atoms, molecules, and condensed matter, and they have enabled past transformative inventions such as the transistor, the laser or magnetic resonance imaging. Quantum physicists are now beginning to harness counter-intuitive quantum phenomena, such as entanglement, to engineer new quantum technology. Envisioned goals include highly sensitive and accurate sensors for forces and fields, secure, unbreakable communication, and quantum information processing. Quantum computers and quantum simulators will enable new approaches to the modeling and understanding of complex systems, such as high-temperature superconductors, that are outside the reach of classical computers.

Biology: Advances have occurred recently in biological sciences that are highly significant towards improving people's health and wellbeing. Some aspects of these advances have been discussed in this session. Such is the case for the identification of the role of stem cells in development, in the process of cell renewal of adult tissues, and their potential for regenerative medicine. The production of a drug against multiple sclerosis is a spectacular example of the direct translation of basic research into medicine. Another highlight of the application of research to human health is the progress in cancer treatment by immunotherapy, together with the hope of novel approaches directly derived from recent results in cell biology. The importance of technical improvements in the process of discovery has been underlined. One example is the spectacular development of new microscope technologies allowing the tracking of molecular processes in living cells. Equally spectacular is the progress in genomics, proteomics, and metabolomics, all of which profit from the availability of huge databases (big data) and the availability of unprecedented computing power. The project for a "Genome information-oriented society" paves the way for personalized medicine. Last but not least, the enormous potential was discussed that stem cell engineering has for the regeneration or replacement of injured tissue and organs. However, particular attention was drawn to the necessity of an ethical attitude in the application of these spectacular scientific advances in order to respect and protect human dignity.

Medicine, Brain: The past decade has seen major breakthroughs in the therapy and even cure of previously fatal diseases, all of which were the consequence of applications of curiosity-driven scientific discoveries to medical problems. Examples are the treatment of Hepatitis C, the development of vaccines against Ebola, the ability to stabilize and sometimes even cure patients infected with HIV, the successes to repress and sometimes even cure cancer by combining immunotherapy and genetic engineering with the classical approaches, the greatly improved success of organ transplantation, and the healing of certain genetically determined diseases by genetic engineering and gene therapy. Much less progress has been made in the treatment of the major psychiatric diseases. The main reason is the still sparse knowledge about the neuronal mechanisms underlying higher cognitive functions. Major challenges are the immense complexity of the nervous system and the fact that its functions are determined not only by genetic but to a large extent also by epigenetic shaping. Here the specific problem is that environmental influences comprise not only biological factors such as nutrition or toxins but to a substantial extent also socio-cultural conditions. Hence, coping with the behavioral and psychological consequences of a diseased brain state requires not only biological interventions but must also consider socio-cultural influences at large. More progress has been made with respect to the substitution of impaired sensory and motor functions using neuronal prostheses or brain-machine interfaces and here is space for promising improvements. To alleviate the symptoms of Parkinson's disease deep brain stimulation with implanted electrodes is now applied in hundreds of thousands of patients and attempts are also underway to use this invasive technique to alleviate psychiatric symptoms. As interference with brain functions, whether with pharmacological, surgical or electrical means, often alters not only motor functions but affects also higher cognitive functions and traits of personality, strict ethical control of such interventions is required but not always implemented. Novel ethical challenges are also created by the progress in reproductive medicine (cloning, therapy of mitochondrial diseases), allo- and xeno-transplantation, and with the introduction of the CRISPR/Cas technology that permits shortcuts to gene editing and gene therapy. As science is international, it is an obligation of the scientific community to make this need transparent and to strive for widely accepted international regulations.

Finally, deeper understanding of the brain mechanisms supporting anti- and prosocial behavior (aggression, greed, hate/altruism, empathy, compassion, cooperativity) will hopefully provide the insight required for the development of effective educational regimes and societal incentives to enhance prosocial and constrain antisocial behavior. Substantial progress in this domain is indispensable in order to confine the dual use problem of scientific discoveries. If progress in science and the ensuing increase in power continues to be perverted for the selfish exploitation of the planet´s resources and the design of ever-effective weapons, the unquestioned benefits of science are jeopardized.

III) Science addressing large humanities issues and their underlying causes

Climate change, energy, sustainability: The new science of climate extremes has made it possible to link many weather extremes to climate change. During the next 25 years, intensification of weather extremes due to climate change can expose more than 1.5 billion people (20% of the population) to deadly heat stress and other attendant health risks. While the poorest among us (numbering over 3 billion) are most vulnerable, climate change has now the potential to adversely impact the wealthy too in the form of intense fires, floods, and droughts. New research has also identified the risk that unabated greenhouse-gas emissions might push the planet into a 'hothouse state', with 5-6°C higher temperatures and up to 60 m sea level rise. Many solutions are still available to avert catastrophic impacts, including mass migrations. The fundamental challenge is to garner massive public support for climate actions. PAS can help immensely by forging an alliance between leaders in science, public health, policy makers, and leaders of all faiths. The glue for such an alliance is the knowledge that both science and religion agree on protecting creation (nature) including the 7.5 billion people; and the knowledge that (because of our inaction to mitigate) climate change has become a huge moral and ethical issue.

SDGs, health, and wellbeing of population: Healthcare is a universal right as recognized by the United Nations charter. The economic, social, and cultural rights are recognized in articles 22 to 27. Science develops the data from which the template/protocol/standards of health care are derived. Hence, the process of standardizing protocols to attain the specified goals is a matter of science. Inequalities and lack of capacities in the production and utilization of science, technology, and innovation (STI) pose a real challenge to many developing countries, especially the LDCs, in their efforts to solve real-life problems and achieve the SDGs. Yet, we also live in a world of unprecedented opportunities. A world in which frontier science and technology innovations, including digitization, internet of things, artificial intelligence, robotics, drones, 3D printing and genomics hold more promise, than ever before, in resolving such fundamental problems as energy, food, and water securities as well as controlling biodiversity loss and curbing the impact of climate change and natural disasters in all countries.

Nutrition: Despite recent progress in tackling malnutrition, last year the number of hungry people in the world rose to 821 million – yet it is estimated that one-third of the food produced annually is lost or wasted. We also face huge challenges to address micronutrient deficiencies, which may harm approximately two billion people. Worldwide obesity is rising, having almost tripled to more than 800 million people between 1975 and 2016. This is not just a high-income, urban phenomenon, but is increasingly impacting lower income groups and rural populations. Overall, the food system is also placing huge pressures on the environment, as a major contributor to deforestation, air and water pollution, and climate change. Science needs to further identify solutions, but important insights are gained and on that basis we urge governments and the private sector, as well as other stakeholders, to undertake scalable and practical solutions, which reflect the central role of safe foods and healthy diets to the Sustainable Development Goals, and to overcome the particularly large burden of unsafe and unhealthy food for the poor.

Ecology and bio-systems (incl. opportunities of genetics): Knowledge about evolution of the universe, of living organisms and of living conditions calls for and offers opportunities to safeguard the very biodiversity that is both our responsibility as stewards of creation as well as the fundamental basis of the life-support systems of the planet. The interdependence of different species of living organisms, highlighted by Pope Francis in *Laudato Si'*, requires more holistic approaches to sustainable development than are currently underway. The biodiversity goals in SDG 14 and 15 underpin most of the other SDGs, enabling humanity, for example, to address poverty, food security, and job creation, and assist with mitigation and adaptation to climate change. Driven by scientific advances, encouraging solutions are now being implemented to help protect biodiversity and enhance the resilience of ocean ecosystems. Specifically, Marine Protected Areas (MPAs) that are fully protected from extractive activities can preserve and restore biodiversity and habitats within their boundaries. Moreover, much of that bounty spills over to adjacent areas outside, helping to restore depleted fisheries. These fully protected areas can also enhance the resilience of ocean ecosystems to climate and other environmental changes. Due to scientific evidence about the benefits of MPAs, there has been an order of magnitude increase in the area of the ocean in MPAs over the last decade. Nonetheless, the area protected is still far less than the international targets set by countries in the SDGs and the area that scientists calculate is likely needed to maintain the health, productivity, and resilience of ocean ecosystems. Hence, in fully protected MPAs, humanity has a powerful, but underutilized tool to help achieve multiple goals.

In parallel to protecting biodiversity and ecosystem functioning through the use of fully protected MPAs, there is new evidence that fisheries can be reformed and restored to greater productivity and resilience to climate change. New science-based approaches to fishery management are demonstrating that it is possible to use the ocean without using it up. Successes in developed as well as developing countries provide models for ways in which science can assist in achieving food security and job creation through the restoration of productive fisheries that bring economic, environmental, and social benefit.

These successes underscore the *connections across the SDGs*, e.g., between biodiversity, health, food security, jobs, and climate change. They also emphasize the importance of science. Moreover, they provide much-needed hope that sustainability is indeed possible when science is used in service to society and when scientists engage with society to tackle big problems.

Another exciting and encouraging development is the availability of cheap miniaturised satellites, enabling monitoring by whole fleets of satellites of land use, urban development, shipping movements, etc. These systems can harvest the data needed for an evidence-based management of our biosphere. In addition, they can be used to bring the internet to undeveloped and isolated regions, thus enabling the less privileged to also profit from accumulating knowledge.

However, human actions are not only jeopardizing the equilibrium of the geo- and biosphere but also their own biotope. We witness the disproportionate and disorderly growth of large cities, whose number and populations are increasing at a dramatic pace. This creates unhealthy living conditions due to pollution, acceleration and overstimulation, anonymity and loneliness, steep gradients between the wealthy and the poor, and the ensuing violence. By contrast, however, big cities also nurture scientific advances, provide a rich cultural environment, professional education, and health care infrastructure and thereby can greatly improve the quality of life of their citizens. Ideally, we should plan new smart cities with a human dimension, containing all the advantages that science can offer, such as clean water, clean environment, connectivity, etc.

IV) Opportunities for consultations among leaders of science organizations, policy makers, religious communities, and Academicians

Taking note of the transformative roles of science in societies, key science policy issues addressed in the consultations were:

Scientific inquiry is constitutive for human culture and has a moral value in itself. As long as humanity actively and intentionally interferes with the world, it is a moral obligation to strive for an evidence-based model of the world as this seems to be the only safe way to judge the consequences of actions.

As *discoveries* are per definition hard to anticipate and as many of them are actually serendipitous, it is epistemically questionable to identify priorities for scientific inquiry solely as a function of short-term applicability. A safe investment is to provide conditions that enhance creativity. Science education of the young, literacy, freedom of thought, and investment in research institutions with flat hierarchies must be priorities. A prerequisite to achieve these goals is the liberation from precarious living conditions. Those struggling for life cannot afford the leisure that nurtures creative thinking.

At the same time, science can also provide immediately *useful solutions to global problems* that require our immediate attention. Investments in both basic and use-inspired (or translational) science are in society's strong interests. Thus, a balance of curiosity-driven and problem-solving science should be encouraged.

Ex-ante identification of *promising fields of science* remains difficult, yet science policy and related financing constantly need to make related decisions. Bold decisions in the face of scientific uncertainties are called for to address uncertain but high-risk global changes.

Science policy choices require consideration of *moral dimensions*. Science communities need to actively engage in shaping and promoting evidence-based worldviews, and in doing so we see synergies between free and responsible natural sciences, the empirical branches of the social sciences, and religion.

Religion harvests and concentrates the collective experience of populations about rules of moral conduct that are helpful to support peaceful co-existence and thus contributes empirical evidence on the validity of moral rules that is complementary to the evidence provided by science. Religion is also a significant expression of human dignity. It can facilitate understanding of short-term trends within the horizon of the existential and eternal questions of humanity. Thus, it contributes to critical analysis and moral discernment as well as to the expression and experience of meaning-making. The urgent questions of our present time call for a framework of resilience, co-existence and hope, to which religious views and practices contribute a robust grounding.

Joint action to preserve and strengthen *trust in sound science*: scientists and science policymakers need to engage with society to foster trust in science and patiently counter the spread of statements that are grossly distorting realities. Sources of trust and mistrust in science must be understood and opportunities to enhance trust in science identified, including science education and communication.

Sharing of science that can help to address global risks across countries for collective action: We note that science itself and its benefits for humanity are not shared sufficiently across nations. As science is fundamental for humanity, this inequality is an ethical issue of growing importance. Developing countries need to be actively included in the advanced international science systems.

Science is partly to be viewed as a *public good*, not only a factor in nations' competitiveness. This especially applies to basic science. The societal and policy demands for short-term translational science need to be critically evaluated and must not marginalize the focus on basic sciences that usually pays off only in the long run. This applies to basic as well as translational (use-inspired) science. Society benefits hugely from the full range of science. Both basic science and translational (use-inspired) science are needed and important.

The *transformative power of science* and technology are obvious (communication, biotechnology, medicine, information processing). However, these goods need to be shared by all countries. Beyond governments and international organisms such as UNESCO and OAS, national and international academies, which are independent civil societies, have a particularly important and responsible function to play in the promotion of knowledge and education among the people of the world.

Final remarks

In accordance with the recommendations of His Holiness Pope Francis in his address to the members of the Pontifical Academy of Sciences and guests, we reexamined the potential of science to identify imminent challenges for our geo- and biosphere and to provide solutions. We left the meeting deeply concerned about the state of the world. Not only that old problems like nuclear arms proliferation seem to re-emerge, but contemporary problems, nearly exclusively generated by human action, keep on aggravating. Nevertheless, we put our hope in our ability to overcome the challenges by combining the rational strategies derived from scientific evidence, provided both, by the natural sciences and the empirical disciplines of the social sciences, with the cultural achievements, that define human dignity, are at the basis of our ethical and moral attitudes and roots in normative systems and religion.

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Thierry Boon Falleur
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William C. Clark
Br. Guy Consolmagno
Michael Heller
Carlo Rubbia
Helen M. Blau

Programme

Monday 12 November 2018

OPENING SESSION
Chair: Joachim von Braun

9:00 *Opening, Words of Welcome and Concept of the Plenary*
Joachim von Braun

Introduction to the Plenary
H.E. Msgr. Marcelo Sánchez Sorondo

BLOCK 1. SCIENTIFIC ASSESSMENT OF A SET OF LARGE GLOBAL HUMANITIES ISSUES (POPULATION, HEALTH, ECOLOGY, AND THEIR UNDERLYING CAUSES)

SESSION I – POPULATION AND SCIENCE APPROACHES

9:10 *World Population Change – Future Dynamics*
Wolfgang Lutz

9:30 *The Complementary Nature of Scientific Experimentation and Thought Experiments*
Werner Arber and Marcel Weber

9:50 Discussion

SESSION II – CLIMATE AND ENERGY
Chair: Edward M. De Robertis

10:00 *Energy for the Nine Billion*
Steven Chu

10:20 *Energies for the Future*
Carlo Rubbia

10:40 Discussion

10:45 Coffee Break

11:15 Audience with Pope Francis, Consistory Hall

13:30 Lunch at the Casina Pio IV

14:30 *What Must Be Sustained to Enable Sustainable Improvements in People's Well-being?*
William C. Clark

14:45 *Where on Earth Are We Heading: Pliocene or Miocene?*
Hans Joachim Schellnhuber

15:00 Discussion

SESSION III – HEALTH

Chair: Klaus von Klitzing

15:25 *The Revolution of Personalized Medicine – Bioethical Obstacles on the Road of Technological Advances*
Aaron J. Ciechanover

15:40 *Organ Transplants*
Francis L. Delmonico

15:55 *The Three-Dimensional Architecture of the Human Genome: Understanding the Physical Mechanisms Controlling Gene Expression*
José Nelson Onuchic

16:15 *Next Generation Antibiotics*
Ada E. Yonath

16:30 Discussion

16:50 Coffee Break

SESSION IV – ECOLOGY AND BIOSYSTEMS

Chair: Edward M. De Robertis

17:20 *Saving Plants from Extinction: How and Why?*
Peter H. Raven

17:35 *Science in a Post-Truth World: Hope for People and the Ocean*
Jane Lubchenco

17:50 Discussion

BLOCK 2. FRONTIERS IN SCIENCE DISCIPLINES

Science community of PAS members and guest speakers highlight science frontiers. Firstly, frontier insights are presented independently from linking them to applications or solution orientation; later and during discussions, new insights may be related to innovations with social responsibility, wellbeing of people and the planet, development of long term perspectives.

SESSION V – PHYSICS

Chair: Theodor W. Hänsch

18:10 *Constants of Nature and Their Applications*
Klaus von Klitzing

18:25 *The Dilemma of Basic Research*
Daniel Kleppner

18:40 Discussion

19:00 Dinner at the Casina Pio IV

Tuesday 13 November 2018

SESSION VI – PHYSICS

Chair: Martin Rees

9:00 *Making the Revolutions of Quantum Technology Deliver for People and Planet*
Massimo Inguscio

9:20 *Science Addressing Questions Not Easily Addressed by "the" Scientific Method. The Origins of Life*
Steven A. Benner

9:40 Discussion

10:00 Coffee Break

SESSION VII – ASTRONOMY, SPACE

Chair: Martin Rees | continued

10:30 *The Space Renaissance and Impacts on Humanity*
Will Marshall

10:50 *The Uses of Small Satellites for Environmental Monitoring, Bringing We-Fi to Africa, and Related Opportunities*
Martin N. Sweeting

11:10 *Exoplanets and Beyond*
Sara Seager

11:30 *Our Place in Space and Time*
John D. Barrow

11:50 Discussion

SESSION VIII – BIOLOGY, GENETICS, BIO-CHEMISTRY, CHEMISTRY

Chair: Vanderlei S. Bagnato

12:10 *Stem Cells and Tissue Regeneration*
Helen M. Blau

12:30 The Role of Microscopy in Improving the Human Condition
Robert Eric Betzig

12:45 Discussion

13:00 Lunch at the Casina Pio IV

14:30 *On Gene Biology and Evolution*
Takashi Gojobori

14:45 *The Dependence Receptor Paradigm: When an Original Cell Death Pathway is Used as a Therapeutic Strategy Against Cancer*
Patrick Mehlen

15:00 *From Basic Research on Amino Acid Polymers to the Most Used Drug Against Multiple Sclerosis*
Michael Sela

15:15 Discussion
15:35 *Cancer Immunotherapy: Improved Treatment and Issues*
Thierry Boon-Falleur
15:45 *Regulation of Protein Degradation and Endocytosis by Wnt Growth Factors*
Edward M. De Robertis
15:55 *The CRISPR-Cas Technique for Gene Editing and its Impact on Society*
Rafael Vicuña
16:05 Discussion
16:30 Coffee Break

BLOCK 3. TRANSFORMATIVE ROLES OF SCIENCE IN SOCIETIES

This block attempts syntheses from Blocks 1 and 2, with presentations and discussions on transformative roles of science in societies and implications for science policy. Discussions with science policymakers address science policy, causes of lack of trust in science and what to do about that; pressure to do translational scienceand to justify basic science with utilitarian rather than epistemic arguments; roles of public and private research; sharing of science across countries; policy choices and their moral dimensions; education for science and curiosity, and fruitful relations between sciences and religions.

SESSION IX – FUTURE SCIENCE POLICY | DISCUSSION AMONG LEADERS OF SCIENCE ORGANIZATIONS, POLICY MAKERS, RELIGIOUS COMMUNITIES AND ACADEMICIANS

Chairs: Wolf Singer and Joachim von Braun

17:00 Jean Pierre Bourguignon | *President of the European Research Council*
Georg Schütte | *State Secretary of Education and Science, Germany*
Lino Barañao | *Former Science Minister of Argentina*
Rev. Antje Jackelén | *The Lutheran Archbishop of Uppsala in Sweden and Primate (inter pares) of the Church of Sweden*
Jürgen Mittelstraß | Academician, The Pontifical Academy of Sciences
Card. Lluís Martínez Sistach | Archbishop Emeritus of Barcelona, Spain
H.E. Msgr. Marcelo Sánchez Sorondo | *Chancellor, The Pontifical Academy of Sciences*

Panelists' statements (10 minutes each, followed by panel interaction with ample amount of time – till 19:00, as well as over dinner)

18:30 Panelists' Discussion with Academicians and Guest Speakers
19:30 Dinner at the Casina Pio IV

Wednesday 14 November 2018

SESSION X – TRANSFORMATIVE ROLES OF SCIENCE, PEOPLE AND EDUCATION

Chair: Jürgen Mittelstraß

9:00 *The Role of Science in the Culture of our Time (Modern or Pre-Aristotelic?)*
Antonino Zichichi

9:15 *Education for a Digital Sustainable Environment*
Antonio M. Battro

9:25 Science Education & Climate Change Authors
Yves Quéré

9:35 Discussion

10:05 Coffee Break

SESSION XI – CONCLUSIONS OF THE 2018 PLENARY

Chairs: Joachim von Braun and H.E. Msgr. Marcelo Sánchez Sorondo

10:35 Brief introductions by teams of Blocks 1, 2, and science policy implications based on a draft statement
Martin J. Rees, Vanderlei S. Bagnato and Theodor W. Hänsch: *New Insights From Basic Sciences* (Block 1)
Wolf J. Singer, Nicole M. Le Douarin and Werner Arber: *Problem Solving Science Opportunities* (Block 2)
Science Policy in Support of Trust in Science (Policy Debates Outcomes)

11:05 General Discussion based on Final Statement

13:00 Lunch at the Casina Pio IV

SESSION XII – CLOSED SESSION FOR ACADEMICIANS

14:00 Self-Presentations
Helen M. Blau
Robert Eric Betzig
Steven Chu
Rev. Guy Joseph Consolmagno SJ
Mohamed H.A. Hassan

14:50 Commemorations
Günter Blobel (Edward M. De Robertis)
Stephen W. Hawking (Martin J. Rees)
Fotis C. Kafatos (Nicole M. Le Douarin)
Félix Malu wa Kalenga (Vanderlei S. Bagnato)
Vera Rubin (Martin J. Rees)

15:40 Award Ceremony of the Pius XI Medal
Noble Ephraim Banadda
David M. Sabatini
Miriam Serena Vitiello

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Block 1 |

Scientific Assessment of a Set of Large Global Humanities Issues

SESSION I – POPULATION AND SCIENCE APPROACHES

World Population Trends and the Rise of *Homo Sapiens Literata*

Wolfgang Lutz[1]

1. Introduction

The population of *homo sapiens* on our planet fluctuated at very low levels of population density throughout most of its history. There may even have been instances when our species was close to extinction. While the Neolithic revolution with the domestication of plants and animals starting some 12000 years ago lead to a marked increase of population sizes, world population up until around 1500 AD stayed below the size of 500 million, i.e. lower than the entire population of the European Union today. Over the last half millennium humankind has experienced many more revolu-

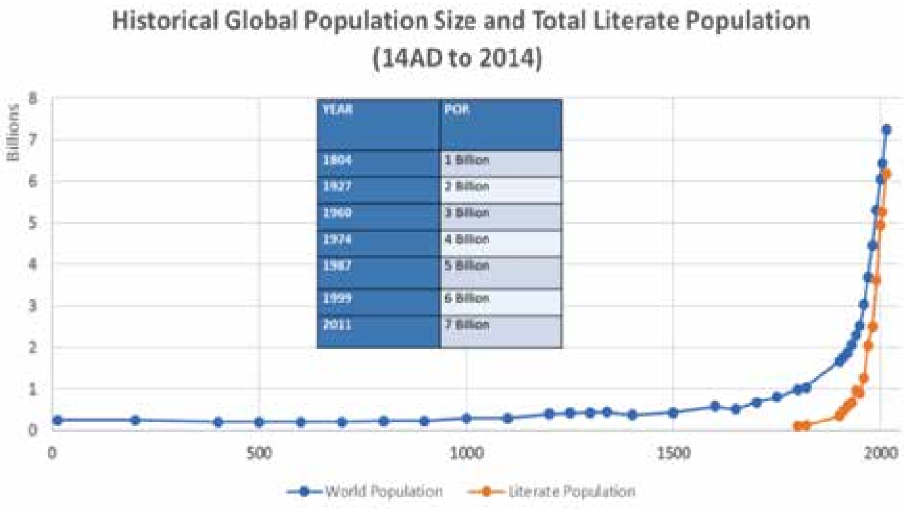

Figure 1. World population size and size of the literate population over the past 2000 years.

[1] Wolfgang Lutz is the Founding Director of the Wittgenstein Centre for Demography and Global Human Capital (Univ. Vienna, IIASA, VID/ÖAW); Leader of the World Population Program at IIASA; Scientific Director of the Vienna Institute of Demography of the Austrian Academy of Sciences; and Professor of Demography at the University of Vienna. Contact: lutz@iiasa.ac.at

tions in demographic, economic, social and technological terms. One of the hypotheses elaborated on in this paper is that these modern revolutions were to a large extent driven by the spread of literacy, and in particular female literacy, from being confined to elites to changing the lives of the general population. I will also argue that the future path of world population growth as well as adaptive capacity to already unavoidable climate change and other challenges will greatly depend on the speed of improvements in the education of women, particularly in the least developed countries. This decisive role of female education in improving the human condition shall be highlighted by introducing the new term "homo sapiens literata".

Figure 1 summarizes the big picture of the remarkable growth in the size of the human population on our planet over the past two centuries and the even more rapid increase in the literate population over essentially the last century. Estimates of past population trends show that the first billion of world population was only reached around 1804 and that it took another century and a quarter to reach the second billion. In contrast, the sixth and the seventh billion took only 12 years each to be added. By the beginning of 2020 the world population is estimated to stand at 7.7 billion and determining when the 8th billion will be reached depends on the projection assumptions made – probably around 2024. However, the growth rate has started to decelerate, and it is an open question – which is discussed towards the end of this paper – whether world population will ever reach 10 billion. As we will also discuss in this paper, both the acceleration of growth (through mortality decline) and the following deceleration (through subsequent fertility decline) are closely linked to and driven by the increase of literacy and basic education among broad segments of the population. Over the past millennia literacy skills have been limited to a small group of elites which at the global level stayed under one percent of the population until the rise of universal literacy started in Northern European countries in the 19th century. Over the first half of the 20th century most of Europe, Japan and the Americas became fully literate and during the second half most of the rest of the world, with some pockets of illiteracy only remaining in parts of Sub-Saharan Africa and Western Asia. This remarkable rise of literacy also was the key driver of remarkable social, economic and cultural changes.

In this paper I will first discuss demographic trends over the past two centuries and introduce the concept of cognition-driven demographic transition, i.e. how the declines in mortality rates and the subsequent decline in fertility were driven by improvements in the average levels of education of the population in interaction with medical and institutional innovations. Next, I will discuss how the increases in human capital turned out to be a key determinant for populations raising out of poverty and achieving economic growth and improvements in more broadly defined aspects of human wellbeing. This will be followed by scenarios about possible population and human capital trends over the coming century. In the conclusion I will discuss how the empowered *homo sapiens literata* has shaped the world, including a visible footprint on the natural environment which also threatens to undermine our own life support systems in the future. But I will also discuss how knowledge and education may offer opportunities for insight and foresight which can bring about a transformation towards sustainable development as well as strengthening our adaptive capacity to already unavoidable environmental changes.

2. Cognition-driven demographic transition

Demographic transition is the universal process of change from a pre-modern demographic regime of essentially uncontrolled high levels of birth and death rates to a modern regime of controlled and low levels of these rates. While in the context of fertility "controlled" refers essentially to the reproductive behavior of individuals/couples, in the context of mortality it also has a strong public health component. Intermediate stages of the demographic transition – when death rates have already fallen while birth rates are still high – are associated with high natural population growth, where "natural" refers to the balance of births and deaths not considering migration which in open populations is a third factor of population change.

While declines in mortality are almost always an object of universal aspiration, high fertility norms are often deeply rooted within cultures and typically take longer to change. Only after birth rates fall below the so-called "replacement level" of two surviving children per woman and a period of time passes when a young age structure results in an increase of women entering reproductive age (positive momentum of population growth) does population growth come to a halt. The precise timing of this process varies from one population to another, but the general process of the demographic transition is considered universal and essentially irreversible.

At the moment, various populations around the world are at very different stages of the demographic transition. While the process has been completed in Europe decades ago, it is now also complete in most countries in Asia and the Americas, but still under way in large parts of Africa, where most countries are still in the phase associated with high population growth. The striking differences in demographic patterns currently observed in different parts of the world are essentially a consequence of different populations being at different stages of this universal process.

The concept of demographic transition was originally triggered by the observation of declining birth rates in many European countries over the first decades of the 20th century. In the early writings, the words "demographic transition" and "demographic revolution" were used interchangeably. Warren Thompson (1929), Adolphe Landry (1934) and Frank Notestein (1945) were the first to classify countries as being at different stages of a universal process that brings them from a condition of high birth and death rates to one that is ultimately characterized by low birth and death rates. In this early literature, the driver of this process was simply called "modernization" without a deeper specification in terms of the relevant causal mechanisms involved. But what they likely had in mind was general socioeconomic development as the reason for a decline in crude death rates (CDR) that was typically followed by a decline in crude birth rates (CBR) after a time-lag of varying length – these rates give the number of births and deaths per 1000 in the population and are called crude because they do not adjust the age structure. As a consequence of the difference between CBR and CDR, the rate of natural increase (RNI) was rising in the process. Disregarding migration, this difference is the reason for population growth in all populations around the world.

Figure 2 illustrates this process for Finland, which has the world's longest national level demographic time series with annual data on death and birth rates since 1722. After strong fluctuations until the middle of the 19th century, in the 1870s a lasting decline in death rates started while the birth rates only entered a steeper decline at the beginning of the 20th century. During this period the population grew at around 1.3-1.4 percent per year. Figure 3 shows the pattern of demographic transition for Mauritius which has long and reliable time-series data and is the country in the African region that is today most advanced in this process. While up until the 1930s birth and death rates were at roughly the same level, death rates first started to decline with a particularly steep fall right after WWII while birth rates stayed high or even increased due to women being in better health status. From the early-1960s to the mid-70s Mauritius then experienced one of the most rapid fertility declines observed in human history with the mean number of children declining from above 6 to below 3 in less than 15 years (Lutz 1994). This comparison illustrates that the demographic transition of latecomers can be much more rapid than the rather gradual historical transitions ex-

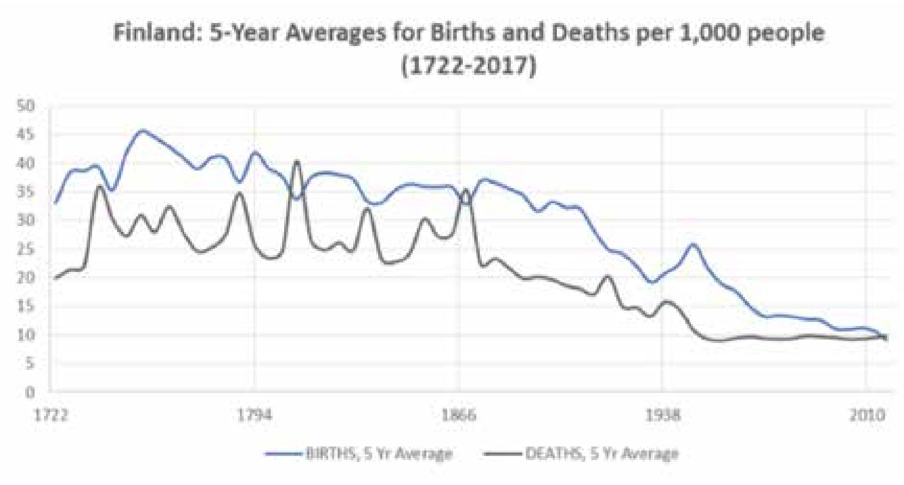

Figure 2. Crude birth and death rates in the territory of today's Finland 1722-2017.

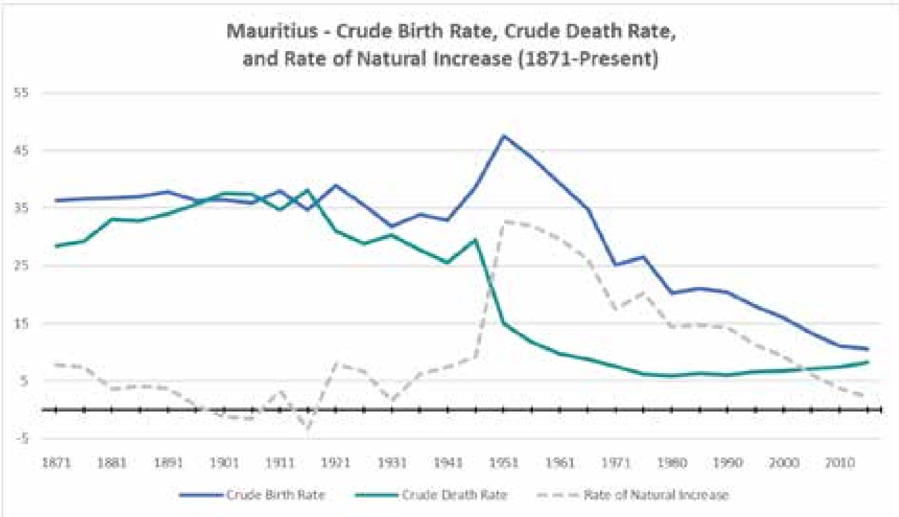

Figure 3. Crude birth and death rates on the island of Mauritius 1871-2017. Sources: Lutz (1994) and Wittgenstein Centre (2018).

perienced in Europe. Consequently, the population growth rates in today's developing countries can rise much higher than they ever were in historical Europe. In Mauritius they were over 3 percent per year in the 1950s which is equivalent to a doubling time of the population of just 23 years.

Much research has been conducted on trying to understand the drivers of the global demographic transition and the specific mechanisms that have caused the mortality and fertility declines. There have also been studies trying to unpack the rather vague notions of modernization and development into its more specific components relating to material/economic changes and cognitive changes related to expanding literacy and general education. There is no space here for a full record of the very extensive literature which has recently been summarized elsewhere (Lutz, Butz, et al. 2014). Instead, I will only give a brief sketch of some of the main arguments. As to the onset of the modern mortality decline in the 19th century in Scandinavia and England, as well as in today's developing countries, there have been two schools of thought associated with the names of McKeown (1976), who puts the emphasis on improving economic circumstances including better food supply, and Caldwell (1976), who emphasizes education and in particular female schooling. Other authors have stressed additional factors, such as medical progress and public health policies that brought down death rates and subsequently helped reduce fertility through declining demand for children (Easterlin 1983; Cleland & Wilson 1987). A recent comprehensive reassessment of the evidence concerning the drivers of global increases in life expectancy since the mid-20th century across all countries of the world shows that improvements in education seem to lie at the root of these increases in terms of improving knowledge and behavioral patterns and can explain the observed changes much better than increasing income, with public health interventions also playing some role, particularly in child mortality decline (Lutz & Kebede 2018).

The study of the drivers of fertility decline has been even more controversial. But there are some generally agreed insights. While in a few cases, such as historical France, the mortality and fertility declines happened only gradually and at about the same time, in most countries there was a distinct time lag of several decades between the observation of falling death rates and falling birth rates. This lag is explained by the fact that in virtually all cultures, norms and institutional settings favoring high fertility are deeply embedded in the normative systems of societies and change only slowly, whereas everybody readily accepts the possibility of higher survival chances as soon as it is attainable. Also widely accepted is the framework of the three basic preconditions for a lasting fertility decline as specified by Ansley Coale (1973):

1. Fertility must be within the calculus of conscious choice, i.e. move from the realm of fatalism to that of consciously planned behavior,

2. Lower fertility must be advantageous, and
3. There must be acceptable means for preventing births.

This framework nicely shows that there is no one-dimensional causation and the cognitive (education-related), economic (also urbanization-related) and contraception-related factors all need to come together in order to result in a lasting fertility decline. This was the case in historical Europe in the same way as it is in today's African populations. While perceived benefits of having fewer children (precondition 2) and the availability of culturally acceptable methods of family limitation (precondition 3) are also necessary for triggering a lasting fertility decline to low levels, the basic precondition 1 of moving from a more fatalistic attitude ("I have as many children as God gives me") to a conscious choice of a specific family size is closely associated with female education, as will be discussed in the following.

Girls' education and fertility decline

Consistent patterns of fertility differentials by mothers' education have been found from medieval times to the present in virtually all countries and at very different stages of economic developments (Skirbekk 2008). The differentials are particularly pronounced in countries during the process of demographic transition when death rates have already fallen and birth rates start to fall after a certain time lag (Fuchs & Goujon 2014). Only in recent years in the Nordic countries does the gradient seem to flatten or show a mild U-shape because more educated women can arrange their lives better in a way to actually achieve the two-child norm which is still almost universal in Europe (Sobotka & Beaujouan 2014). More generally, the empowering effect of education brings women in high fertility settings to want fewer children and find effective ways to have fewer children. They generally want fewer children for health reasons, as many births at short intervals can be a major risk in the absence of effective health services, and because of value change preferring fewer children who each will have better life chances, and possibly because of higher opportunity costs. Also, better educated women can better resist the traditional pro-natalist norms in their societies and resist the often higher fertility desires of their husbands (Lutz 2014).

The empirical evidence for a strong fertility reducing effect of education in today's high and medium fertility countries is overwhelming, although there are some country-specific peculiarities. Figure 4 shows comparable data based on recent Demographic and Health Surveys (DHS) for 58 developing countries with fertility levels (TFR) given for six different groups of women according to their highest educational attainment ranging from no formal schooling at all to post-secondary education. It shows that within the same countries there is a wide spectrum with, in some cases, uneducated women having on average six or more children while highly educated women have less than two children, levels similar to Europe today. Averaged across all countries (dotted lines) there is a consistent ordering of fertility levels according to the level of education. The highest fertility levels today are in Africa, where studies on the causes of educational fertility differentials consistently show that better educated women want fewer children, have greater autonomy in reproductive decision-making, more knowledge about and access to contraception, and are more motivated to practice family planning (Bongaarts 2010).

These pervasive education differentials have also been incorporated into models of population dynamics that stratify populations not only by age and sex but also by levels of education (Lutz & KC 2011). Because female education is associated with lower fertility at the individual level, populations with higher proportions of better educated women have lower overall fertility rates. This fertility factor by far outweighs the higher child survival rates associated with better education of mothers which works in

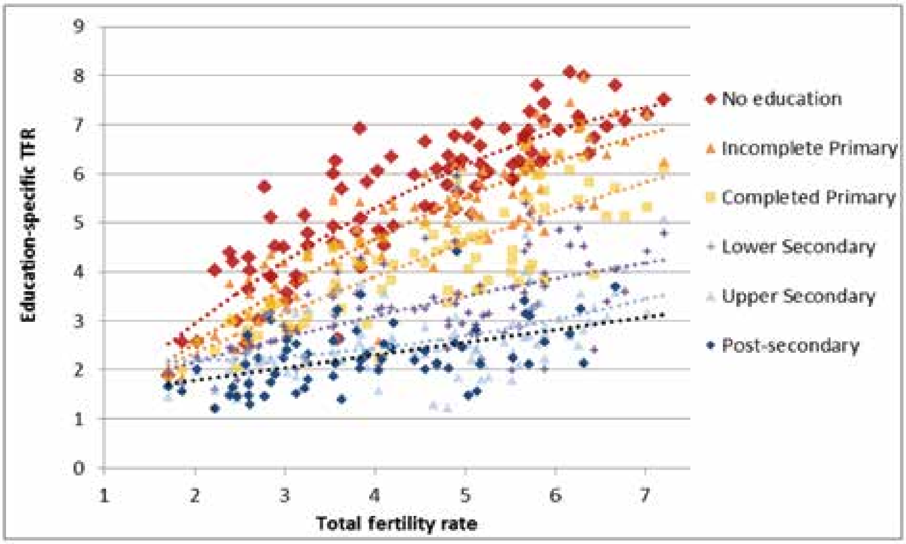

Figure 4. Fertility by level of female education in high fertility countries. 58 DHS (Demographic and Health Survey) countries (multiple time points), sorted by aggregate TFR in country.

the direction of higher population growth. Combining both forces, better female education will lead to a sizable long-term reduction in the population growth rates. A quantification of the pure education effect has shown that assuming identical sets of education-specific fertility trajectories for all countries a scenario assuming constant school enrollment results in a world population size by 2050 that is one billion higher than under a scenario of rapid school expansion (Lutz & KC 2011).

In concluding this section, the above brief survey of the literature and the data on the drivers of the demographic transition has made it clear that both for the onset of the mortality decline that resulted in ever increasing life expectancies around the world and for the onset and the further course of fertility decline from uncontrolled high to low levels education – and for the case of fertility, in particular female education – has been the essential driver, with many other factors also contributing in a more secondary role. But the real driver is not the fact that children spend a certain time in school, but it is what this schooling does to their brains, how it changes their synaptic structure and thus affects their cognition. And such empowering cognitive changes can in principle also be acquired outside the formal school system. For this reason, I prefer to speak of cognition-driven demographic transition rather than education-driven demographic transition.

3. Literacy and development

Few people in developed countries would dispute the importance of education in our lives and those of our children. We need education in order to be professionally successful, to broaden our horizons, to be able to question the status quo and to choose what kind of life we want to lead. Education even allows us to influence our health. Indeed, education is what enables us to lead a self-determined existence at all. It is fundamental for the complex organisation of modern societies and it serves higher goals such as freedom and justice. Better-educated people become more involved in political decision-making processes, thus helping to further democracy. In most countries across the globe extending education to broad sections of the population by following the principle of "education for all" and seeking the attainment of ever higher qualifications has brought about a marked improvement in living conditions over a period of decades or even centuries. All over the world the prosperity of nations is closely connected with their citizens' level of education. For this reason, modern societies are also called knowledge societies.

For most of the 5000 years since writing was introduced in Mesopotamia and Egypt to keep simple accounts about stocks of grain delivered and other administrative purposes, literacy skills tended to be restricted to a tiny elite. For the first millennia, literacy was primarily limited to religious leaders, state servants, far-travelling traders, members of specialized guilds, and certain nobility (UNESCO 2016). There are two known exceptions to this: In ancient Athens in the 5th century B.C.E. and in 15th century towns in Tuscany. In both cases, there were interesting interactions with democracy in the way in which being able to write (e.g. the name of a person who should be ostracized by the assembly of the demos of Athens) was a prerequisite for exerting democratic rights, and conversely. The rights were an incentive to acquire basic literacy (Missiou 2011). It should be noted, however, that in both cases the skills and rights were limited to the male population that held rights of citizenship, a minority of the total population. But the reformation took this a step further. In spring 1524 Luther wrote his pamphlet "To the Councilmen of all cities in the German lands, that they should establish and maintain Christian schools" (Aland 1990, p. 70). In it he called for children to be taught more than was necessary for earning their daily bread. This is a very important foundation for the later spread of literacy in the Protestant territories where it preceded economic growth, thus challenging the frequent assumption made by economists that the spread of education was a consequence of responding to economic incentives. It can be shown that almost universally the spread of literacy for non-economic reasons preceded economic growth. It was for religious and not economic reasons that Luther and his closest associate Melanchton wanted every boy and girl – including "das geringste Mägdelein" (the lowest level maid) – to be able to read the Bible.

As a consequence of this emphasis on universal literacy, the Protestant territories in Northern Europe gradually became the most literate populations of the world, though there were some interruptions, such as the Thirty Years' War. In fact, one could argue that the rise of the Netherlands and England as colonial powers and the parallel decline of the powers of Spain and Portugal with much less educated populations were in part due to this factor (Klingholz & Lutz 2016). Statistics from the Netherlands show that already around 1600, two-thirds of men in the cities could read and write. Around 1850, about 80 percent of the population, including those in rural regions, were literate. The same happened in England, where around 1800, 60 percent of all men and 40 percent of all women could read and write (Broadberry & O'Rourke 2010). Looking at a map of

Europe around 1870, the clear association between literacy and religion is evident (Broadberry & O'Rourke 2010). The Protestant territories of Sweden, Germany, the Netherlands and Great Britain are undisputed leaders with literacy rates of around 80 percent at this time. They are followed by France, which after the French Revolution managed to raise its literacy rate to 69 percent. Austria and Ireland rank after France. Italy and Spain lag a long way behind with rates below 35 percent. Russia reaches 15 percent literacy and Turkey 9 percent.

This ranking by level of literacy in 1870 matches almost exactly the degree of economic development at that time. Interestingly, recent research suggests that this association of religion and development is not so much attributable to Max Weber's famously hypothesized effect of "Protestant Ethics" but that the economic head start of Protestant regions can be more easily and more directly explained by their better educated populations (Becker & Woessmann 2009). In fact, the French sociologist Emmanuel Todd (1987) describes the progress of humankind as a direct function of the spread of literacy in populations. Comparing the evolution of literacy rates around the world, he suggests that a critical threshold for socio-economic change and even political revolutions is reached around the point when 50 percent of male adults are literate. He sees the progress of human history as driven by the progress of the human mind with the slow rise of literacy being even more influential in the long run than the industrial revolution.

Human capital – defined as the combination of education and health – is a fundamental prerequisite for economic progress and good institutions – key components of sustainable development. At the level of individuals, empirical evidence shows beyond any reasonable doubt that more years of schooling on average lead to higher income. This pattern can be found in virtually all countries, and discussions only concern the specific patterns or changes over time in this so-called education premium. At global macro-level economic growth regressions, however, until recently did find the same significant positive effects of education due to the education data used (Barro & Lee 1996; de la Fuente & Doménech 2006; Cohen & Soto 2007; Benhabib & Spiegel 1994; Pritchett 2001). Indeed, the usual human capital indicator in the form of mean years of schooling of the entire adult population does not adequately reflect recent improvements of the education of younger cohorts. Under conditions of very rapid education expansion the young adult cohorts who are decisive for economic growth can already be highly educated while the mean years of education indicator can still be depressed through the still uneducated older cohorts. In analyses that explicitly consider the age structure of human capital growth, regressions unambiguously confirm the key role of human capital in economic growth (Lutz et al. 2008). In addition, utilizing in economic growth regressions the full range of the educational attainment distribution by age results in findings of great policy relevance: For poor countries with very low levels of education, only the combination of universal primary education with broadly-based secondary education results in the kind of rapid economic growth that has the potential to push countries out of poverty (Lutz et al. 2008). This important new insight is also reflected in the SDGs (Sustainable Development Goals): While the earlier MDGs (Millennium Development Goals) only called for universal primary education, SDG4 calls for universal high-quality primary and secondary education (Lutz & Muttarak 2017).

While the historical macro-level evidence described here tells a convincing story about how literacy and education of broad segments of the population drive development, one also has to ask what are the individual level mechanisms through which literacy changes our brains and in consequence our perceptions and behaviors. In this paper I can do no justice to the vast amount of research in cognitive science and neuro-psychology as well as experimental economics that tries to understand these mechanisms. Instead I will highlight a few key findings that I found myself to be helpful in explaining how education influences our cognitive function, attitudes and behaviors as well as equips us with better social and economic opportunities. Directly, schooling enhances cognitive development through increasing the synaptic density in relevant parts of the brain. Not only experimental and observational studies have provided confirmation of a robust effect of education on executive functioning and cognitive abilities (Blair et al. 2005; Baker et al. 2012; Brinch & Galloway 2012), neurocognitive and neuroimaging studies have also shown strong associations between adaptive changes in the brain and learning experience in classrooms (Lewis et al. 2009; Welberg 2009). Abstract cognitive skills such as categorization and logical deduction acquired through schooling enhance the way educated individuals reason, solve problems, assess risks and make decisions (Bruine de Bruin et al. 2007; Peters et al. 2006) – those skills and qualities that are also highly relevant for adapting to climate change. Similarly, since education improves knowledge, understanding of complex information, efficiency in allocation of resources and capacity to plan for the future (Cutler & Lleras-Muney 2010; Kenkel 1991; van der Pol 2011), this can help in making better choices in a broad spectrum of choices affecting one's health, income and other aspects of one's personal life as well as the functioning and thriving of society and economy at large.

4. Demographic scenarios and sustainable development

World population currently – at the beginning of 2020 – stands at around 7.7 billion people. While the absolute increments per year still are at a peak level of about 83 million per year – it takes about 12 years to add another billion – the rates of growth have been already declining in the past decades as the demographic transition progresses around the world. World population growth peaked in the late 1960s at a level slightly above 2 percent per year. This kind of growth, if maintained, implies that the population would double roughly every generation. On a planet with limited resource of food, fossil fuel and fresh water this gave rise to a number of highly influential alarmist studies ranging from *The Population Bomb* and *The Population Explosion* of Paul Ehrlich (Ehrlich 1968; Ehrlich & Ehrlich 1990) to *The Limits to Growth* by the Club of Rome (Meadows et al. 1972). But there were also opposing voices mostly by economists who believed in the substitutability of resources and the innovative capacity of humans. Prominently among them was Julian Simon whose book *The Ultimate Resource* (1981) stressed that there could never be too many people because there always would be enough geniuses who would come up with solutions for all problems.

These two opposing views on future world population growth remained essentially unreconciled until it became clear that focusing on simply the number of people without considering their heterogeneity and differential human capital and adaptive capacity was unproductive and misleading (Lutz 1994; Lutz 2014). Once educational attainment was explicitly factored into the population models. A new paradigm could be developed that could reconcile both seemingly opposing views: Innovations tend to come from more educated people and not from starving illiterate ones (Simon) and without sufficient education population growth rates are likely to stay high and limits to food supply and other feed-backs from the environment may well result in increasing misery and death rates (Malthus and Ehrlich). A key to overcoming this unproductive polarization of the discussion thus lies in the fact that female education is a main determinant of lower fertility rates and that education enhances the adaptive capacity to environmental change (Lutz & KC 2011; Lutz & Muttarak 2017).

World population projections for the 21st century as produced by the United Nations Population Division and by IIASA (International Institute for Applied Systems Analysis) have changed quite a bit over time as a function of different long-term fertility and mortality assumptions and the incorporation of most recent observed empirical trends and analysis. While the UN uses the conventional cohort-component method which models the populations by their age and sex structures, IIASA has developed the methods of multi-dimensional population dynamics which in addition to age and sex also explicitly models the changing educational composition of populations in each age and sex group (Lutz & KC 2011). In their most recent assessments the UN (2019) in their medium variant projects continuous growth of world population reaching 10.9 billion people by the end of the century whereas IIASA (Lutz et al. 2018) in its medium scenario (SSP2) projects a peak population being reached at around 9.7 billion in 2065-75, followed by a slight decline to 9.3 billion by the end of the century (see Figure 5). This difference is mostly due to different methods of deriving long-term fertility assumptions for the different parts of the world where the UN relies primarily on statistical models that derive assumptions from the experience of other countries, whereas IIASA gives more weight to expert arguments and region-specific scientific reasoning about the drivers of these trends. While the two sets of projections are quite similar for the coming decades, toward the end of the century they differ in an important qualitative way, with the UN suggesting continued population growth whereas IIASA anticipating the end of world population growth during this century.

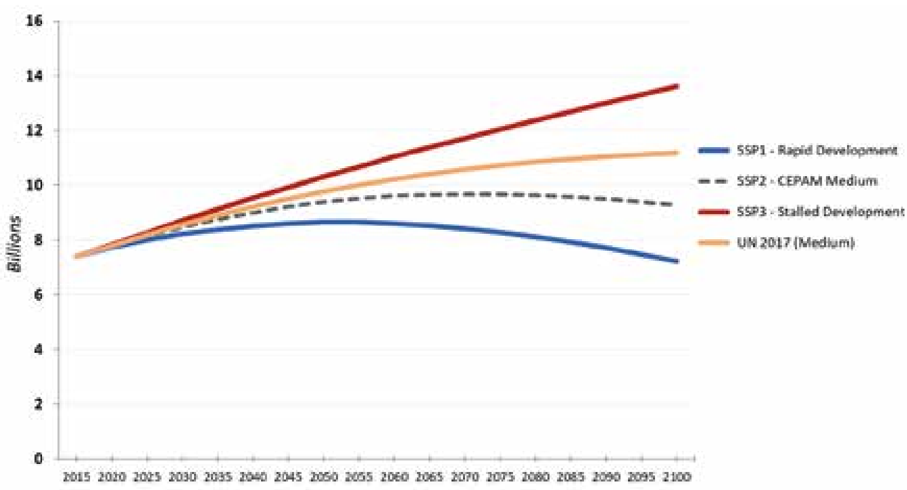

Figure 5. Comparison of different scenarios for world population growth over the 21st century.

The notion of an "end of world population growth" was first introduced in an article in the pages of *Nature* presenting the first set of fully probabilistic world population projections (Lutz et al. 2001). Based on empirical information up to the late 1990s these projections showed that there was a high probability of over two thirds that world population would peak and then start to decline over the course of the 21st century. This was qualitatively not so different from the UN medium projection at the time which also saw a levelling off of world population over the last decades of the century. The main difference was in the level of assumed ultimate fertility which for the UN was around replacement and for IIASA a bit lower. Subsequently, an unexpected stall in the fertility declines of some important African countries was observed where, around 2000-2005, fertility rates interrupted their earlier declines or even increased somewhat. While the exact measurement and explanation of this stall is still controversial, one plausible hypothesis is that it is a late consequence of the interruptions of the education increases of female cohorts born around 1980 in the context of the so-called structural adjustment programs (Goujon et al. 2015; Kebede et al. 2019). More recently, demographic surveys show that the declining trend has picked up again which is also associated with a continued increase in the education levels of young women in most African countries.

Figure 5 shows the results of the 2018 IIASA projections carried out in the context of CEPAM (Centre for Population and Migration Analysis, a joint venture between IIASA and the Joint Research Centre of the European Commission). While the long-term fertility and mortality assumptions of these projections were derived from the major 2014 assessment of the scientific state of the art in terms of drivers of fertility, mortality and migration (Lutz, Butz, et al. 2014), the baseline data were updated and a specific focus was on the long-term impact of alternative migration assumptions which matter significantly for national populations but are irrelevant at the global level. Figure 5 also compares this projected trend (SSP2) to the UN medium variant as well as to two alternative high (SSP3) and low (SSP1) scenarios that were developed in the context of the Shared Socioeconomic Pathways (SSPs) widely used in the climate change research community (KC & Lutz 2017).

The SSP3 scenario assuming stalled social development and thus lower female education and higher fertility rates for each education group already reaches the 10 billion mark around 2045 and then continues to grow over the rest of the century reaching 13.4 billion in 2100. According to the narrative underlying this scenario this will be a very unpleasant future in which the world will be strongly fragmented, there will be widespread poverty, mortality will be rather high and the adaptive capacity to already unavoidable climate change will be very weak. This pretty much resembles a Malthusian scenario as described above.

The SSP1 scenario assuming rapid social development results in markedly lower population growth showing a peak population of around 8.9 billion in 2055-60 and a decline to 7.8 billion by the end of the century. This is just a bit higher than the population estimated for today and the same as expected for 2020. In terms of the underlying narrative this resembles a global development under which the sustainable development goals are met in most countries and significant progress in education and poverty reduction is made. As has been shown elsewhere (Abel et al. 2016) meeting SDG4 (on education) and SDG3 (on health, including reproductive health) will help to bring the SSP2 scenario closer towards the SSP1 scenario in terms of the total world population growth resulting from these trends.

Under all scenarios the world population will get significantly older as a consequence of low fertility rates and increasing life expectancy (see Figure 6). In the medium (SSP2) scenario the proportion above age 65 increases from currently 8.3 percent to 17 percent by mid-century and 29 percent by 2100. Under the rapid social development scenario (SSP1), which assumes faster increases in life expectancy, this proportion of elderly

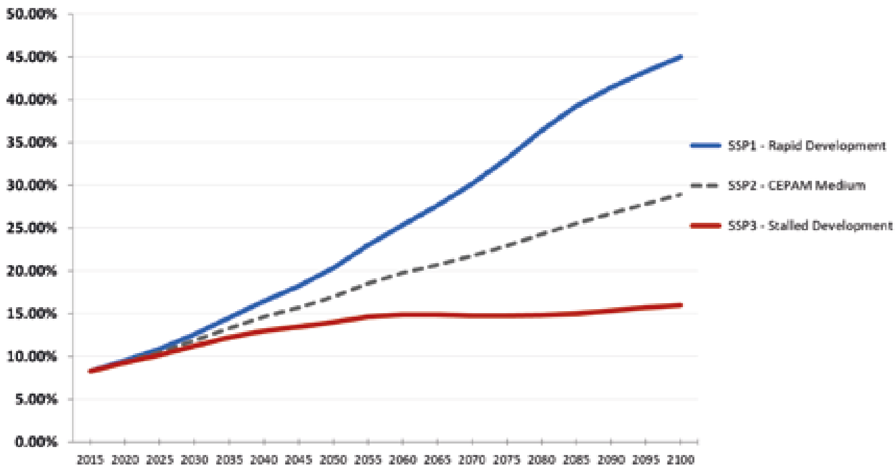

Figure 6. Global trends in the proportion of the population above age 65 according to different scenarios.

reaches around 20 percent in mid-century and 43 percent in 2100. The stalled development scenario (SSP3) on the other hand will see a much slower increase, reaching only 16 percent by the end of the century.

When interpreting these different scenario results in terms of changing proportions of the populations above the age of 65 one has to keep in mind that a cut-off point at age 65 is rather artificial and reflects a static notion of being "old". The typical 65-year old in the 1960s had on average a much worse health status than the average 65-year old today. Also, in terms of the remaining life expectancy the 65-year old has many more years to expect today. This is also reflected in the saying "70 is the new 60" for which there is a lot of evidence. In terms of demographic ageing indicators this is also covered by new indicators such as the proportion of persons that have a remaining life expectancy of 15 or less years, an indicator that increases much more slowly than the proportion above age 65 plotted here (Sanderson & Scherbov 2019).

This also needs to be taken into account when comparing the scenarios. SSP1 partly results in much more population ageing because it also assumes more rapid increases in life expectancy. And this is only likely to happen when at the same time disability-free life expectancy continues to increase. Hence, when thinking about a world population at the end of the century where possibly 40 percent of the population will be above age 65, we should not think in terms of the 65-year-olds we know today. If such a scenario should indeed materialize it could be expected that a majority of these people above age 65 would be not-so-elderly healthy and active people. But still it will pose challenges to adapting existing institutions including systems of social security.

In terms of educational attainment (Figures 7-9), in 2016 10.3 percent of the world population had no formal education at all and 10.9 percent had some sort of post-secondary education. Under the medium (SSP2) scenario significant progress will happen, with the proportion without any education declining to 5 percent by mid-century and on 1 percent by 2100, while at the same time the proportion with post-secondary increase to 20 and 38 percent respectively. Under the rapid development (SSP1) scenario the proportion with post-secondary education increases to 32 percent in 2050 and 65 percent in 2100.

But further long-term progress in education is not guaranteed, despite of the fact that today in virtually all countries the young generations are better educated than the older ones. As illustrated by the stalled development (SSP3) scenario in Figure 9 the combination of high population

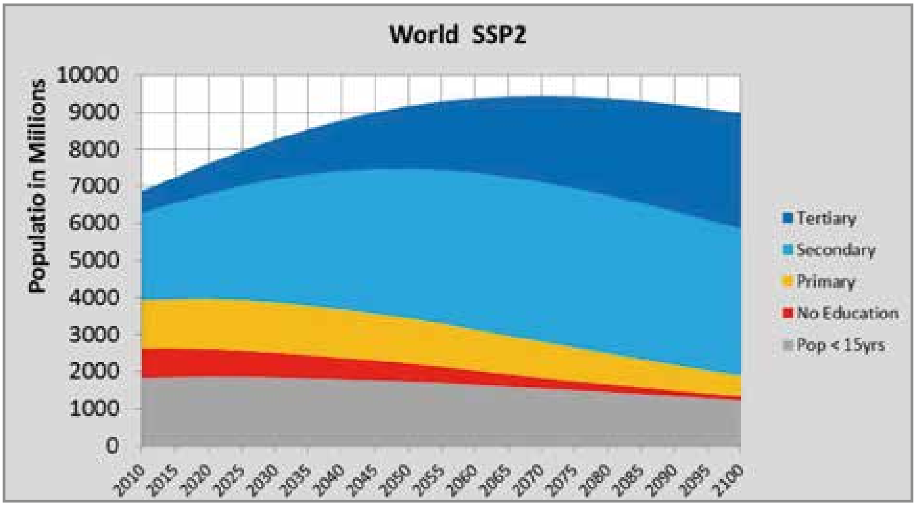

Figure 7. World population by level of educational attainment, Medium Scenario (SSP2).

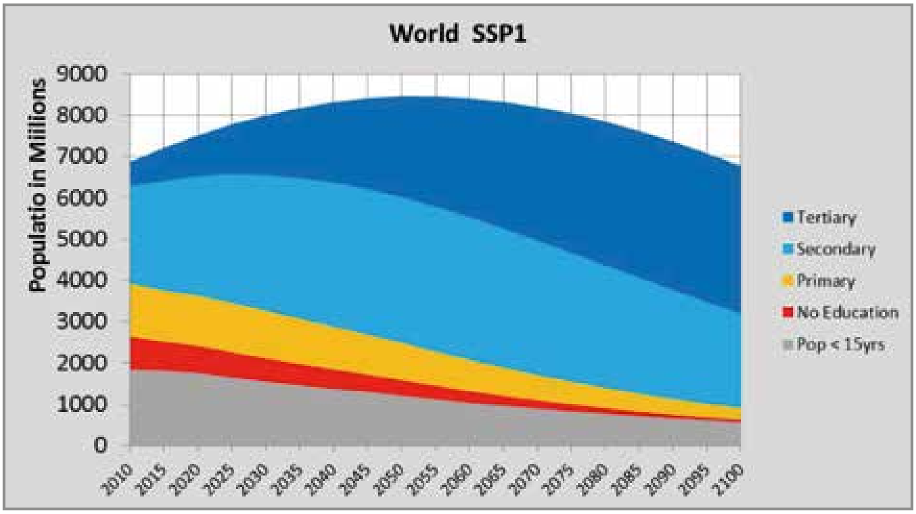

Figure 8. World Population by level of educational attainment, SSP1 Scenario – Rapid Development.

growth with little further schooling expansion can actually result in an increase of the proportion without any formal education from 10 to 22 percent by the end of the century. This scenario also shows a stall in the proportions with post-secondary education below 12 percent. This scenario will also a result in a greatly polarized world. While the countries in today's developed world and the emerging economies where the young generations are already fairly well educated will continue to enjoy high levels of education, the African and South Asian populations may actually become less educated because school expansion will not be able to keep pace with the rapid population growth.

Viewed together these population and education scenarios clearly illustrate that still two very different futures are possible: (a) One resembling the Malthusian trap which is captured by the SSP3 scenario in which low education investments and continued high fertility in Africa and parts of South Asia reinforce each other and lock the world into a trap of very high population growth and poverty, and low adaptive capacity to environmental change; (b) another optimistic one captured by SSP1 where these feedbacks result in a virtuous cycle of further strong improvements in education together with lower fertility and an end of world population growth and thus more healthy and wealthy people who are better empowered to adapt to already unavoidable environmental changes.

Whether the world will move towards one of these two opposing directions or will end up somewhere in the middle will depend largely on policy choices made over the coming years.

These different population and education scenarios are highly relevant for different aspects of sustainable development. An important field of application is in assessing the likely future resilience and adaptive capacity to

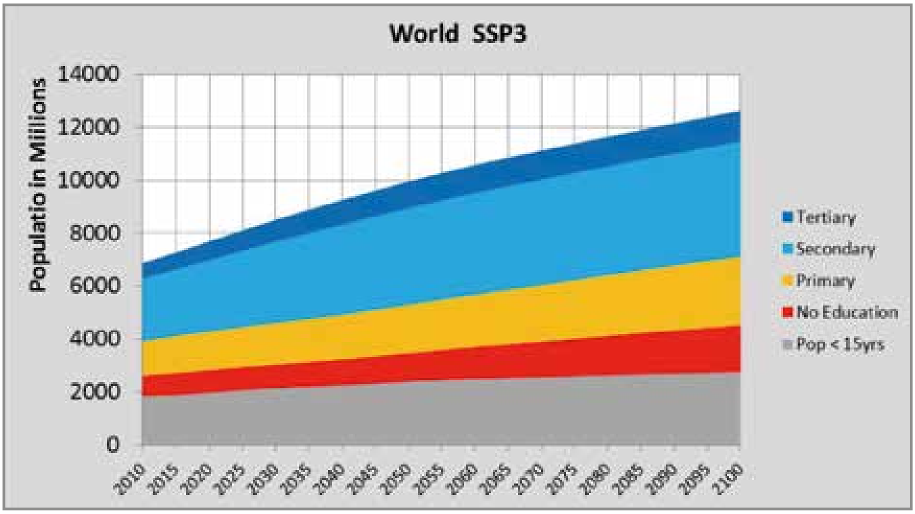

Figure 9. World population by level of education, SSP3 Scenario, Stalled Development.

all kinds of potentially disruptive changes, including global environmental change. Recently, in the analysis of climate change, the attention has shifted from an earlier almost exclusive focus on mitigation to adaptation that will be necessary when coping with already unavoidable changes of the climate. However, much of the ongoing research in the field superimposes projected biophysical conditions for the end of this century onto present-day socio-economic conditions (IPCC 2014), when we know that societies are also changing over time in dimensions such as public health capabilities that are essential for their adaptive capacity. Disregarding such future social change would be misleading. It has been demonstrated recently that education is a key determinant of differential vulnerability both at the individual and societal level (Butz et al. 2014). Hence, the above described SSP scenarios are an effective way for also forecasting societies' future adaptive capacities to climate change (Muttarak & Lutz 2017). Contrasting the SSP1 and SSP3 scenarios for the rest of the century (Lutz et al. 2014) it was recently shown that due to the educational expansion under the rapid social development path in SSP1, disaster mortality will be much lower – even in the case of increasing climate related hazard – than in the SSP3 scenario where under-investment in education leads to high population growth and heightened vulnerability. Given the uncertainty about the precise manifestations of climate change in specific areas, there is a strong case to be made for general empowerment through education which increases human and social capital to flexibly and effectively react to upcoming challenges rather than investing in massive concrete infrastructure projects.

More generally, for the interactions of humans with environmental change, education has been shown to matter for behavioral changes necessary to mitigate human impacts such as changing behaviors in terms of choosing greener technologies, switching to public transport or recycling waste (Muttarak & Lutz 2017). Since education improves knowledge, understanding of complex information, efficiency in allocation of resources and capacity to plan for the future (Cutler & Lleras-Muney 2010; Kenkel 1991; van der Pol 2011) it is conducive for making better choices at the individual and societal level that will make a transition toward sustainability more likely.

5. Conclusions: Population growth and brainpower for sustainable development

The future trends in population and education greatly matter for many dimensions of sustainable development and all of its three social, economic and environmental pillars. With respect to trying to identify the impact of population growth on environmental change the combined effects of population growth (P), affluence (A) and technology (T) on environmental impact (I) has sometimes been expressed through the "I=PAT" equation. Called the Ehrlich-Holdren or Kaya identity, it lends itself to efforts to quantify the contribution of the individual components on environmental impact. The decomposition literature based on this identity has, however, been inconclusive due to the fact that the three components tend to work in different directions, are not independent from each other, and not all consumption can be meaningfully attributed to individuals. In particular, it has been pointed out that households and not individuals should be taken as the consuming units and that the consumption or impacts of big companies or the military cannot be meaningfully attributed to individuals. But despite some of these problems, the literature mostly agrees that population change and change in consumption patterns are both relevant aspects, even though the latter tends to dominate the picture (O'Neill et al. 2005).

The number of people on this planet not only matters with respect to their consumption and impact on the natural environment and thus the life support systems of future generations, it also matters in terms of human rights and basic needs to be met. It is clearly more difficult to leave no one behind and secure basic entitlements under continued rapid population growth associated with stalled development (SSP3) than under a scenario of rapid fertility decline together with fast socioeconomic development (SSP1). But while the human headcount on our planet clearly matters, the analysis summarized in this paper also shows that what is inside the heads matters more than the mere number.

Much more research is needed in this field, in particular to better understand the mechanisms by which enhanced cognitive abilities (brain power) can contribute to changes in our behavior at the individual and collective level toward achieving sustainable development. Many of the solutions are readily available on the table but they are not being implemented due to blockades at various levels, including the links between perception and behavior in our brains. Recognizing this, the German National Academy of Sciences Leopoldina has recently held two symposia in support of the Global Sustainable Development Report 2019 (Messerli et al. 2019) to explicitly address the cognitive preconditions for a successful sustainability transition. Under the heading "Brainpower for sustainable development" (Lutz et al. 2019) it has been affirmed that "brain power comprises the competences, abilities, traits and motivational skills that enable people to make sound decisions and adapt their behavior. Brain power is a key prerequisite for a successful transition towards sustainability. Individual brain power develops out of a continuous, lifelong interaction between genetic dispositions, maturation processes, environmental conditions and social experience. The most obvious way to strengthen brain power is to provide positive supportive environmental conditions in early childhood, both formal and informal high-quality education as well as lifelong learning. Furthering general cognitive and motivational competences proves to be more effective than specialized programs" (cited from Lutz et al. 2019, page 1). Again, this points to the overriding and fundamental importance of universal literacy and continued education for both women and men to assure future human wellbeing on this planet.

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The Complementary Nature of Scientific Experimentation and Thought Experiments

Werner Arber, Marcel Weber

Introduction

As intelligent living organisms, humans possess curiosity, which is a driving force both for scientific research and for reflections on the encountered living conditions and their origin. This leads them to carry out theoretical and experimental scientific research and to make thought experiments. The outcome of these approaches represents important contributions to the worldview, which provides us with orientation knowledge that gives us an important basis for our life activities.

Nature and examples of thought experiments

Thought experiments are fictive scenarios imagined in order to explore the implications of some theory, for example a scientific theory or a philosophical account ([1], [2], [3]). Philosophers widely use thought experiments in order to check whether some philosophical account accords with widely held intuitions, for example, intuitions about the moral acceptability of actions. By contrast, scientists use thought experiments in order to check whether their theories are internally consistent, or whether they agree with everyday experience. An example of the latter kind can be found in Galileo's dialogues, when he shows that falling objects can still appear as if they were moving in a straight line perpendicular to the surface of the Earth, even if the Earth moves ([4]). He shows by this asking his interlocutors to imagine that they are standing on a moving ship and looking at the ship's rigging. Even though the ship moves, to the observer moving along with it the rigging would appear as being at rest. In a similar way, when we watch a rock falling from a tower we cannot perceive the tower's horizontal motion due to the Earth's orbital motion. And the same is true of the horizontal component of the falling rock's motion. Therefore, the rock appears to be falling perpendicularly to the surface of the Earth.

In a similar way, the physicist James Clerk Maxwell imagined a microscopic demon who operates a shutter between two containers of gas, letting only the fastest molecules pass. This thought experiment exposed certain limits of the Second Law of Thermodynamics ([5]).

But thought experiments are not only used in the history of science. In the journal *Nature Communications* we can find an article published 18 September 2018 where two contemporary physicists, Daniela Frauchiger and Renato Renner, describe a thought experiment that is supposed to prove that quantum theory cannot consistently be applied to itself, i.e., to an agent performing a quantum measurement ([6]).

Thought experiments can also be found in other areas of science such as economics ([7], [8]) or biology ([9], [10]). For example, the British economist Thomas Malthus [11] famously imagined what would happen if the human population reproduced unrestrictedly. Because this leads to geometrical, i.e., exponential growth while the productivity can only grow arithmetically, starvation, poverty and disease would ensue. This thought experiment is known to have been an important influence on Charles Darwin's idea of natural selection.

Darwin struggled to provide proof for his principle of natural selection. One line of evidence he provided in the *Origin of Species* consisted in showing how much artificial selection could change an organism's heritable traits, for example, in domestic dogs or pigeons. But this was *artificial* selection and what he needed to prove was the possibility of *natural* selection. As he had no experimental data or field observations available, he resorted to thought experiments [9]. An example of such a thought experiment can be found in the following citation from the *Origin of Species*:

> Let us take the case of a wolf, which preys on various animals, securing some by craft, some by strength, and some by fleetness; and let us suppose that the fleetest prey, a deer for instance, had from any change in the country increased in numbers, or that other prey had decreased in numbers, during that season of the year when the wolf is hardest pressed for food. I can under such circumstances see no reason to doubt that the swiftest and slimmest wolves would have the best chance of surviving, and so be preserved or selected … Now, if any slight innate change of habit or of structure benefited an individual wolf, it would have the best chance of surviving and of leaving offspring. Some of its young would probably inherit the same habits or structure, and by the repetition of this process, a new variety might be formed which would either supplant or coexist with the parent-form of wolf ([12], 90-91).

Thus, Darwin imagined what *would* happen under certain conditions in nature, and this was one of his chief arguments for the occurrence of natural selection.

It should also be noted that some contemporary accounts of the origin of life are also thought experiments, for example, the idea that life started out with ribonucleic acids (RNAs) that can catalyze their own synthesis [13], which came to be known as the "RNA world hypothesis". Such molecules are known to exist but their presumed role in the origin of life is nothing but a thought experiment.

Of course, it could be argued if all of these examples really constitute thought experiments or if some are better viewed as hypotheses, theories or theoretical models. Indeed, the cases are different. Some of the examples mentioned (Galilei, Maxwell) involve a concrete experiment that is imagined rather than performed. The case of Darwin involves what may be called an imagined natural experiment. The cases of Malthus and the RNA world may also be viewed as just hypotheses. However, it should also be noted that all these cases also have something in common, namely that they imagine possible worlds that are in some respects unlike the world we know. In these imagined worlds, certain suppositions are assumed to be true. Scientists then intuit (or in some cases calculate) what the consequences would be. Indeed, thought experiments have been characterized as "expeditions to possible worlds" ([2], p. 135). Hypothesizing and model-building may also be characterized in this way. Both thought experiments and model building involve idealizations, even though perhaps to different degrees. Thus, the difference between thought experiments, hypothesis and theoretical models may just be a difference of degrees rather than of kind [8].

We hope these examples suffice to illustrate the point that, while all scientific knowledge must be ultimately based on empirical data, imagination and thought experiments can nonetheless play a role in scientific research. They help the human mind to chart our scientific knowledge and make sure that it coheres with rest of our knowledge, including our common experience. Indeed, a considerable part of our scientific worldview is based on thought experiments.

Can we consider creation myths as thought experiments?

Reflections on people's lives under convenient living conditions are likely to have been made by curious early farmers and their compatriots already a few thousand years ago. Various resulting creation myths took their origin at a number of locations on our planet [14]. Often a divinity was seen to act as creator of living conditions and of living organisms. One of these accounts is included in the Genesis chapter of our Bible. Religious people interpret this kind of insights into our existence as divine revelations. But this does not exclude that one can count creation myths as resulting from a kind of thought experiments based on intelligence.

Creation myths also had an undeniable impact on science, as can be seen in the case of Darwin. A theologian and Anglican priest, he started out as an ardent follower of the English tradition of physico-theology that sought to prove the existence of God by studying the ingenious ways in which organisms appeared to be adapted to their form of life. Darwin absolutely needed to find an alternative explanation, which was his main motivation for elaborating a theory of natural selection.

We think that these cases also use fiction in scientific reasoning, exactly like thought experiments.

Scientific research and thought experiments can enrich our available knowledge on natural properties and functions

In the course of time, scientific research improved gradually our available knowledge on the nature in which we live. Tribes living several thousand years ago could not know the presence of cohabiting microorganisms, nor did they know that they lived on a planet with the shape of a ball representing only a minute part of the immense Universe.

Without going into details, we can conclude that thought experiments can stimulate scientific research into particular directions, whereas results from scientific research can stimulate humans to carry out novel thought experiments. The two approaches to understand nature are complementary.

Recent astrophysical research has shown that some stars in the Universe are surrounded (like our sun) by planets ([15], [16]). These are called exoplanets. Actual research investigates whether some exoplanets offer convenient living conditions. A relevant thought experiment that predicts the existence of living organisms on other planets raises the question whether intelligent organisms could travel as aliens to our planet Earth. It would be a very difficult task for our scientific researchers to explore whether some exoplanets showing living conditions are inhabited by living organisms. If we define living organisms, as we have the habit on our planet, to be able to reproduce and to undergo biological evolution, exploration of the existence of living organisms can be very difficult in view of the great distances between the Earth and the relevant exoplanets. However, if such scientific investigations should become possible, interesting additional questions are whether living organisms on exoplanets possess genes that are carried on nucleic acid molecules and whether all kinds of organisms on a given exoplanet possess an identical genetic code.

Acquired knowledge on evolution processes

Available scientific insights lead to the conclusion that natural evolution generally proceeds extremely slowly. This renders these ongoing evolutionary processes at the levels of the Universe, of our planet and of its living populations hardly visible to us in our lifetime. This slowness ensures relatively good stability of living populations and of their living conditions. Available knowledge from studies on biological evolution, on geology and on astrophysics forms a basis for these conclusions. Some natural scientists see these processes providing remarkable stability as pointing to a self-organization by nature.

Scientific and religious views on creation processes

So far, scientific attempts to create a simple living organism *ex nihilo* have failed. In contrast, our available knowledge on biological evolution processes indicates that all living organisms present on our planet must have evolved stepwise in the past from one or more primitive microorganisms. One can consider this process as continuous permanent creation by nature's self-organization. Thanks to self-organisation the Creator did not have to bring into existence each individual species, but he may have laid down principles that allow the components of the universe to become ever more diverse in the course of time.

Christian faith in general makes widespread use of thought experiments [17]. In the cultural history of mankind, individual deities were often assumed to act as creators in favor of humanity. This led to the concept of Polytheism. However, more recently a single God became seen in the concept of Monotheism to act in all these events. We appreciate the Christian view of the Trinity [18] in which God is "Three in One and One in Three", i.e., the Father, the Son, and the Holy Spirit. The Son is Jesus, the founder of the Christian religion, who provides to human believers useful stimulations for their life activities. In contrast, God Father and the Holy Spirit are not living organisms but rather conceptual entities. In this concept, the Trinity acts not only on Earth, but it is the Divinity for the entire Universe.

Conclusions

Thought experiments can be seen as the results of human reflections that are based on available knowledge and on ideas how the studied objects might contribute to the process under study. Thought experiments were already carried out a few thousand years ago. In contrast, serious scientific investigations have a shorter history and have become intense only in the last few hundred years. At present, solid scientific knowledge can beneficially contribute to thought experiments and thought experiments can stimulate to carry out scientific research projects. The two approaches are complementary and they can help obtain deeper insights into various natural properties and functions.

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SESSION II – CLIMATE AND ENERGY

Where on Earth Are We Heading: Miocene or Pliocene?

Hans Joachim Schellnhuber and Lila Warszawski

The evidence of our rapidly changing climate – and the Earth System as a whole – is literally raining down around us. Over the past few years, it has been almost impossible to ignore the growing list of tropical storms and severe precipitation events that have devastated communities across the globe. Mother Nature has spared neither modern metropolises (e.g. Tropical Storm Harvey, around Houston USA, August 2017), nor more vulnerable parts of the developing world (e.g. cyclone Idai in south-east Africa, March 2019). As scientists, we greet these human and natural catastrophes with sadness, but not surprise. This increase in extreme storm activity is a prediction of our modern understanding of the Earth System's response to rising global temperatures, which are in turn the result of the burning of fossil fuels, and the degradation of the Earth's natural compensatory systems (e.g. carbon sinks in the biosphere). In other words, we are collecting abundant evidence that we have entered the *Anthropocene*, an epoch in which human activity is disrupting essential planetary processes, and where human interference is driving the Earth out of the Holocene epoch in which agriculture, sedentary communities, and socially- and technologically-complex human societies emerged.

Scientists are now asking themselves, where is this all headed? And what can we do to influence the path we, as a global community, are taking? To answer the first of these questions, we must quantify the driving forces (how much carbon dioxide will be emitted into the atmosphere over the coming years and decades), and require a deep understanding of how the Earth System will respond to these driving forces.

The publication in 2018 of the Intergovernmental Panel on Climate Change's (IPCC) Special Report on the impacts of 1.5°C anthropogenic global warming and related greenhouse gas emissions pathways made clear that "every half degree of warming matters" (Hoesung Lee, IPCC Chair), and that even 1.5°C warming will have dire consequences for many vulnerable communities. And yet a stocktake of current political ambition in terms of greenhouse gas emission reductions on a country-by-country basis puts us on a path to anywhere between 2.5° and 4.7°C global mean temperature rise by 2100 (Climate Action Tracker, September 2018).

It will not be a smooth ride towards a new state of the Earth System in a warmer world. The road is dotted with thresholds, beyond which key systems may be tipped into an irreversible and self-perpetuating new state (Lenton *et al.* 2008; Schellnhuber *et al.* 2016), such as the ice sheets, the tropical rainforests and global circulation patterns in the ocean and the atmosphere (see Figure 1). A set of these 'tipping elements' may already be activated by global temperature rises within the range set by the Paris Climate Agreement (1.5°-2°C). These include the West-Antarctic Ice Sheet, which may enter a state of self-amplifying melting, resulting on average in around 3m of sea-level rise (Bamber *et al.* 2009); or the permanent demise of coral reefs, which will not have time to recover between the increasingly frequent bleaching events (Zemp *et al.* 2017; Lucht *et al.* 2006). Between 3°C and 5°C global temperature rise, irreversible systems changes such as a weakening of the Indian summer monsoon (Schewe and Levermann

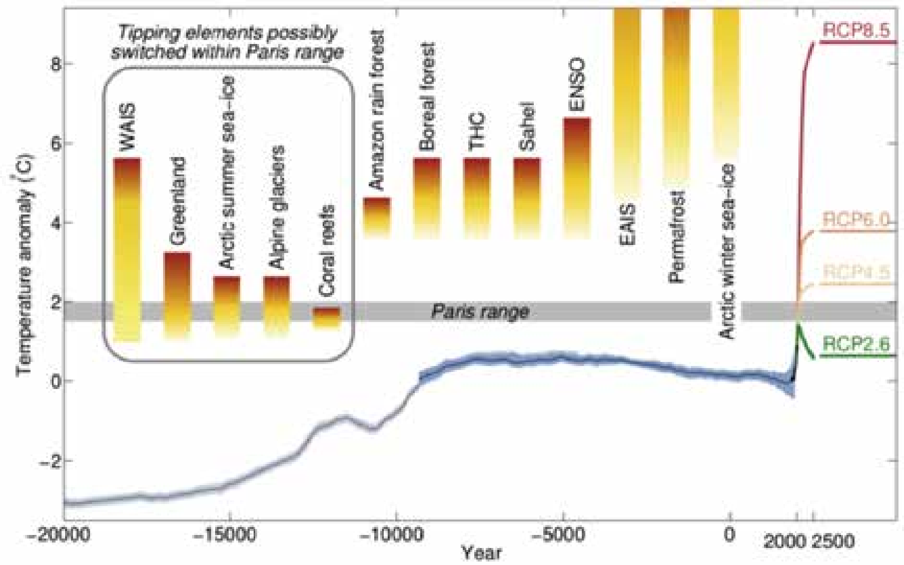

Figure 1. This graph (taken from Schellnhuber et al. 2016) shows the global-temperature rise (above pre-industrial levels) at which certain tipping elements could be triggered. The colour scale of the vertical columns depicts the temperature *range* in which the tipping element could be triggered with increasing probability (from yellow to red). The blue curve shows the history of the development of mean global temperature from 200 000 in the past, and projected 500 years into the future based on four global greenhouse gas emissions scenarios (RCP2.6, RCP4.5, RCP6.0 and RCP8.5).

2012), the dieback or functional change of the Amazon or boreal forests (Zemp *et al.* 2017; Lucht *et al.* 2006), or a transformation of the jet stream (Petoukhov *et al.* 2013) are on the cards. And beyond 5°C warming, permafrost thawing, the disappearance of the Arctic winter sea-ice, and runaway melting of the East Antarctic Ice Sheet may be triggered.

Nota bene that this global-warming-dependent landscape of risks should not be seen as a decision-making tool. There is no compelling evidence to support the belief that the Earth System can be 'parked' safely at a chosen level of global warming, even at the relatively low warming levels addressed in the Paris Agreement. In fact, some of the relevant tipping elements, especially those linked to the global carbon cycles, have the potential to accelerate the climate change that pulled the trigger in the first place (Steffen et al. 2018). Such runaway processes would have a devastating effect on human settlements and the natural world.

Moreover, these tipping elements do not present isolated threats, but are rather part of a network of interdependent components of the Earth System. Their interconnectedness, whilst fascinating in its intricacy, delicate balance and resilience thus far, will become a point of vulnerability as global temperatures rise. Triggering a 'low-temperature' tipping element, could lead to further temperature rise, which in turn triggers a higher-temperature tipping element. These domino-like cascades could see global temperatures skyrocket, with no time or opportunity for the global community to react. We might be standing at a fork in the road, with paths defined by a rapid assumption of human stewardship towards a 'Stabilized Earth'; or an unchecked trajectory across a planetary threshold towards a 'Hothouse Earth' (Steffen et al. 2018 and Figure 2 below).

On a stabilized Earth, global temperature rise does not exceed 2°C, keeping the likelihood of triggering a given tipping element, and subsequent cascade, relatively low. However, this risk reduction can only be achieved with the rapid adoption of policies and practices to protect and enhance natural marine and terrestrial carbon sinks, deep cuts in greenhouse gas emissions, and promotion of sensible efforts to remove carbon dioxide from the atmosphere. In other words, this future is only achievable if humankind becomes a steward of its own future.

Without that stewardship, we will hold the path towards a potential planetary threshold, beyond which a Hothouse Earth may become unavoidable. We only need to look into the past to understand the acuteness of the Hothouse vs. Stabilized Earth dichotomy. A Stabilized Earth would experience conditions similar to those in a period known as the Pliocene

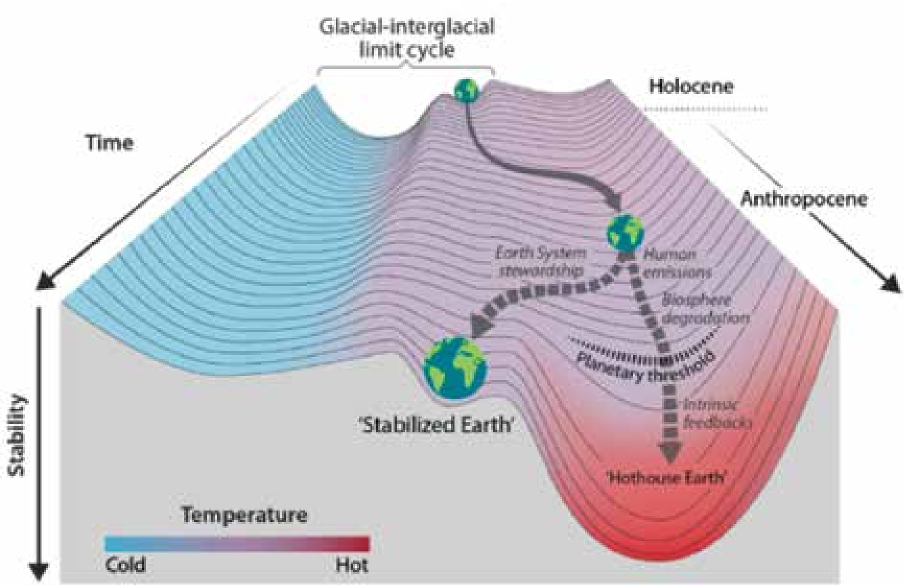

Figure 2. The trajectory of Earth from the Holocene into the Anthropocene, and thus away from the glacial-interglacial dynamics of the past 10 000 years. The Earth system stands at a cusp, which, depending on action (not) taken by the global community, could lead us towards a planetary boundary, beyond which we may face a 'Hothouse Earth'; or towards a 'Stabilized Earth', reached via human stewardship of the Earth system (Graphic taken from Steffen *et al.* 2018).

(some three to four million years ago, see Figure 3 below), with global temperatures between 2°C and 3°C above pre-industrial levels (another 1°-2°C higher than today), and sea levels between 10m and 22m higher than today. Even this sobering 'best-case' scenario is only accessible if humankind immediately acts to ensure the promises of the Paris Agreement, signed by 195 nations, but as yet implemented by very few, are kept.

However, we are still on a trajectory towards a much higher global temperature rise. If a planetary threshold does indeed exist, the current trajectory might lead us directly towards a Hothouse Earth, without the possibility to park the Earth System at intermediate global-warming levels (see Figure 2). This would put the Earth System in a state similar to that of the Middle Miocene (some 15-17 million years ago) (Burke et al. 2018, see Figure 3 below). At this time, global temperatures were 4°C-5°C higher than in pre-industrial times, and sea levels 10m-60m higher. In such a world, severe risks would be posed to political and economic stability, human health (especially for the most vulnerable), efforts to establish global equality, and ultimately to the habitability of planet Earth for humans.

Depending on the path taken, we may be on the cusp of being catapulted, in just 200 years of industrialization, into conditions last seen on Earth between 3 and 17 million years ago! While looking into the past offers an insight into a near-equilibrium state of the Earth System under particular climatic conditions, we are facing a situation in which these conditions will be imposed in the blink of an eye, subjecting ecosystems to an unwinnable game of catch up.

Since entering the Anthropocene, human activity has taken the wheel in determining the state of the Earth System. The efficacy of this takeover is demonstrated in the analysis of the interplay between the variations of solar forcing due to tiny changes in Earth's orbit around the sun, and global CO_2 concentration, which shows that human activity has already delayed the onset of the next glaciation by some 50 000 years (Ganopolski, Winkelmann, and Schellnhuber 2016). So the potency of human interference is being understood in ever finer detail, and our understanding of the paths that lay ahead is becoming increasingly sophisticated. And yet, the stewards at the helm of our shared future have fallen asleep at the wheel. There is no better evidence of this than the insufficient pledges being offered by industrialized countries to reduce emissions of greenhouse gases, whose

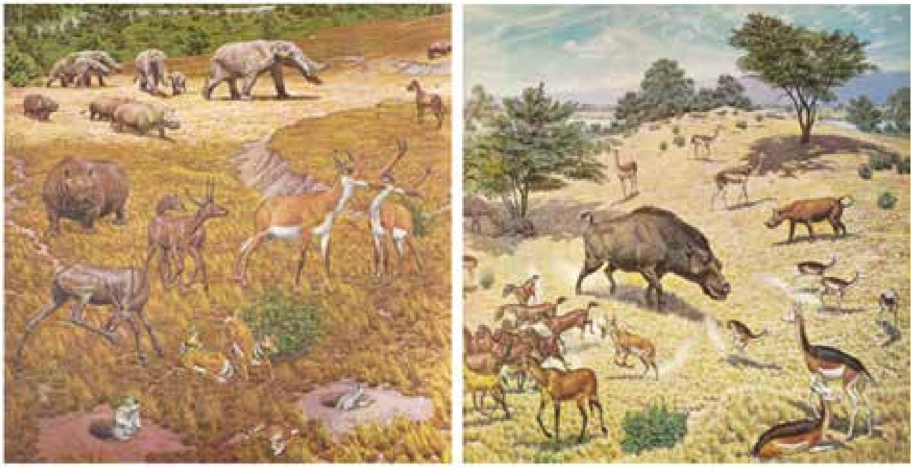

Figure 3. Wall paintings from the Smithsonian Museum depicting the flora and fauna of the Pliocene (left) and Miocene (right). In the Pliocene, global mean temperature was 2°-3°C warmer than pre-industrial conditions, compared to 4°-5°C warmer in the Miocene.

cumulative effect would launch us on a terrifyingly fast journey 15 million years into the past.

Despite vociferous warnings from scientific and lay communities, international bodies tasked with curbing greenhouse gas emissions are currently too slow to divert us away from a potentially Hothouse Earth. It seems that we are living in an age of global cognitive dissonance, in which imminent threats, laid out in graphic and meticulous detail in internationally agreed-upon reports, have become a driver of inaction.

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SESSION III – HEALTH

Organ Transplants

Francis L. Delmonico

Organ transplantation is a lifesaving and cost-effective treatment for organ failure but there is an insufficient supply of transplantable organs available worldwide to address those in need. In 2016, approximately 136,000 organ transplants were performed throughout the world. Most of these transplants are performed for either kidney (approximately 90,000) or liver (approximately 30,000 candidates). Most of these transplants (greater than 60%) are performed from deceased donors but there are locations of the world such as Japan and India, in which there are either relatively few or no deceased donors (Egypt and the Philippines).

With a world population of over 7 billion, it is estimated that there are approximately 60 million deaths annually. From that proportion of those dying there is a total of only 30,000 deceased donors worldwide for a rate of 0.05% donors per deaths. To accommodate the need which is 10 times the number of annual transplants performed, the rate of deceased donation must increase to 0.5% donors per deaths. The inadequate supply of organs has led to a desperation by patients to obtain organs through illegal or unethical ways – victimizing the poor as a source of organs.

Organ Trafficking

Organ trafficking is occurring day by day throughout the world in economically underdeveloped countries with the destitute selling their kidneys to provide for themselves or for their families. Organ trafficking is a form of human trafficking and a violation of human rights. The migrants fleeing from Syria or along the Nile corridor are selling their organs in Turkey and in Egypt. The media reports regarding these illegal activities are current. But organ trafficking is not limited to those locations. It is the experience of transplantation in India. It is the experience of transplantation in Mexico when a wealthy journalist can travel from Germany accompanied by a young man from Africa to sell his kidney. It is the experience of a Syrian woman compelled to sell her kidney so her children can reach an environment free of war.

The doctors who perform these procedures are trained but do so in locations that are not monitored by proper governmental oversight. Although the doctors rationalize the concern for a patient with organ failure in need of a transplant, that rationale is discredited by the reality of greed. Money is the motivation. Organ trafficking is now defined by the Council of Europe as a monetary transaction as the basis for the organ transplant. Monetary gain is the objective of the vendor who sells an organ; monetary gain is the objective of the doctors who enable the transaction. The vendor is exploited. A large sum of money is provided to a broker and to the doctor but in contrast virtually nothing to the donor vendor. The vendor is stigmatized within his or her own culture – illustrated by the organ market in Iran. However, the motivation of the vendor in obtaining money usually does not achieve the reason needed for the money. The vendor remains destitute with one less kidney. There is no sustained care of the vendor if complications arise – and they do. There is no awareness of a donor death; if the donor dies, it is only the family that has to reconcile the loss.

Organ transplantation is a societal event – different than any other practice of medicine. It requires the oversight of society to protect the well being of the living donor and to make certain of the equitable distribution of organs that derived from the deceased. Governments are not exercising their responsibility to provide a sufficient number of organs from the deceased within their jurisdiction nor are they monitoring the practices of transplant doctors in exploiting vendors for their organs. As a result, patients in need are traveling to locations in which organs are readily obtainable – economically underdeveloped countries where the source of organs is plentiful. Alternatively, patients in need will secure a donor and travel with that individual to a location that has no ethical framework to prohibit the exploitation. The demand for organs will continue unless governments act to achieve self-sufficiency for their own patient populations who are otherwise compelled to participate in organ trafficking.

The World Health Organization

The issue of organ trafficking has been a concern of the WHO for three decades, expressed initially in 1987, but reaffirmed by the adoption of a World Health Assembly Resolution (WHA63.22) on 21 May 2010 to promote *"principles of human dignity and solidarity which condemn the buying of human body parts for transplantation and the exploitation of the poorest and most vulnerable populations and the human trafficking that result from such practices"*.

The WHO has also urged Member States *"to strengthen national and multinational authorities and/or capacities to provide oversight, organization and coordination of donation and transplantation activities, with special attention to* *maximizing donation from deceased donors and to protecting the health and welfare of living donors with appropriate health-care services and long-term follow up".*

The 2010 Resolution of the 63rd World Health Assembly (WHA) that embraced the Guiding Principles of the World Health Organization set forth the following objectives to be accomplished by Member States:

– *to improve the safety and efficacy of organ donation and transplantation by promoting international best practices;*
– *to promote a system of transparent and equitable allocation of organs, guided by clinical criteria and ethical norms, as well as equitable access to transplantation services in accordance with national capacities, which provides the foundation for public support of voluntary donation;*
– *to strengthen national and multinational authorities to provide oversight, organization and coordination of donation and transplantation activities, with special attention to maximizing donation from deceased donors and to protecting the health and welfare of living donors with appropriate health-care services and long-term follow up;*
– *to collaborate in collecting data including adverse events and reactions on the practices, safety, quality, efficacy, epidemiology and ethics of donation and transplantation.*

The Declaration of Istanbul

On April 30, 2008 The Transplantation Society (TTS) and the International Society of Nephrology (ISN) convened in Istanbul, Turkey a Summit Meeting of more than 150 representatives of scientific and medical bodies, government officials, social scientists, and ethicists from around the world to take a stand on the urgent and growing problems of organ sales, transplant tourism, and trafficking in organs. The meeting adopted the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism", which has since been endorsed by 130 medical societies, government bodies, and other groups involved with organ transplantation. Although the Declaration was widely disseminated in medical journals and online beginning with a seminal article published in *The Lancet* on July 5, 2008. TTS and ISN were determined that the Declaration would be more than merely a statement reported in the medical literature. Therefore, in 2010, they created the Declaration of Istanbul Custodian Group (DICG) as a means of actively promoting, sustaining, and monitoring the implementation of the Declaration's principles.

The Pontifical Academy of Sciences Summit on Organ Trafficking and Transplant Tourism

In February 2017 PAS convened a Summit on the topic of organ trafficking by the direction of Pope Francis. A definitive statement was made by participants from throughout the world (inclusive of China) that all nations and all cultures recognize human trafficking for the purpose of organ removal and organ trafficking, which includes the use of organs from executed prisoners and payments to donors or the next of kin of deceased donors as crimes that should be condemned worldwide and legally prosecuted at the national and international level. Organ trafficking is a crime against humanity.

The participants also emphasized that nations provide the resources to achieve self-sufficiency in organ donation at a national level with regional cooperation as appropriate by reducing the need for transplants through preventive measures and improving access to national transplant programs in an ethical and regulated manner.

Development of WHO Task Force on Organ and Tissue Donation and Transplantation

To fulfill the WHA commitment to disseminate WHO Guiding Principles, that would ensure ethical practices of organ and tissue donation and transplantation worldwide, the Delegation of People's Republic of China proposed at the 70th World Health Assembly of 2017 that the WHO establish an Organ and Tissue Donation and Transplantation Task Force to implement the WHO Guiding Principles in Member States with organ and tissue transplantation services.

National Self-Sufficiency

Countries have a responsibility to provide a national supply of transplantable organs by ethical and legal practices. The role of government is now clear to support organ and tissue transplantation:

- Enact legislation to define death that enables recovery of organs and tissues;
- Enact legislation to support ethical, efficient and sustainable tissue donation, banking and transplantation;
- Establish a National Agency that:
  - oversees the practice of organ donation and transplantation;
  - oversees the practice of tissue donation, banking and transplantation;
  - certifies transplant centers, training programs and transplant personnel;

- certifies organ and tissue procurement agencies and personnel;
- certifies histocompatibility laboratories;
- certifies tissue processing and distribution facilities;
- develops registries for donors, potential recipients and transplant patients;
- reviews outcome data;
- reviews the burden of disease that necessitates organ and tissue transplantation.

The Challenges Ahead

Scientists and scientific policymakers must be engaged to develop a common understanding of death to enable a sufficient supply of organs to be available. National authorities must regulate donation and transplantation activities, maximizing donation from deceased donors and protecting the well-being of living donors with appropriate health-care services and long-term follow up.

Governments must promote a system of transparent and equitable allocation of organs and tissues, guided by clinical criteria and ethical norms, as well as equitable access to transplantation services in accordance with national capacities, which provides the foundation for public support of voluntary donation. Governments must also address the disproportionate use of dialysis as renal replacement therapy impeding access to kidney transplantation which is comparatively cost-effective and improves the quality of life. Governments must also combat the trafficking of human organs defined by the Council of Europe as commercialization – the buying and selling of organs; and human trafficking for organ removal which is a human rights abuse of exploitation of the poor.

The national agencies overseeing organ transplantation must collect data to evaluate the practice, safety, quality, efficacy and ethics of organ donation and transplantation and promote organ donation as a standard of end-of-life care.

The Three-Dimensional Architecture of the Human Genome: Understanding the Physical Mechanisms Controlling Gene Expression

José N. Onuchic[1]

Introduction

The human genome lives inside the cell nucleus and it is composed of 46 DNA molecules. These molecules are called chromosomes and have a combined length of about 2 meters. Chromosome structures vary for different cell types. Their three-dimensional architecture plays a central role in transcriptional regulation and its loss of functionality may be associate to disease. In this manuscript we describe a theoretical approach for determining the physical mechanism governing genome architecture. This is an interesting challenge since the DNA contained in every human cell is identical, and therefore this information has to be located somewhere else.

Towards answering this challenge, we have demonstrated that the architecture of interphase chromosomes is encoded mostly by its epigenetic marking. This one-dimensional sequence information is sufficient to determine its three-dimensional structure. This epigenetic information can be rewritten during cell differentiation, and therefore determining for each cell type both the three-dimensional structure and gene expression. [1,2]

In vivo, regions of chromatin characterized by different epigenetic markings go through a process similar to phase separation during its three-dimensional spatial organization. This process forms liquid droplets, which rearrange dynamically by breaking and fusing, which characterize the chromosomal architecture.

Our theoretical approach, combined with the respective computational tools, is able to predict the spatial conformation of genomes with unprecedented accuracy and specificity and, at the same time, it understands the

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physical mechanisms governing this organizational process. This physical understanding and modelling provide the initial tools towards understanding the functional aspects of genome architecture.

Exploring the energy landscape of chromatin and establishing the connection between genome conformation and phenotypes

Chromatin is not only composed of DNA. Its structure and dynamics also require hundreds of structural and regulatory proteins that interact with this genetic material. This provides what is called epigenetic information. As we have described above, in the cell, chromatin has partially organized structures, which are essential in controlling the transcription of genes1-2 and disrupting them often leads to diseases.[3-6]

In the recent past, new experimental techniques have been developed which combine DNA proximity ligation with high-throughput sequencing. These techniques are making it possible to learn much about chromatin organization.[7] These chromosome conformation capture[7,8] experiments provide rich data sets that have been used to develop structural models of chromosomal organization.[9,10] The most advanced of these approaches, Hi-C, provides a high-resolution contact map of the genome. These experiments show that chromatin structure gives rise to segregation of different types of chromatin in compartments (see discussion below). This information is very coarse-grained, with a representation of the chromosomes as a necklace of beads of 50 kilobases in size. Our goal is to determine the physical mechanism by which local interactions lead to the 3D fold observed in chromatin.

In earlier work, we have shown that energy landscape theory and the funnel concept are powerful tools in understanding protein folding.[11-13] A similar approach can be developed to investigate chromosome structure and function.[10,14] Any landscape theory is based on the fact that biomolecules do not have only a single folded structure but live in a dynamical ensemble of a large number of structures. In the case of proteins, they have a funnel landscape, i.e., convergent kinetic pathways that guide folding to a unique, stable, native conformation. There is a strong correlation between protein order and free energy stabilization. This landscape, therefore, is not only responsible for folding the protein but also governs its function since many of the protein functional states live higher in free energy in the funnel. This correlation between order and energetic stabilization allows for a connection between kinetic pathways and free energy minimization. Inspired by this framework, we have built an energy landscape approach for chromatin folding which is described in the following section. Utilizing the Hi-C data, we have been able to construct this coarse-grained energy landscape with the help of a maximum entropy Bayesian approach. Despite its limitations, these landscapes reproduce well the experimental information, particularly all the contacts predict by Hi-C between different genomic segments. It also reproduces different experimental results, such as contacts predict from FISH microscopy, even though this information was never used while building this model.

Predicting Genome Structures

In 2016 we proposed a physical model (the Minimal Chromatin Model (MiChroM)) for chromatin folding that has shown unprecedented accuracy in predicting the structure of chromosomes.[15] MiChroM is based on the assumption that chromatin can be subdivided into a handful of structural types based on its biochemical properties. We proposed that selective binding of nuclear proteins to these few distinct types of chromatin is the driving phenomenon behind chromatin folding. Again, chromatin types, which are distinct from DNA sequence, are at least partially epigenetically controlled and change during cell differentiation, thus constituting an intriguing link among epigenetics, chromosomal organization, and cell development. Using molecular dynamics simulations, we showed that micro-phase separation of chromatin structural types is capable of generating 3D configurations that are strikingly similar to chromosome conformations found *in vivo* by the DNA ligation assays such as Hi-C. We also showed that differential binding of proteins generates an equilibrium ensemble of unknotted structures, a finding that stands in contrast to the long-held belief that these structures must be the result of a non-equilibrium process. We now present a summary of this model (details can be found in reference 15).

MiChroM is based on several physical assumptions informed by experiments. It is known that chromosome interactions are mediated by a cloud of proteins, each of which interact with DNA with a different selectivity. Our initial assumption is that these biochemical interactions can be represented by only one of a few "types" of chromatin. These types are determined by different histone modifications and other protein mediated interactions. In its most current version, utilizing high resolution Hi-C data, we utilize six distinct interaction patterns, corresponding then to six sub-compartments (A1, A2, B1, B2, B3, and B4). A and B types tend to phase separate into different compartments as described above. The second assumption is that some specific pairs of loci strongly interact to form particularly frequent contacts or loops Most of these loops are intra-chromosomal and require the presence of a binding factor (CTCF), which identifies the DNA bases CCCTC motif, and the cohesin protein complex. The final assumption is called the ideal chromosome potential. It assumes that there is an additional free energy that only depends on the genomic distance between the two loci. This term is responsible for the local chromatin structure. Figure 1 shows a schematic representation of MiChroM.

A real challenge is to determine these structural types utilizing only epigenetic information without any previous structural knowledge. Therefore we developed a method (Maximum Entropy Genomic Annotations from Biomarkers Associated with Structural Ensembles (MEGABASE)) to determine the structural type of a segment of chromatin using its epigenetic marking patterns.[16] A neural network was used to convert chromatin immuno-precipitation (ChIp-Seq) data into chromatin types annotations. These annotations became an input to MiChroM to produce structural ensembles for chromosomes of a *lymphoblastoid* cell line (GM12878) for which high resolution Hi-C data is available. These predictions were extensively validated using experimental data from Hi-C and FISH microscopy. Details of this approach can be found in reference 16 and a schematic representation is shown in Figure 2.

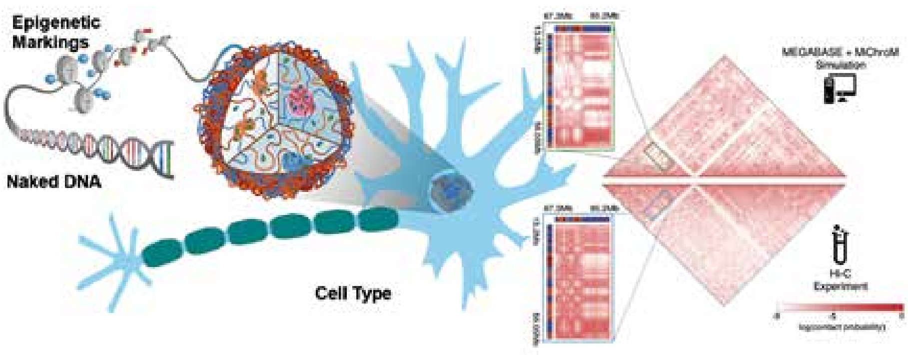

Figure 1. (left) Naked DNA is decorated by proteins and epigenetic markings that differ between cell types. Our results indicate that these markings carry enough information to determine the 3D architecture of the genome, which is also cell-type specific. (right) Validity of MiChroM is checked by direct comparison to Hi-C maps. It is particularly important to check predictions for contacts between loci at large genomic distances since they are vital to determine the success of the model.

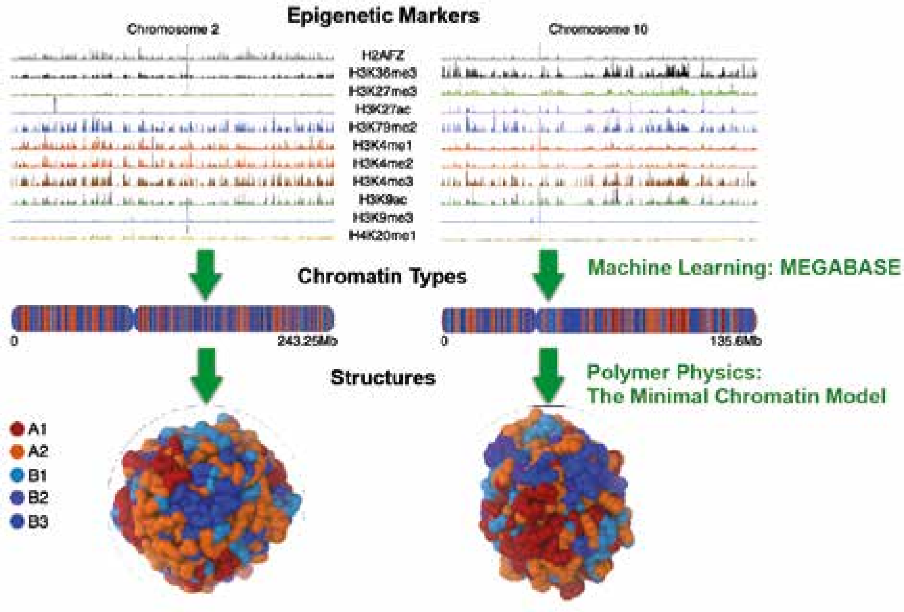

Figure 2. Schematic representation of the MEGABASE+MiChroM computational pipeline. Initially, we utilize chromatin Immuno-precipitation Sequencing (ChIP-Seq) assays which contain the epigenetic markings of a cell type. This information is publicly available from the NIH ENCODE Project database. Utilizing these data, our machine-learning MEGABASE method generates annotations for the chromosomal types. Finally, molecular dynamics simulations are utilized to create the ensemble of 3D chromosome structures.

The MEGABASE+MiChroM computational pipeline allows simulating the conformation of entire genomes using only the sequence of epigenetic marking patterns without the need for any additional experimental information. Using a combined approach of machine learning and physical modeling, we were able to achieve a degree of quantitative accuracy that makes our model not only able to predict 3D conformations but also a viable explanation of the mechanism behind chromatin folding.

Conclusion

The MEGABASE+MiChroM computational pipeline makes it possible to extensively investigate the ensemble of structures of genomes in many different cell lines. Experimental data from ligations assays show that the structure of chromosomes changes accordingly to the phenotype[17,18] as observed, for example, during cell differentiation. Structural changes have also been detected in cancer cells.[19] Using this new theoretical approach, the 3D genome conformations for a large number of human cell lines can now be generated and the results validated by comparing to information from ligation assays, whenever such data is available. A systematic study of the relationship between structural ensembles and the expression patterns in each phenotype is now becoming possible.

It is important to keep in mind that this theoretical model is based on the three physical assumptions described above: compartment formation by type segregation, loop formation, and the ideal chromosome. Although most of the current experimental information supports them, much more work is needed to determine their validity. Also, most of the parameters used in this model have been learned from experimental data. Additional work is still need to link them to detailed physical descriptions. The quality the current predictions, however, provides us with sufficient confidence that the basic physical mechanisms governing genome folding are well described by this theoretical framework.

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Contemporary Challenges in Medical Usage of Antibiotics

Giuseppe Cimicata, Tanaya Bose, Gil Fridkin,
André Rivalta, Moshe Peretz, Anat Bashan and Ada Yonath[1]

Introduction

The severe increase in antibiotic resistance and cross-resistance among many pathogenic bacterial strains[1] presents a significant health threat.[2] The marginal attention to severances of the results from antibiotics usage led to a rapid increase in the appearance of multi-drug resistant pathogenic bacterial strains.[3] Moreover, the extremely slow progress (actually negligible) in developing new antibiotics by pharma companies worldwide causes extreme contemporary issues.[4] Consequently, it seems that along with the traditional attempts to improve current antibiotics and the intensive screening for additional natural compounds, this field should undergo substantial conceptual revision. For example, the common preference for broad-spectrum antibiotics should be challenged, as it triggers the development of antibiotic resistance in a large variety of bacteria, including those that are not involved in the particular disease. In addition, many antibiotics do not distinguish between pathogens and some of the bacteria of the microbiome may thus alter the microbiome population.[5] Furthermore, most antibiotics are chemically substituted non-digestible and non-biodegradable small molecules that upon leaving the patient's body and reaching the environment, may escape the purification systems and cause ecological and environmental complications,[6] which in turn contribute to further resistance development. Here we describe our studies towards reducing and/or controlling antibiotics resistance, focusing on the identification of species-specific and environmentally-friendly protein synthesis inhibitors, which may be used as lead compounds for the development of novel drugs.

Expected Lower Rate of Resistance

The ribosome is the biological macromolecule responsible for protein synthesis according to the genetic code in all the living cells. In prokaryotes it consists of two ribosomal subunits, namely the large ribosomal subunit,

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called 50S (according to its sedimentation coefficient), and the small ribosomal subunit, or 30S (Fig. 1).

Owing to the vital role played by the ribosomes, many antibiotics target them.[8] Most ribosomal antibiotics obstruct the key ribosomal functions, namely decoding and peptide bond formation. As these sites are rather limited in number and chemical options, we initiated studies, based on our previous attempts to identify particular ribosomal structural motifs,[9] aiming at the development of novel antibiotics. Particularly we focus on "pathogen-specific antibiotics", in contrast to the current preference of broad range antibiotics. For this aim, we identified species-specific ribosomal structural motifs that may be exploited for the design of novel antibiotics of controllable chemistry.

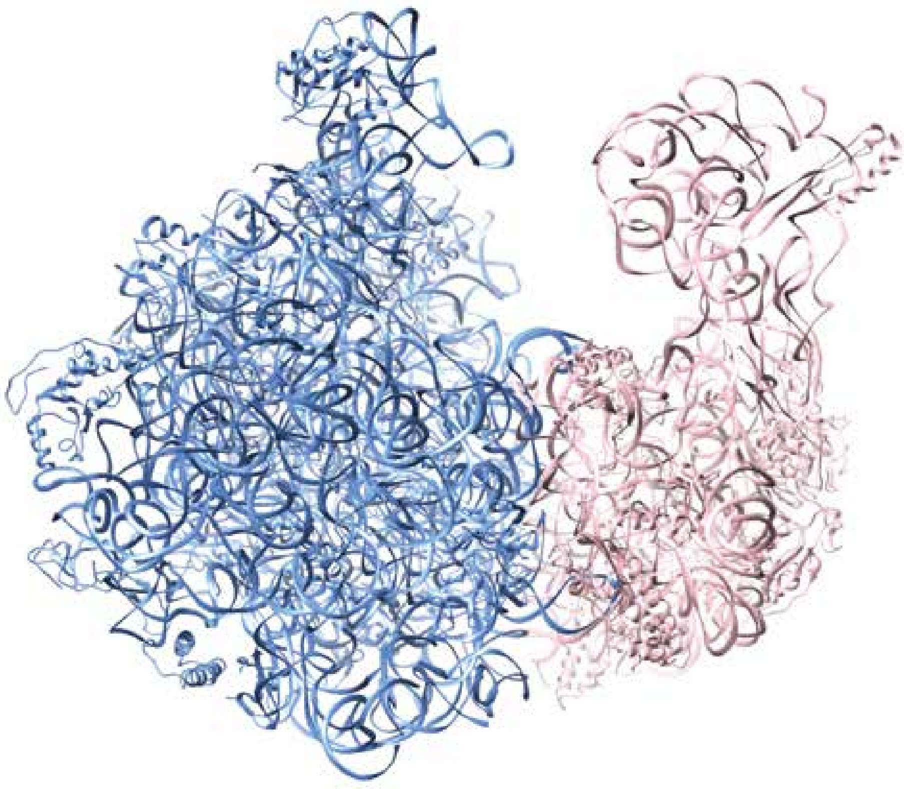

Figure 1. The skeleton of the ribosome from Staphylococcus aureus:[7] the large ribosomal subunit is represented in blue, the small ribosomal subunit in pink.

In principle, for each bacteria several such sites could be identified, and for each of these sites a specific matching molecule could be designed as a lead compound. Hence, for each pathogen we will have in hand a collection of lead compounds, each of which can be further developed into an antibiotic drug. These are planned to be used one at the time. Thus, the usage of species-specific instead of broad range antibiotics, alongside the expected variety of these antibiotics, which can be used consequently, are bound to lead to a slower pace of resistance appearance.

We are focusing on surface exposed sites, with chemical structure and composition allowing the design of matching compounds with favorable chemistry. These sites were discovered mainly by comparing the sequences and the structures of the large ribosomal subunit of the pathogenic bac-

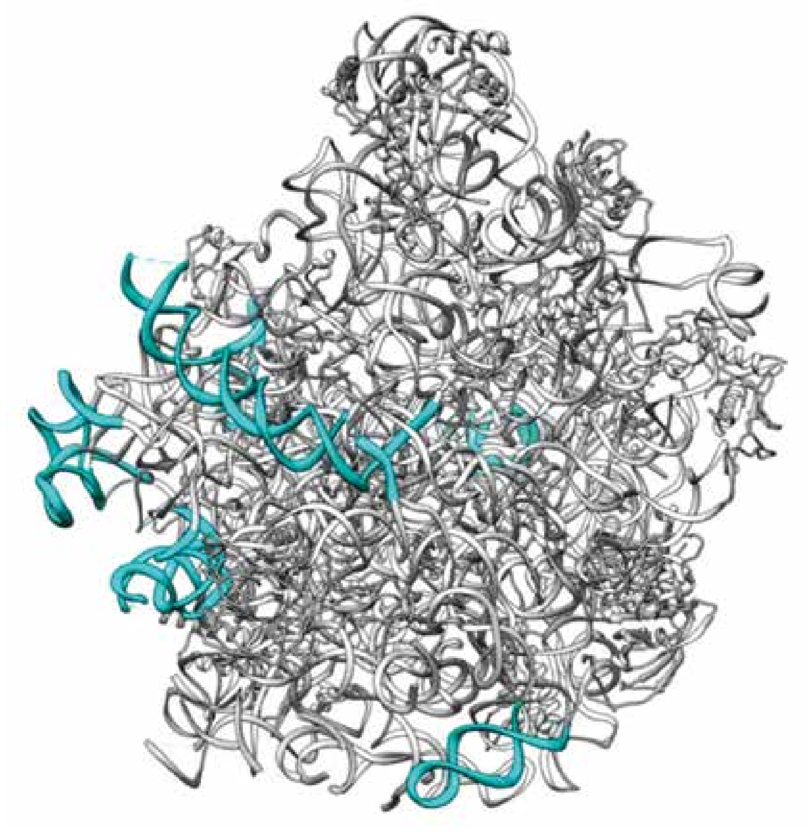

Figure 2. The skeleton of the large ribosomal subunit from Staphylococcus aureus.[10] Potential target sites for antisense therapy are shown in cyan.

teria of interest to those of other non-pathogenic bacteria. Our approach became feasible thanks to the recent year's availability of cryo-electron microscopy for the determination of high-resolution structures of large biomolecules like the ribosomes. Once the explicit pathogen unique sites were identified, solvent exposed regions of rRNA (Fig. 2) were selected. These were targeted by antisense oligonucleotides in a cell free *in vitro* transcription-translation activity assay, using luciferase as reporter gene to check protein synthesis inhibition.

The interactions between the inhibiting antisense oligonucleotides and their designed targets were then assessed by running fluorescein labelled versions of the oligonucleotides in an agarose gel, along with both the ribosomal subunits from the bacteria of interest, using a fluorescein labelled Shine-Dalgarno sequence[11] as positive control. In this way we observed selective binding of our designed antisense oligonucleotides to the large ribosomal subunit. These interactions, paired with a selective binding of the Shine-Dalgarno sequence to the small ribosomal subunit, represent a proof that the designed sequences are indeed binding to their predicted target sites.

Conclusions

Our studies are leading towards the design of "pathogen-specific antibiotics", in contrast to the current preference of broad-spectrum antibiotics usage. The discovery of the unique species target that can lead to antibiotics that will be used sequentially, alongside the speeding up of the procedures for the identification of the actual clinical pathogen (by a few companies) open new, untraditional path towards species specific antibiotics, of which sequential application should reduce and slow down the appearance of resistance.

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SESSION IV – ECOLOGY AND BIOSYSTEMS

What Should We Try to Do in an Age of Extinction?

Peter H. Raven[1]

Because its loss is irreversible, and since we depend on it completely for every aspect of our lives, the extinction of biodiversity is actually the most important problem that we face today – but few realize that fact, much less take action adequate to prevent it. In our Academy we held a study week on this subject in spring 2017, the results of which will be published as a book in 2019 by Cambridge University Press. Here I have used the results presented there, and by Raven (2019), largely without specific attribution.

The evolutionary line to which we belong, the hominids, diverged from the African apes about 6-8 million years ago, with our species, *Homo sapiens*, first appearing in the fossil record about 300,000 years ago, in Africa. Concerning our appearance on Earth, *Genesis* 2: 15 reads "The Lord God then took the man and settled him in the garden of Eden, to cultivate and care for it". In fact, we had relatively little impact on the planet and its ecosystems until we began to cultivate plants and domesticate animals as sources of food about 11,000 years ago – barely a blink of an eye in the 4.54-billion-year history of the Earth. When crops were first domesticated, our total human population is estimated to have amounted to about one million people, spread out over all of the habitable continents, with only about 100,000 people, a number that could be accommodated in a single large sports stadium, living in Europe.

Where have we come during the 400 human generations that have succeeded one another since that time? By 1562, when the lovely building in which we are meeting was completed as a summer home for Pope Pius IV, the global population had grown to about 500 million people, equivalent to the present population of Europe. In 1936, when Pope Pius XI revived our Academy and dedicated this building to the use of our Academy, there were 2.5 billion of us! Subsequently, our numbers have now climbed to more than 7.6 billion, growing by about 200,000 per day, and projected to reach 9.9 billion by mid-century, 30 years from now.

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In terms of our hopes for future stability it is particularly important to remember that the 1 billion people currently living in Sub-Saharan Africa are projected to grow to approximately 2.2 billion people within the next 30 years and perhaps 4.4 billion by the end of the century. Given the fact that 24 of the world's poorest countries in the world are located in Africa, and that many of them, with increasing poverty, are starting to fall into what Mathis Wackernagel has begun to term an "environmental poverty trap", a situation in which these countries have nothing left to export to earn money, the future certainly looks bleak for the continent. This is particularly true in view of the growing selfishness and nationalism that are all too evident among the world's rich countries today: can we count on them to intervene massively to help alleviate the problems of Africa?

Today, human beings completely dominate the earth and are destroying its prospects for sustainability through a combination of the impact of our sheer numbers and our activities magnified by the runaway consumption of perhaps the top ten percent of the world's people. The total mass of human bodies and that of our domestic mammals, cattle, sheep, pigs, currently amounts to *twenty times* the mass of all other mammals on earth. Our domestic fowl weigh more collectively than all other birds on earth. About 800 million of us are hungry, even on the edge of starvation, with about a third of the human population lacking at least one essential nutrient. At the same time, eight people currently possess as much wealth as do the poorest 3.6 billion people on earth. Apparently they are unfamiliar with the words of Matthew 25:40, "And the King shall answer and say unto them, Verily I say unto you, Inasmuch as ye have done *it* unto one of the least of these my brethren, ye have done *it* unto me".

In such a connection, I am also reminded of the words of US Secretary of State Adlai Stevenson, who said in 1965, "We travel together, passengers on a little spaceship, dependent upon its vulnerable reserves of air and soil, all committed for our safety to its security and peace; preserved from annihilation only by the care, the work, and I will say, the love we give our fragile craft. We cannot maintain it half fortunate, half miserable, half confident, half despairing, half slave to the ancient enemies of man, half free in a liberation of resources undreamed of until this day. No craft, no crew can travel safely with such vast contradictions. On the resolution depends the safety of us all".

We are currently consuming an estimated 175% of the world's capacity for sustainable productivity (www.footprintnetwork.org), a proportion that has more than doubled, from 70%, over the past 50 years. In the grip of this clearly unsustainable situation, we exhausted the earth's total sustainable productivity on "Earth Overshoot Day", August 1, 2018, and for the past 3.5 months have been drawing down our planet's ultimate capacity to support us and other living beings. Much of this is related to our dependence on fossil fuels, which we clearly must rein in soon or face disaster for us all. Within the overall pattern of consumption, most industrialized nations consume much more than their "share" of the world's productivity, making it extraordinarily difficult for the poorer countries to catch up.

The Role of the Catholic Church

The Industrial Revolution, which reached full force about two centuries ago, has played a major role in exacerbating human inequality and social injustice and at the same time led directly to widespread environmental destruction. Virtually no uncut forests remained in Europe by 1840: these forests re-grew only when their use as the primary source of fuel was shifted to coal. By 1891, Pope Leo XIII, in his Encyclical *Rerum Novarum*, was calling attention to the growing social problems and proposing ways to rectify them. As our global population swept up from its Napoleonic level of 1 billion people to the current 7.6 → 9.8 billion in just two centuries, more than 200 million people were killed in wars, while social inequality grew rapidly both within and between nations.

Selfishness and nationalism are still the dominant ambitions driving us on, the kind of tribalism so well described in the Bible gaining strength rapidly, with the world completely divided into nations by the early 19th century, each of them striving for more than its neighbors possessed. By the second half of the 20th Century, the signs of environmental deterioration had become evident and were increasingly emphasized by religious and national leaders. The 1971 Stockholm Conference on the environment, when Pope St. Paul VI participated and spoke out strongly on the environmental problems facing humanity, was effectively the first true global conference on the environment, with evidence for global warming just becoming convincing and biological extinction starting to attain major levels. From that point on, the Roman Catholic Church has been deeply and outspokenly concerned with the environment, the Popes often emphasizing its attendant problems, but never more convincingly or thoroughly than Pope Francis, in his Encyclical *Laudato si'* of 2015, promulgated just two and a half years ago.

In that document, Pope Francis not only forcefully emphasized the enormous danger of climate change for humanity but also devoted a significant section of his message to the irreversible problems relating to the accelerating loss of biodiversity. His words brought that second problem into sharper focus than any earlier official Church pronouncement had done, and it is on that complex problem that I shall focus my presentation today.

In chapters 32-41 of *Laudato si'*, the ways in which the earth's resources are also being plundered because of our shortsightedness in economic development are emphasized both in relation to the loss of functionality in both terrestrial and marine ecosystems and also in relation to the attendant loss of species at a rate that has grown to many thousands per year. Pope Francis emphasizes that we have no right to drive those species to extinction, but rather an obligation to try to save them so that they will be able to continue to give glory to God by their existence and at the same time "convey their message to us". As species are lost, ecosystems often malfunction and we attempt to intervene in ways that often make the situation worse. The Pope calls for aggressive action to learn about species and the ways in which they support the functioning of ecosystems, which is certainly insufficiently known at present. As they lose their constituent species, the ecosystems will function increasingly poorly; as we wreck whole ecosystems, they will continue to lose their species rapidly. Thus our greed for short-term gain can only place unfair burdens on the majority of poor who live among us now, and seemingly intractable problems that future generations will need to try to solve with the curtailed resources that we are leaving them (*Laudato si'*, Chapter 34-35).

The Encyclical continues to point out that some countries are trying hard to preserve their biological diversity and relatively intact ecosystems, establishing sanctuaries both on land and in the oceans, and often in areas where species diversity is relatively rich, but that these efforts need to be greatly amplified for our common benefit. It also emphasizes the great importance of the tropics and the rapidity of extinction there as their forests are being cut, largely to benefit wealthy individuals or international corporations. It recommends that each country carry out its responsibility to preserve its environment and natural resources, a subject to which I shall return later in this paper. Equally strong measures are urged to protect the abundant life and ecosystems of the oceans, both because of their role in global ecology and in supplying food to so many of us. They are certainly more fragile than they seem, and ignoring them could easily lead to changes in the whole planet in ways that we understand incompletely (*Laudato si'*, Chapters 38-40). In addition, the Encyclical stresses that many of the individual species being lost may constitute extremely important resources for the future, not only for food but for medicines and many other purposes that remain unknown to us as they disappear.

In relation to with modern methods of breeding improved crops, domestic animals, and other organisms to serve our needs and regulating environmental problems, it is pointed out that different species contain genes that could become key resources in years ahead. Indeed, the deeper modern molecular probes, the more impressive the differences between entire genetic systems in different organisms become. This relationship constitutes yet another reason for not throwing away the diversity that we have inherited simply because of our short-term greed and the further enrichment of those who are already wealthy.

Extinction Rates and their Consequences

First of all, let us consider the extent of biodiversity that exists on earth today. There are two major kinds of living organisms, Eukaryotes, which include animals, plants, fungi, and complex microorganisms, and Prokaryotes, which are the bacteria, and Archaea (the latter might better be viewed as their own distinct branch of life). Eukaryotes, all of which are made up of complex cells like ours, appear in the fossil record about 2 billion years ago, and Prokaryotes, possibly Archaea, about 4 billion years ago, with our planet having originated and started cooling 4.54 billion years ago.

The number of Eukaryotes inhabiting our planet now is estimated by various authorities to amount to some 8-12 million species, and the actual total could be much larger. What is striking is that only between 1.7 and 2 million species have been detected by science and given names, so that the great majority of existing species are unknown – and likely will remain so as they disappear forever. Only birds, mammals, and other terrestrial vertebrates; land plants; and a few other groups of organisms, such as butterflies and mosquitoes, are reasonably well known, but probably still have 10-20% of their species to be discovered. The simple, and at the same time awful, relationship that this reveals can be demonstrated by pointing out that most of the species that are forecast to become extinct during ours and the next two generations will never even have been seen by any scientist – we are literally throwing them away. It as if we not only are burning the Library of Alexandria, but a library in which relatively few of the books have been examined by anyone before they vanish permanently.

For Prokaryotes (bacteria and Archaea), the story is even more difficult to imagine. Only a few thousand species have been given names, and yet estimates of the total number on Earth range all the way up to *one trillion* kinds! We know that individually and in the aggregate they are of fundamental importance for the functioning of ecosystems, of soils, or aquatic systems – of everything living – and yet we are scarcely trying, in relation to the immensity of the problem, to know anything about them, or indeed about Eukaryotes, while they are still supporting our lives and every other living system on our planet.

Given this base, how fast are we losing species? Using the fossil record of well-represented groups, we calculate a rate of extinction for them of about 0.1 species per million per year. Comparing these rates with those observed now for the same groups leads us to the conclusion that they have already increased by about 1,000 times, to about 100 species/million/year. Because of the factors discussed earlier in this paper and below, we have become certain that these numbers are accelerating rapidly (summaries in Dasgupta, Raven, and McIvor, 2019; Raven, 2019).

A second way that we may approach the problem of estimating probable biological extinction in the remainder of this century is as follows. Comparing IUCN Red List rankings (IUCN 2016) with extinction probabilities determined in alternative ways for particular groups, including vertebrates and flowering plants, leads to an estimate that perhaps 20% of species in these groups are in danger of extinction during the next several decades. This, if actually attained, would be a much higher rate than the likely present one we calculated comparing actual extinctions with the fossil record.

If that rate (100 species/million/year) were to remain constant, and assuming that there are about 10 million species of Eukaryotes, about 50,000 of them would be expected to disappear over the next 40 years. If, instead, 20% of all species were to become extinct during this period, 40 times that many species, some 2 million, would have to be lost, that would mean an average rate of extinction of 40 times as high as the one we have calculated. This would amount to losing 50,000 species per year (higher in the future, lower now, of course). Whether our destructive activities will actually drive such a high rate remains to be seen, but we are clearly heading in that direction. By the end of the century then, the actual loss would certainly be cataclysmic. Considering these trends, it seems to many scientists likely that we may already be entering a Sixth Major Extinction event, with a large proportion of all species likely to be lost by the end of this century and in the decades immediately following.

What are the principal factors involved, and how could we slow them down?

The first and most important since the invention of agriculture has clearly been habitat destruction. Crops are currently being grown on about 11% of the Earth's land surface, with grazing, mostly on natural grasslands and therefore largely unsustainable, on another 30% of the land. Current estimates are that we would have to produce 70-100% more food by 2050 to feed the 9.9 billion people projected to be living then adequately, but the actual growth in production amounts to only about half that rate. Estimates of the amount of additional food necessary to feed 9.9 billion (Gustafson *et al.*, in press). At the same time that our numbers are increasing rapidly, people want to consume more and more, and the problem of hunger and starvation remains intractable or continues to grow. The probable effects on biodiversity of the drive to solve those problems will likely be enormous.

In synchrony with the expansion of agriculture, natural habitats everywhere are being destroyed rapidly too. Tropical forests are home to the richest and most poorly know biodiversity anywhere on earth, and their destruction is accelerating. Since the implementation of the highly-regarded Convention on Biological Diversity 25 years ago, a quarter of all tropical forests have been cut, mainly for industrial-scale agriculture. Considering the relationship between species numbers and our knowledge of the plants and animals that inhabit those forests, it is likely that 19 out of 20 of the kinds of Eukaryotes living there and subject to extinction are currently unknown to science, an appalling thought in relation to our future.

Particularly since the development of international commerce over the past five centuries, the introduction and establishment of weeds, pests, and pathogens has expanded rapidly worldwide and is clearly an important factor accelerating extinction and ecosystem disturbances worldwide.

Humans gathering medicines, wood, and other forest products from natural communities is driving many of them to very low population levels and potentially extinction also. To the extent that these products could be obtained from cultivated crops must be worked out for each of them, and of course would compete with food production, as we are seeing in the case of biofuel production in the US and elsewhere.

Coming strongly into view recently as a cause of species extinction is global climate change, which we are certainly managing inadequately so far. Larger than anticipated changes are perfectly feasible, and it has become almost certain that agriculture will be substantially disturbed or even displaced over the coming several decades. And in the so-called "biological hotspots", areas with large numbers of species found nowhere else that have already been substantially disturbed by human activities (e.g., Madagascar, California, the Mediterranean generally), the risk of large amounts of rapid extinction is extremely high, as would be the case along the southern edges of the world's southern lands, in coastal areas, and on islands generally. Estimates offered to date for the additional extinction due to climate change in this century mainly range from 15 to 40% – and they do not depend on any further habitat loss!

Whether the loss of species is caused by global warming or another factor, there are many possible, poorly-understood global consequences that may ensue. Thus Lenton (2018) inquires to what extent the projected high levels of species loss would compromise the function of ecosystems and the biosphere. Changes at a certain order of magnitude could certainly result in the loss of entire biomes by the tipping of critical balance points. In the seas, acidification resulting from increases in carbon dioxide concentration have already become a major problem. Marine anoxia resulting from the runoff of nitrogen and phosphorus from agricultural systems on land is leading to increased ocean warming and thus further reducing the capacity of the water to absorb oxygen. Changing temperatures for offshore currents could certainly cause massive change both on land and in the seas, certainly with consequences for increasing biological extinction.

Summary

Following the appearance of *Homo sapiens* about 300,000 years B.P. cultural evolution led eventually to the development of agriculture as the last ice age waned, about 11,000 years B.P. About one million of us existed then, and now there are 7.6 billion growing rapidly, with more than a third of the earth's surface devoted to agriculture. As a result of this and our other activities we are estimated to be driving the species of organisms to extinction at about 1,000 times the historical rate, with about 20% of all species endangered now and many more likely to disappear before the end of the 21st Century. Since the functioning of our planet depends on biodiversity, so do our lives; and, in addition, we obtain virtually everything we use from it, including our food and many of our medicines. We need to feed the 800 million hungry people on earth now, and to take care of the 2.3 billion projected to be added in the next 30 years, and yet to keep our planet functioning. No result of our activities will harm our future prospects more decisively than biological extinction, which is irreversible.

Nothing we are doing to damage the functioning of the living world and the stability of its ecosystems will do more harm than biological extinction. We must find effective ways to address the loss before it is too late

(e.g., Tilman *et al.*, 2017; Lovejoy, 2017). While pollution and global warming are obviously directly hurting us badly today, our ability to recover will depend to a large extent to whether we save the biological units, species, that interact to produce the habitable earth we are damaging so radically at the present time.

As Dasgupta & Ehrlich (2018) have concluded, seeking to limit the proximate causes of extinction will not ultimately prevail unless the basic drivers are addressed – "continued population growth, policies seeking economic growth at any cost, overconsumption by the rich, and racial, gender, political, and economic inequality (including failure to redistribute). Collectively addressing these are possibly the greatest challenges civilization has ever faced".

Achieving the goals just outlined clearly must be taken as our common responsibility; without doing so we simply haven't got a chance. Learning about how to achieve them and then working to achieve them ultimately will be responsible for our survival, and we must learn, teach, act, and vote in such a way as to advance our common cause, the search for a sustainable world. Doing so will require a degree of humility, compassion, and love that we have yet to exhibit, but which is indicated very clearly in our topical Encyclical *Laudato si'*. We do not seem likely to do so on the basis of facts and logical reasoning alone, and therefore highly praise the leadership of Pope Francis in contemplating the beauty and importance of life as it is and the urgency of working to preserve it for the future. As Pope Francis has stated so clearly in *Laudato si'*, Chapter 43, "Because all creatures are connected, each must be cherished with love and respect, for all of us as living creatures are dependent on one another".

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Block 2 |

Frontiers in Science Disciplines

SESSION V – PHYSICS

Basic Research and a Moral Responsibility of Scientists

Daniel Kleppner

The history of the living world
is an elaboration of ever more perfect eyes
in a cosmos in which there is always something new to be seen.
Teilhard de Chardin

Teilhard was a paleontologist, geologist, philosopher and Jesuit priest; his epigram provides a stunning description of the evolution of science. Teilhard's phrase "ever more perfect eyes", for instance, accurately describes the evolution of telescopes from the crude optical devices at the dawn of the 17th century to today's space telescopes. This fabulous development was driven by curiosity about the nature of the universe, which is to say that it was the product of basic research. I would like to discuss issues related to basic research in the physical sciences that relate to the central concern of this session of the Pontifical Academy of Sciences. By "basic research" I mean research motivated by the joy in understanding nature in contrast to solving a particular problem. When Teilhard talked about "ever more perfect eyes in a cosmos in which there is always something new to be seen", he was talking about basic research

Einstein's search for a theory of gravity – his General Theory of Relativity – is an iconic example of basic research. The problem he struggled to solve – to create a theory of gravity that avoided some inconsistencies in Newton's theory of gravity – worried hardly anyone else and had no conceivable use, at least not at that time.

A startling consequence of Einstein's theory is that gravity affects time. A clock on top of a mountain runs faster than an identical clock at sea level, but not by much: a clock on the peak of Mt Everest should run fast only by about a millionth of a second a month.

The quest to observe Einstein's prediction for the effect of gravity on the rate of a clock has a remarkably well documented starting date: January 11, 1944. That day, a New York Times article carried the headline "Cosmic Pendulum for Clock Planned". It was the report of a speech at an American Physical Society meeting in New York City, by I.I. Rabi, a physicist at Columbia University. Rabi proposed creating a clock whose ticks were governed not by the swing of a pendulum but by pulsations within an atom that could be measured by a technique he had invented: molecular beam magnetic resonance. The accuracy of such an atomic clock could be fabulously high. The NY Times article reported that "Professor Rabi said that he would like to see someone build an atomic clock that would be capable of providing for the first time a terrestrial check on the Einstein postulate that the gravitational field produces a change in the frequency of radiation".

The creation of atomic clocks sprung directly from the quest to see whether gravity affects the rate of a clock, that is, whether gravity affects time. Lacking any other conceivable application for such an accurate clock, the quest provides an ideal example of basic research.

Nobody rushed to build an atomic clock following Rabi's talk in 1944: the research establishment was in disarray from World War 2 and there was a technical barrier. That barrier was breached in 1949 when Norman Ramsey, a former student of Rabi's who had just joined the physics faculty at Harvard University, proposed a technique with the cumbersome name of "the separated oscillatory field method". Serious work on an atomic clock started then and in 1954 the first experimental clock was demonstrated in England. It came to be known as the cesium beam atomic clock.

In 1953 I went to Cambridge University, England, with a two-year Fulbright Fellowship. My tutor, Kenneth Smith, did something tutors generally did not do at Cambridge in those times: he talked with me about his research. His work centered on studying the properties of atomic nuclei using Rabi's technique. Smith told me about Rabi's proposal to observe the effect of gravity on clocks. I remember being stunned by the idea that gravity affects time but I could only store the thought among the clutter of possibly interesting ideas rattling around in my head.

In September 1955 I entered graduate school at Harvard University. Ramsey was on the faculty and the following spring I joined his group. In the fall of 1956 he told me about his idea for the hydrogen maser, a frequency standard fundamentally different from the cesium frequency standard but which had some potential advantages. Naturally, I jumped at the opportunity. The first hydrogen maser was demonstrated in August 1960.

When Rabi proposed that "somebody ought to build a clock", he was referring to what became known as the cesium-beam clock. The first cesium clock was demonstrated in 1956 and within a few years a practical device had been produced. The hydrogen maser is comparable in accuracy to the cesium beam clock and most time standards laboratories have one or more.

Although the hydrogen maser was created specifically to verify Einstein's conjecture about time and gravity, its unanticipated applications are noteworthy. The hydrogen maser made the radio-astronomy technique known as Very Long Baseline Interferometry (VLBI) possible.

VLBI allows astronomers to make radio telescope antennas that are effectively the size of the earth. VLBI enables astronomers to create maps of hydrogen in the universe with astonishing detail, and allowing them to look further back in time than by any other technique. Recently progress has been reported on the Event Horizon Telescope. This telescope combines data from about 15 radio telescopes around the world. Working together, these are powerful enough to make an image of the event horizon as matter disappears as it falls into the massive black hole at the center of our galaxy. Once inside the event horizon, material disappears forever but as it falls in it radiates intensely. Images of that radiation make it possible to study the predictions of General Relativity under conditions never previously observed.

The greatest impact from the development of atomic clocks, however, is the creation of the Global Positioning System (GPS). The GPS is a technical marvel of the Space Age. It is fundamentally a timing system and atomic clocks are at its heart. General Relativity is also at its heart: GPS would not work if Einstein's theory of gravity were ignored. To my knowledge, nobody had thought about such a system before atomic clocks became a reality and nobody could have imagined the powers of today's GPS.

Today the GPS is ubiquitous: it is at the heart of the air control systems that guide planes in flight and the navigational systems in smart phones and automobiles. The GPS keeps our communication networks and power grids synchronized. It is crucial for medical emergency systems. Above all, the GPS is crucial for understanding the existential threat to humanity that is the focus of this Plenary Session: Climate Change.

Understanding the global climate requires data on a vast number of variables: radiant energy flow to and from Earth, vertical and horizontal temperature profiles, cloud covering and temperature, sea and land surface profiles, ocean surface temperature and wind speed, global precipitation, water content of the atmosphere and troposphere. The list goes on and the data are enormous.

The primary source of data on Earth's climate is a fleet of eight weather satellites in polar orbits, four from the U.S., and four from the European Space Agency. This fleet scans the entire surface of Earth four times a day. Often, the satellites work together in pairs, exchanging radar and lidar ("light radar") signals to look through the troposphere to measure its water content. This particular measurement is crucial to a global analysis because most of the atmospheric water is stored in the troposphere. In addition to the polar fleet of weather observatories, there are clusters of synchronous satellites from various nations that continuously view Earth. The U.S. has two clusters viewing the entire country; one extending to points east, the other to points west.

Because hardly any of these global climate measurements would have been possible without GPS, it is valuable to keep the origin of the GPS in mind: mere curiosity about General Relativity. Basic research was the driving force for the GPS it is often the driving force for transformational advances, advances that broadly affect society.

Here are two other examples of transformational discoveries from basic research:

The invention of the maser and the laser by Charles H. Townes originated in his research on the temperature of molecules in space. His research contributed to the discovery that space has a temperature and that discovery triggered a revolution in cosmology. To measure the feeble signals of molecules in space, Townes invented a new type of molecular signal amplifier called the *maser* (the acronym for *microwave amplification by stimulated emission of radiation*). Townes and his colleagues then extended the maser concept from microwave frequencies to optical frequencies, which led to the invention of the laser (acronym for *light amplification by stimulated emission of radiation*).

The laser has transformed communications, manufacturing, and lighting. Lasers can be found in essentially every scientific and industrial research laboratory. Applications range from lidar systems at the heart of automobile collision avoidance devices to surveying systems that monitor Earth strains in volcanic and earthquake-prone areas.

Nuclear magnetic resonance (NMR) provides a second example of basic research generating a transformational technology. NMR was invented independently by Felix Bloch at Stanford University and Edward M. Purcell at Harvard University. NMR was invented primarily to study the properties of atomic nuclei but it quickly became an essential tool in chemistry. The major impact of NMR came about twenty-five years after its invention when powerful computers had become practical. Combining these technologies led to the invention of Magnetic Resonance Imaging, (MRI) by Paul C. Lauterbur in the U.S. and Sir Peter Mansfield in England. MRI makes it possible to take non-invasive pictures anywhere within the human body. It is now a standard imaging technique.

I stress these unexpected rewards from basic research because society urgently needs new ways to deal with the ominous threats of climate change. Research on many aspects of energy production and usage is underway but I want to emphasize the importance of new ideas coming from basic research unrelated to any perceived need.

There is no way to predict which area of research will suddenly bloom and possibly create a transformational technology but the conditions for such discoveries are well known: a research environment in which the search for new knowledge is respected, research is supported, and institutional structure encourages communication and collaboration.

Today, in the United States, support for basic research is dwindling. Opportunities for a career in basic research are decreasing and our ability to attract excellent students from home or abroad is declining. When considered in the context of the most recent report of the Intergovernmental Panel on Climate Change (IPPC), neglect of basic research could be disastrous.

It has been known for decades that there is a possibility of a runaway situation in which an increase in global temperature feeds back to accelerate the global heating. The process could lead to a massive change in climate and a catastrophic elevation of sea level. The latest report of the IPPC concludes that previous reports erred in being too cautious: the time to stem the flow of greenhouse gases is shorter than had been estimated. We are facing a truly existentialist threat to civilization. New technologies need to be fostered, but in the rush to develop them a reasonable level of basic research must be maintained if we are to hope for new transformational technologies.

Vigorous international leadership is required if we are to make a rapid change in greenhouse gas emission. The United States should be capable of leading but the current President of the United States is opposed to science and mocks the concept of scientific truth. He and his followers take comfort in a policy of denial. Denial is guaranteed to make matters worse. Until the U.S. recovers its moral bearings we will continue to waste the precious short time we may still have for effective action.

This creates a personal dilemma that I imagine many scientists share with me. Ever since the creation of the atomic bomb there has been a tradition of scientists involving themselves in science policy and public affairs. In the U.S. the list from physics includes Leo Szilard, Eugene Rabinowitch, Hans Bethe, I.I. Rabi, Viki Weisskopf, and Richard Garwin, as well as organizations such as the American Association of Atomic Scientists and the Union of Concerned Scientists. How can scientists honor that tradition today?

If our civilization succeeds in learning how to live in harmony with the natural world, science will have played a crucial role in the transition. The immediate problem in the United States is to convince Congress of the urgency of the situation. Happily, the years of developing STEM education in the U.S. are starting to pay off. There is a growing number of scientifically literate citizens and members of Congress. These people will listen if scientists speak up. Speaking up for science is surely high on the list of the moral responsibilities of scientists today.

Science Addressing Questions Not Easily Addressed by "the" Scientific Method. The Origins of Life[1]

Steven A. Benner[2,3]

1. A multidisciplinary workshop built a model for the geochemical formation of RNA

In October 2018, a group of planetary, biological, and molecular scientists gathered in Atlanta for an unusual three-day workshop. On its last day, the scientists closed their PowerPoints, set aside individual projects, and opened an interactive discussion with just one goal: To resolve paradoxes that prevent the "origins of life problem" from being studied as "normal science" (Kuhn 1966).[4]

The interactive discussion moved beyond talks that had been presented by individual participants from their individual laboratories in their individual fields. Freed from constraints, for three hours, the group built a model for origins that combined all three fields. The "Atlanta Model" that emerged included a chemical path-hypothesis to make RNA from starting materials that were likely available on a Hadean Earth. It identified geological events that would have made those materials available. It estimated dates when those events most likely made oligomeric RNA.

The Atlanta Model is detailed in a joint publication of the participants (Benner et al. 2019). The discussion that generated the model was summarized by Robert Service, a science journalist who witnessed the interactive discussion (Service 2019).

In brief, the Atlanta Model hypothesizes that life on Earth most likely emerged 4.36 ± 0.1 billion years ago (Ga) via an abiotic synthesis of oligomeric RNA that served as its first informational biopolymer. That RNA

[1] Adapted from a presentation to the 2018 Plenary Session of the Pontifical Academy of Sciences at the Vatican in November 2018.

[2] Foundation for Applied Molecular Evolution, 13709 Progress Blvd. Box 7, Alachua, FL 32615, USA.

[3] Firebird Biomolecular Sciences LLC, 13709 Progress Blvd. Box 17, Alachua, FL 32615, USA.

[4] The Origins of Life 2018 Conference http://templetonorigins.ffame.org/OriginsConference2018.aspx

arose from:

(a) formaldehyde ($H_2C{=}O$) and trace amounts of glycolaldehyde (HOCH-$_2$HC=O) generated by ultraviolet light and/or electrical discharge in a Hadean atmosphere rich in carbon dioxide (CO_2). These
(b) reacted with volcanic sulfur dioxide (SO_2) to form carbohydrate-bisulfite adducts that
(c) rained into constrained aquifers that intermittently evaporated, where
(d) the carbohydrate-bisulfite adducts, constrained by minerals containing borate, silicate, and phosphate, matured to give 5-carbon sugars (such as ribose). These then
(e) reacted with phosphorus species to generate carbohydrate cyclic phosphates, which
(f) gave nucleosides via direct reaction with nucleobases, which had
(g) been formed from precursors having reduced nitrogen atoms, which had been generated in
(h) an atmosphere that had been transiently reduced by a large impact, which was
(i) date-estimated from various geological clocks.

The nucleosides were then converted to phosphorylated materials in

(j) aquifers evaporating and re-hydrating to support
(k) reaction between nucleosides and phosphate, phosphite, nickel, and borate minerals to give nucleoside 5'-polyphosphates. The polyphosphates then
(l) reacted on silicate minerals to form mineral-stabilized oligomeric RNA.

Our task today is to ask, with much incredulity: How is it possible to say such things about events that occurred billions of years ago, none of which are directly observable?

We also consider the more general question: Can such models ever enjoy the respect that we give models emerging from "the" scientific method?

Over the past century, many have introduced methods and demarcation criteria, including logical positivists (Smith 1986), Popper (2002), Quine (1953), Hempel, and others (Benner & Gutterson 1976). As we were taught for our 8th grade science fairs, a "scientific" activity requires careful observations, precise measurements, and tests of well-structured hypotheses. None of these seem directly possible when seeking to understand the origins of life.

However, science has long recognized that such "big" questions can be indirectly studied by asking other, hopefully related, "small" questions (Benner 2009). Indeed, almost no one found on a list of scientists said to be investigating the "origin of life" is actually and directly investigating the origin of life. Rather, they are investigating microbial metabolism or synthetic organic chemistry that, at funding time, they *say* is relevant to the origin of life.

For such scientists, problem selection becomes very (very) important. Scientists generally continue to do research in the future that is similar to research that they have done in the past. Funding agencies encourage this. Thus, it is easy for scientists to go down rabbit holes in their work. Even if a project began with the intent to indirectly study how life originated, it often moves away from that goal, drilling deeper and deeper into narrower and narrower problems that are more and more distant from the initial intent.

Most importantly when working off-target, we must remember the Feynman dictum: "People are easy to fool, and the easiest person to fool is ourselves" (Feynman 1974). Scientists are like all humans. We are good at rationalizing, especially when it comes time to raise funds for our laboratory. We easily rediscover old ideas and brand them as our own (Saladino et al. 2018). We easily advocate for our ideas by cherry picking data that agree with them, excluding or suppressing data that disagree.

Indeed, origins of life research holds many examples of the "anything goes" description of science provided by Paul Feyerabend, my former colleague at the ETH. Paul noted that scientists use "any trick, rational, rhetorical or ribald" to get a community to accept their views, with the publications, grants, and awards to follow (Feyerabend 1975).

2. Background. RNA as the first genetic molecule to support Darwinism

The Atlanta workshop discussion started with a "Standard View" for the origin of life on Earth (Neveu et al. 2013). That view holds that Darwinian evolution began when abiotically-created RNA molecules became the informational part of a system that catalyzed the template-directed synthesis of RNA, with replicable errors (Rich 1962). This is a minimalist, molecular, and reductionist view of evolution. An "existence proof" for such RNA molecules comes from the laboratory of Philipp Holliger in Cambridge, which found examples of RNA molecules that catalyze the template-directed synthesis of RNA (Attwater et al. 2013).

This Standard View has long enjoyed support because it manages a key "origins" problem emerging from the details of modern molecule biology.

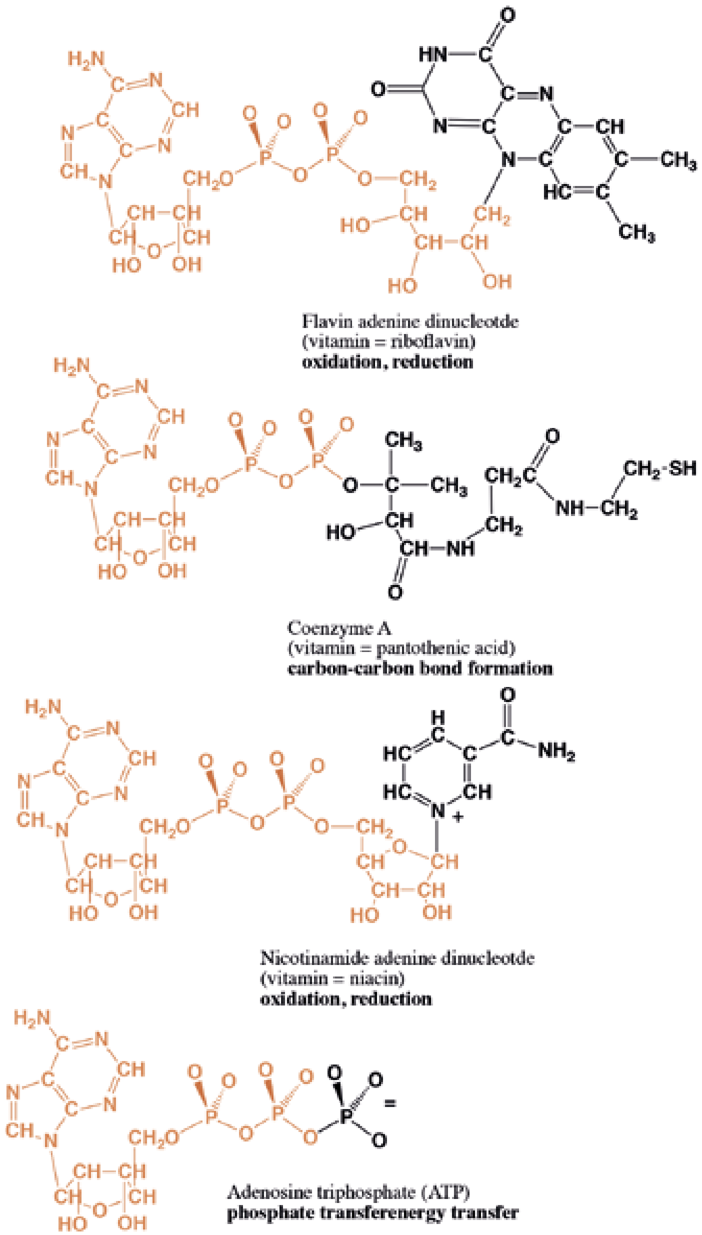

Figure 1. Four representative cofactors that have a part (in black) that delivers reactivity not available in the 20 standard amino acids attached to a piece of RNA (in orange) that appears to have no chemical purpose. While this does not demand that Darwinism began on Earth through the abiological formation of RNA, it does provide evidence that RNA played a bigger role in the past than today.

Today on Earth, in contemporary molecular biology, the information in DNA encodes the information of RNA, and the information in RNA encodes the information in catalytic proteins. If RNA emerged first in a form able to perform both genetic and encoded catalytic roles in the first forms of life on Earth in an RNA World (Gilbert 1986), this avoids the chicken-or-egg problem (which came first, DNA for genetics, or proteins for catalysis?).

Other chemistry from the modern biosphere also implicates RNA in early episodes of life on Earth. The ribosome, the molecular machine that *makes* proteins, is itself an RNA catalyst. Ada Yonath, in her contribution to the Atlanta workshop, provided information about the performance of ancient RNA from ancient ribosomes, consistent with the Standard View.

An RNA World model also accounts for the chemistry of RNA cofactors in modern metabolism (White 1976; Visser & Kellogg 1978a,b). In life on Earth today, various chemical reactivities required for metabolism are not enabled by the encoded amino acids in our proteins. Rather, they are provided by cofactor moieties that are attached to small pieces of RNA (Fig. 1). The RNA appendage is seen as a vestige of a handle that held the reactive moiety to RNA catalysts in the RNA World. An analysis of these cofactors and modern genomic sequences adumbrated models for the genomic and metabolic activities in the RNA world at the time when encoded synthesis of proteins first emerged (Benner et al. 1989).

3. The "scientific method" and the origin of life

3.1. The "RNA First" model for the origins of life is ripe for philosophizing

The "RNA First" model for the origin of life on Earth might be viewed as a hypothesis. However, it would not serve well an 8th grader participating in a science fair, as it contains few of the instructed elements required for a blue ribbon. Where is the experiment that would confirm a historical model, something that would fit a "positivist" model? What experiment might "falsify" the model, to satisfy Karl Popper and Gunther Wächtershäuser (1995)? Thomas Kuhn (1966) might remark on the absence of opportunities for "normal science" in the field. However, pointing out that a field needs a revolution is hardly a prescription for getting one.

The difficulty of placing origins research into standard "scientific methods" has been noted by its more philosophical participants. For example, one of many philosophical (and quotable; Krishnamurthy 2018) aphorisms from Albert Eschenmoser, also of the ETH, who noted that the origin of life "cannot be discovered; it must be re-invented" (Eschenmoser 2007, 2009). "Re-invention" is outside of the 8th grade science fair canon.

John Sutherland has also contributed richly to the philosophy of the discipline. For example, in 2011, Powner and Sutherland (2011) suggested "a new *modus operandi*" for prebiotic chemistry. Seeking to formulate a broad new approach to the origins problem, Sutherland (2016) criticized a view, attributed to Gerald Joyce (2002), that "Darwinian evolution needs informational molecules, so RNA must have come first". Sutherland then criticized another view, attributed to Wächtershäuser (1992), that "[y]ou can't get by without building blocks and energy, so metabolism must have come first". He then criticized another view, attributed to Plankensteiner et al. (2005), that "[g]enetics and metabolism without catalysis is hard to imagine, so proteins must have come first". He then criticized another view, attributed to Segré et al. (2001), that "[t]he development of Darwinian selection is hard to imagine without compartments, so membranes must have been there at the outset".

Sutherland then advised the community to pursue a "more holistic approach" to the origins problem. His advice was to let "chemical results … constrain geochemical scenarios", and allow the geochemical scenarios to "back-inform the chemistry [leading] to refinements in both the [geological] scenario and the chemistry". Sutherland (2017) noted that by doing so, the field might not be at its end, or even the beginning of its end, but at the end of its beginning.

The need for geological and chemical models to interact under such a *modus operandi* has been recognized in this community for over a half a century (see, for example, Bernal 1961, Cairns-Smith 1977, 1982, 2005; Scorei et al. 1999, Cimpoiasu et al. 1999, Prieur 2001, Ricardo et al. 2004). Indeed, the Atlanta workshop brought together many scientists who followed this *modus*. Let us see how the Atlanta discussion developed.

3.2. Paradoxes as a tool to focus research effort on the most important problems

As its goal, the interactive discussion in Atlanta sought to resolve *paradoxes* that prevent the origins of life problem from being studied as a "normal science". Several prominent researchers in the field have disputed this approach, arguing that paradoxes are no different from statements of "difficult problems". Let us develop the concept of "paradoxes" so that we (at least) understand such a dispute.

Paradoxes are distinguished from simple propositions by a logic that interrelates their propositions. Paradoxes are constructed, using logical formalism, to move from universally accepted facts via Aristotelian deductive logic to a conclusion that its constructors may find to be unacceptable. To be a paradox, as opposed to simply a statement that a problem is "difficult", formal logic must be invoked.

It is best if the target of the paradox is a model that the constructors themselves like. For example, for those liking the RNA-first model for the origin of the Darwinism, a useful paradox moves via deductive logic from "obviously correct" premises to the conclusion that RNA cannot possibly have emerged abiologically. This is a way that a paradox can mitigate human confirmation biases, which source the issues raised by Feynman. Indeed, science students may be taught to construct paradoxes as a "game" to train them to these ends.

Constructing paradoxes is also a way to productively focus research effort. This use is well understood in physics. As Niels Bohr once remarked (Moore 1966), "How wonderful that we have met with a paradox. Now we have some hope of making progress". That remark reflects the ability of paradoxes, even if they turn out to be misperceived, to focus attention on important things, and direct our attention away from activities that will have little impact.

Paradox construction thus offers a tool to prevent research from going down rabbit holes. If the outcome of an evolved research programme, even if it is fully successful, will have no impact on the logic of the paradox, one should perhaps select a different programme.

4. Illustrating the role of paradoxes in guiding origins research

4.1. A Miller-inspired paradox. Ribose, and therefore RNA, cannot emerge abiologically

Let us illustrate the value of paradoxes by considering ribose, the "R" in RNA. Ribose is rather unstable to self-reaction to give complex mixtures of products. This is a property of most carbohydrates, compounds that contain carbon, hydrogen, and oxygen atoms in the ratio of 1:2:1.[5] Indeed, this propensity of carbohydrates to decompose is known to anyone who has ever heated sugar in the kitchen and watched it caramelize.

A quarter century ago, Stanley Miller, a founder of modern prebiotic chemistry, quantitatively measured the instability of ribose (Larralde et al. 1995). This is an excellent example of quantitative and observational science, good for a science fair project. Miller found half-lives for the decomposition of ribose in water to be 44 years on ice at neutral pH 7, but only

[5] Carbohydrates are also often called "sugars". Ribose is the carbohydrate, or sugar, found in RNA.

73 minutes at 100°C at pH 7. This is, of course, the caramelization that is known to every chef (amateur and professional).

Miller concluded that the instability of ribose "*preclude[s] the use* of ribose and other sugars as prebiotic reagents except under very special conditions. It follows that ribose and other sugars *were not components of the first genetic material*" [emphasis added]. With more Aristotelian formality, Miller inspired a paradox whose conclusion is incompatible with an RNA First model for life's origin, unacceptable to scientists who *want* that model to be true:

(a) Ribose decomposes at a quantitatively measured rate,
(b) Molecules decomposing at this rate cannot be part of abiotically-formed genetic materials,
(c) Therefore, ribose could not have been part of an abiotically-formed genetic material.

Those of us who accept these premises and accept Aristotelian logic are compelled, it would seem, to abandon the Standard View for the origin of life. The only hope we might find in Larralde et al. (1995) is the qualification: "except under very special conditions".

4.2. The instability of sugars is rooted in the C=O carbonyl group

Of course, scientists rarely accept logic that contradicts a preferred theory, as many have noted (Feyerabend 1985, 1993), (Boyd 1991). Instead, scientists are inclined to try to rescue the theory. This inclination is not necessarily bad, Feynman aside. The premises of the paradox may be flawed in a non-obvious way. Auxiliary factors might render a "disproof" of an observation not a disproof (Quine 1954). If an attempt to rescue a theory makes obvious such flaws to give new insights, it is worthwhile.

Here, physical organic chemistry puts the instability of ribose into a broader context. Instability is not a problem just with ribose *specifically*. Rather, ribose has a feature of its molecular structure that causes its propensity to decompose. This feature is a carbon atom doubly bonded to an oxygen atom (C=O). This "carbonyl group" confers special reactivity upon a molecule if its carbon atom is bonded to another carbon atom that is itself bonded to a hydrogen atom. This allows any molecule having this structural feature (not just ribose) to "enolize" (Fig. 2).

Enolization is the first step in a manifold of processes that destroy carbohydrates (Fig. 2). First, the "enolate" can react with another carbonyl molecule to give an "aldol" reaction. Alternatively, the enolate can suffer

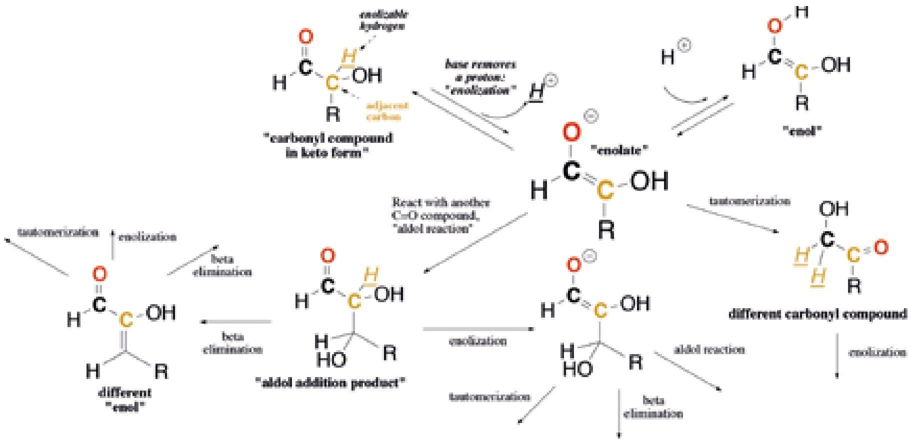

Figure 2. Compounds that contain a carbonyl group (C=O) whose carbon atoms are attached to another carbon atom that carries a hydrogen atom can undergo enolization. This initiates a series of reactions that include reaction with the C=O group of a second carbonyl compound in an “aldol reaction”. The propensity of carbohydrates (often called sugars) to form tar derives from the fact that products of these aldol reactions often (but not always) contain their own carbonyl groups whose carbon atoms are attached to another carbon atom that carries a hydrogen that can undergo further enolization. Unless these reactions are stopped promptly by an attentive graduate student, the mixture can become quite complex. The rate of enolization is a function of pH. For simple carbohydrates like glycolaldehyde and glyceraldehyde, at pH 10.5 in room temperature, the rates of enolization are measured in minutes.

“elimination”, “tautomerization”, and reaction with other “electrophiles” (Fig. 2). The rate of enolization increases as the temperature increases and as the pH moves away from neutrality. For example, at pH 10.5, rates of enolization of carbonyl compounds at room temperature are not measured in years, but in minutes (Illangkoon 2010).

The “aldol product” arising from the reaction of a carbohydrate molecule with an enolate often (but not always) ends up having a carbonyl group of its own (Fig. 2). Further, often but not always, the carbon of the C=O group in the product is attached carbon bonded to a hydrogen atom. In this case, the product can itself *again* enolize, tautomerize, eliminate, and undergo aldol reactions, leading to more products, and eventually to caramel. These self-reactions prevent the accumulation of most carbonyl compounds, except perhaps under “very special conditions” (Larralde et al. 1995).

Enolization occurs in water, but many compounds can encourage (catalyze) this process and participate in it, including acids, bases, and those that contain reduced nitrogen (e.g. ammonia, NH_3). If the products become large enough to absorb ultraviolet light, the manifold of complexifying reactions becomes larger and larger. The result is "tar", the natural fate on Earth of biological organics removed from Darwinism, including oil, coal, asphalt and graphite.

Miller was not alone in recognizing that ribose and other C=O carbonyl compounds might be too reactive to have participated in an abiological process that led to the formation of RNA, at least not in amounts that might self-react. For example, a bit earlier, Sutherland and Weaver (1994) noted that the reactivity of the C=O group in glycolaldehyde phosphate required the C=O moiety be introduced *last* in a laboratory synthesis of this compound. Eschenmoser had proposed glycolaldehyde phosphate to be an intermediate in the abiological synthesis of ribose (Wagner et al. 1990), in part because he expected the phosphate group to diminish the rate of the intrinsic base-catalyzed enolization of glycolaldehyde.

5. Descending rabbit holes unconstrained by paradoxes. Examples in origins research

With this understanding of physical organic chemistry, even non-chemists can evaluate a sequence of reactions that is proposed to have occurred abiologically. They must inspect a path-hypothesis to find any C=O compounds that it might contain.

5.1. An Orgel-hard problem: The formation of cytidine from two pieces: cytosine and ribose

For example, Fig. 3 contains a path-hypothesis for a prebiotic synthesis of cytidine, one of the four building blocks of RNA (Powner et al. 2009). You can play along. Identify in Fig. 3 all of the compounds containing a C=O carbonyl group, and circle those if the carbon of the C=O group is attached to a second carbon having a carbon-hydrogen bond.

Players of this game find three carbonyl compounds in this particular path-hypothesis that fit the rules. One of these is glycolaldehyde (labeled 10 in Fig. 3). Another is glyceraldehyde, labeled 9 in Fig. 3. The third, labeled 5, is not on the specific path that concerns us at the moment, and we will set this aside.

It turns out that glycolaldehyde 10 and glyceraldehyde 9 actually enolize *more rapidly* than ribose. This is because they cannot form the 5-membered cyclic ring that ribose can (see Fig. 5 for reactions that C=O can undergo that transiently control its reactivity). Therefore, glycolaldehyde 10

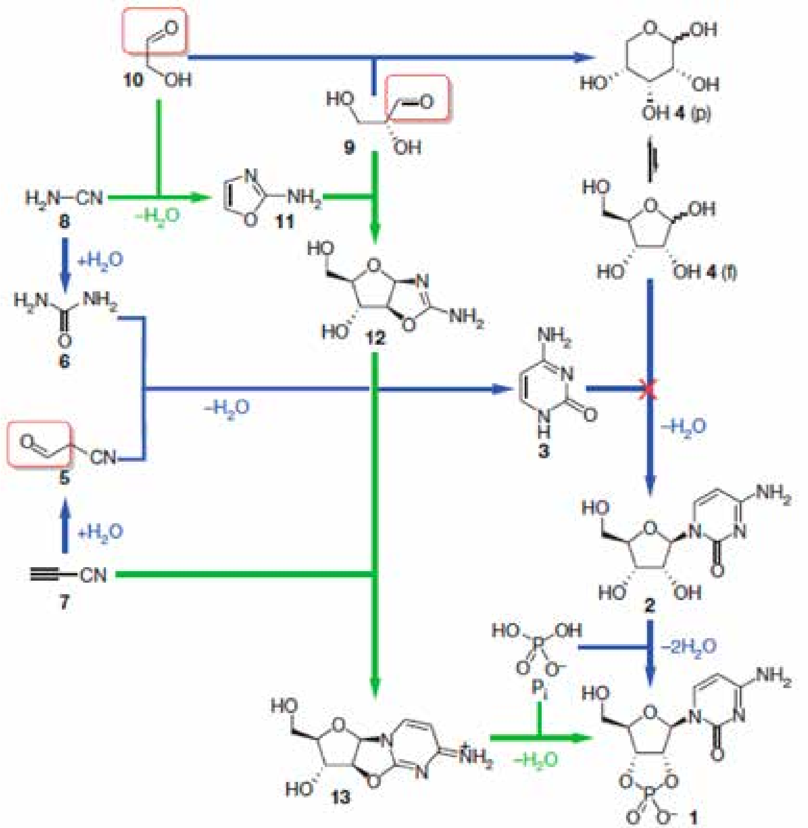

Figure 3. The path-hypothesis to make a cytidine derivative, adapted from Powner et al. (2009). Carbonyl C=O groups are boxed in red. The "Orgel-hard" formation of a glycosidic bond by direct reaction of ribose specifically with cytosine is marked with a red x.

and glyceraldehyde 9 decompose *faster than ribose*. Thus, the reasoning that generates the Miller-inspired paradox, which precludes *ribose* as a prebiotic reagent, would seem to also apply *even more strongly* to glycolaldehyde and glyceraldehyde. From this, it appears that the path-hypothesis in Fig. 3 does not solve the Miller-inspired paradox; instead, it would seem to aggravate it by requiring pools containing large amount of two *less stable* carbonyl compounds.

Work suitable for a high school science fair confirms this. This work studied in detail the reactions of glycolaldehyde 10 and glyceraldehyde

9, both free in solution (Harsch et al. 1984) and in the presence of borate (Ricardo et al. 2004; Kim et al. 2011), a species that has long been considered in prebiotic chemistry (Cimpoiasu et al. 1999; Scorei et al. 1999; Prieur 2001; Scorei & Cimpoiasu 2006).

We start by discussing the "self-reaction" of each. What happens if many molecules of glycolaldehyde 10 or glyceraldehyde 9 are present in solution without any other molecules?

The answers are well known (Ricardo et al. 2004) (Kim et al. 2011). Specifically, if the enolate of 10 encounters an unenolized molecule of 10, the two react in the aforementioned aldol reaction (Fig. 4, top). Adding carbon atoms, the two carbons in 10 would sum with the two carbons in the enolate to give one of two 4-carbon carbohydrates, which are called threose and erythrose (Fig. 4, top). Likewise, if the enolate of compound 9 encounters an unenolized molecule of 9, the two react also in an aldol reaction (Fig. 4, top). Adding the three carbons in 9 to the three carbons in the enolate give one of many 6-carbon carbohydrates; fructose is one of these (Fig. 4, top).

The path-hypothesis in Fig. 3 does not mention these self-reaction possibilities, both of which drain resources from the desired product (cytidine). We can ourselves, however, add these to Fig. 3 to give Fig. 4. This makes clear that the path-hypothesis in Fig. 3 requires glycolaldehyde 10 to wait without enolization until a molecule of 8 arrives. Compound 9, glyceraldehyde, must wait without enolization until a molecule of 11 arrives.

This creates a new problem. Enolization is, in the jargon of the physical organic chemist, a "pseudo-first order reaction". Its rate depends only on the pH of the aqueous solution. The reaction of 10 with 8 and 9 with 11 are "second order reactions". The reactions desired in Fig. 3 occur in competition with enolization only if the pH is near neutral and the concentrations of 8 and 11 are high.

In the published work (Powner et al. 2009), the concentrations of glycolaldehyde and glyceraldehyde were high, the materials were pure, and the mixing of reagents was timed by a graduate student. How was this to be managed without a graduate student? In an earlier paper reporting part of the Fig. 3 path hypothesis, Sutherland speculated that the aminooxazole 11 might be synthesized in separate location, with the synthesis "followed by [its] evaporation, sublimation, and subsequent rain-in" at a "separate location" to get the desired sequential order of addition (Anastasi et al. 2007). The geological likelihood of this sequence of events has been questioned (see below).

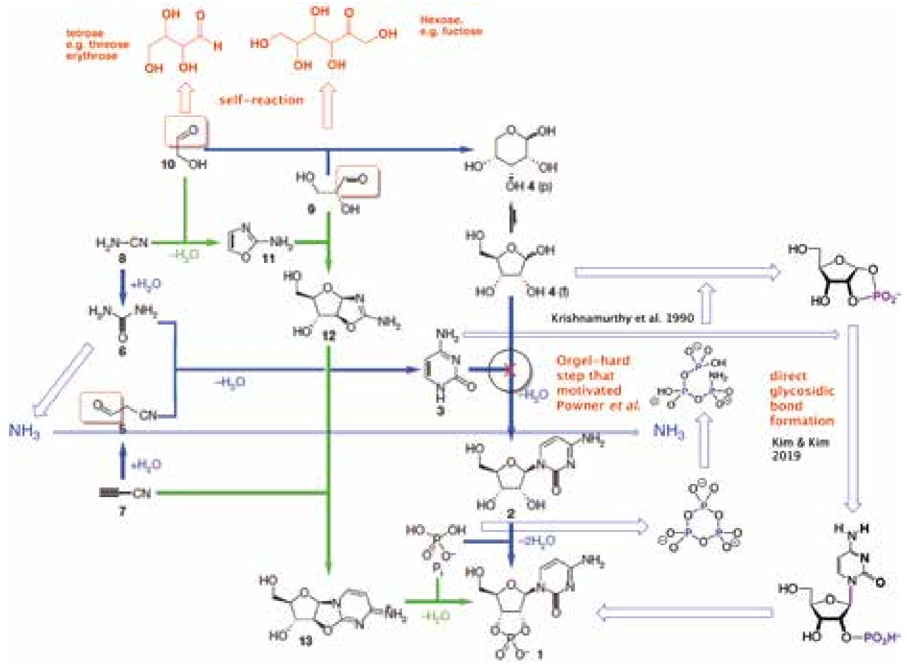

Figure 4. The path-hypothesis to make cytidine, adapted from Powner et al. (2009), to which are added reactions that likely occurred under conditions specified by Powner et al. (2009). Reactions in red are destructive. Reactions in blue are constructive. If we accept the premises of Powner et al. (2019), cytidine is available prebiotically *without* the novel process proposed here. By introducing two new carbonyl compounds, both less stable to self-reaction than ribose, the path does nothing to resolve the Miller-inspired paradox. Indeed, it makes it worse.

This notwithstanding, even if the Hadean had sources of 9 and 10, the path-hypothesis does not resolve the Miller-inspired paradox. On the contrary, it doubles it by replacing *one* unstable carbonyl compound (ribose) with *two* even less stable carbonyl compounds (glycolaldehyde and glyceraldehyde). Having lost our focus on the paradox, we have gone into a rabbit hole.

One might propose to resolve these new problems by having scarce glycolaldehyde 9 dropped into a large amount of cyanamide 8. This way, perhaps scarce glycolaldehyde might encounter 8 before it has a chance to enolize. This raises a new problem, however: 8 is itself a reactive molecule. In particular, cyanamide hydrolyzes in water (half life of 1 day at pH 12 and 50°C) to give 6 (Buchanan & Barsky 1930); it also reacts with itself.

So cyanamide also cannot accumulate to wait around to react with scarce glycolaldehyde 9.

In laboratory experiments controlled by graduate students, Powner et al. managed the competing enolization of glycolaldehyde 10 and glyceraldehyde 9 by providing a phosphate buffer to maintain the pH at about 7, where enolization is the slowest. Importantly, their work found several unexpected ways that phosphate influences the fates of various species in this path-hypothesis.

However, the requirement for phosphate generated another problem. Its influence was seen at only high concentrations (1 molar, 1 M). Most phosphate salts have low solubility, far below 1 M; sodium and potassium phosphates are the only ones that routinely deliver 1 M phosphate to a solution. In contrast, the salt of phosphate with the ferrous ion (which features in other path-hypotheses, Bray et al. 2015) is the largely insoluble mineral vivianite.

Thus, your analysis of the path-hypothesis in Fig. 3, even as a beginner, recognizes that it does not resolve the Miller-inspired paradox in any general way. The path-hypothesis avoids ribose, which is good. However, it requires large amounts of two less stable carbonyl compounds, glycolaldehyde and glyceraldehyde. And it requires phosphate at concentrations that are incompatible with most common counterions, giving us a new problem to solve.

5.2. Path-hypotheses to solve these "Orgel-hard" problems need not be necessary

The path-hypothesis in Fig. 3 was criticized specifically by Robert Shapiro (Wade 2009) immediately after it was published, along these lines. Before his untimely death, Shapiro served as the needed gadfly for much other self-uncritical prebiotic chemistry. Shapiro (2007) likened such multistep pathways to "a golfer who had successfully played a golf ball around an 18 hole course, could assume that the ball could then play the same course by itself, through a combination of the wind and other natural forces".

What motivated Powner et al. (2009) to develop this path-hypothesis to create cytidine in the first place? It was not to get prebiotic ribose. In 2004, Ricardo et al. showed that in a Hadean environment with borate, glycolaldehyde and glyceraldehyde in the amounts required by the Fig. 3 path-hypothesis would have reacted with each other via enolization to give large amounts of borate-stabilized ribose and other pentoses. This was an example of borate *both* controlling the reaction of the two molecules *and* stabilizing their product, the first time that such a combination had been reported (compare with Cimpoiasu et al. 1999; Scorei et al. 1999; Prieur 2001; Scorei & Cimpoiasu 2006). Indeed, absent the formation of the glycolaldehyde and glyceraldehyde in different locations, it would have been difficult for ribose and other pentoses *not* to be formed if glycolaldehyde and glyceraldehyde were present in the amounts specified by Powner et al. (2009). This alternative path is captured in Fig. 4 (arrow at top going to the right).

Indeed, borate alone partly resolves the Miller-inspired paradox with respect to ribose (Cimpoiasu et al. 1999; Scorei et al. 1999; Prieur 2001; Scorei & Cimpoiasu 2006). Borate forms a stable complex with the cyclic form of ribose that is formed in the presence of borate (Chapelle & Verchere 1988). As noted in Fig. 5, the cyclic form of ribose lacks a C=O carbonyl group. Stabilization of the cyclic forms of ribose by complexation with borate offers additional stability by reversibly locking ribose into this cyclic form. Analogous cyclic forms are not available for glycolaldehyde 10 or glyceraldehyde 9.

Nor was the Fig. 3 path-hypothesis motivated by a need for a route to create prebiotic cytosine, the nucleobase portion of cytidine. Cytosine is itself formed in respectable yields from cyanoacetylene or cyanoacetaldehyde 5 and urea 6, the compounds involved in the path-hypothesis in Fig. 3 (Ferris et al. 1968).[6] Thus, if the nitrogen-containing compounds in Fig. 3 had been available in a Hadean environment, it would have been difficult *not* to form cytosine.

If cytosine and ribose are both available, the question arises: Would it not be simpler to just make cytidine (the ribonucleoside) by combining some derivative of cytosine with some derivative of ribose? This would directly form the glycosidic bond joining the base to the sugar.

Powner et al. (2009) considered this possibility, but felt that it presented an "insuperable" chemical problem. Indeed, they placed in Fig. 3 an "x" over a conjectural step that might combine cytosine and ribose directly. To account for this "x", Powner et al. (2009) cited a paper by Leslie Orgel (2004) to suggest that "the condensation of ribose 4 and cytosine 3 does not work".

This citation of Leslie Orgel indicates his well-deserved place in the culture of prebiotic chemists. Indeed, problems in that culture can be dis-

[6] But see Shapiro's criticism (Shapiro 1999), Miller's reply (Nelson et al. 2001), and Shapiro's comments to the reply (Shapiro 2002).

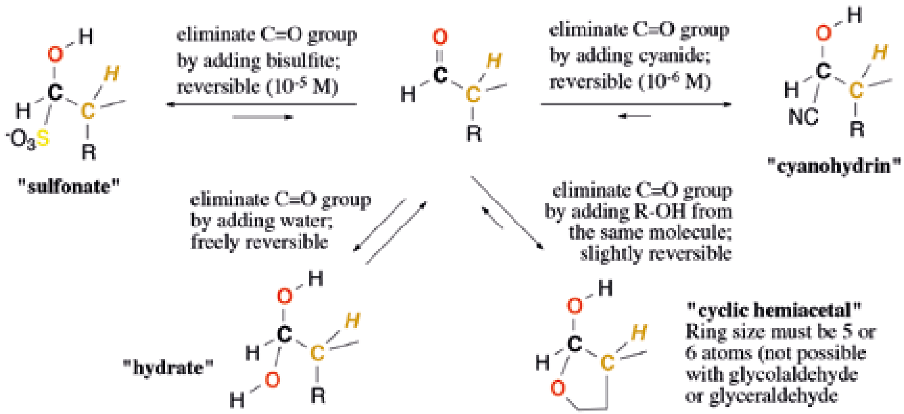

Figure 5. Ways to stabilize C=O carbonyl compounds that involve a reversible reaction that generates a compound that lacks a C=O group. Some products (e.g. sulfonates) cannot further react. Others, like the cyanohydrin, can hydrolyze irreversibly to act as a sink for the C=O compound. The cyanohydrins are key to the path-hypothesis in Fig. 6.

tinguished as "Orgel-easy" or "Orgel-hard". This distinction is made by examining literature from the Orgel laboratory starting a half-century ago. If Orgel's lab showed that a compound *could* be formed under what it felt were "plausibly prebiotic" (Benner 2018) conditions, then the culture sees this compound as being available in the Hadean. If Orgel's lab stated that a compound could *not* be formed under what it felt were "plausibly prebiotic" conditions, then the culture sees this compound as being *un*available in the Hadean.

This is the source of the "x" in the path hypothesis in Fig. 3. The x-ed out step is "Orgel-hard". This was the premise that motivated the development of the path hypothesis in Fig. 3.

Historians of science will ask: What experiments did Orgel *actually do* to support the conclusion that problems in directly forming a glycosyl bond between cytosine and ribose (to make cytidine directly) are "insuperable"? The specific reference that Powner et al. (2009) cite states that "[n]o direct synthesis of pyrimidine nucleosides from ribose and uracil or cytosine has been reported". This may indicate (or not) that someone in Orgel's laboratory had attempted this reaction without success. This statement is a few logical steps removed from the conclusion that this process is problematically "insuperable".

Sanchez and Orgel in 1970 did publish a work-around that differs from the path proposed by Powner et al. (2009) in using ribose, rather than glycolaldehyde and glyceraldehyde, as a starting material (Sanchez & Orgel 1970). Here, the downstream steps of Powner et al. (2009) follow closely those of Sanchez and Orgel (1970).

However, seeking to form a bond between cytosine and ribose without activating either reactant is likely to be difficult on energetic grounds. The reaction formally involves the removal of water in a process that is likely to have occurred in water as a bulk solvent present in large excess. As Powner et al. (2009) point out, this reaction is thermodynamically unexpected. This supports the inference that the direct reaction between cytosine *specifically itself* and ribose *specifically itself* would be unlikely under many conditions.

However, formation of cytidine (or a derivative) via direction reaction of a *derivative* of cytosine and/or a *derivative* of ribose is not excluded by this inference. For example, in 2000, Krishnamurthy et al. pointed out that amidophosphates could convert sugars such as ribose into their 1,2-cyclic phosphates (Fig. 4, right) (Krishnamurthy et al. 2000). Any Hadean aquifer having 1 M phosphate (as required for the path-hypothesis in Fig. 3), certainly had polyphosphates, upon evaporation. Any Hadean environment having cyanamide (as required for the path-hypothesis in Fig. 3) certainly had the ammonia needed to react with polyphosphates to give amidophosphates. Thus, the cyclic phosphates of Krishnamurthy et al. (2000) seem likely to have formed in any environment sharing the conditions with those in Fig. 3. As these cyclic phosphates have no C=O carbonyl group, they mitigate (at least in part) the Miller-inspired paradox; they could have accumulated without self-reaction (Fig. 4).

Further, the cyclic phosphates could have reacted directly with cytosine to give the Orgel-hard glycosidic bond. Indeed, Kim and Kim (2019) showed that such cyclic phosphates react with many nucleobases, including cytosine, to form the corresponding nucleoside (including cytidine) upon evaporative heating (Kim & Kim 2019). Thus, if the *premises* of Fig. 3 are accepted, cytidine can form *even without the novel parts of the path-hypothesis* in Fig. 3.

Thus, there was no need to go down the rabbit hole in the first place. If we presume that the Hadean had large amounts of phosphate, cyanamide, cyanoacetylene 7, glycolaldehyde 10, and glyceraldehyde 9, it had not only ribose 4 and cytosine 3, but also cytidine derivative 1 in reaction processes that are as workable in the laboratory as those in Fig. 3.

5.3. Selecting between closely alternative path hypotheses using Occam's razor

This does not mean, of course, that the path-hypothesis in Fig. 3 did *not* operate in the Hadean. Prebiotic chemists like Gerald Joyce, who describe RNA as a "prebiotic chemist's nightmare" (Joyce & Orgel 1999), will have better dreams with either path-hypothesis. They might even prefer having both, with one being a backup for the other.[7]

However, advocates for the path-hypothesis in Fig. 3 have argued that their model is preferred over one involving borate based on an "Occam's razor" argument (Sutherland 2016). Those familiar with the Sagan-Druyan film *Contact* are aware of scientists seeking to explain their preference for one model over an alternative using a concept of "simplicity". For example, Ellie Arroway, played by Jodie Foster in the film, made such an argument to support her hypothesis that an alien intelligence has sent plans for a super transporter that she used after it was built in Japan.

Occam's razor is actually not a good criterion for comparatively evaluating very different models in science, since different people having different worldviews have different opinions about what is "simple". From *Contact*, Ellie Arroway may have been transported 130 light years in 10 seconds to converse with (fictional) human-shaped aliens who had invaded her brain. Or she may have been a dupe of a hoax of the (equally fictional) billionaire S.R. Hadden. Which modeler is "simpler" depends on one's view of the world.

If one *must* apply Occam's razor, it is best done when the competing models are similar, and if they share premises. For example, the path-hypothesis in Fig. 3 requires large amounts of glycolaldehyde and glyceraldehyde. Never mind where they come from. A world with large amounts of pre-formed glycolaldehyde and glyceraldehyde would also have had access to large amounts of ribose (if borate were present) by simple mixing (Ricardo et al. 2004). A world having access to one molar phosphate and reduced nitrogen (such as NH_3) would have had access to amidophosphates to make the 1,2-cyclic phosphate from that ribose (Krishnamurthy et al. 2000). A world with abundant cyanamide and cyanoacetylene most likely offered abundant cytosine, which forms cytidine by condensing with ribose 1,2-cyclic phosphate.

[7] In various of his writings (Sutherland 2016) (Ritson et al. 2018), Sutherland appears to desire that path-hypotheses other than his own be removed from discussion. We have no such agenda. Our agenda is to resolve paradoxes that prevent origins-of-life research from being "normal science". In this view, the more ways to perhaps resolve such paradoxes, the better, regardless of who proposes them.

The two models are identical in their premised environments. Which is simpler? This is simply a matter of perspective. And as Feyerabend and others have noted, scientists often find simpler the model that they themselves wish to have the community accept.

6. Going further down the rabbit hole adds paradoxes

Sutherland's group then set out to find path-hypotheses to make glycolaldehyde 9 and glyceraldehyde 10 under "plausibly prebiotic" conditions. One recent path-hypothesis is summarized in Fig. 6, adapted from Xu et al. (2018) and Ritson et al. (2018). It features:

(a) the reaction of atmospherically-formed hydrogen cyanide (HCN) with dissolved ferrous iron (Fe^{2+}), which is thought to be the dominant oxidation state of iron in the Hadean oceans (Bray et al. 2018), to form ferrocyanide complexes,

(b) the reaction of cyanide ion (CN^-) containing one carbon atom, with formaldehyde to form a "cyanohydrin" ($HOCH_2$-CN), which lacks a C=O moiety,

(c) the photochemical reduction using ultraviolet (UV) light of the -CN group in the cyanohydrin with ferrocyanide as the photochemically active species to give – by way of an intermediate imine ($HOCH_2$-C=NH) – glycolaldehyde, with sulfur dioxide (SO_2) as reductant,

(d) repeating the cycle to add a carbon from cyanide to glycolaldehyde to give glyceraldehyde.

Again, non-chemists can play an evaluation game by circling all of the C=O carbonyl compounds in Fig. 6 that might suffer enolization. There are several. The non-chemist then asks a chemist about the expected rate of enolization of these relative to other processes, in particular, their reaction with cyanide.

It is again important to remember that the rate of enolization is "pseudo first order", depending on the pH of the solution. The reaction of a C=O compound with cyanide is second order; its rate depends on the concentration of total cyanide as well as pH. Cyanide itself is unstable in water, hydrolyzing to give formamide and (then) ammonium formate (Fig. 7). The rate of HCN destruction is lowest at about pH 4, and rises as the pH increases until reaching a plateau at about pH 9 (Miyakawa et al. 2002).

The path-hypothesis in Fig. 3 managed problematic enolizations of glycolaldehyde and glyceraldehyde by keeping the pH near neutral, about 7. This was done by presuming the presence of large amounts of inorganic

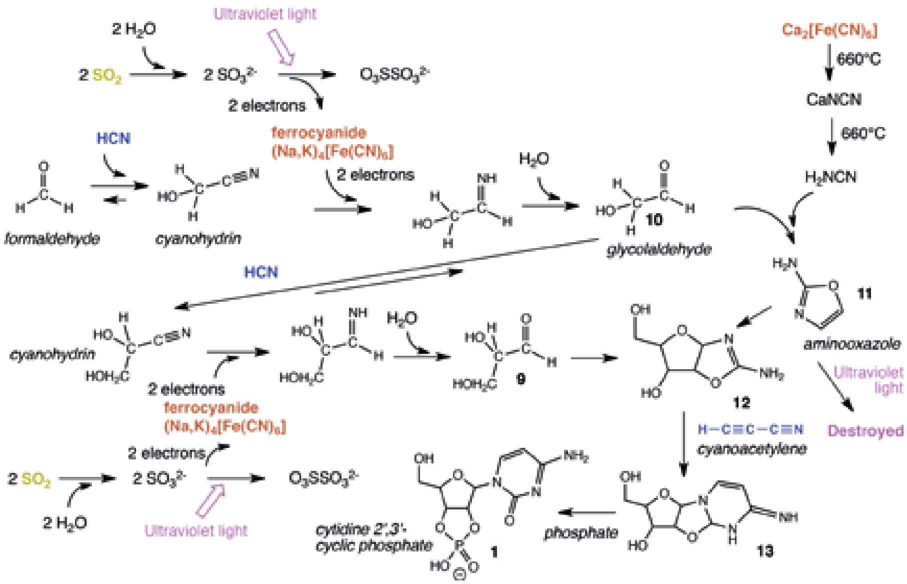

Figure 6. The "cyanosulfidic" path-hypothesis exploits the ability of Fe^{2+} to sequester cyanide, the ability of sulfite from volcanic SO_2 to serve as a reductant, and high-energy photons to allow the photoreduction of intermediate cyanohydrins using ferrocyanide as the photoactive species. Reduced HCN, proposed to have atmospheric origin (here, from the late heavy bombardment at 3.8 Ga, much later than the dates proposed from the Atlanta discussion) is used with metals (Na^+, K^+, Ca^{2+}) to create ferrocyanide (Keefe & Miller 1996). Here, the atmosphere is an indirect source of the cyanamide needed to generate an aminooxazole. Purine ribonucleosides would presumably be made by other processes (Kitadai & Maruyama, 2018). Adapted from Xu et al. (2018) and Ritson et al. (2018).

phosphate buffer. With the path-hypothesis in Fig. 6, neither a low pH nor large amounts of phosphate rescue those enolizable species. Phosphate (even in small amounts) precipitates with Fe^{2+} to give the aforementioned mineral vivianite. Toner and Catling (2019) suggest that ferrocyanide might become stable at pH not much above pH 7 in lakes that are rich in carbonates, which make also make phosphate available. The propensity of HCN to itself undergo hydrolysis prevents the problem from being solved by adding scarce C=O compounds to an excess of cyanide.

Adding further to the challenge is the requirement in the path-hypothesis in Fig. 6 for high-energy photons at each reductive step. In their 2009 contribution, Powner et al. (2009) remarked on the unexpected stability of beta-ribocytidine-2',3'-cyclic phosphate upon UV irradiation. They noted that "irradiation ... destroy[s] most other pyrimidine nucleosides and nucleotides". Here, they *require* this potentially destructive irradiation throughout the process.

Further, chemists also expect aminooxazole to be degraded by ultraviolet light. Interestingly, Todd et al. recently confirmed this photodecomposition (Todd et al. 2019).[8] If UV light is necessary for a process to make glycolaldehyde and glyceraldehyde by sequential photochemical reductions, and if UV irradiation destroys the precursor 11 and most other RNA building block products, a paradox that *now* needs resolution might be:

- UV photons at 254 nm must be present for the path-hypothesis in Fig. 6 to operate, as they must be present for certain steps.
- UV photons at 254 nm must *not* be present for the path-hypothesis in Fig. 6 to operate, as they destroy molecules that must be present for certain steps.

But we are still not free from paradoxes. The photoactive ferrocyanides that participate in this path-hypothesis must be on the surface of the Hadean Earth; indeed, they must be unshielded on the surface. That surface must be below an atmosphere that must be delivering substantial amounts of HCN (and, hence, cyanide), if only to balance the loss of HCN by hydrolysis. However, HCN is synthesized in large amounts only in atmospheres where the amounts of reduced compounds are substantial relative to the amount of atmospheric CO_2 (Zahnle et al. 2019). Such atmospheres are mostly hazy.

Again, those evaluating the path-hypothesis note that while we have gone further down the rabbit hole for the purpose of getting glycolaldehyde and glyceraldehyde, the Miller-inspired paradox related to the intrinsic instability of these carbonyl compounds has not been touched. At least in Fig. 3, we had only two unstable C=O compounds to worry about, glyceraldehyde in glycolaldehyde. Their instability was controlled by a phosphate

[8] Todd et al. do not abandon the path-hypothesis, hoping that a photostable molecule might be found to act as a sunscreen to protect the aminooxazole that is used for the path-hypotheses in Fig. 3 and Fig. 6. A challenge then emerges to find a screening molecule that can selectively block photons that cause the *undesired* decomposition of the aminooxazole (and other species) without screening out photons needed to perform two *desired* photoreduction steps involving ferrocyanide. If the photons for both the destructive and the non-destructive steps have the same wavelength, a paradox can be written.

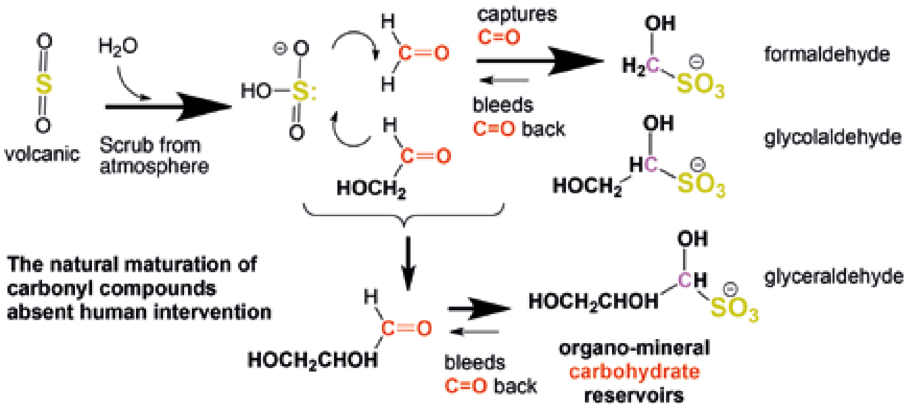

Figure 7. Volcanic sulfur dioxide becomes sulfurous acid in water aerosol particles, giving them a pH of ca. 4. When rained on to a surface having alkaline pH, the bisulfite anion is formed. This reacts with carbonyl C=O groups to give their bisulfite addition products, which are sulfonates. This reaction is general, as discussed in the text. The sulfonates are quite stable to self-reaction and other degradation paths. Their only reaction at lower temperatures in water is their reversible dissociation to give back the carbonyl compound. Therefore, sulfonates slowly bleed reactive species into aqueous mixtures. When formaldehyde is in excess, it captures enolates of carbohydrates before they can unproductively react to give tars.

buffer at neutral pH. And if the path-hypothesis in Fig. 3 struck us as not being "Occam-simple" enough, we could get cytidine directly from the ribose that unavoidably would form, the aminophosphates that unavoidably would form, the nitrogenous compounds to make cytosine that unavoidably would form, and the processes proposed by Krishnamurthy et al. (2000) and Kim & Kim (2019).

In Fig. 6, the glyceraldehyde and glycolaldehyde are transient intermediates, not pre-formed reservoirs. This is good. However, we have moved in Fig. 6 to a pH where they both enolize in minutes. We also now require an atmosphere to make HCN that is perhaps opaque (but see Zahnle et al. 2019) to the photons required in the ferrocyanide-mediated cyanohydrin reduction invoked twice. The paradoxes write themselves.

7. The path-hypothesis emerging from the Atlanta workshop

This example is illustrative enough about how a field can go down rabbit holes, after its beginning (and reasonable premise) was found in later work to be unnecessary. This is a problem with research projects, entire fields, and entire cultures. It is certainly not limited to origins of life.

Avoiding it requires a discipline that we seek to train in students: Every now and then, we ask students to return to first principles to understand *why* they are doing what they are doing. Formulating paradoxes that (apparently) stand between the state-of-the-art and the "big picture" is a useful way to train scientists to do this. This is why the discussion in the Atlanta workshop was set to resolve paradoxes.

Here, we looked for inevitable chemistry, which Prof. Carell termed "privileged" and Prof. Benner termed "bespoke". As examples, it is well accepted that photochemistry high in a Hadean atmosphere with CO_2 generates substantial formaldehyde ($H_2C=O$). The amount of $H_2C=O$ formed is largely independent of the amount of methane (CH_4) or other reducing agents in the atmosphere (Harman et al. 2013). Further, various quantitative estimates for the amounts of $H_2C=O$ formed in the Hadean atmosphere are available (Pinto et al. 1980)

Lacking a carbon carrying a hydrogen atom adjacent to the C=O group, formaldehyde cannot enolize. Further, unlike HCN, $H_2C=O$ cannot be destroyed in water by hydrolysis. Aqueous pools of $H_2C=O$ are stable against self-reaction, if the pH (and the concentration of $H_2C=O$) is not so high as to support the Cannizzaro reaction (pH>>10). Thus, we can regard $H_2C=O$ as being reliably available in the Hadean atmosphere at amounts estimated by Pinto et al. (1980). Formaldehyde is a "privileged" carbonyl compound.

Much smaller amounts of the 2-carbon glycolaldehyde ($HOCH_2$-HC=O) were also unavoidably formed by analogous processes in the Hadean atmosphere. However, the amount of glycolaldehyde formed is quite dependent on the amount of reduced species in the atmosphere (Harman et al. 2013). So how we proceed depends on how "reduced" we think the Hadean atmosphere was.

In the current consensus model for the Hadean Earth, Earth's mantle had already approached its modern oxidation state (Wade & Wood 2005). Measurements on surviving zircons place the redox state of the terran mantle at about 4.36 Ga near the fayalite-magnetite-quartz redox buffer (FMQ -0.5 $\pm$ 2.3) (Trail et al. 2011). This means that only a very little glycolaldehyde was formed in the standard Hadean atmosphere. Even if substantial reducing power was present, $HOCH_2$-HC=O was likely to be only 1 ppm relative to $H_2C=O$. This means that absent another way to form it, glycolaldehyde can participate in prebiotic chemistry only as a catalyst, not as a stoichiometric reagent (as in the path-hypothesis in Fig. 3).

Critical to the fate of both formaldehyde and glycolaldehyde, sulfur emerging from the FMQ Hadean mantle was predominantly SO_2 rather than H_2S. Indeed, the rate of SO_2 likely to emerge from Hadean volcanoes is on the same order of magnitude as the rate of formation of formaldehyde in the Hadean atmosphere.

An atmosphere that had both SO_2 and $H_2C=O$ could not have avoided a reaction between the two. In aerosols, $H_2C=O$, $HOCH_2$-$HC=O$, and other C=O compounds, react reversibly with SO_2 to form "bisulfite addition products" (Fig. 5) (Graedel & Weschler 1981). These products are sulfonates having the general formula R-CH(OH)SO_3^- (Fig. 5). This reaction requires no intelligent guidance. Indeed, these sulfonates are formed in atmospheric aerosols above Earth today, where $H_2C=O$ and SO_2 are products of human activities (e.g. coal burning).

What forms first with $H_2C=O$, the sulfonate ($H_2C(OH)SO_3^-$) or the cyanohydrin (HOH_2CCN)? This depends on the ratio of bisulfite and cyanide, making the redox state of the Hadean atmosphere again important. With volcanoes producing SO_2 and a comparably oxidized atmosphere producing very little HCN, the sulfonate (HMS) must have dominated. The same for glycolaldehyde. Another aphorism of Albert Eschenmoser, that "the answer [to the origins of life] has to come from revisiting the chemistry of HCN" (quoted in Sutherland 2016), is not relevant to a Hadean atmosphere that lacked much HCN.

Neither sulfonate ($H_2C(OH)SO_3^-$ or $HOCH_2$-$CH(OH)SO_3^-$) is volatile; both are soluble in water. Therefore, both must rain out into any aquifer that the Hadean offered (as indeed they do today). If the aquifer and the water evaporate, the two form evaporite sulfonate minerals, similar to borates and halites (Kawai et al. 2019). Neither has a C=O group. Therefore, even in water, evaporite sulfonate minerals do not directly react. In dry form, the sulfonate minerals are quite stable, even at relatively high temperatures (e.g. 100°C). Therefore, they must accumulate, absent their being washed into a global ocean.[9]

Depending on the precise environment, the expected estimated accumulation is ca. 0.1 milligram of precipitated $H_2C(OH)SO_3^-$ per century per cm^2, or about one gram/m^2. This estimate is based on the classical model (Pinto et al. 1980) that ~ 3×10^8 molecules of formaldehyde were formed per cm^2 every second in the Hadean atmosphere; with 3×10^9 sec/century, this corresponds to 10^{18} molecules, or 10^{-6} moles.

[9] Of course, today, the sulfonates are food for life on modern Earth, and so are rapidly eaten.

However, addition reaction between C=O compounds and bisulfite arising when SO_2 dissolves in water is reversible (Fig. 7). The rates of the forward and reverse reaction are well-studied functions of temperature and pH (Sorensen & Andersen, 1970; Kok et al. 1986; Dong & Dasgupta 1986). Thus, if a bed of evaporite sulfonate minerals is rehydrated, $H_2C(OH)SO_3^-$ slowly bleeds free $H_2C{=}O$ into the aquifer. In much smaller (ppm) amounts, $HOCH_2\text{-}CH(OH)SO_3^-$ slowly bleeds glycolaldehyde into the same aquifer.

We can play the "carbonyl game" again (Fig. 8). Glycolaldehyde that leaks from its sulfonate derivative can enolize with a rate depending on the pH, temperature, concentration of dissolved borate, and other features of the environment. Regardless of its rate of formation, if the enol of glycolaldehyde *does* form, it is a million fold (or more) more likely to encounter a $H_2C{=}O$ molecule (which cannot enolize) than a second glycolaldehyde molecule.

This means that the enolate of glycolaldehyde will react essentially exclusively with formaldehyde in a 2+1=3 carbon reaction to yield glyceraldehyde (Kim et al. 2011). The 2+2 formation of erythrose or threose is a million-fold disfavored because of the low concentration of glycolaldehyde.

The rates of these processes are well measured, especially in the presence of borate (Kim et al. 2011) (Fig. 9). Indeed, high reactivity (even recognizing that it forms hydrates) and relative abundance of $H_2C{=}O$ means that $H_2C{=}O$ traps enolates arising from *any* enolizable C=O compound. Even at low concentrations (10 mM), $H_2C{=}O$ prevents other aldol reactions, beta eliminations, hydride shifts (Appayee & Breslow 2014), and other processes that give tars (Fig. 2) (Kim et al. 2011). It even prevents protonation of the enolate at pH values greater than ~ 9. Thus, in a quantitative study, even at pH>11 with $Ca(OH)_2$ and temperatures as high as 80°C, $H_2C{=}O$ prevents tar formation of carbohydrates. Only after $H_2C{=}O$ is consumed does tar formation begin (Ricardo et al. 2006).

The fate of the glyceraldehyde is likewise constrained. It can itself react with the bisulfite necessarily in the environment to form its own bisulfite addition product (Fig. 7). This product again lacks a C=O group; it can accumulate. However, should it enolize, the glyceraldehyde enolate will encounter $H_2C{=}O$ first, again because of its high concentration, not glycolaldehyde or another molecule of glyceraldehyde. In the presence of borate, the predominant product arising from this encounter is erythrulose (with 4 carbons, from a 3 + 1 = 4 reaction) (Fig. 8).

Erythrulose cannot cyclize to stabilize itself, or to form a stable complex with borate. However, erythrulose can enolize after it forms a weak

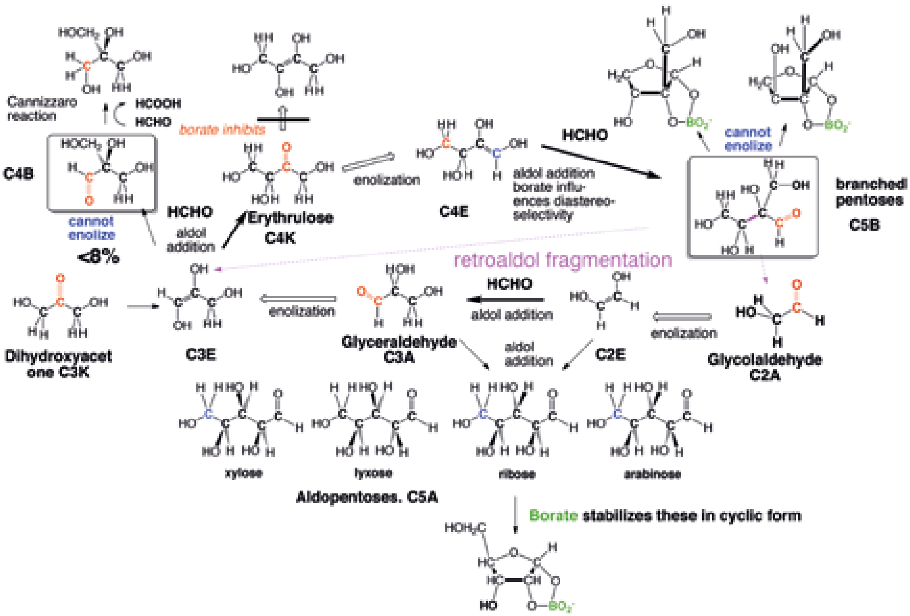

Figure 8. Maturation of carbohydrates when formaldehyde is in excess.

complex with borate. Here, borate controls the direction of enolization (Fig. 9); borate also controls the products that arise when its enolate reacts with $H_2C{=}O$. Again, if $H_2C{=}O$ is present in any significant amount, the enolate of erythrulose reacts largely to form one of two diastereomeric branched 5-carbon sugars, from a 4+1=5 reaction. Borate and formaldehyde suppress other reactions (Fig. 2) that give tar.

This is a "maturation" process. It is what formaldehyde and small amounts of other carbohydrates must do in the environment that we have proposed for the Hadean, if left to themselves, in the presence of borate, bisulfite, and in a constrained aquifer. It does not require the intervention of graduate students; it is a hard-to-avoid outcome of a carbohydrate pool under the conditions that would have been present on a sub-aerial Hadean surface intermittently exposed to water in a constrained aquifer.

Now, this maturation, if prolonged, gives caramelization. This leads to the key question: If maturation is to yield any species useful in an abiological synthesis of RNA (such as the ribose of Larralde et al. 1995), how might the maturation be naturally constrained before tar forms?

The answer to this question lies in part in the structures of the molecules that emerge via this maturation. In particular, the branched pentoses are privileged in several of their structural features. First, they are the *first* compounds in the maturation process that can form a cyclic structure that lacks a C=O group, all by themselves (Fig. 8, top right). Glycolaldehyde, glyceraldehyde, and erythrulose all cannot. Thus, the branched pentoses can accumulate for this reason alone, while glycolaldehyde, glyceraldehyde, and erythrulose all cannot.

Further, as the first compounds in the maturation process able to form cyclic species, these branched pentoses are also the first molecules in the maturation of a carbohydrate pool that are able to form a tight complex with borate (Fig. 8, top right). Indeed, the borate is required for the controlled maturation in any case; it is therefore present to do the stabilizing. This is a second reason why the branched pentoses can accumulate; their borate complex would have been a Hadean organic mineral that serves as a reservoir for pentoses.

Finally, for those playing the carbonyl game, these branched pentoses, even in their ring-*open* form that has a C=O moiety, *do not have an adjacent carbon carrying a hydrogen atom* (Fig. 8, top right). Thus, the branched pentoses are the *first molecules to emerge in the process that cannot enolize*, even in the absence of borate. This is the third reason why they are privileged to accumulate as stable organic minerals.

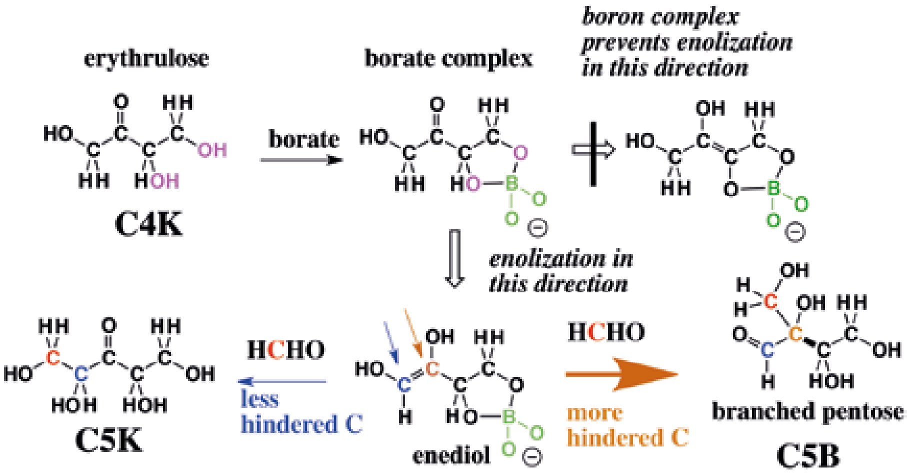

Figure 9. Carbohydrate maturation in the presence of borate, which guides enolizaton of four carbon carbohydrates and directs the regiochemistry of the attack of HCHO on their enol.

Another feature of the maturations process is worth noting. If the carbonyl compounds mature from their bisulfite adducts, this maturation is self-quenching. Every time a new carbon-carbon bond is formed via an aldol addition of carbonyl compounds arising from the dissociation of a sulfonate precursor, a dissolved bisulfite molecule is released *without* a C=O partner. Thus, as the aldol reactions proceed in a constrained aquifer, the matured products encounter higher and higher concentrations of bisulfite. These increasingly higher bisulfite concentrations increase the reversible conversion of carbonyl compounds to sulfonates, slow further reactions, creating bisulfite-carbohydrate reservoirs, and slow the formation of tar.

Thus, maturation limited by bisulfite, borate, and formaldehyde mitigates the Miller-inspired paradox arising from the measured instability of ribose discussed a quarter century ago (Larralde et al. 1995). Further, this process follows directly from current models for the Hadean atmosphere, the Hadean Sun, and the Hadean FMQ mantle. Even the early view that borate minerals were not present in adequate abundance in the Hadean crust due to insufficient plate tectonics has been set aside (Hazen et al. 2008; Grew et al. 2011). Sizeable amounts of borate are present on the accessible surface of Mars, which has never had plate tectonics (Gasda et al. 2017). Further, the very recent report of the observation of ribose in meteorites (Furukawa et al. 2019) suggests that this specific maturation may occur in natural environments.

8. What happens next?

8.1. The fate of carbohydrates that are stabilized

Sutherland has criticized this model by suggesting that the metastability of the borate complex of the branched pentose is a flaw, not an asset, of the maturation (Sutherland 2016). He wondered how that complex would be mobilized to form nucleosides. That criticism assumed that to release the pentoses from borate required "acidification and repeated addition and evaporation of methanol", something that certainly requires attention of a graduate student.

This criticism, of course, disappears with a physical organic chemical perspective. The formation of borate:diol complexes is dynamic and reversible, with the precise rates for both processes depending on the concentration of borate, pH, and other factors. Thus, the fate of the borate complexes of the branched pentoses depends on the balance between incoming $H_2C{=}O$, borate, and bisulfite. If $HOH_2CSO_3^-$ continues to precipitate into a constrained aquifer, the amount of branched pentose will come to exceed the amount of stabilizing borate. A free branched pentose will emerge when it lacks a borate partner. Its steric crowding discourages bisulfite adduct formation.

Again, the branched pentose molecules that are freed from a borate ligand cannot enolize; they lack an adjacent carbon with a C-H. They can, however, undergo a retroaldol fragmentation reaction (Fig. 8). That 5→2+3 fragmentation gives the now-familiar glycolaldehyde and glyceraldehyde (Fig. 8). Indeed, the fact that these branched pentoses cannot enolize is the reason why the normally slower retroaldol reaction manifests itself in these branched pentoses; the second is their steric crowding

In the absence of $H_2C{=}O$, glycolaldehyde enolate and glyceraldehyde formed from this fragmentation can combine directly to give ribose and other linear (not branched) pentoses (Ricardo et al. 2004). Thus, if $H_2C{=}O$ is absent, the branched pentose-borate complex will gradually mature to give the more stable borate complexes of the linear pentoses. These too can accumulate as reservoirs for future prebiotic synthesis, as they lack a C=O group in their cyclic forms complexed by borate. The ribose:borate complex is the most stable of the aldopentoses.

Alternatively, if $H_2C{=}O$ is present, the glycolaldehyde enolate and glyceraldehyde enolate can fix more $H_2C{=}O$. The result is a catalytic cycle, where multiple molecules of $H_2C{=}O$ are fixed for each molecule of glycolaldehyde that was originally presented. This overall cycle was shown experimentally by Neveu et al. (2013) and Kawai et al. (2019), who studied the reaction manifold using ^{13}C-labeled formaldehyde. To make the reaction rates large enough to be conveniently measured, the reactions were followed at pH 10.5, a bit higher than that expected in aquifers exposed to serpentinizing basalts.[10]

[10] To address the remaining criticisms of Sutherland (2016) and Ritson et al. (2018), these overlook the privileged structures and consequent reactivities of branched pentoses, misunderstand the physical organic rates and concentration-dependence of various reactions, and mistakenly confuse the path-hypothesis in Fig. 7 with the "formose reaction", which is the formation of a sweet-tasting material (formose) by the self-reaction of $H_2C{=}O$ upon heating in $Ca(OH)_2$ (Butlerov 1861). This process has mechanistic challenges missing from the path-hypothesis in Fig. 7. Likewise, many physical organic studies are done at a pH higher than likely allowed by atmospheric CO_2. This is done for convenience. Even at lower pH, the reactions still occur, but at rates less easy for a student to measure. Nevertheless, those criticisms are worth reviewing in the context of the Feynman dictum.

8.2. The Atlanta discussion combined the carbohydrate maturation with other ideas

Thus, the October 2018 Atlanta workshop participants had at their disposal some privileged chemistry that would have delivered linear pentoses, like ribose, in mineral stable forms via "hands free" maturation of bisulfite-trapped C=O compounds emerging from the Hadean atmosphere. This control comes from the special reactivity of $H_2C=O$, mineral species such as borate, and SO_2, that emerged from an FMQ mantle. Fig. 10 summarizes this chemistry.

Further, the workshop participants had available a process to transform the matured carbohydrates to their cyclic phosphates, provided that the conditions required by Krishnamurthy et al. (2000) were available. It also had chemistry able to form the "Orgel hard" glycosidic bonds of the nucleosides. It also had available multiple ways to phosphorylate nucleosides to give mono-, di-, and triphosphates, stereoselectively in the presence of borate. And it had multiple possible ways to convert those phosphorylated nucleosides into oligomeric RNA that might be stabilized on silica phases (Biondi et al. 2017).

The overall model is captured in Fig. 10. However, astute readers (as well as the Atlanta workshop participants) can recognize a paradox. We already noted that the Hadean Earth likely had an FMQ mantle delivering correspondingly oxidized minerals to the surface of the Earth beneath a redox-neutral atmosphere with little methane, carbon monoxide, ammonia, H_2S, or H_2. This explicitly excluded the production of substantial amounts of HCN, HCCCN, H_2NCN, and other compounds that make the formation of the nucleobases "Orgel-easy". Our focus on the Miller-inspired paradox related to the instability of enolizable C=O compounds had not solved *another* paradox; the path-hypothesis in Fig. 10 needs reduced species that are not present, according to the premises of the path-hypothesis.

The multidisciplinary Atlanta group understood, however, that the Hadean environment was neither static nor placid. Rather, it was interrupted by impacts, some rather large. Much literature views the impactors as *sources* of HCN, glycolaldehyde, and other reduced compounds directly. This itself generated its own paradox; an impactor large enough to deliver these needed precursors in (apparently) the quantity needed would create the heat that destroyed them. Here, attempts to resolve this paradox have focused on local environments.

The Atlanta group therefore turned to the view that the impactors were not the sources of the needed reduced organic materials themselves, but

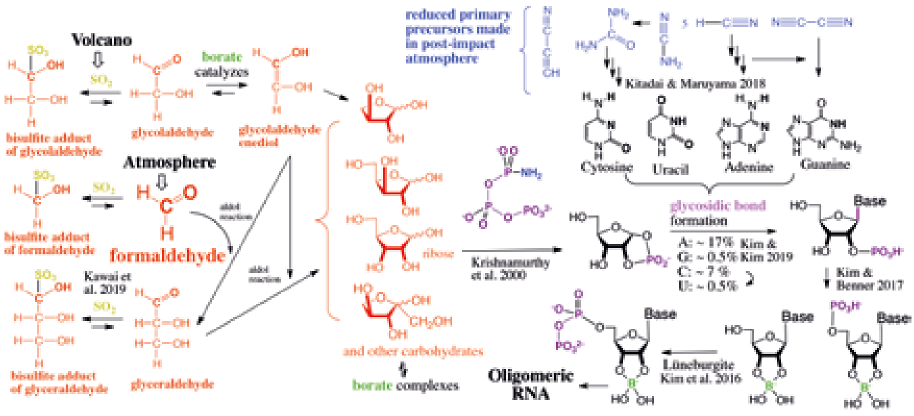

Figure 10. Schematic for a path-hypothesis that yields RNA nucleotides by direct joining of preformed canonical nucleobases to preformed ribose derivatives via a glycosidic bond (magenta) (Kim & Benner 2017) (Kim & Kim 2019). The stereochemistry of various chiral molecules is arbitrary. This path-hypothesis invokes reservoirs of carbohydrates (red) arising from formaldehyde and traces of glycolaldehyde stabilized by SO_2 (yellow) (Kawai et al. 2019) emerging from a Hadean mantle having an oxygen fugacity (redox state, f_{O_2}) near the fayalite-magnetite-quartz buffer (f_{O_2} = FMQ -0.5 ± 2.3) (Trail et al. 2011). Black lines (left) indicate aldol reactions that carbohydrates undergo if released from their bisulfite adducts in the presence of borate and trimetaphosphate transformed with ammonia (Krishnamurthy et al. 2000). This path-hypothesis requires sub-aerial surfaces intermittently submerged by water. Last, it requires HCN, HCCCN, H_2NCN, and other reduced atmosphere-generated primary precursors (in blue, not all shown). Formation of these depends strongly on the redox state of the atmosphere. For one critique of this path-hypothesis, see the Supplementary Information from Ritson et al. (2018).

rather a source of *reducing power that would create a reduced atmosphere that would allow the reduced organic materials to be made there*. Substantial impacting bodies (>10^{21} kg) would have had their own iron cores, which would have likely shattered on impact with the Hadean Earth. This shattering would deliver molten iron (Fe^0) to the Hadean atmosphere.

The Fe^0 delivered by the impactor must have reduced water, N_2, CO_2, and other gases in the atmosphere. It must also have delivered the Ni^{2+} (about 20% of a typical iron meteorite) to allow nucleoside triphosphate formation (Benner et al. 2019a). Any NH_3 generated from the reduced iron would have been available for the Krishnamurthy-Eschenomser process to activate cyclic trimetaphosphate (or a reactivity equivalent) to generate ribose-1,2-cyclic phosphate. It would also have delivered phosphite, whose relevance to prebiotic phosphorylation is well known from Pasek's work (Gull et al. 2015).

And, of course, the reduction due to the impactor would have allowed the atmospheric formation of HCN, HCCCCN, NCCN, H_2NCN, and other well recognized precursors of the nucleobases, as well as their hydrolysis products, including formamide, urea, and cyanoacetaldehyde (Kitadai & Maruyama 2018). All of these are invoked in many path-hypotheses to make the formation of RNA nucleobases Orgel-easy. A productive atmosphere would have been hazy, although Zahnle et al. (2019) have noted that production of HCN (if not the other, larger, species) may have continued for a short time after the haze had cleared.

The model is agnostic with respect to the size and the date of the relevant impactor. Important only is that the impact that enables RNA formation not be followed by a subsequent impactor that sterilized the planet.

Participants at the Atlanta workshop pointed out that the last sterilizing impactor may have been a Moon-sized body (10^{23} kg, Moneta). Moneta would have been big enough to deliver the late veneer heavy metals (like platinum and gold) that arrived on Earth after Earth's core closed (Mojzsis et al. 2019). Moneta was very sterilizing, would have created a lava ocean, and woud likely have re-set most of the geological clocks that we have on Earth.

A smaller 10^{21} kg Ceres-sized impactor would also have been sterilizing. However, it would not have reset all of the clocks that we find on Earth, but it would have delivered a productively reducing atmosphere. A still smaller 10^{20} kg Vesta-sized impactor would not have sterilized the Earth or reset the clocks, but still would have generated a productively reducing atmosphere, albeit for a shorter time.

Inspired by the output of the Atlanta workshop, Zahnle and his coauthors modeled a spectrum of outcomes of impactors of different sizes (Zahnle et al. 2019) and the productivity of the reducing atmosphere that they generated. This work estimates the amount of time following an impact that the Hadean atmosphere remained productively reduced, how hazy the atmosphere was during its productive period, and how much material it would generated.

Here, the important word is "transiently". An atmosphere that gets reducing power from the dispersion of molten iron from an impactor does not keep that reducing power forever. Gases continue to come from the mantle, which is not reduced by any impactor smaller than the hypothetical Moneta, and not significantly reduced even with Moneta itself.

Further, the reducing property of the atmosphere is lost as H_2 escapes to space. With Moneta, which is modeled to have generated as much as 90 bars of H_2 (Genda et al. 2017a, 2017b), the half-life for the restoration of an unproductive redox neutral atmosphere is measured in the tens of millions of years. For a Vesta-sized impactor, the time constants for the loss of a productive atmosphere are measured in the tens of thousands of years.

To accumulate more RNA precursors, bigger impactors are better. However, most recent models for the impact history of the Earth have impactor size decreasing over time monotonically. Thus, a Ceres-sized impactor may have occurred 1 ± 1 times after a Moneta-sized impactor. If it occurred, it was sterilizing, and therefore is the impactor most likely to be relevant to the abiotic formation of RNA. In contrast, if this impactor did not arrive, and Moneta was the last sterilizing impactor, it created the longest-lived productively reducing atmosphere. The later Vesta-sized impactors (of which there were likely several) are conceivably important for the generation of a reducing atmosphere to generate RNA precursors, but RNA formation would need to have occurred rapidly after their impact. Further, the longer the persistence of the reducing atmosphere, the longer it could have productively fed the emerging RNA life before it became autotrophic.

8.3. Dating when RNA most likely emerged

The highlight of the Atlanta discussion then came as Ramon Brasser (a planetary scientist) pointed out to the chemistry and molecular biology participants that by combining the chemical and geological information, we might estimate *when* this chemistry most likely occurred. The impact energy of a Moneta would likely have reset the radiogenic clocks in the crust (Abramov et al. 2013). A survey of ~ 200,000 detrital zircons from the Jack Hills in Western Australia shows the oldest of these at ~ 4.38 Ga (Harrison et al. 2017) (Valley et al. 2014). This places a latest date for the arrival of Moneta.

An earliest date might be found by considering the date for the onset of the migration of the giant planets (Mojzsis et al. 2019). Relating radiometric ages from asteroidal meteorites to dynamical models that account for late accretion may confine the onset of this migration to no later than about 4.48 Ga, with planetesimals and asteroids continuing to strike the inner planets in agreement with crater chronology. This suggests a starting constraint on when the window of opportunity for RNA formation opened, no earlier than 4.48 Ga, and no later than 4.36 Ga, perhaps later if a Ceres-sized sterilizing impactor was in Earth's natural history.

With H_2 loss following a simple exponential with a half-life of 40 million years for a Moneta-sized impact occurring at 4.48 Ga, atmospheric production of primary nucleobase precursors might be half at 4.44 Ga, a quarter at 4.40 Ga, and an eighth at 4.36 Ga, if the rate of formation of primary precursors is a linear function of H_2 partial pressure. This estimates a date for the optimal accumulation of RNA precursors at ~ 4.36 Ga ± 0.1 Ga. This, according to the model, is the time when the formation of RNA was most probable, and the formation of RNA-based Darwinism under an RNA-First model.

Smaller impactors, as noted above, could also have transiently made the Hadean atmosphere productive for the formation of RNA nucleobase precursors. These would have supported Orgel-easy processes to make the nucleobases themselves (Kitadai & Maruyama 2018), nucleobases that would then react with cyclic phosphates via the Kim & Kim (2019) process. However, the time would have been shorter, and the amounts of material would have been smaller. This implies that these are less probable as geological events to initiate an RNA world. This consideration is especially true given a model where the first RNA organisms were heterotrophic, relying on the environment to provide them their first foodstuffs.

9. The next generation of paradoxes

This is how the multidisciplinary discussion in Atlanta identified a chemical path to make RNA from starting materials likely available on a Hadean Earth, identified geological events to make those materials available, and estimated dates when those events most likely made RNA. With the delivery by an impactor of reducing power to the Hadean atmosphere, the natural maturation of carbonyl compounds to accumulate pentoses as their borate complexes, and various sources of phosphate (and phosphite, with reduced phosphorus from an impactor as outlined by Gull et al. 2015), resolutions were offered for a generation of paradoxes. Indeed, possible resolutions (in some cases, multiple resolutions) are now available for most of the paradoxes that had been mentioned in the call for proposals issued by the Foundation for Applied Molecular Evolution in a grant program supported by the John Templeton Foundation. RNA is much less of a "prebiotic chemistry nightmare" (Joyce & Orgel 1999).

Problems remain, of course. One relates to the amount of semi-arid dry land at the relevant time on Earth; this is needed for constrained aquifers. Estimates for the amount of continental crust in the Hadean are poorly constrained (Korenaga 2018), and the amount of continental crust need not translate directly into the amount of dry land available. Of course, a very large impactor, by reducing water, would have increased the amount of available semi-arid dry land.

Further, more studies are needed of the carbohydrate maturation processes to understand how the product manifold depends on pH, temperature, and other conditions. Further, amidophosphates can phosphorylate glycolaldehyde and glyceraldehyde as well as ribose. Work must be done to see if this competing process generates a paradox demanding resolution. Analytical methods remain difficult.

Likewise, our understanding of the status of phosphorus on the Hadean surface also needs development. Many processes for the formation of, for example, cyclic trimetaphosphate require high temperatures, for example 600°C (Gard 1990). While these were almost certainly available on a Hadean surface with volcanism, little of this parameter space has been explored.

Also missing from this path-hypothesis is a mechanism to obtain homochirality. As discussed elsewhere (Benner 2017), homochirality is required for an evolvable informational molecule. Because the Simons Collaboration had team members addressing this issue, the Templeton Foundation consortium had not focused in this area. We are awaiting insights from the Simons Collaboration into this very important problem.

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SESSION VI – ASTRONOMY, SPACE

The Global Sensing Revolution

Will Marshall

We're in the middle of a global sensing revolution – wherein we are covering the surface of the Earth, and the skies and space above it, with sensors: mobile phones, drones, satellites, the list goes on. The picture of global change that these sensors paint are ushering in a new era of planetary awareness and transparency. They can help us measure things we couldn't measure before, and measure them in a more cost-effective, reliable and accurate manner. These technologies help us make the invisible visible and fill in critical gaps in our understanding of our changing planet.

It's this perspective that powers all of us at Planet, a company that operates the largest Earth-imaging constellation of satellites in history. Our goal is to image the entire Earth every day, and make change visible, accessible and actionable.

From accelerated vertebrate species loss[1] to food production concerns[2] relating to increased populations, our data can play a key role in helping us to grasp the effects that humanity has on our planet's complex environments and ecosystems and take actions toward positive change.

Earth Observation (EO) enables us to identify illegal gold mining in the Peruvian Amazon; monitor the development of military installations in the South China Sea; gauge trade levels between China and North Korea; and more. EO is documenting events on land and at sea at an unprecedented scale and speed and this global monitoring capability is being driven by a new crop of aerospace companies that are delivering more high quality data per kilogram than ever before.

[1] Gerardo Ceballos, Paul R. Ehrlich, Anthony D. Barnosky, Andrés García, Robert M. Pringle, Todd M. Palmer, Accelerated modern human-induced species losses: Entering the sixth mass extinction, *Science Advances* 19 Jun 2015: Vol. 1, no. 5, e1400253 DOI: 10.1126/sciadv.1400253, available online at https://advances.sciencemag.org/content/1/5/e1400253

[2] FAO, 2050: Water supplies to dwindle in parts of the world, threatening food security and livelihoods, available online at http://www.fao.org/news/story/en/item/283255/icode/

Meeting Challenges with Sensors

The growth in sensors and data collection has been discussed at length, and often focuses on personal technology[3] like self-driving cars and smart refrigerators. But these sensors will help humans in other ways too, enabling us to overcome some of our greatest global challenges. A good summary of the world's challenges are encompassed in the Sustainable Development Goals.[4]

A global sensing revolution can help solve these challenges. In any system, measurement is required on a timescale that is faster than the timescale of the change. Let's imagine we are on a spaceship, and our ship begins to uncontrollably spin, or the CO_2 levels start increasing. As this is happening, we have to measure these events quicker than the timescale of change. We need to know how fast we're spinning and in what direction, or the rate at which CO_2 is rising, to know how to stop them. This paradigm is clearly applicable to humans on Earth: we are all on a spacecraft – and it's called Spaceship Earth!

Comparably, then, if we are to understand change on Earth, identify its causes and stabilize it by caring for humanity and other life on our planet, then we must collect planetary data faster than the timescale of change. The only way to achieve this is through a global network of sensors.

The ability to drastically increase the rate at which we collect data and measure change on Earth is why small, affordable sensors are powering a global sensing revolution. These new sensors are largely operated by commercial companies and are increasing the role the private sector plays in collecting data for science. The commercial market has stepped forward to help lead the charge of advanced data collection. It will play an important role in helping to deliver detailed, unbiased, data to society, further exposing the powerful impacts of climate change.

Deforestation is a great example. To date, people have used satellites to monitor forests every year by taking images at sufficient resolution to observe Earth's trees. At this pace, experts have been able to see what *has happened*, but have been too late to stop the changes from *happening*. Instead of measuring the forests annually, if experts were to measure or monitor all

[3] Internet-Of-Things Heat Maps For Operational Excellence, 2019, https://www.forrester.com/report/InternetOfThings+Heat+Maps+For+Operational+Excellence+2019/-/E-RES122661

[4] Sustainable Development Goals https://www.globalgiving.org/sdg/

the trees every day, illegal deforestation could be stopped in the act. Instead of just being *aware* of the problem, *action* can be taken to stop it.

A global sensing revolution is underway and it will yield tremendous benefits, helping us address climate change, help humanity and protect living things. It will help all of us astronauts – seven billion of us – to take care of our precious Spaceship Earth.

Small Satellites – Bringing Space Within Reach

Martin N. Sweeting

Earth orbiting satellites come in a wide range of shapes and sizes to meet a diverse variety of uses and applications. Large satellites with masses over 1000kg support high resolution remote sensing of the Earth, high bandwidth communications services and world-class scientific studies but take lengthy developments and are costly to build and launch. The advent of commercially available, high-volume and hence low-cost microelectronics has enabled a different approach through miniaturisation to produce physically far smaller satellites that dramatically reduces timescales and costs and that are able to provide operational and commercially viable services. These developments have catalysed a new approach to access to and exploitation of space.

1. Introduction

In the early decades of the space era, space was the preserve of the wealthiest and most technically advanced nations who enjoyed the ad-

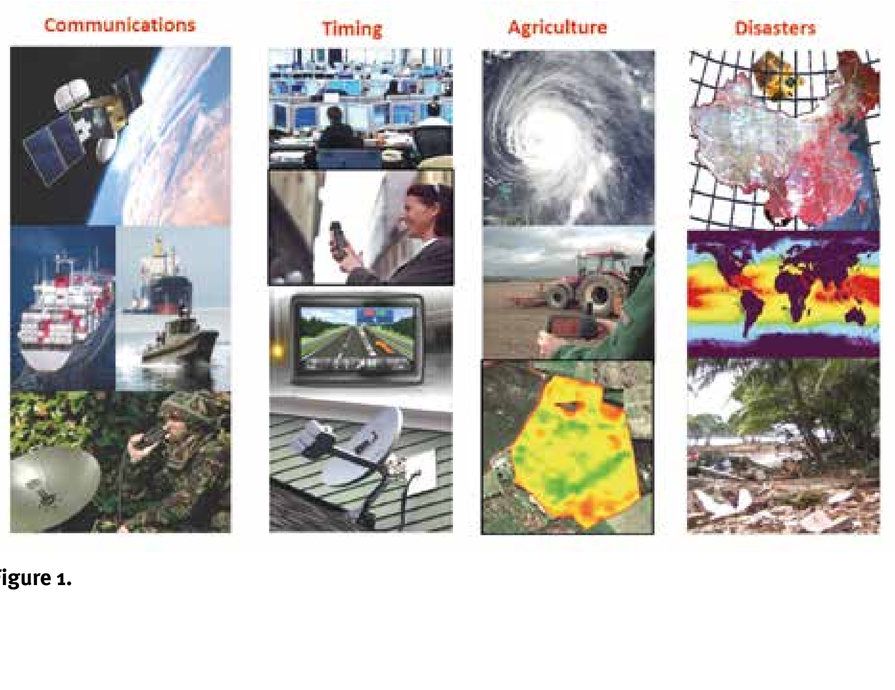


Figure 1.

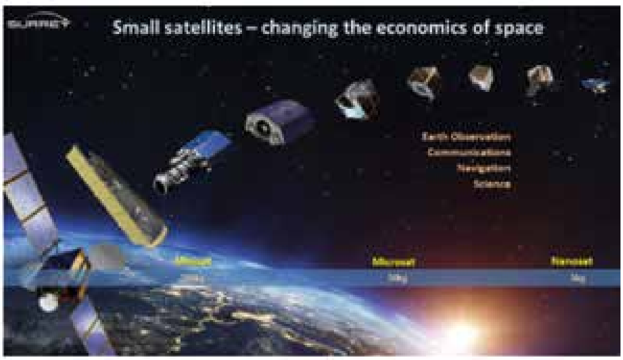
vantage and benefits brought from the high vantage-point of Earth orbit, primarily for observation and communications.

The use of space is expanding. It is now an essential infrastructure supporting national economies, their security and population well-being. Space provides global communications, pin-point positioning and navigation aids, the ability to optimise agriculture and the use of increasingly scarce land and water resources, and enables the monitoring and mitigation of natural and man-made disasters.

Earth orbiting satellites come in a wide range of shapes and sizes to meet a diverse variety of uses and applications. Large satellites with masses over 1000kg support high resolution remote sensing of the Earth, high bandwidth communications services and world-class scientific studies but take lengthy developments and are costly to build and launch.

The advent of commercially available, high-volume and hence low-cost microelectronics has enabled a different approach through miniaturisation to produce physically far smaller satellites that dramatically reduces timescales and costs and that are able to provide operational and commercially viable services. The University of Surrey (UK) pioneered the development of 'microsatellites' in the 1980s by taking advantage of the capabilities of 'commercial off-the-shelf' components to achieve a high performance to cost ratio.

These developments have catalysed a new approach to access to and exploitation of space and, by 2018, these small yet sophisticated and capable satellites have enabled everyone to have direct access to space – whether it be a developing economy, small companies, universities and even high schools.



Class	Mass (kg)
Large satellite	>1000
Small satellite	500 to 1000
Mini-satellite	100 to 500
Micro-satellite	10 to 100
Nano-satellite	1 to 10
Pico-satellite	0.1 to 1
Femto-satellite	<0.1

Table 1. General classification of femto-pico-nano-micro-mini-small-large satellites. [1]

Following the launch of Surrey's first microsatellites (UoSAT-1 & 2) in 1981 and 1984, the University formed a spin-out company, Surrey Satellite Technology Ltd (SSTL), to transfer the results of their academic research in small satellites across to industry for commercial exploitation. Over the following decades, Surrey has built and launched some 60 small satellites using 10 different launch vehicles working with international partners from 22 countries. Eighteen of these programmes involved know-how training alongside the design and construction of the satellites in order to assist developing space nations gain knowledge and build indigenous capacity for space activities.

#	Partner	Start	Duration	Team size	Mission
18	Algeria, ASAL	2014	2y	18	ALSAT-1b
17	Ghalam, Kazakhstan	2014	2y	15	KazSTSAT
16	KGS, Kazakhstan	2012	2y	18	KazEOSat-2
15	USA, NASA / MSU	2007	1y	3	Magnolia
14	Nigeria, NARSDA	2006	2y	25	NigeriaSat-2, NX
13	Nigeria, NARSDA	2001	2y	12	NigeriaSat-1
12	Turkey, Bilten	2001	2y	12	BILSAT-1
11	Algeria, CNTS	2000	2y	12	AlSAT-1
10	China, Tsinghua Uni.	1998	2y	12	Tsinghua-1
9	Malaysia, ATSB	1996	2y	9	TiungSat-1
8	Singapore, NTU	1995	3y	2	UoSAT-12 (payload)
7	Thailand, MU	1995	3y	12	Thai-Phutt
6	Chile, FACH	1994	5y	8	FASAT-A&B
5	Japan, Fujitsu	1992	2y	3	(FjSAT)
4	Portugal	1992	2y	6	PoSAT-1
3	S.Korea, KAIST	1989	4y	12	KITSAT
2	S.Africa	1989	3y	2	UoSAT 3/4/5
1	Pakistan, Suparco	1984	5y	10	BADR-1

Table 2. International training & capacity building programmes with Surrey.

2. Small Satellite programmes

The early microsatellite programmes focussed on providing digital store-&-forward communications between remote regions – before the advent of the internet infrastructure. Pilot projects provided daily email connectivity between health workers in Africa and Southeast Asia with medical centres in Europe and the US, and email communications with scientific outposts in the Antarctic where geostationary communications satellites were inaccessible due to being below the local polar horizon.

However, Earth observation became the prime application for small satellites – starting with fairly modest capabilities but improving rapidly from mission-to-mission through the use of increasingly capable COTS components. The combination of affordable satellite cost and corresponding launch opportunities as secondary payloads made it possible, for the first time, to launch a constellation of remote sensing microsatellites to achieve daily revisit over any specific area of the Earth's surface at least once each day – indeed more frequently at higher latitudes.

Taking advantage of this, 6 nations collaborated with Surrey in 2003 to construct the international Disaster Monitoring Constellation comprising 7 microsatellites carrying multispectral Earth observation cameras and solid-state on-board memories. Each of the participating nations funded a satellite, several including capacity-building training programmes, at Surrey and once launched into low Earth orbit the image data collected by the constellation was shared between the participants. Thus, by funding a single affordable satellite, the participants were able to benefit from data from a constellation of 7 satellites, increasing both data quantity and timeliness.

Table 3. The international disaster monitoring constellation (DMC) with Algeria, China, Nigeria, Turkey, UK & Spain.

The DMC responded to many major natural disasters, such as forest fires, flooding, snow storms and earthquakes – particularly responding to the Indian Ocean tsunami and Chinese Wenchuan earthquake disasters and the hurricane Katrina inundation in the USA. The DMC became a member of the International Charter on Space and Major Disasters, contributing regular data on a 'no cost' basis in response to formally-declared major incidents.

In addition to providing rapid response imagery in response to disasters worldwide, the DMC partners provided excess data onto the commercial Earth Observation market for agricultural, mapping and water management, thus recouping some of their initial investment. The DMC collected forest cover information in the Amazon on a 6-monthly basis to assist in the assessment of the rates of de-forestation.

Figure 2. The international disaster monitoring constellation (DMC) responding to the Indian Ocean tsunami and the Chinese Wenchuan earthquake disasters.

The DMC satellites also advanced several associated techniques for small satellites, notably communicating with their ground stations using the Internet Protocol for payload data transfer and command and control, so extending the Internet into space – including the first use of the 'bundle' protocol in space where Sensor data was successfully delivered from the satellite using this disruption- and delay-tolerant networking protocol designed for the Interplanetary Internet. The UK-DMC satellite included a GPS reflectometry experiment and on-board Internet router.

The success of the DMC stimulated the first fully commercial operational EO satellite constellation, RapidEye, comprising five 150kg microsatellites with 5-band multispectral imager (RGB, red edge, and near IR bands) with 6.5m GSD to generate land information products downlinked at 80 Mbit/s at X-band.

Figure 3. DMC3 high resolution optical Earth observation image and the 3 minisatellites on Indian PSLV launcher.

The demand for higher resolution and improved spectral fidelity for agricultural monitoring, precision farming and smart city management led to the need for more capable small satellite platforms with increased power, data handing and pointing requirements to carry larger aperture telescopes.

Three 450kg ‘minisatellites’ were built by SSTL and launched in 2015 to provide an optical imaging service with a ground resolution of 1-metre and were followed in 2018 by a fourth satellite and a synthetic aperture radar (SAR) minisatellite for all-weather, day/night monitoring for storms, deforestation and maritime surveillance.

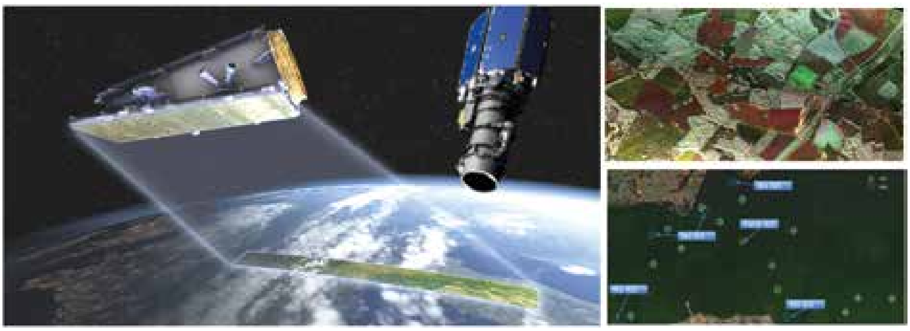


Figure 4. NovaSAR radar with 4th optical high resolution minisatellites SAR and AIS ship monitoring data.

Whilst higher fidelity minisatellites were launched, technology demonstrator missions showing the potential for 100kg microsatellites to provide high resolution (1-metre) full real-time video were launched – Carbonite-1 & 2.

3. The space environment and space debris

Unfortunately, debris from spent rockets and defunct satellites are littering space to an increasing degree – especially in the popular low Earth orbits below 2000 km. At altitudes below ~500 km, the natural decay into the Earth's atmosphere results in an 'auto-cleaning' function that reduces the lifetime of debris to manageable levels, however above that altitude the debris lifetimes can be measured in centuries and poses a serious threat to operational satellite systems. The density of debris is close to the threshold of the "Kessler Effect", in which collisions lead to a runaway increase in numbers of pieces of debris.

The recent proposals for 'mega constellations' exacerbates this problem and mechanisms to 'clean up space' are being actively considered. It is impractical to remove the 500,000+ pieces of sizable debris in low Earth orbit, however potential chain reactions of debris generation can be reduced if even relatively few large objects or items that might potentially fragment could be removed.

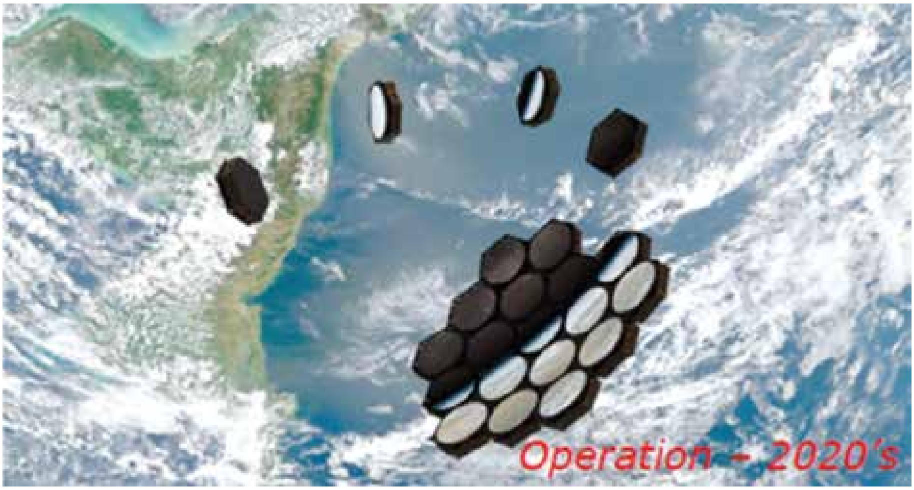


Figure 5. RemoveDebris mission net debris capture demonstrated in orbit in 2018 drag sail for orbit re-entry.

Surrey has been developing means both to reduce the natural orbital lifetime of satellites after the end of their operational life by extending a drag sail ('parachute') for speed up re-entry and by active removal using nets or harpoons deployed from a mothership that then forces a controlled re-entry.

There are now several companies proposing commercial services to remove debris or defunct satellites – particularly relevant for the proposed mega-constellation – as debris would represent a significant risk to their operational business.

4. What next for small satellites?

The physical design and construction techniques for satellites have been dictated and constrained by the launcher volume under the fairing and ascent phase dynamics (vibration, noise, shock) necessary to survive the aggressive first 20 minutes or so of ascent to orbit. An effective means of constructing large apertures in space could be through robotic assembly in orbit of numbers of small satellites Lego-like to form physically larger structures that could be used for optical, radar or communications applications – for business, scientific or exploration objectives. The structures can be reconfigurable in orbit to meet changing mission objectives – such as spare apertures trading resolution against signal-to-noise. The small and relatively robust 'lego-satellites' can be launched in space-efficient stacks on a number of launchers meaning, in principle, an unlimited size of assembled structure in orbit. The challenges associated with precise autonomous robotic assembly in orbit are not trivial, especially if optical alignments are required. In order to demonstrate this concept, the "Autonomous Assembly of a Reconfigurable Space Telescope" (AAReST) mission has been developed by CalTech, JPL, Surrey, IIST.

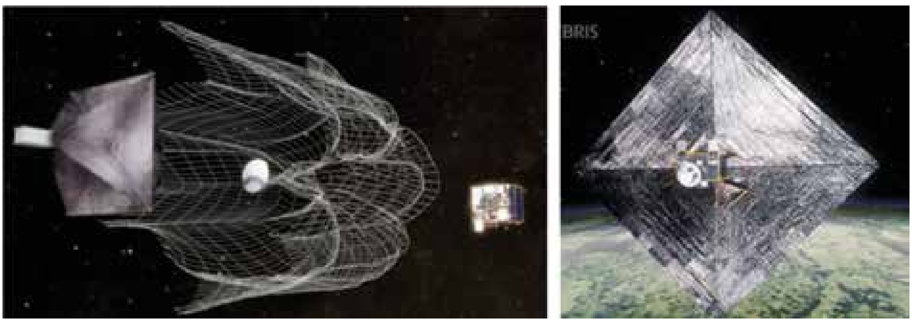


Figure 6. In-orbit assembly of a large aperture from individual microsatellites.

The logical next step is to exploit terrestrial developments in additive (and subtractive) manufacturing techniques (so-called 3-D printing) to move the manufacturing of spacecraft into orbit where eventually raw materials alone are launched and then design software uploaded to manufacture the required functions on 'gossamer' spacecraft – thus completely bypassing the structural constraints of the launch phase and, possibly, also simplifying the demands on the launcher itself leading to lower launch costs.

5. Conclusions

Small satellites have exploited advances in microelectronics to create a more affordable and timely access to space for a wider international community bringing space and its opportunities within the affordable grasp of every nation, commercial business and university. This has created new markets for space and its applications stimulating over 500 new start-up companies that, together with the proposed 'mega-constellations' have attracted some $25Bn investments. The resulting 'NewSpace' community is stimulating new approaches to space business and its applications to society. There is an opportunity to reduce the 'digital divide' and bring under-developed communities into the global economy. Persistent EO/RS will enable nations to have a more direct view and better manage their resources and the impact of human activity on their environment – reduce international tension.

New materials combined with robotics have given rise to new satellite/spacecraft manufacturing techniques that enhance small satellite capabilities and also further reduce cost and timescales. Robotic additive (and subtractive) manufacturing techniques now make possible product geometries that were previously physically impossible by human hands and digital manufacturing provides freedom of location and dramatically increased speed of the design evolution and the product innovation cycle.

Robotics and software-defined satellites manufactured in orbit will fundamentally change the space industry, access to and exploitation of space, and further increase our dependence on space – with an accompanying responsibility to manage properly that unique environment.

Exoplanets and Beyond

Sara Seager[1]

Thousands of exoplanets have been discovered in the last two decades, uncovering a wide diversity of planets that are very different from those in our own solar system. Now the push is to smaller and smaller planets down to those of Earth-size that orbit in the so-called "habitable zone" of their host stars. Ideas for how to detect signs of life in the variety of planetary possibilities, by way of biosignature gases, are expanding, although they largely remain grounded in study of familiar gases produced by life on Earth and how they appear in Earth's spectrum as viewed as an exoplanet. What are the chances we will be able to observe and identify biosignature gases on exoplanets in the coming two decades? I review the upcoming ground- and space-based telescopes and their opportunities in the search for habitable planets and biosignature gases.

1. Motivation

A longstanding goal in modern astronomy is to discover an exoplanet with suitable conditions to host life. That is, a planet with surface temperatures suitable for liquid water (needed for all life as we know it). An even more grand vision is to find an exoplanet with atmospheric gases that might be attributed to life, "biosignature gases". New ground- and space-based telescopes coming online in the next decade or two will give astronomers the capability to realize the grand goal, but only if Nature has co-operated in the form of providing a multitude of nearby habitable worlds.

2. Upcoming Telescopes at the Frontiers

An organizational framework describing each of three categories of concepts to search for habitable exoplanets is shown in Figure 1, and described in the below subsections. The categories are: transiting exoplanet transmission spectroscopy; direct imaging from large ground-based telescopes now under construction; and sophisticated direct imaging space-based telescopes. Each category of techniques includes capabilities of observing exoplanet atmospheres, needed to estimate the planetary surface temperature and search for biosignature gases by way of spectral features.

[1] Massachusetts Institute of Technology, 54-1718 77 Mass. Ave., Cambridge, MA, USA.

Figure 1. Organizational framework to describe the observational search for biosignature gases.

2.1. Transiting Planets with the James Webb Space Telescope

Transiting exoplanets are incredibly valuable [1]. A transiting planet's size and mass and hence average density can be measured or constrained. Furthermore, a transiting planet's atmosphere can be measured, given a bright enough host star and suitable planet characteristics. These values are in contrast to many other planet-finding techniques where only a planet mass can be measured or estimated. Transiting exoplanets are those that pass in front of their parent star as seen from the telescope. Only a small fraction of planets have the required fortuitous alignment; stars' rotation axes (and to some extent the planet orbits) are randomly oriented with respect to our line of sight.

The dominant transit survey mission operating today is the MIT-led NASA mission the Transiting Exoplanet Survey Satellite (TESS) [2], currently in its two-year prime mission (August 2018 through June 2020). TESS carries four identical, specialized wide-field CCD cameras, each with a 100-mm aperture and covering 24° × 24° on the sky. In a two-year, nearly all-sky survey, TESS will cover 400 times as much sky as NASA's pioneering Kepler space telescope [3] did. In the process, TESS will examine millions of stars at 30-minute cadence and 200,000 stars at two-minute cadence to likely find thousands of exoplanets with orbital periods (i.e., years) up to about 50 days. TESS will not be able to detect true Earth analogs (that is, Earth-sized exoplanets in 365 day orbits about sun-like stars), but it will be capable of finding Earth-sized and super Earth-sized exoplanets (defined as planets up to 1.75 times Earth's size) transiting M dwarf stars, stars that are significantly smaller, cooler, and more common than our Sun. The TESS search for habitable planets that may be followed up for signs of life is, therefore, focused on M dwarf host stars. (Several other ground- and space-based transit surveys are ongoing or planned for host stars of all types).

TESS may be called a "finder telescope" for the James Webb Space Telescope (JWST [4]; launch scheduled for 2021). The JWST will be capable of observing small exoplanet atmospheres for planets transiting small M dwarf stars. As the planet transits the star, some of the starlight passes through the planet atmosphere – but not all of it. At some wavelengths the planet atmosphere absorbs starlight more than at other wavelengths. By carefully observing wavelength-by-wavelength, we can identify which gases and in some instances how much of them are present in the planet atmosphere. This technique is called transit transmission spectroscopy [5]. Most transiting planets also go behind their parent star, called a secondary eclipse. As the planet disappears behind the host star, the combined planet and starlight drops by a tiny amount related to the planets thermal emission which can be converted to an estimated top-of-the-atmosphere brightness temperature. Dozens of exoplanets have been observed in transmission and thermal emission [6], though most are limited to giant and or hot exoplanets, which are more favorable to observation with the Hubble Space Telescope and with some large ground-based telescopes.

The JWST will bring the capability to observe small rocky planet atmospheres via transmission spectroscopy and secondary eclipse spectroscopy, but challenges remain. With an optimal target, a large amount of observing time, and some luck – the JWST could detect habitable conditions on a rocky transiting exoplanet in the habitable zone of a nearby mid-to-late-type red dwarf star. The habitable zone is the zone around the star where a rocky planet with a thin atmosphere, heated by its star, may have liquid water on its surface. Liquid water is needed for all life as we know it, and detection of atmospheric water vapor as a proxy for surface liquid water on a small exoplanet is key.

Small planets transiting small red dwarf stars for this first category already exist: the Trappist 1 planets [7] and LHS 1132b [8].

Despite their extensive current popularity, transits are only the first part of a long story. Transiting planets must be fortuitously aligned, which eliminates most planetary systems. While atmospheres of small planets transiting small M dwarf stars are within reach, the same small planet transiting a larger sun-like star is out of reach.

2.2. Direct Imaging with Extremely Large Telescopes

Very large ground-based telescopes are now under construction and anticipating "first light" in the 2020s. The USA is pursuing two telescopes, the 20 m mirror diameter Giant Magellan Telescope[2] [9] in Chile, and the Thirty Meter Telescope[3] [10] on Mauna Kea in Hawaii. The European Southern Observatory is building the 40 m mirror diameter European Extremely Large Telescope[4] [11] in Chile. With the right instrumentation

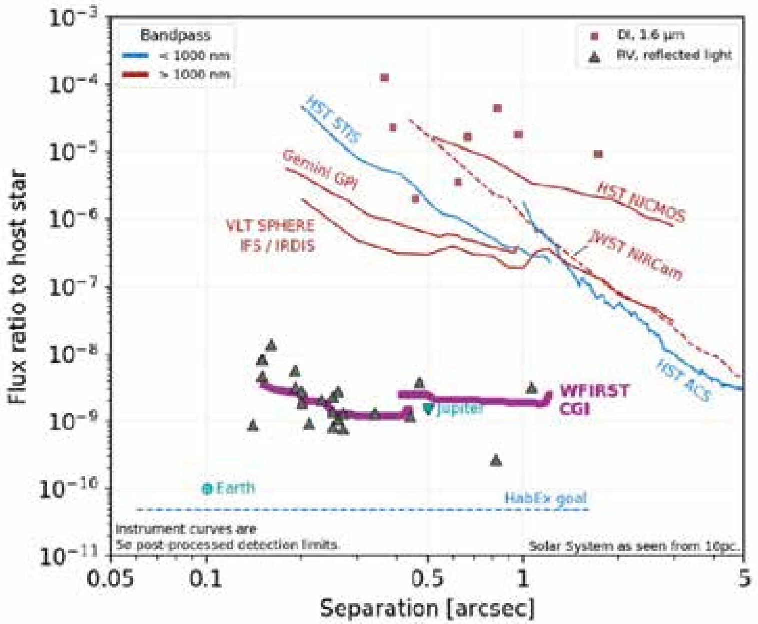


Figure 2. Planet-to-star flux ratio performance goal in the context of known planets and existing and planned high-contrast direct imaging instruments. Shown is the flux ratio between a planet and its star (points for individual planets) or between the dimmest source detectable (solid and dashed lines, assuming a 5σ detection after post-processing) and its star (for instrument performance curves) versus the projected separation in units of arcsec. The black triangular points are estimated reflected light flux ratios for known gas giant radial velocity-detected planets at quadrature, with assumed geometric albedo of 0.5. Red squares are 1.6 μm flux ratios of known self-luminous directly imaged planets. Cyan points represent the Earth and Jupiter at 10 pc. Figure courtesy of K. Stapelfeldt, T. Meshkat & V. Bailey. This version of the figure and caption are taken from the HabEx Final Report.[5]

[2] https://www.gmto.org/
[3] https://www.tmt.org/
[4] https://www.eso.org/public/usa/teles-instr/elt/

and extreme adaptive optics to correct for the blurring effects of Earth's atmosphere, these telescopes will be able to study rocky planets around M dwarf stars by direct imaging.

Direct imaging is a planet-finding technique whereby the starlight is blocked out, enabling any orbiting planets to be detected. To date direct imaging has succeeded for self-luminous planets (that is very young and/or massive planets) orbiting far from the star (top right in Figure 2).

Planets orbiting in the habitable zone of a red dwarf star will shine in reflected light at the tiny level of about 10^{-7} to10^{-8} planet-star flux ratio, about thousands of times more challenging than current capabilities. Equally challenging will be the small projected separation from the host star, on order of 0.1 arcseconds or smaller. A planet in the habitable zone of a red dwarf star orbits much closer to the star than a planet in the habitable zone of a sun-like star because the red dwarf star gives off lower energy than a sun-like star. The ELTs will have capability on the middle, left side of Figure 2. A couple of hundred M dwarf stars are suitable for the ELT search for and atmospheric characterization of small rocky exoplanets.

Nearby red dwarf stars with a suitable exoplanets separation already exist: Proxima Centauri b [12] and Ross 128 b [13].

2.3. Direct Imaging with Space-Based Telescopes

The ultimate goal to many working in exoplanet astronomy is to discover a true Earth analog – that is an Earth-size planet in an Earth-like orbit about a sun-like star. While other planet finding techniques (namely radial velocity and transits) are pushing down to the sensitivities to uncover Earth analog, only direct imaging affords the possibility of atmosphere study. Atmospheres are critical to identifying a habitable world – Venus and Earth would appear the same to all planet-finding techniques that have no atmosphere study capability. Venus and Earth are about the same size and same mass, yet the Venusian surface is completely inhospitable to life because a massive greenhouse atmospheres makes the surface temperatures far too hot for life.

NASA recently concluded two studies on sophisticated space telescopes with starlight-blocking capability to operate in space above the blurring effects of Earth's atmosphere. The challenge for direct imaging an Earth analog is tremendous, the planet-star flux ratio is one part in ten billion. Two decades of serious work of lab demonstrations have shown this astonishing starlight blocking capability is within reach. One study is called Large UV

Optical IR Surveyor (LUVOIR)[5] [14] where UV means ultraviolet wavelengths, optical means visual wavelengths, and IR means infrared wavelengths. LUVOIR uses a coronagraph, an internal starlight-blocking device first invented in the 1920s by the French astronomer Lyot. LUVOIR would be huge, one version has an effective 8 m mirror diameter and a second version 16 m. LUVOIR would be the most ambitious space telescope ever built, with the ability to search a few hundred of sun-like stars.

The second concept studied by NASA is the Habitable Exoplanet Observatory (HabEx)[6] [15]. HabEx houses a coronagraph but also includes a starshade. A starshade has its own spacecraft and is a giant specially-shaped screen tens of meters in diameter that would fly in formation tens of thousands of km from a space telescope, blocking out starlight to the required 1 part in 10 billion so that only planet light enters the telescope. The starshade's technology development is anchored in NASA's Exoplanet Exploration Program's effort called "S5" (Starshade to Technology Readiness Level 5),[7] an activity to address all critical starshade technologies and raise them to TRL 5 by 2023. The fiducial HabEx design has a 4 meter diameter "off axis" mirror and a 52 m diameter starshade. HabEx would closely survey about fifty of the nearest neighboring sun-like stars.

In addition to HabEx is a smaller starshade mission with the starshade at 26 m diameter, the Starshade Rendezvous Probe[8] [16]. The Starshade Rendezvous Probe would be built and launched on its own, then rendezvous on orbit with NASA's planned WFIRST telescope (itself anticipated to launch in the mid 2020s).

3. The Frontiers of Biosignature Gas Research

The material in this section is adapted from [17].

3.1. Earth's Biosignature Gases

Life on Earth has completely reengineered Earth's atmosphere, specifically making it 20% oxygen (O_2) by volume. Without plants and photosyntheric bacteria, Earth would have almost no O_2, about orders of magnitude less than present today [18]. O_2 is so reactive it should not be present in the

[5] https://asd.gsfc.nasa.gov/luvoir/

[6] https://www.jpl.nasa.gov/habex/

[7] NASA Exoplanet Exploration Program Technology Overview, 2018; Available from: https://exoplanets.nasa.gov/exep/technology/technology-overview/

[8] https://smd-prod.s3.amazonaws.com/science-red/s3fs-public/atoms/files/Starshade2.pdf

atmosphere in any significant quantity unless continually generated. It is therefore not surprising that O_2 has been considered a biosignature gas for nearly a century [19]. If we observe O_2 in a small rocky exoplanet atmosphere spectrum, we will want to attribute it to life, with the caveat of false positives in the form of exotic geological or atmospheric processes [20]. We should keep in mind, however, that while O_2 may be unique in being both abundant and non-geological, life on other worlds may not make O_2.

Life on Earth produces not only oxygen but literally hundreds of thousands of other chemicals (see review in [21]), estimated from plant natural products, microbial natural products, and marine natural products. A subset of hundreds are both in gas form and present in Earth's atmosphere in at least trace concentrations. A further subset of tens of gases are present in the atmosphere in high enough concentrations to consider as being remotely detectable for astronomical purposes. A further subset of gases are spectroscopically active enough to be considered as potential biosignature gases on an Earth-like exoplanet.

Out of the promising numbers and variety of gases produced by life on Earth, there appears to be a conundrum when considering their potential as biosignature gases for exoplanets [22]. On Earth, the most abundant biosignature gases (e.g. CH_4) can also be produced from abiological sources, and will therefore have false positives in an exoplanet context. These are gases produced when life exploits a chemical potential energy gradient that is geochemically stable. In more detail, two materials (such as hydrogen and carbon dioxide) are produced by different geochemical processes and come together in one place. Their reaction is thermodynamically favored but kinetically inhibited – their reaction cannot happen at ambient temperatures and pressures. Life catalyzes the reaction. Gas products of such reactions include CH_4, N_2O, and H_2S. Such gases are abundant because they are created from chemicals that are plentiful in the environment. However, not only does geology have the same molecules to work with as life does, but in one environment where a given redox reaction will be kinetically inhibited and thus will proceed only when activated by life's enzymes, in another environment with the right conditions (temperature, pressure, concentration, and acidity) the same reaction might proceed spontaneously. Small common molecules produced as biosignature gases will therefore be fraught with false positives.

In contrast to the category of simple gases produced by life exploiting chemical potential energy gradients, a second category of biosignature gases are larger more complex molecules that appear to be unique to life.

In other words, they are unlikely to have false positives. For example, dimethylsulfide released by oceanic plankton. These unique-to-life gases are present only in tiny quantities that in most imaginable exoplanet scenarios may be too low for the gas to accumulate to detectable levels. This category of biosignature gases appear to be special to particular species or groups of organisms, and require energy for their production). They are produced for organism-specific reasons and are highly specialized chemicals not directly tied to the local chemical environment and thermodynamics. Some biosignature gases in this category of energy-requiring specialized byproduct gases include methanethiol CH_3SH [23], methyl chloride CH_3Cl [24], and organic sulfur compounds (CS_2, OCS, CH_3SH, CH_3SCH_3, and $CH_3S_2CH_3$ [25]). The thought is that some of these gases, under the right conditions of excess production or favorable UV flux conditions, might accumulate to hypothetically detectable levels.

3.2. Thousands of Biosignature Gas Possibilities

My research team aims for as general a view as possible – so as to explore all possibilities to increase our chances of identifying signs of life on planets beyond Earth (Figure 3). We have curated a detailed database of all volatile molecules, not just those that are produced by life on Earth, but all of those that are both stable and volatile at a wide range of habitable atmospheric temperatures and pressures [21].

The appeal of the "all small molecule" approach is that it is independent of terrestrial biochemistry. The only assumption is that life beyond Earth uses chemistry and metabolism to store energy and outputs metabolic byproduct gases. After all, astronomers will only be able to see the byproducts of metabolism and not any life forms themselves.

To proceed, we are taking molecules, or classes of molecules based on functional groups, and assessing first how likely they are to accumulate in an exoplanet atmosphere of a specified composition, and second whether or not they are spectroscopically detectable by a remote space telescope (Figure 3). The first point depends on the UV radiation environment from the host star that drives photochemistry, the atmospheric composition and atmospheric mass, and the surface chemistry (including sources and sinks). In other words, we take classes of molecules and aim to determine if they are stable and can accumulate in different planetary environments by integration into existing computer models of planetary chemistry and photochemistry. The spectroscopic detectability relies on molecular line lists, which for many molecules do not exist yet. We have therefore developed

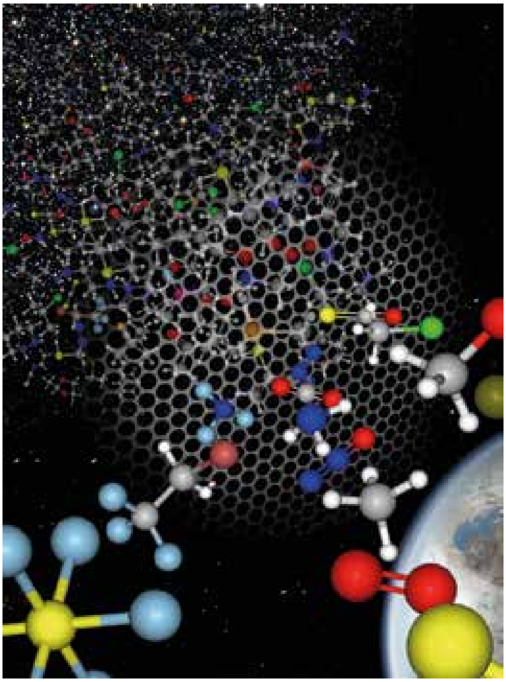


Figure 3. Schematic for the concept of considering all volatile molecules in the search for biosignature gases. The goal is to start with chemistry and generate a list of all small molecules and filter them for utility as biosignature gases, based on atmospheric models with surface source and sink input details, strengths of spectroscopic features, and context with other gases in the atmosphere. The figure shows a sea of molecules that fill chemical space, as shown in the distance. A subset of choice molecules make it through the shaker filter into three different streams. Two of the streams include molecules produced by life on Earth and reach near an exoplanet, illustrating the hope that some of these molecules are relevant for the search for life on other worlds. Atoms correspond to the following colors: C: light grey; O red; N blue; S yellow; P orange; Cl green; Br reddish brown; F light blue; B (and other rare elements) dark pink; and Se olive green. Figure originally published as the cover for the journal Astrobiology in June 2016. Figure credit: J. Petkowska.

a complimentary approach to quantum mechanical model generated precise line lists, by estimated functional group spectral features [26]. In the assessment we must also consider false positives, that is how a gas could be produced by non-biogenic processes, such as in volcanoes or via various chemical reactions in the atmosphere. We could, in some cases be highly confident that a gas might be produced by life, and in others less so, perhaps even assigning a probability after detailed atmosphere calculations.

4. Outlook

Astronomers are exuberant about the extensive progress in exoplanetary science and in the promise of the future for finding and characterizing other Earths. The new telescopes coming online have the capability of detecting biosignature gases, if they exist on a planet favorable for observation around a nearby star.

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Our Place in Space and Time

John D. Barrow

Other speakers have talked eloquently about some of the contributions of the astronomical sciences to human progress and well being. We recognise that Einstein's special and general theories of relativity are essential for accurately functioning GPS and the guidance of satellite and probes dedicated to observation of the earth's topography, flora and fauna, predicting weather, and monitoring our vulnerability and responses to disasters of many sorts; lasers and masers were developed with astronomical uses in mind; sensitive receivers and mirrors, new materials, as well as optical instruments for medical and practical deployment have all emerged from astronomical imperatives; techniques for mining information from huge data sets; indirect astronomical determinations of the constants of nature that surpass the accuracy achievable by laboratory metrology, and limits on elementary particle physics that are beyond the reach of terrestrial experiments. All are by-products of astronomy.

Yet, I do not want to revisit those direct benefits from astrophysics and cosmology. Instead, I want to highlight the potentially larger impact on human thinking of the ideas of modern cosmology. Cosmology is an attractive shop window for all of science. It attracts the attentions of young school students and engages a far wider public. It is one of the few sciences that is able to rise above political and nationalistic wrangling to stress the unity of humanity and reveal our shared cosmic environment. It raises longstanding and outstanding questions about the nature of the universe and our existence within it that places it at a crossroads where physics, biology, philosophy and theology meet.

Cosmology is currently in a golden age of discovery. New developments in quantum electronics, optics, and satellite instrumentation have fuelled a succession of dramatic discoveries, culminating in the recent direct detection of gravitational waves from colliding black holes and neutron stars.

Cosmology shapes our worldview and defines the cosmic canvas on which we try to place ourselves. It not only tells us where we are and when we are, it helps us understand who we are and where we might be heading. Although cosmology is an ancient human speculation, it only became a branch of science after Einstein's creation of the general theory of relativity in 1915. Previously, there was no theory of gravity that allowed us to consistently describe entire universes, whether they were finite or infinite in extent [1]. Cosmology was really just a branch of art history. You could imagine any type of universe that took your fancy and there was no way to test whether it might be right or wrong.

For thousands of years, philosophers, astronomers and scientists thought of the universe as rather like a stage setting – a fixed, unchanging system within which the planets, stars and other heavenly bodies had been set in motion. Einstein changed all this and showed that space and time are dynamic entities whose nature, rate of change and flow are shaped by the material contents of the universe. Instead of a fixed stage, space is more like a trampoline, shaped by the movement of mass and energy upon it. Einstein's equations determine the link between the shape of space, the rate of flow of time, and the distribution of mass and energy upon them.

Every solution of Einstein's remarkable system of ten partial differential equations describes an entire universe: a map of space, time and matter. There are in principle infinitely many of them and only a few of the simplest, most symmetrical solutions can be found. Fortunately, one of the simplest solutions fits observations very well and provides an accurate description of an expanding universe with very high levels of symmetry and spatial uniformity on the average just like the one we see. The visible universe is almost the same in every direction and at every place to an accuracy of about one part in 100,000 over its largest scales of more than 14 billion light years.

Cosmology is not like laboratory sciences: we can't experiment on the universe so we look for correlations between properties that are predicted to coexist. Moreover, everything we see in the astronomical universe is, to a greater or lesser extent, as it was in the past when the photons left their sources towards us. We see the universe as it was long ago. Some of the things we see will no longer exist.

The universe is expanding as Edwin Hubble, Milton Humason and Georges Lemaître first revealed to us by interpreting the shifting of spectral lines in light from distant stars towards the red end of the optical spectrum as a Doppler shift produced by a receding light source. This was arguably the greatest scientific discovery of all time – the expansion of the universe. It is important to realise that there is no centre and no edge to this expansion: the universe is not expanding into anything. We can't be at the centre of the universe because there isn't one. Nor are we, or the solar system, or our Milky Way galaxy, expanding. All of those structures are bound together by other gravitational or non-gravitational forces that are stronger than the effect of the expansion over their scale. You have to go out to the scale of great clusters of hundreds of galaxies before you find the markers that trace the expansion of the universe.

The visible part of the universe contains about 100 billion galaxies and each of them contains about 100 billion luminous stars. Yet there is evidence throughout the universe of another dark form of matter, unimaginatively dubbed *dark matter* – probably some weakly interacting elementary particle population as yet unknown to laboratory physics but suspected to exist by theorists – that contributes nearly seven times more material and gravitational pull that everything that shines in the dark.

In 1998, two large teams of astrophysicists led by Saul Perlmutter, Brian Schmidt and Adam Riess observed that distant supernovas were dimmer than expected, and hence much further away than predicted by existing models of the universe. This led to the dramatic (and ultimately Nobel Prize-winning) discovery that, instead of slowing down under the effect of gravity, cosmic expansion is now proceeding at an ever-accelerating rate. A new universal force had caused the universal expansion to switch from deceleration (governed by gravitational attraction) to acceleration (governed by some source of gravitational repulsion) when the expansion had proceeded to about 75% of it present extent. What is the reason for this mysterious force – the so-called *dark energy* – that makes up about 70% of the mass-energy in the universe today? Is it the quantum vacuum energy of the universe, some new type of matter with a very strong negative pressure, some feature of quantum cosmology, or simply another part of the gravitational force that Einstein knew to be a possibility back in 1915. All of these options are possible descriptors of the dark energy. Each has the challenge of explaining why it began to dominate the dynamics of the universe a few billion years ago. None has succeeded so far.

Modern cosmology has taught us that we should not longer expect our position in the universe to be privileged in every way. We couldn't exist anywhere in the universe, of course – the hot centres of stars are hardly conducive to living complexity. However, when it comes to *when* we exist we can see that we do live in a special cosmic time interval. This determines our entire picture of the universe and many of the philosophical and psychological responses we have to it.

As far as elements go, the early universe was almost exclusively made up of hydrogen and helium when it was three minutes old, with only tiny traces of everything else. Carbon, oxygen and all the other heavier elements that make up complexity and life today did not appear ready-made at the beginning of the universe. They were forged in the explosive nuclear furnaces of dying stars, where helium atoms combined into beryllium, beryllium and helium into carbon, and carbon and helium into oxygen. These reactions, which yielded the basic building blocks of biochemistry, took many billions of years to complete. Thus, we shouldn't be surprised to find ourselves in a universe that is more than 10 billion years old, since younger ones would not yet contain the building blocks needed for biochemical complexity.

Neither should the size of the universe surprise us; its immensity is simply a reflection of its great age. In fact, we could not exist in a universe that is significantly smaller than the one we find ourselves in. While a universe the size of the Milky Way, with its billions of stars and planets, might seem a sufficiently large setup for life to emerge, it would be little more than a month old – barely enough time for you to pay off your credit card bill, let alone evolve complex life. People often point to the vastness of the cosmos to argue that life surely must exist somewhere other than Earth. While this might very well be the case, it is striking that the universe would still have to be almost as big as it is just to support one lonely outpost of life.

The large time needed to produce the building blocks of living complexity leads not only to the large size of the universe but also to its low temperature (just 2.7K) and remarkable scarcity of matter. If all the atoms in the universe were evenly spaced out then there would only be about one atom in every cubic metre of space – emptier than any laboratory vacuum chamber on Earth. Gather atoms together, and this tiny material density corresponds to finding about one Earth-sized planet every 10 light years, or one star like the Sun every 1000 light years, and one galaxy like the Milky Way every 10 million light years. Thus we see why the other planets, stars and galaxies are so far away: there is too little material to form them with greater spatial density in the universe.

The last dramatic consequence of the low density of stars is that the sky is dark at night. There is too little matter and energy in the universe to make the sky bright as Edmund Halley first thought it should be, around 300 years ago. For if your every line of sight ends on a tree trunk when you look into a wood containing just a few hundred trees, why doesn't your line of sight end everywhere on a star when you look out into the countless field of stars in the universe? Why is the sky not completely bright all the time?

The large age of the universe needed for life has led to so much expansion that the density of matter and light is far too low today to illuminate the sky. There was a time when the sky was always bright but it was in the distant past, when the universe was about a million years old. But no one could be there to see it because the temperature then was too great for any atoms and molecules to exist. So, the dark night sky you see today, witnesses to the expansion of the universe.

Thus, we are faced with a curious, almost philosophical set of consequences: to develop the broad-brush ingredients required to produce biochemical complexity, the universe must be big and old, almost empty, dark and cold. Paradoxically, these stark properties, which do not sound at all conducive to sustaining living things, turn out to be necessary for the creation of the building blocks of life upon which evolution can act.

Since 1981, a unifying idea has been that the universe underwent a surge of *accelerated* expansion for a finite period of time in its very early history – this phenomenon is called *inflation* [2]. It can be caused by new types of matter with negative pressure (called 'scalar fields') that were predicted to exist in new theories of elementary particles that emerged after the emergence of gauge theories including asymptotic freedom 1974. The recently discovered Higgs boson is an example of such a scalar field.

The surge of early inflation accelerates the expansion to such an extent that it allows the whole of our visible part of the universe to be the expanded image of a part of space that at the time inflation began was small enough for light signals to traverse it and keep its properties correlated and smooth – up to quantum statistical fluctuations. In the absence of an early period of accelerated, this is not possible: the smooth regions would only have expanded to be a few metres in size today, far smaller than the size of the visible universe (about 1025 metres across).

This appealingly simple idea allows us to understand the expansion rate as well as the symmetry and smoothness of the expansion today; it also gives rise to quantum statistical fluctuations which seem able to produce the seed fluctuations that led to galaxies. These possibilities all allow the theory of inflation to make predictions and be tested by astronomical observations made from the ground and by satellites like COBE, WMAP and Planck.

Remarkably, our universe is expanding within about one per cent of the critical divides that separates a future of indefinite expansion (exceeding its escape velocity) from one (at less than its escape velocity) that will reverse into contraction back towards a 'big crunch' of ultra high density and temperature in the future. That our universe seems to be balanced on a knife edge separating two radically different futures is not the only unlikely feature of the cosmic expansion that inflation naturally predicts. The expansion of the universe is also isotropic, meaning that it proceeds at the same rate in every direction. In addition, the universe is extremely smooth, but not completely so – it has a graininess level of one part in 105, just lumpy enough for stars and galaxies to form. Had the universe been just ten times more or less grainy, it would host no habitable regions where stars could form and the chemical elements needed for life would be missing. The elegance of the inflationary picture is that a brief period of accelerated inflation drives the expansion so close to the critical divide that even after 14 billion years of subsequent expansion it should still be tantalisingly close to the divide. Moreover, any pre-existing directional asymmetries in the expansion rate, due to rotation or shear, will be driven to become imperceptibly small as the acceleration pushes the expansion rate in every direction towards the same rate of isotropic expansion [3]. Two of the longstanding problems of cosmology could therefore be solved and a third, the origin of the galaxies, might also be answered by the quantum fluctuations created during inflation which then grow by gravitational instability to become significant over-dense islands of matter billions of years later. This third hope can be checked to an accuracy of a part in 100,000 by observations of the pattern of variations in the background radiation temperature with wavelength. So far, there is a very impressive agreement between the predictions and the observations: some version of inflation seems to have occurred when the universe was about 10-35 sec old. It is remarkable that microwave receivers in space are now easily able to observe the effects of processes occurring so close to the beginning of the universe's expansion across the whole microwave spectrum. In the future, the detection of cosmological gravitational waves also produced by the surge of early inflationary expansion may contribute more information to our picture of the very early universe.

Cosmic inflation is now the standard working model for the earliest stages of the universe – the one that we try to shoot down. As we mentioned earlier, this requires that the whole of the visible part of the universe (and probably much beyond our horizon as well) grew from a tiny patch of space measuring about 10-25 cm across. But what about the rest of the early universe that lay beyond that tiny patch when inflation commenced? We can imagine many (perhaps infinitely many) similarly sized regions, each internally coordinated but potentially very different from each other. They might have all inflated by different amounts to create a universe that was globally extremely different in structure from place to place (maybe also in its underlying physical forces and constants of nature in some versions of this scenario). This is called *chaotic inflation* [4]. It invites us to think of the universe during the period of inflation as being analogous to a great foam of bubbles, some of which get inflated a lot, others not very much, and others perhaps not at all. We live in one of those bubbles that has inflated enough, and over sufficient time, to become old enough and big enough for stars, biological elements, planets, and ultimately people, to form [5]. If we could see far enough in the universe, beyond our horizon imposed by the speed of light, 42 billion light years away, this elaboration of inflation predicts that we should find the universe to be very different from place to place. Geography is a much more complicated subject than when we were school! While the idea of a universe varying in space like this is not a new one, this is the first time that it has emerged as a positive prediction of a cosmological scenario.

Alarmingly, it seems that history may also be a more complicated subject than we are used to. For each one of those inflating 'bubbles' can rather easily create within itself the conditions for tiny sub-regions to undergo further inflation of their own. They, in turn, can create the further sites for continuing inflation, ad infinitum. This *eternal inflation* is a self-replicating fractal process that appears to have no end [6]. Whilst any bubble, like the one that expanded to encompass our entire visible universe, will have a beginning, the entire eternally self-reproducing network of which it is a (possibly infinitesimal) part has no end and need have no beginning – it may be continued like an exponential function ex forever into the past as $x \to -\infty$.

Our visible universe is just part of one of these inflating bubbles that has the features of large age and size needed for life to be possible. So, the question of "Did the universe have a beginning?" now has a much more nuanced answer. Our visible universe had a beginning, when some sort of quantum fluctuation initiated its career of expansion. But we don't know, and probably can never know, if the same was true for the entire (possibly infinite) multiverse of all the expanding or contracting bubbles.

Chaotic and eternal inflation have produced a multiverse perspective. They are simple extensions, that may be inevitable consequences, of the standard simple inflationary picture of the fate of a single inflating 'bubble' that has been astronomically so successfully tested by observations. Modern theories of high-energy physics, like string theory, need to tell us whether the classes of self-interacting matter fields, or particles, that give rise to these exotic behaviours do indeed exist with the right properties within their theories, or whether their existence would be in contradiction with other features of the elementary particle world that we know exist. In this respect, the recent study of the so called 'swampland conjectures' [7] is interesting. Particular constraints on the speed of change of the types of matter field that can give rise to inflation and eternal inflation have been proposed in order that the whole theory have an acceptable vacuum state. These constraints on the 'landscape' of all possible theories seem to be extremely restrictive. Their significance remains a research topic of great current interest.

The discovery that the universal expansion started accelerating again, a few billion years ago, has far-reaching consequences for the future of the universe and the extent to which it can be comprehended. The acceleration will ultimately bring to an end all information processing in the universe [5]. Structures will not be able to bind and survive in the face of acceleration that stretches all spatial separations exponentially rapidly in time. The acceleration also introduces a new feature. During the earlier stages of the universe's life, the distance that we can see with a perfect telescope increases steadily, in proportion to the product of the speed of light times the age of the expansion. Each day we can, in principle, see a little (one light-day) further. But the acceleration now imposes a fixed limit to how far we can see. Light can never beat the effect of the acceleration and reach us from outside this fixed horizon surface around us. After about 100 billion years all the other galaxies we see today will pass beyond this surface [8]. If we have descendants studying the universe at that time, they will no longer be able study cosmology like we do. They will not be able to see other galaxies or discover that the universe is expanding. Ironically, they will not be able to see the evidence we have for the accelerating expansion that is responsible for the horizon around them. Trapped in a nutshell they will be prisoners in a finite space. Their knowledge of the vastness of the expanding universe will have to come from books. For them cosmology will have become a branch of literary history.

Just as there is a period of cosmic history during which life can arise and evolve, so there is a period during which the universe can be studied and understood. It is strange and sobering to think that in the distant future, the only way to learn about aspects of the universe that are easily observed today would be to pore over old astrophysical books and journals from a long-gone era, when the galaxies were still within our reach.

Finally, we see how our conception of the universe has been elaborated and extended. This forms part of a familiar historical trend which see the particular become part of a wider spectrum of possibilities. For example, once we believed that Euclidean geometry was the only logically consistent possibility – part of the absolute truth about reality – but an infinite number of non-Euclidean geometries can be consistently formulated (what mathematicians mean when they say that they 'exist'). Later, we found that there were many possible logics, unending scales of infinities [9]. None is unique. In the future we may have to find a place for human intelligence amongst a population of 'artificial' intelligences or see life on Earth amongst forms of life that evolved independently elsewhere in the universe. These challenges will require varieties of judgement that are broader and deeper than those provided by science alone.

Acknowledgements

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SESSION VII – BIOLOGY, GENETICS, BIO-CHEMISTRY, CHEMISTRY

Stem Cells and Tissue Regeneration

Helen M. Blau[1]

Stem cells have great potential to increase the function of defective or aged tissues through replacement and rejuvenation. Aging is often depicted as in the painting by Gustav Klimt "The three Ages of Woman" – as a progression from a wondrous child to a mature radiant woman to a stooped elderly individual – decrepit and aged. Although longevity, or lifespan, is increasing for both men and women, quality of life, or healthspan, is not. As posed in *Nature* (Bellantuono, 2018), increased longevity means "more years of what?" Indeed, longer lifespan is associated with more years with chronic disease. Regenerative medicine aims to change that and to increase healthspan, the quality of life, so that one can enjoy life – jog, ski, dance and do all the things one likes to do, even when aged.

The overarching goal of stem cell biology and tissue engineering is to replace or regenerate damaged or diseased tissues, for instance to treat Parkinson's, myocardial infarction (heart attack) or stroke (Blau and Daley, 2019). Additionally, stem cells can be used to deliver genes that are missing in inherited diseases, like Duchenne muscular dystrophy or hemophilia. Finally, stem cells afford a unique opportunity to improve our understanding of early human development by modeling it in tissue culture. The ability to model human disease processes in culture facilitates screens for drugs in an unprecedented manner. There are three fundamental types of stem cells (Figure 1 and Table 1): embryonic stem (ES) cells, induced pluripotent stem cells (iPSC), and adult tissue-specific stem cells, each with its relative advantages and disadvantages.

Embryonic stem cells

Stem cell biology began with embryonic stem cells. As is well known, the cells of the embryo are pluripotent, capable of specializing into the diverse range of cell types that comprise the human body. Once the oocyte is fertilized, it divides multiple times, giving rise to a blastula with an inner cell mass. These cells, if isolated and cultured, give rise to embryonic stem cells. Embryonic stem cells are pluripotent – they can be directed to

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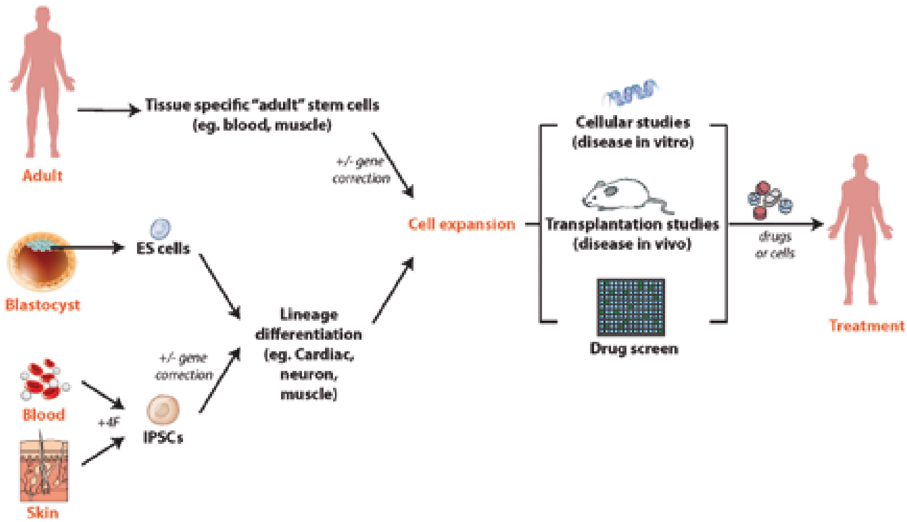

Figure 1. There are three main sources of human stem cells: adult tissue-specific stem cells, embryonic stem cells (ES), and induced pluripotent stem cells (iPSCs). Each source has distinct advantages and disadvantages.

	ES cells	**iPS cells**	**Adult Stem Cells**
Pro	– Unlimited cell source – Pluripotent – Easy to culture and maintain	– Unlimited cell source – Pluripotent – Patient-specific (in theory)-no immunologic problems	– Limited to small biopsy – Specialized – Patient-specific origin-no immunologic problems
Con	– Embryo destruction and ethical issues concerning egg donors – Potential for tumors – Difficult to direct--limited to fetal gene expression	– Genetic correction of patient mutation possible – Potential for tumors – Difficult to direct--limited to fetal gene expression	– Cell type restricted – Limited cell numbers – Hard to maintain in culture – Not present in all tissues

Table 1.

become any cell type in the body – for example skeletal muscle, cardiomyocytes, neurons or epidermal cells.

ES cells have distinct *advantages* (Blau and Daley, 2019) (Figure 1 and Table 1). They divide extensively, provide an almost unlimited cell source, and can be differentiated into almost any given cell type. The *challenges* of using ES cells are that they are obtained by dissociating the inner cell mass which involves destruction of the embryo created by in vitro fertilization. Accordingly, there are ethical concerns regarding exploitation of egg donors. Additionally, there are challenges to their use, as directing ES cells to become mature cell types is not readily achieved. Indeed, cells differentiated from ES cells usually express fetal genes, not adult genes, and there is an inherent risk of tumorgenicity, as the cells are often karyotypically unstable (Figure 2).

Plasticity of the differentiated state

I entered the field with a quest to discover if the differentiated state of a cell could be changed. In the 1980s, cells specialized for specific functions were thought to be stably and irreversibly committed. The dogma at the

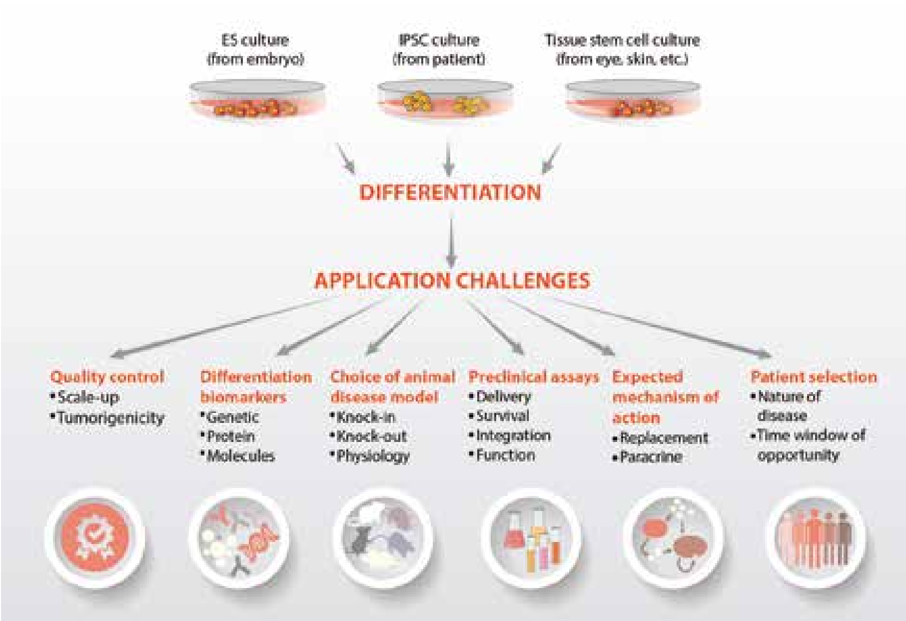

Figure 2. Challenges in the clinical use of stem cells.

time was that once a cell became a liver cell or a skin cell, that was its destiny. A cell's fate was thought to be fixed and set for life. I decided to challenge this premise and probe if specialized cells could be induced to change and adopt properties of other cell types. Specifically, I asked the question: is the destiny of a skin or liver cell terminal or is it reversible? Can it be changed? To address this, I devised a cell fusion system called a heterokaryon wherein multiple mouse muscle cells were fused with human liver cells (hepatocytes) to form a mixed species non-dividing syncytial cell (Figure 3). In this microenvironment, there was no loss of chromosomes and all genetic material remained stably intact. Such heterokaryons are advantageous over hybrid cells, dividing interspecies cell fusion products, in which genetic instability and chromosome loss are pervasive. The use of hybrids allowed genes to be mapped to chromosomes, but precluded conclusions as to whether de novo gene expression in mammalian cells resulted from the activity of activators or the loss of repressors, a question of major interest at the time. Using heterokaryons, Cecelia Webster, Choy Pik Chiu and Grace Pavlath showed that hepatocytes could be induced to express muscle genes that they would never normally express. Further, we found that this held true for a number of human differentiated cell types representative of all three embryonic lineages. We were able to show definitively that this occurred by transactivation, because all chromosomes remained stably intact and the human and mouse

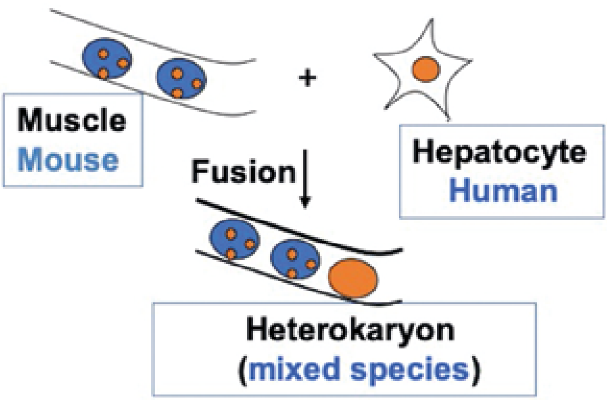

Figure 3. Plasticity of the differentiated state. Schematic of an experiment showing heterokaryons: stable fusion products of multinucleate mouse muscle cells and human hepatocytes with no chromosome loss or rearrangements. Heterokaryon experiments provided novel evidence that the reprogramming and activation of silent mammalian genes is possible and that the human differentiated state is not fixed and irreversible.

muscle gene products could be distinguished. Our experiments provided evidence that reprogramming of the nuclei of highly specialized human cells was possible and resulted in the activation of previously silent genes in specialized mammalian cells (Blau et al., 1983, 1985; Chiu and Blau, 1984). Our discovery provided early evidence that John Gurdon's elegant Nobel Prize winning nuclear reprogramming experiments in frogs had relevance to mammals. This demonstration of the "Plasticity of the Differentiated State" was highlighted in *Science* in the Frontiers in Biology issue for the year 1985 (Blau et al., 1985).

Other scientists were also addressing this question using different experimental paradigms. A particularly creative approach was developed by Nicole Le Douarin in Paris, reviewed in (Le Douarin and Dupin, 2016). She showed the plasticity of cells derived from the brain using a very elegant method for following and monitoring cell fate, wherein nuclei of quail cells transplanted into chickens could be distinguished microscopically. Her experiments revealed that neural crest cells are multipotent and change in response to alterations in their microenvironment in the developing avian embryo.

Induced pluripotent stem cells

A major breakthrough in the stem cell field was achieved by Shinya Yamanaka in 2006, which led to the development of an artificial pluripotent cell type, known as "induced pluripotent stem cell" (iPSC), an alternative to embryonic stem cells (Takahashi and Yamanaka, 2006). This discovery was transformative, as it enabled pluripotent cells to be obtained without sacrificing embryos. It also revolutionized the field by creating cells that could be envisioned, not only as sources for cell therapy, but also for studying the development of human disorders in vitro. iPSCs can be derived from a patient's readily accessible tissues: blood, urine, or skin. Yamanaka identified four transcription factors in a clever screen, that if overexpressed in such cells, converted them into pluripotent cells with features similar to ES cells and the potential to differentiate into essentially any differentiated cell type, as shown in Figure 1 and Table 1 and reviewed in (Blau and Daley, 2019). iPSCs are *advantageous,* as they comprise an unlimited cell source and are, in effect, immortal. iPSCs can be converted into diverse cell types such as beating cardiomyocytes or electrically coupled neurons, and if derived from a patient with a heritable disorder, will manifest features of the disease in culture. They enable experiments in which CRISPR-corrected controls have an identical genetic background and rescued mutation. iPSC, like ES cells, constitute an unlimited cell source for in vivo tissue replacement. In contrast to ES cells, if donor-derived, they can be immunologically matched to the patient, thereby avoiding immune rejection or lifelong immunosuppression. Obtaining the cells entails a simple basic procedure – obtaining blood, urine or a piece of skin. iPSCs afford an unprecedented opportunity to study human disease mechanisms in tissue culture and perform screens for drugs with therapeutic potential.

The *challenges* of using iPSC clinically are that, like embryonic cells, they are difficult to differentiate beyond the fetal stage of gene expression (Figure 2 and Table 1). They also have a tendency to be tumorigenic, as they characteristically express oncogenes, harbor an unstable chromosome composition, and have elongated telomeres. Thus, safety is a major barrier to their use in cell therapy. Additionally, it is difficult to scale up production, as rendering the quality control of the cells at a reasonable cost is an immense challenge. As a result, autologous cells, which would overcome immune mismatches, are currently impractical and the current focus of research is on generating non-autologous cell banks lacking major histocompatibility antigens in the hope that they will evade immune clearance.

As an example of "disease in a dish" using iPSC, I will draw on work from my own laboratory where we have been modeling heart failure due to Duchenne Muscular Dystrophy (DMD). DMD affects 1 in 3,600 boys and is due to a mutation in the gene encoding dystrophin, a large structural protein that connects the cytoskeleton with the extracellular matrix. We obtained blood cells from DMD patients, converted them to iPSC by overexpressing the four Yamanaka transcription factors with the help of collaborators at Stanford, and then differentiated them into contractile cardiomyocytes. A talented mechanical engineer, Gaspard Pardon, in my laboratory generated hydrogel patterns with an aspect ratio of 1:7, the typical dimensions of a cardiomyocyte in vivo. This causes the cardiomyocytes to align and form well-organized sarcomeres that aid in their maturation and contractile function. Additionally, using traction force microscopy, Gaspard was able to determine the contractile strength, based on displacement of fluorescent beads within the hydrogel (Figure 4). Video-microscopy and an analysis of Fourier transforms revealed contractile defects due to a single mutation in a gene encoding the contractile protein, dystrophin, on gels of a stiffness comparable to that of a fibrotic heart.

In 2013, Alessandra Sacco, Faye Mourkioti and Alex Chang in my laboratory made the unexpected discovery that telomeres are 50% shorter in the cardiomyocytes of DMD patient hearts relative to other cell types in

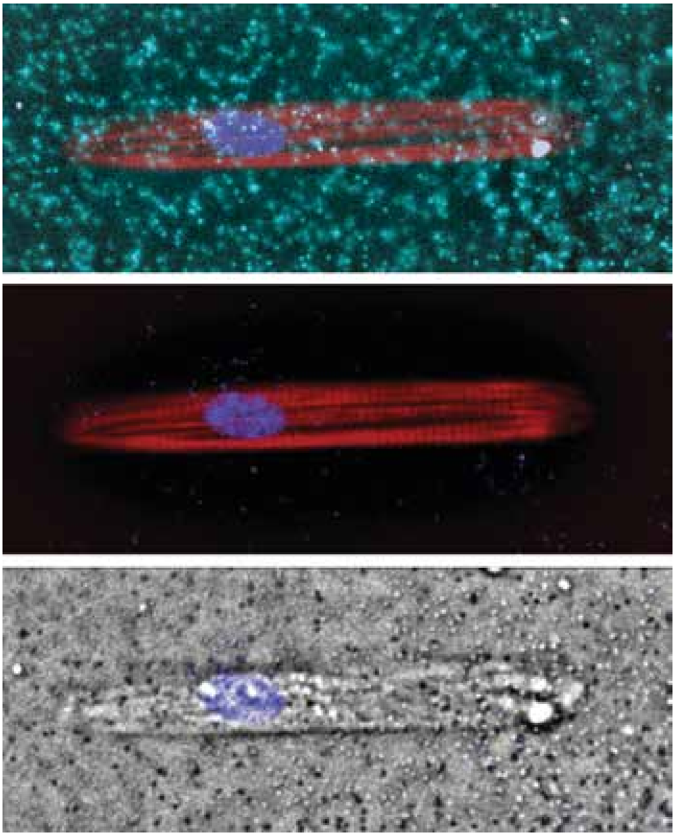

Figure 4. IPSC-derived cardiomyocytes grown on patterned hydrogels exhibit well-organized sarcomeres that generate force that can be measured by traction force microscopy. Images of a cardiomyocyte embedded in a hydrogel are shown. Fluorescent beads (top, cyan) enable visualization of the hydrogel and facilitate monitoring and quantification of cardiomyocyte contraction. The sarcomere, the contractile apparatus of the cell, is labeled red and the cell's nucleus is blue (middle). Brightfield image of the experimental setup (bottom). Contributed by Gaspard Pardon.

the same tissue, such as smooth muscle cells, which do not normally express dystrophin and are not affected by its absence. Telomeres are protective caps at the ends of chromosomes that shorten with aging – usually in the course of cell division. The mdx mouse, which lacks dystrophin like DMD patients, does not manifest the cardiomyopathy from which patients succumb. We reasoned that mice might be protected from cardiac failure by the length of their telomeres. When we bred the mice with mice lacking the RNA component of telomerase, they exhibited all of the features of DMD dilated cardiomyopathy, including early mortality due to heart failure (Chang et al., 2016; Mourkioti et al., 2013; Sacco et al., 2010). We can recapitulate the telomere shortening seen in the cardiomyocytes of mouse and in DMD cardiac tissues in the cardiomyocytes differentiated from DMD patient-derived iPSC. The telomeres or iPSC are uniformly long, whether derived from DMD patients or normal controls. Upon differentiation, the telomeres progressively shorten (Chang et al., 2018). We have now determined that a similar telomere attrition is characteristic of both tissue cardiomyocytes and iPSC-derived cardiomyocytes from patients who succumbed from dilated cardiomyopathy due, not only to dystrophin deficiency, but also to troponinT or titin deficiencies(Chang et al., 2018). Remarkably, this telomere shortening occurs independent of cell division in differentiated cardiomyocytes, recapitulating 30 years of life in 30 days in culture. This modeling of "disease in a dish" now enables elucidation of the cause and effect and the underlying molecular mechanisms by which replication-independent telomere attrition occurs, in a manner not previously possible. To date we have found that a DNA damage response is induced by contraction in the absence of a crucial contractile protein, which in turn leads to increased reactive oxygen species (ROS) and mitochondrial failure, culminating in cardiomyocyte death. Tests of interventions that could arrest telomere shortening and serve as a therapeutic intervention are now currently underway in my laboratory. This example highlights the potential for the human iPSC model system to provide fundamental insights into human diseases and serve as a potent platform for drug discovery.

Applications of ES cells and iPSC to the treatment of disease

A major cause of blindness with aging is age-related macular degeneration (AMD), of which the dry form comprises 90% of cases and is associated with loss of vision (Figure 5). ES or iPSC are being used to regenerate the lost retinal pigment epithelial cells (RPE). ES or iPSC are differentiated to RPE and transplanted as a suspension or sheet just below the photoreceptor layer of the eye, which they support. Although not as advanced as corneal transplants, several studies suggest substantial promise for restoring sight to individuals with AMD (Stern et al., 2018) (da Cruz et al., 2018)(Davis et al., 2017)(Song et al., 2015) (Mandai et al., 2017) There are still challenges to overcome, as one clinical trial was halted in Japan due to the acquisition by iPSC of potentially oncogenic mutations (Garber, 2015; Merkle et al., 2017).

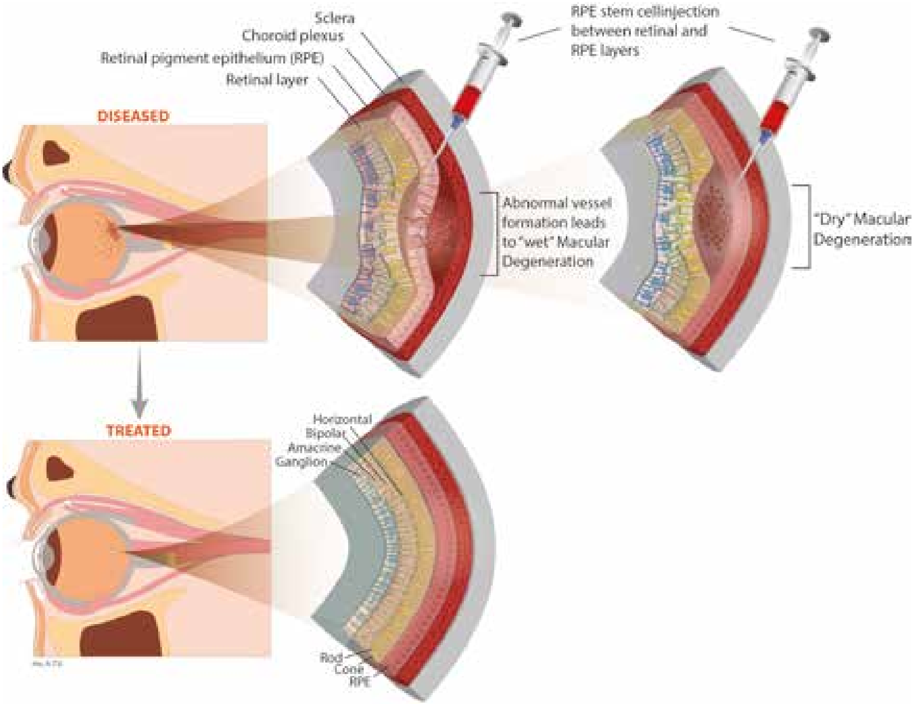

Figure 5. Regeneration of the retinal pigment epithelium (RPE) that supports the photoreceptors of the eye and is lost due to age-related macular degeneration (AMD) is possible with ES or IPSC-derived RPE.

Applications of tissue-specific stem cells in the treatment of disease

Significant therapeutic advances have been achieved using adult tissue-specific stem cells – the third stem cell type (Figure 1). These are stem cells that reside in tissues like muscle, skin or blood and are dedicated to replacing those tissues throughout life. These stem cells spring into action upon injury, proliferate and regenerate the damaged tissue. They constitute a cell source for isolation, cultivation, and transplantation, serving as a cell therapeutic. Additionally, a major focus is to identify drugs that stimulate and rejuvenate the function of the endogenous tissue-resident stem cells, enlisting them in tissue replenishment, for example in aging.

A striking therapeutic success entails regeneration of the cornea following physical damage or chemical burn. The injured cornea becomes opaque, leading to loss of vision. When limbal cells, the stem cells that give rise to the cornea, are isolated from a 1-2 mm biopsy taken from the unaffected cornea of the other eye, minced and directly injected or cultured on a hydrogel contact lens and implanted into the damaged eye, sight is restored (Hirsch et al., 2017) (Hayashi et al., 2016)(Shukla et al., 2019) (Rama et al., 2010) (Figure 6).

Another landmark example of a successful stem cell therapy was achieved for a disorder of skin, entailing the bodywide replacement of 80% of the epidermal layer of a 7-year old boy. de Luca and colleagues in Modena, Italy, identified the quintessential stem cell for the epidermis, the holoclone, and showed that it was capable of longterm tissue reconstitution, enabling a boy with a severe rare genetic skin blistering disease, Epidermolysis Bullosa (EBD) to assume a normal life. EBD is due to the absence of a crucial extracellular matrix protein encoded by one of 18 genes, a laminin or collagen, that is integral to skin function and if missing results in chronic skin erosions and ulcers (Figure 7). Affected children typically live in the hospital and die at a young age, as minor injuries or fric-

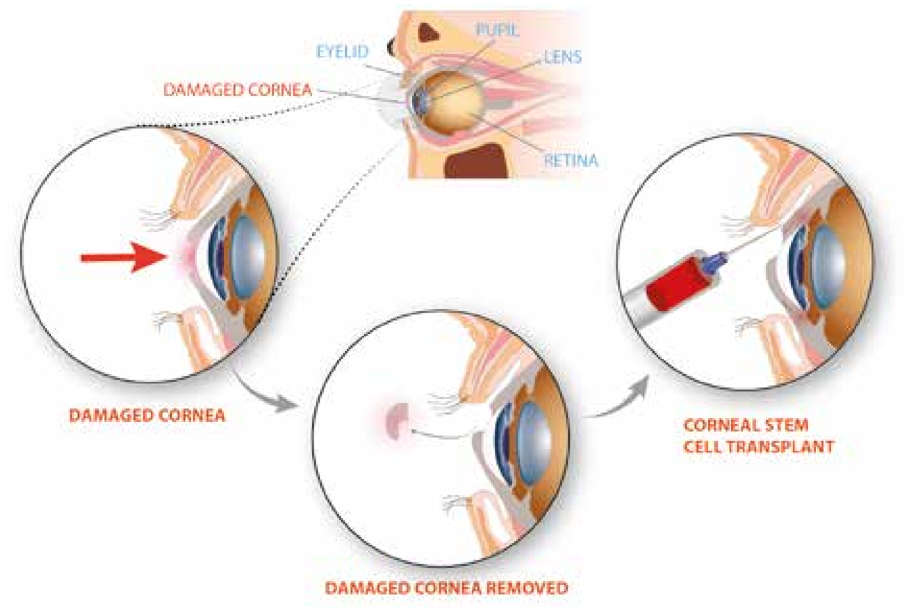

Figure 6. Replacement of corneal tissue subjected to physical or chemical damage can be achieved by transplantation of limbal tissue-specific stem cells from the unaffected eye.

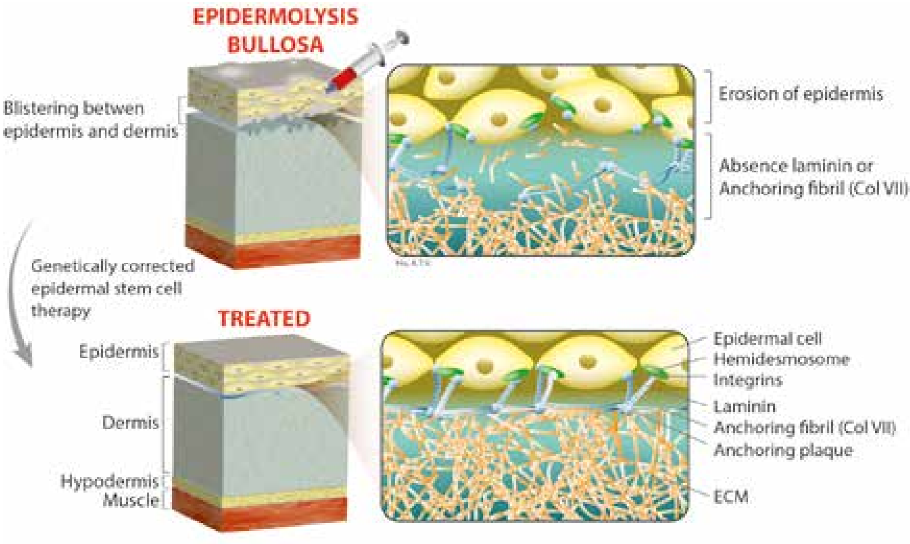

Figure 7. 80% of the epidermis of a boy with a rare heritable highly disabling blistering disorder, Epidermolysis Bullosa, was replaced longterm by transplanting the boy's genetically corrected tissue-specific stem cells (holoclones), allowing the boy to assume a normal life.

tion yields blisters that readily become infected. Holoclones were isolated from an unaffected region of the boy's body and engineered to express the gene encoding the missing protein, a laminin, and then transplanted to cover all affected skin regions (Hirsch et al., 2017). Three years later, this child is playing soccer. During this period, it is estimated that the epidermis underwent approximately 30 cycles of self-renewal. This success highlights the need to characterize the true tissue-specific stem cell with longterm self-renewal and differentiation potential, a major challenge in the adult stem cell field. Although this is now known to be a holoclone in the case of skin and cornea, the identification of specific cell surface markers enabling prospective isolation of the stem cells by fluorescence activated cell sorting has yet to be achieved. Notably, in some cases, such as the heart, the very existence of a tissue-specific stem cell remains in question, despite claims to the contrary.

In my laboratory, we focus on skeletal muscle stem cells (Figure 8). 40% of the body mass is muscle and with age muscles atrophy and become weaker, compromising quality of life, leading to an increasing incidence of

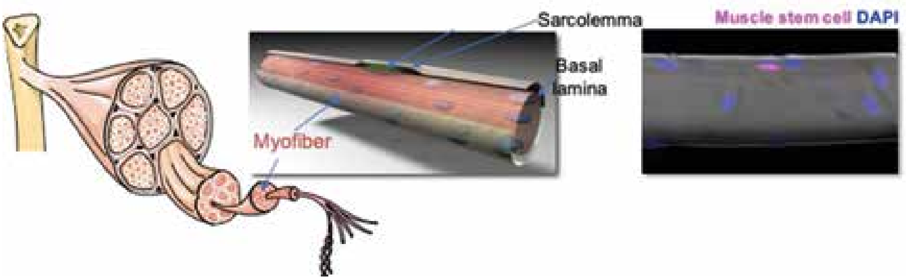

Figure 8. Muscle stem cells (satellite cells) that reside in niches along the length of the myofiber, can be envisioned as a cell therapeutic to treat a wide variety of muscle-related disorders, such as muscular dystrophies. An alternative strategy entails identification of drugs to activate and rejuvenate endogenous tissue-resident stem cells to treat disorders such as sarcopenia, progressive muscle wasting with aging.

falls, loss of mobility, and an associated increase in morbidity. The muscle stem cells, known as satellite cells, reside in a membrane-enclosed niche juxtaposed to the myofiber. They express the hallmark transcription factor, Pax7. In response to injury, these cells become activated, divide and become committed progenitors that fuse into the muscle fibers and restore muscle strength. Alessandra Sacco in my laboratory defined cell surface markers that enable the prospective isolation of muscle stem cells (MuSCs) capable of self-renewal, engraftment and differentiation, as we showed by using single-cell transplants monitored by dynamic bioluminescence imaging (Sacco et al., 2010). We encountered a problem in their further study, as the stem cell properties were rapidly lost when isolated MuSCs were grown on tissue culture plastic. By fabricating hydrogels with an elasticity mimicking the muscle tissue, Penney Gilbert and Karen Havenstrite were able to overcome this limitation and maintain the stem cell state of MuSCs (Gilbert et al., 2010), enabling experiments not previously possible. We identified intrinsic regulators that become dysfunctional with aging, including the acquisition of phosphorylated p38 MAP kinase. Ben Cosgrove showed that by inhibiting this kinase with a small molecule drug in aged MuSCs grown on elastic hydrogels, we could rejuvenate the function of the aged MuSC population and restore strength upon transplantation into injured muscles (Cosgrove et al., 2014). We sought to discover an extrinsic regulator of MuSC function that could target and augment the function of the stem cells in situ. Since the first response to wound healing is an inflammatory response, Andrew Ho and Adelaida Palla performed an in silico screen, a bioinformatics analysis, of the transcriptome of activated MuSCs and identified the EP4 receptor on the surface of the stem cell. EP4 is the receptor for prostaglandin E2. We found that a transient 24-hour exposure to PGE2 led to a robust increase in muscle stem cell numbers a week later (Ho et al., 2017). A timelapse microscopy analysis revealed that PGE2 acts as a potent mitogen and pro-survival metabolite. This signaling pathway is essential to the function of MuSCs, as if the EP4 receptor is genetically ablated on MuSCs in mice, they lose strength post-injury. In addition, if the natural synthesis of PGE2 is blocked by giving mice a non-steroidal anti-inflammatory agent, like ibuprofen, strength drops by 50% post-injury. A major focus in my laboratory now is to capitalize on this natural wound healing regenerative response to determine if we can rejuvenate muscle stem cell function, counter muscle atrophy, increase strength, and increase quality of life of the elderly.

Although challenges remain, the promise of stem cells for regenerative medicine is beginning to be realized (Blau and Daley, 2019). Stem cell therapeutics are now in clinical trials for two major disorders of vision, age-related macular degeneration and corneal damage. In addition, the epidermal layer of the skin can be effectively regenerated longterm. Efforts to identify the stem cell that regenerates the dermal skin layer are underway and essential for the treatment of burn victims, as both the epidermis and dermis are damaged. Treatment of Type I diabetes is in clinical trials using ES- or iPSC-derived pancreatic beta-cell progenitors, cleverly encapsulated to evade the immune response, while allowing diffusion of glucose into and secretion of insulin out of the capsule. Advances in the differentiation of dopaminergic cells and their integration into the host striatum of the brain has reduced symptoms of Parkinson's disease in primates. The derivation of engraftable hematopoietic stem cells represents an as yet unattained holy grail for addressing the immense need for blood transfusion due to accidents or disease, as allogeneic bone marrow transplants are associated with a high risk of death. The loss of heart muscle, most commonly through myocardial infarction is life-threatening, and constitutes perhaps the most daunting challenge of electrical and mechanical integration. Nonetheless, the hurdles facing stem cells and their use in the treatment of disease are likely to be surmounted with regenerative medicine assuming an ever-increasing role in the therapeutic armamentarium.

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The Role of Microscopy in Improving the Human Condition

Robert Eric Betzig

Thank you for the opportunity to be with you today. The optical microscope was developed early in the 17th century and, after 50 years of improvement, microscopists such as Hooke and Van Leeuwenhoek were opening up an entire new micro world of living systems, beyond the ability of what the naked eye could see. Microscopes steadily improved until the end of the 19th Century through, oftentimes, with fits and starts and a lack of reproducibility. Then, in the 19th century, a microscope manufacturer named Carl Zeiss teamed up with physicist Ernst Abbe and chemist Otto Schott to make a science of microscopy. Together they figured out exactly how images are formed in the microscope and how to create lenses to optimize these. One of the consequences of their work was that Abbe discovered that there was a fundamental limit to the smallest object you could resolve in an optical microscope, which was half the wavelength of light. Because they were able to make a reproducible scientific instrument, optical microscopy became ubiquitous in the 20th Century. In fact, it is so ubiquitous today that if you did the deletion test and erased optical microscopes, there's no branch of science and technology that would not be impacted by their absence. However, because they attained the predicted resolution of the microscope at the end of the 19th Century, in some ways the technology stagnated, so that the microscope you could buy from Zeiss in 1880 was really not all that different from the microscope you could buy from them in 1980. There were additional contrast mechanisms and better light sources and such, but it was basically the same instrument.

As a result, in the 20th Century, it was the developing fields of Biochemistry and Molecular Biology that became predominant. In fact, they've been so successful that today most biologists have a worldview where they look at living systems through the eyes of biochemistry or molecular biology. But that started to change, starting around 1980, thanks to a series of unrelated technical innovations. The first was the transistor, which led to the personal computer, so that you could control microscopes automatically. It also led to semiconductor cameras that could detect light very efficiently in digital images, and these could be processed and analyzed by computers. The next innovation was immunofluorescence technologies where, instead of seeing ghost-like images in black and white of cells, you could illuminate any one of the tens of thousands of different types of proteins specifically, and see them individually. That had another big boost in the 90s, with the development of fluorescent proteins, where you could coax live cells to produce their own fluorescent labels. The third was a development of lasers, which allowed us to illuminate these fluorophores very precisely and sculpt their light in different ways in space and time to create new microscopes.

As a result, by stirring these technologies together in different ways, there has been a Cambrian explosion of microscopy technology since the 80s, first with the confocal microscope, then spinning disk confocal microscopes that look at live cells, two-photon microscopes that look in scattering tissue, super-resolution microscopes, like the ones I developed, that see beyond Abbe's limit, light sheet microscopes that can look at 3D dynamics, and adaptive optical microscopes that can look into aberrating multicellular tissues.

What these microscopes have revealed is that the cell is incredibly complex and incredibly dynamic and, if you don't take into consideration the fact that it's the dynamism that defines life, you are missing a critically important aspect of what's going on.

I'll give you a couple examples of that. First (Figure 1A), using a super resolution technique that I had a hand in developing, one of our collaborators looked at the Huntingtin protein, which is involved in Huntington's disease. Here you see the nuclei of two live cells. The one on the left with the normal or "wild-type" form of the Huntington protein, creates only very small, intransient aggregates, but when you have the glutamine repeat of the mutation in the disease, you get these large aggregates in the nucleus.

Now, people have known about these aggregates for a long time, but by imaging in a second color our collaborators were able to show that individual transcription factor molecules get bound up in within the aggregates like they're caught in quicksand. This suggests a previously unconsidered possibility that the capturing of these molecules may lead downstream to the underproduction of certain important proteins critical to normal cell metabolism, because the transcription factors can never get to the DNA to produce the necessary RNA to produce these proteins. Thus, a new possible avenue of attack on the disease was found that would be hard to discover without the sort of direct imaging done here.

In a second example (Figure 1B), the textbook picture of a cell shows its key components, or organelles, such as its mitochondria and endoplas-

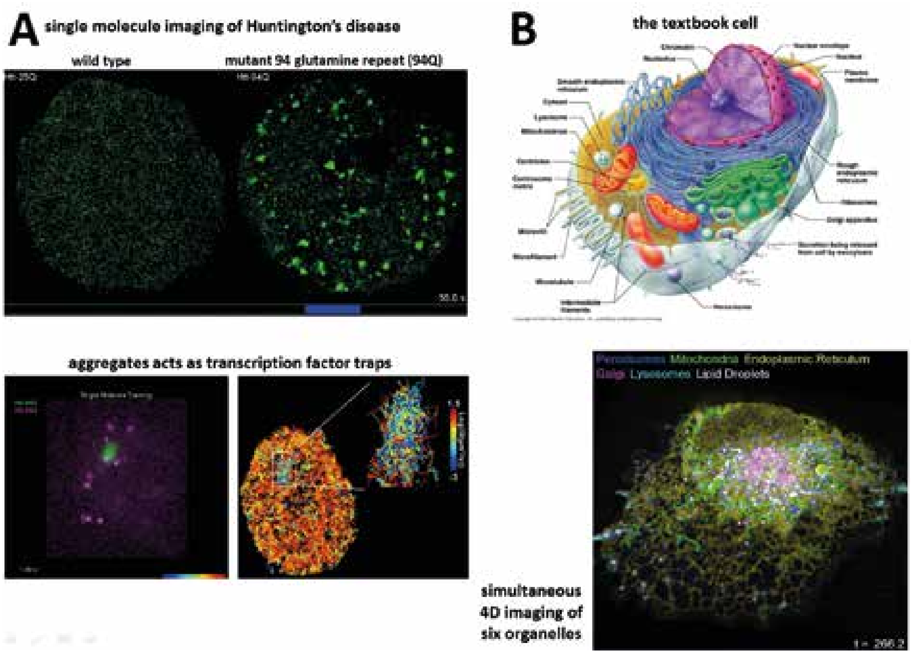

Figure 1. Surprises in Live Cell Imaging. A) Protein aggregates (green) in Huntington's disease trap transcription factor molecules (purple) needed for the normal, physiological operation of neurons. B) Subcellular compartments called organelles do not operate in isolation, but rather are in constant mutual interaction with one another.

mic reticulum (ER), as independent bodies floating passively within the cytoplasm. The reality is not like that at all. Using a high-speed super-resolution method known as structured illumination microscopy, we found that the microtubule cytoskeleton constantly remodels the ER, sometimes under the influence of protein-degrading lysosomes that track along the microtubules like railway cars and push the ER around. Similarly, when we looked at a cell with six labeled organelles using yet another microscope that excels at imaging dynamics in three dimensions, we found that contacts between organelles are ubiquitous. In particular, contacts between mitochondria and the endoplasmic reticulum act as organizing centers for other organelles to come and dock temporarily for biochemical reactions. So the cell isn't a bunch of individual isolated components, but rather a bunch of constantly interacting components with transient interactions happening everywhere which are essential to its function.

The problem with the techniques I've shown so far is that they look at cells in isolation. However, biologists know that the appearance, or phenotypes, that we observe are the result of gene expression, and gene expression is influenced by the local environment. Therefore, when we look at cells on a coverslip, we're far removed from the multicellular environment where they evolved, and we can expect them to look and act different than they do in whole organisms. In order to see them in their true physiological, multicellular context, we've borrowed the technique of adaptive optics from astronomers, which we use to cancel the optical aberrations present in multicellular systems to be able to study their dynamism in vivo with full, unperturbed resolution. For example, we can follow the complex movements of an immune cell as it migrates through the inner ear of a fish. In your body you have 37 trillion cells all undergoing that type of choreography at the same time. Furthermore, inside each one of those cells, several billion protein molecules are stochastically buzzing around and interacting in a way similar to that I showed in the Huntington's example earlier. Inside each human body there is an entire universe of complexity, and inside the collective brains of all of humanity there are more synapses than there are stars in the universe. The most complex matter in the known universe is us.

The upshot is that we've made remarkable progress in the past thirty years in developing microscopes that allow us to see and understand living systems in ways we've never been able to before. The bad news is that it remains a herculean task to make these microscopes accessible. That's true not only for the advanced microscopes I've introduced here, but also the simplest microscopes that have been around for decades – microscopes that could have an impact in third world countries, particularly for the diagnosis and treatment of infectious diseases.

Here (Figure 2) you see examples of some of these diseases, which afflict many millions of people every year. Often you can identify them directly by the outward phenotypic changes they induce to the appearance of the afflicted, but if you want to understand what specific infective strains are involved, the degree of infectious progression, and the efficacy of treatment, access to basic microscopy would be a huge help. That's routine in developed countries with the extensive resources they have. Several groups, particularly over the last decade, have taken on the challenge of making extremely inexpensive microscopes to make them broadly accessible in the third world. The Foldscope, for example, from Manu Prakash at Stanford, is less than a dollar. It's very much like Van Leeuwenhoek's old microscope

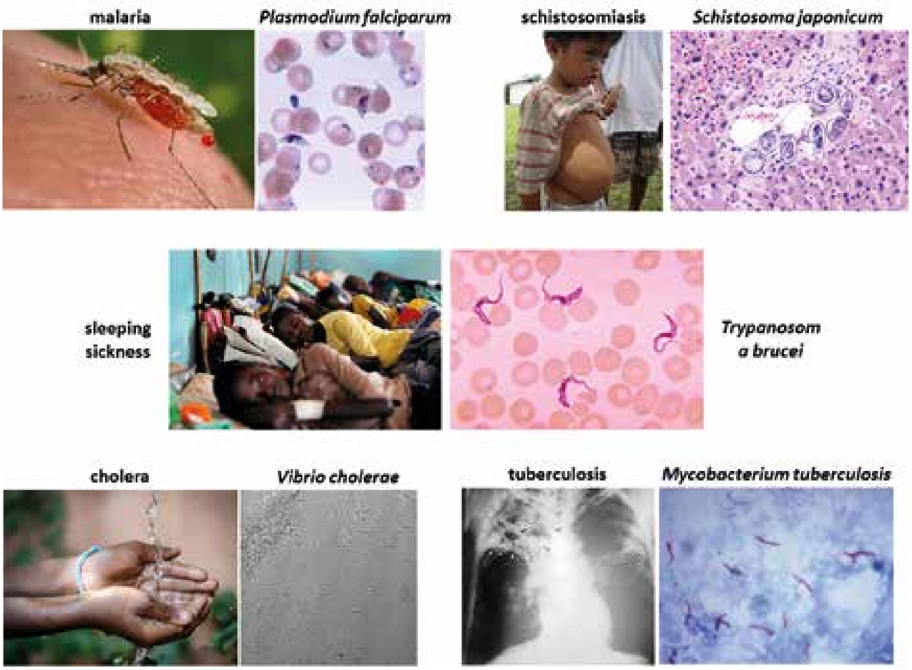

Figure 2. Infectious diseases and the microorganisms that cause them.

hundreds of years ago. Nevertheless, there are many problems other than just cost that have limited the impact of such efforts, such as surrounding technical infrastructure, training, and resistance to seek treatment. I think these problems are solvable, but they require a concerted effort by a number of different communities.

At the other end of the technological spectrum, we have an analogous problem with the adoption of the microscopes we make. While they're very powerful and can routinely reveal biological processes never seen before, they're also very complex and expensive. We want them to be in the hands of many biologists, but there are very few optical engineers in the world who can build them, and the overlap between these two groups is even smaller. With our lattice light sheet microscope, we've worked very hard to try disseminate the technology to others, but while we've sent detailed plans to ~90 groups and offer significant support on top of that, so far only ~ 20 are operational in four years of effort. Ultimately, the only way biologists are going to broadly adopt these technologies is if they can be commercialized and made turnkey. You heard from Helen Blau's talk that biologists have many, many other things to worry about than whether their microscope is working properly, so they need something that is easy to use and works routinely. To do that, you need market forces to provide the incentive to invest in the necessary product development and thereby cross the common valley of death between a research idea and a commercialized product. This usually becomes a chicken-and-egg problem, because companies aren't going to invest the money to make these microscopes until they know there's a sizable market for them, and biologists won't tell them there's a market until there's a useful microscope for them to work with. To get around this problem, at Janelia we founded an Advanced Imaging Center where we have a suite of pre-commercial microscopes we've developed, which we offer free for use to visitors from around the world. This has been very successful, and in a couple of instances it's been enough to get a couple of these microscope technologies into the commercial pipeline.

Beyond that, we face other problems as microscope developers. Just as you can't build a car that can take the kids to daycare on Friday and then win at the Indianapolis Speedway on Sunday, you can't build one microscope that can do everything. Microscopes have to differentiate. That's a problem, because, if you have an imaging core for biologists, that means they need to have many microscopes of different types there and they don't know which one the biologists are going to need on any given day. As a result, most of them are underutilized. The final project I've been working on at Janelia is to make a Swiss Army knife microscope that takes almost all of those technologies I've told you about, and puts them in one four-foot by four-foot box. We worked hard to design the microscope to be affordable and exhaustively documented and, while initially it will again only attract the small subset of people with the skills to both build it and use it, hopefully the ideas within it will eventually hit the commercial sphere. At that point, imaging cores could have a suite of identical microscopes, where the operator could push a button to reconfigure the system to whatever mode of microscopy works best for any particular biological user.

Yet another problem created by our microscopes is that they can produce terabytes of data per hour. We have one paper that was just accepted that includes nearly a petabyte (one million gigabytes) of data. Most scientists do not have access to the computational resources needed to extract biological meaning from data at this scale. You can create beautiful movies of animated cells, but you're not going to gain a detailed understanding of transient interactions happening across the cell over a wide range of spatial and temporal scales without massive computational resources. I've recently moved to Berkeley and we're trying to attack this problem with a new Advanced Bioimaging Center, modeled after the Center we founded at Janelia, but with a much greater emphasis on developing open-source algorithms so that scientists can get quantitative biological insights from the massive data sets these microscopes produce.

To conclude, as a physicist I come to biology as an outsider. Modern biology reminds me of the old parable of the blind men and the elephant: when you're trying to understand living things, the molecular biologists are holding the tail, the biochemists are holding the trunk and perceive something different, and the structural biologists are hanging onto an ear and sense a third thing. The thing that defines life is that it's animate, so the only way we're really going to understand life is to understand dynamic interactions, which is what modern optical microscopy brings to the table. It may never reveal the whole elephant, but at least we can hold another part of it to understand biology in a new way.

Thank you.

The CRISPR-Cas Technique for Human Gene Editing and its Impact on Society

Rafael Vicuña

From time to time, the biological sciences undergo a technological breakthrough. Examples of this type of innovation in recent decades are the advent of the recombinant DNA techniques, the cloning of the first mammal from adult cells, the establishment of the first cultures of stem cells derived from human blastocysts and the generation of induced pluripotent stem cells from adult cells.

These advances have given rise to active debates that have transcended the scientific community. The most frequent concerns have been the bioethical implications of the use of the novel technologies with humans and their possible impact on the environment. The media, both written and visual, disseminate these breakthroughs to the general public, sometimes with fruitful creativity and imagination. In turn, scientists normally take the initiative in convening committees and proposing guidelines for the proper application of the new technologies. A paradigmatic case of this type of response was the Asilomar conference in 1975. Noteworthily, this Pontifical Academy has played a leading role organizing workshops on topics such as GMOs and stem cells, publishing statements with conclusions and recommendations. On the other hand, governments dictate public policies to assure safety benefits to society. For example, there are regulations for genetically modified crops issued by the FDA and the European Commission. The protocols for human gene therapy and the use of human embryonic stem cells are also subject to strict oversight. The challenge for the regulatory agencies is to respond in due time with guidelines that are supported on solid scientific evidence.

We are now witnessing another breakthrough that seems to surpass the traditional recombinant DNA techniques in terms of versatility and accuracy, namely, the so-called CRISPR-Cas technology. CRISPR is an acronym for Clustered Regularly Interspaced Short Palindromic Repeats. These correspond to DNA sequences in bacteria and archaea that, in conjunction with Cas (CRISPR-associated) proteins, participate in the recognition and elimination of invading foreign DNA species, thus acting as an adaptive immune system. In particular, the CRIPR-Cas9 system offers a simple procedure for introducing various modifications at targeted loci in all kinds of living cells. This system relies on base complementarity between an engineered guide RNA and a specific DNA sequence in the genome, followed by double strand cleavage by Cas9. The double strand breaks are later repaired by one of several pathways that may lead to gene mutation or replacement.

Recent developments have allowed the expansion of the genome-editing repertoire of the CRISPR-Cas system. These include modification of the guide RNA to improve recognition specificity, amendment of the Cas9 enzyme to create new docking sites in the genome and deactivation of the nuclease activity of the Cas protein. A nuclease deficient Cas enzyme can be fused to another enzyme to correct a mutant base or to introduce nonsense mutations at selected sites, without cleaving the genome.

Both social media and the scientific community reacted very quickly upon the advent of the CRIPR-Cas technology. Their main apprehension is the possibility of editing the human germ line,[1] either for therapeutic or enhancement purposes. The scientific community has taken several initiatives, consisting mainly in deliberations comprising both scientific and bioethical arguments, while at the same time encouraging further scientific research. A milestone in these actions was a meeting held in Napa, California, in January of 2015, which is reminiscent of the Asilomar meeting. Convened by the Innovative Genomics Institute,[2] the group released a statement in which, among other recommendations, it proposed not to conduct germline genome modification, at least for the moment. A similar conclusion was reached at the First International Summit on Human Gene editing, convened in Washington DC in December of 2015 by the U.S. National Academies of Sciences and Medicine, the Chinese Academy of Sciences and the Royal Society. The second version of this meeting will take place in Hong Kong later this month.

A voluntary moratorium as an effective way to discourage human germline modification has been supported by several scientists. For example, Edward Lanphier and four colleagues have argued that heritable human genetic modifications pose serious risks and the therapeutic benefits

[1] Early-stage embryos, eggs, sperm and the cells that give rise to them.

[2] Academic partnership between UC Berkeley and UCSF whose mission is to develop and deploy genome engineering to cure disease, ensure food security and sustain the environment for current and future generations.

are tenuous.[3] The NIH, for its part, has announced that, although it will continue to support a wide range of innovations in biomedical research, it will not fund any use of gene editing technologies in human embryos.

However, there are some disagreements among scientists, as illustrated with these headlines taken from *Nature* magazine. Thus, Henry Miller from Stanford University claims that germline gene therapy should be used sparingly and with scrutiny, pushing the frontiers of medicine to rid families of monstrous genetic diseases.[4] In a similar stance, geneticist George Church argues that banning human germline editing could put a damper on the best medical research, driving the practice underground.[5] In a more cautious position, Jennifer Doudna, a prominent leader in the field, calls for urgent ethical discussions and avers that a complete ban is impractical given the ease of use of the technique.[6]

In view of these disputes, it may be worthwhile to find out what science academies and societies have said in this respect. I have selected two of them based on their ample representativeness. According to the US National Research Council,[7] the ethical norms and regulatory regimes developed for somatic cell therapy are appropriate for the management of somatic genome-editing applications. In the case of germline editing for therapeutic purposes, research trials might be permitted, but only following much more research and, even then, only for compelling reasons and under strict oversight. In contrast, genome editing for enhancement should not proceed at this time, and public discussions should precede any decisions about such applications. On the other hand, The European Society of Human Reproduction and Embryology and the European Society of Human Genetics released a joint report asserting that although clinical germline gene editing would be totally premature, it might become a responsible intervention in the future, but only after adequate preclinical research conducted under societal oversight. It adds that the present prohibition in Europe[8] of germline modification needs renewed discussion among relevant stakeholders.

[3] Lanphier, E. *et al.*, Don't edit the human germ line. *Nature* 519, 410.411, 2015.

[4] Miller, H. Germline Gene Therapy: Don't let good intentions spawn bad policy. *Issues in Science and Technology*, Volume XXXII (3), Spring 2016.

[5] Church, G. Encourage the innovators. *Nature* 528, S5, 2015.

[6] Doudna, J. Embryo editing needs scrutiny. *Nature* 528, S6, 2015.

[7] The USA National Academies of Sciences, Engineering and Medicine.

[8] Clinical Trials Regulation EU N° 536/2014, article 90.

In the meantime, while these deliberations have been taking place, some research centers have dared to take the first steps. One would have thought that since somatic gene therapy offers much less bioethical apprehensions than germline gene editing, the first attempts would be directed to treat or prevent disease in infants and adults. Indeed, Companies such as Editas Medicine, CRISPR Therapeutics and Intellia Therapeutics, as well as research groups at various universities, are engaged in programs aimed at treating patients suffering from different diseases. To my knowledge, there are no publications in the scientific literature reporting actual trials. There is only a very short note that appeared in *Nature* describing the treatment of a cancer patient in Chengdu, China, and a report in the Wall Street Journal earlier this year noting that there are presently in China 86 cancer or HIV patients being treated using the CRISPR-Cas technology.

In contrast, scientific journals disclose that gene editing in human embryos is an active area of research, especially in China. To date, experiments have been intended to test the efficacy of the technique rather than to establish pregnancies by transferring the modified embryos. The first report appeared in 2015,[9] implying that experimentation started as soon as the CRISPR-Cas technique was harnessed for genome editing in eukaryotic cells.[10] Early results obtained in this work and a couple of subsequent attempts[11,12] revealed several non-targeted gene modification events, as well as mosaicism when the embryos were allowed to further develop *in vitro*. The protocols applied in subsequent instances were aimed primarily at overcoming these flaws.

One of them involved the simultaneous injection into oocytes of sperm plus the editing components.[13] This particular work, conducted by Shoukhrat Mitalipov's team in the USA,[14] resulted in more efficient ed-

[9] Liand, P. *et al.*, CRISPR/Cas-mediated gene editing in human tripronuclear zygotes. *Protein Cell* 6, 363-372, 2015.

[10] Cong, L. *et al.*, Multiplex genome engineering using CRISPR/Cas systems. *Science* 339, 819-823, 2013.

[11] Kang, X. *et al.*, Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. *J. Assist. Reprod. Genet.* 33, 581-588, 2016.

[12] Tang, L. *et al.*, CRISPR/Cas-mediated gene editing in human zygotes using Cas9 protein. *Mol. Genet. Genomics* 292, 525-533, 2017.

[13] Ma, H. *et al.*, Correction of a pathogenic gene mutation in human embryos. *Nature* 548, 413-419, 2017.

[14] Oregon Health & Science University.

iting, although the interpretation of the results was openly debated by another group. In turn, a report by Junjiu Huang's group from Guangzhou, China, deals with the amendment of the mutation responsible for thalassemia, a 'recessive' disease that is caused by having two faulty copies of a gene.[15] Because it would be difficult to find dozens of embryos that have this rare double mutation, the team developed embryonic clones from their patient's skin cells. There is also a publication by a British team in which, rather than targeting a disease, they investigate the function of the pluripotency transcription factor OCT4 during human embryogenesis.[16]

The CRISPR-Cas technique exhibits some improvements, but it is still far from reaching a safety stage that would permit the transfer of the modified embryos, or even its application in adult gene therapy. For example, it has recently been shown that cleavage of the DNA by Cas nuclease induces the p53-mediated DNA damage response leading to a selection against cells with a functional p53 pathway.[17,18] The authors showed that inhibiting DNA damage signaling improves the efficiency of editing in normal cells. However, inhibition of p53 leaves the cell transiently vulnerable to the introduction of chromosomal rearrangements and other tumorigenic mutations. In addition, work conducted with mouse and human cells has shown that CRISPR/Cas editing leads to large deletions and complex rearrangements both at target and distal sites.[19] Still another setback to be solved, at least in protocols aimed at somatic gene therapy, is the identification in humans of pre-existing immunity to Cas9 proteins.[20] It is for reasons such as these that *The New York Times* felt compelled to publish an extensive article cautioning about the present limitations of the CRISPR-Cas technology.[21]

It is likely that several features of CRISPR-Cas are still unknown to us.

[15] Liang, P. *et al.*, Correction of b-thalassemia mutant by base editor in human embryos. *Protein Cell* 8, 811-822, 2017.

[16] Fogarty, N.M.E. *et al.*, Genome editing reveals a role for OCT4 in human embryogenesis. *Nature* 550, 67-73, 2017.

[17] Haapaniemi, E. *et al.*, CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. *Nature Med*. 24, 927-930, 2018.

[18] Ihry, R.J. *et al.*, p53 inhibits CRISPR-Cas9 engineering in human pluripotent stem cells. *Nature Med* 24, 939-946, 2018.

[19] Kosicki, M. *et al.*, Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnol*. 36, 765-771, 2018.

[20] In the form of both anti-Cas9 antibodies and T-cells: Porteus *et al.*, bioRxiv preprint first posted online Jan. 5, 2018; doi: http://dx.doi.org/10.1101/243345

[21] Zimmer, C.A. Crispr conundrum: How cells fend off gene editing. *New York Times*, June 12, 2018.

Hence, it would be advisable for the moment to moderate expectations and proceed with caution, especially when it comes to extrapolating the results obtained in the lab to the treatment of adult patients or human embryos. In particular, human embryo editing constitutes a clear example of science advancing faster than ethical reflection and legislation, with the further complication that due to different views regarding the moral status of the human embryo, general agreements are difficult to reach. More than ever before, the scientific community should be aware of its great responsibility in guiding society in safeguarding human dignity.

Wnt Signaling as a Regulator of Cellular Endocytosis and Protein Stability

Edward M. De Robertis, Nydia Tejeda-Muñoz and Lauren Albrecht[1]

Introduction

Protein degradation plays a key role in cellular homeostasis. The topic of how cellular components are turned over has been one of great interest to members of the Pontifical Academy of Sciences. Academician Christian De Duve discovered that membrane proteins and external nutrients acquired through endocytosis are digested in acidic vesicular organelles called lysosomes (De Duve and Wattiaux, 1966). Cytosolic proteins are mostly degraded in proteasomes, which consist of cytosolic cysteine proteases. Proteins are targeted to proteasomes after being modified by a small 76 amino acid protein called ubiquitin (Ciechanover, 2005). When a protein is marked by a chain of ubiquitin molecules, called Lysine-48-linked polyubiquitin, it was thought to be invariably degraded in proteasomes. Ubiquitin is also involved in the targeting of membrane proteins for trafficking into lysosomes either by addition of a monoubiquitin or of Lys63-linked polyubiquitin. I had the privilege of discussing with De Duve and Ciechanover here at the Casina Pio IV the relationship between the lysosomal and proteasomal pathways, and both Nobel laureates thought there was none.

In this paper we present work from our laboratory showing that cytosolic proteins phosphorylated by Glycogen Synthase Kinase 3 (GSK3) can be degraded inside lysosomes by the process known as microautophagy, and that the transition from proteasomal to lysosomal degradation is regulated by an extracellular growth factor called Wnt. Wnt causes a great increase in non receptor-mediated endocytosis and this requires the prior activity of Protein Arginine methyltransferase (PRMT1). These studies lead to the conclusion that the proteasomal and lysosomal degradation pathways are not independent of each other as previously thought, and that the switch between them is physiologically regulated by the Wnt signaling factor.

[1] An early version of this work was presented in *Cell Biology and Genetics*, De Robertis, E.M. and Sánchez Sorondo, M., Eds. *Pontificiae Academiae Scientiarum Scripta Varia*, Vol. 137, pp. 177-186 (2018). Libreria Editrice Vaticana, Rome.

1. Wnt signaling causes the sequestration of GSK3 inside multivesicular bodies

1.1. Wnt signaling in development and disease

The canonical Wnt/GSK3 signaling pathway was discovered by Roel Nusse and is now known to be a key regulator of tissue regeneration, stem cells, and cancer (Logan and Nusse, 2004; Nusse and Clevers, 2017). Multiple loss-of-function mutations in this pathway, in genes such as Axin, APC and β-Catenin cause stabilization of β-Catenin, increasing cell proliferation and leading to cancer.

1.2. Wnt decreases GSK3 activity

The Wnt growth factor binds to the cell surface co-receptors LRP6 (LDL-receptor related protein 6) and Frizzled. Activated receptors are phosphorylated by GSK3 and other kinases and recruit a cytosolic β-Catenin destruction complex consisting of Axin, Adenopolyposis Coli (APC), Dishevelled (Dvl), GSK3 and Casein Kinase 1 (CK1). In the absence of Wnt, the amino terminal region of β-Catenin is phosphorylated first by CK1 and then by three phosphorylations by GSK3. This generates what is called a phosphodegron. When regions of proteins are modified by multiple phosphates in Serines or Threonines in close vicinity, these phosphodegrons are recognized by ubiquitin ligases that catalyze the polyubiquitination of these proteins targeting them for degradation in proteasomes (Ciechanover, 2005). The phosphorylation of β-Catenin by GSK3 makes it an unstable protein. However, in the presence of Wnt β-Catenin is no longer phosphorylated and becomes stabilized. The accumulation of newly made β-Catenin causes its translocation into the nucleus where it binds to T-Cell Factor (TCF) on DNA, eliciting the many transcriptional effects of Wnt signaling on gene expression.

The mechanism by which Wnt signaling blocks GSK3 phosphorylations long was an enigma. We performed measurements of the enzymatic activity of GSK3 using lysates containing the detergent Triton X-100 and were surprised to find that Wnt addition did not inhibit GSK3 enzyme activity (Taelman *et al.*, 2010). How could this be?

1.3. GSK3 is sequestered into multivesicular endosomes

We then remembered the classical work of Stanley Cohen, who had treated cultured cells with labelled Epidermal Growth Factor (EGF) and found that this growth factor became localized inside multivesicular bodies a few minutes after the endocytosis of its receptor (McKanna *et al.*, 1979).

If GSK3 were to follow its receptors into the endolysosomal pathway its sequestration inside membrane-bounded organelles could explain the reduced activity GSK3 in the cytosol while maintaining total levels of enzyme activity in detergent-treated lysates (Figure 1).

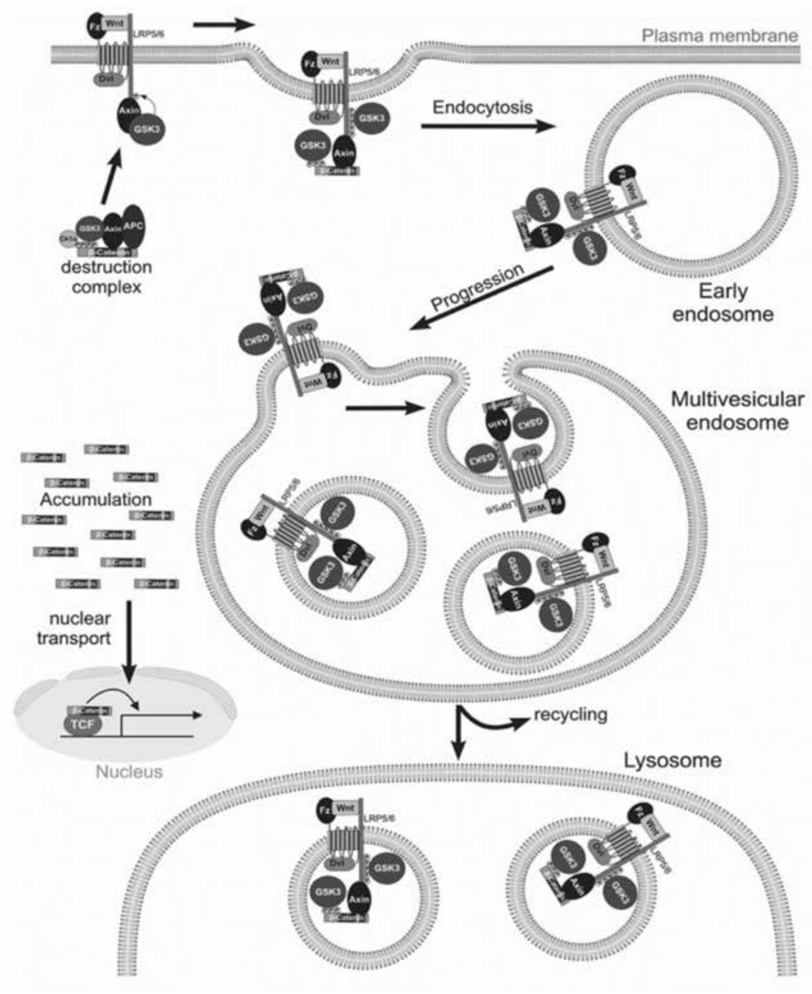

Figure 1. The Wnt growth factor signals through the sequestration of GSK3 and Axin inside multivesicular bodies. The activated Wnt receptors bind to Axin, a scaffold protein that brings bound to it APC, Dvl, phospho-β-Catenin. All these proteins, together with the Wnt coreceptors Frizzled and LRP6, are substrates for phosphorylation by GSK3. Following endocytosis, GSK3 becomes engulfed inside the intraluminal vesicles of multivesicular endosomes. This process is called microautophagy. The sequestration of GSK3 causes many proteins in the cytosol to become stabilized since GSK3 phosphodegrons are no longer formed. From Taelman *et al.*, Cell 2010.

1.4. Wnt addition increases endocytosis

When cultured cells were treated with purified preparations of Wnt3a, after 10 minutes we observed the formation of prominent vesicular structures visible by phase-contrast optical microscopy (Figure 2). Thus, Wnt causes a large increase in endocytosis. When stained with antibodies against endogenous GSK3, it was clear that large amounts of GSK3 are translocated from the cytosol into these vesicles. Cryoimmuno electron microscopy, done in collaboration with David D. Sabatini of New York University, showed that GSK3 was localized inside the intraluminal vesicles (ILVs) of multivesicular bodies. Protease protection assays in cells made permeable with Digitonin showed that GSK3 and Axin were translocated into membrane-bounded organelles by Wnt signaling (Taelman *et al.*, 2010; Vinyoles *et al.*, 2014; Albrecht *et al.*, 2018).

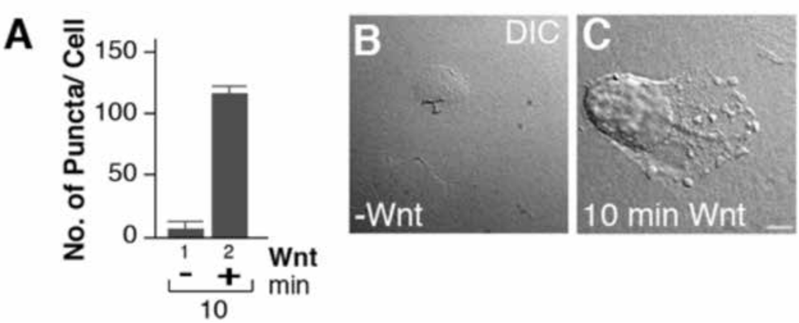

Figure 2. HeLa cells treated for short periods with Wnt protein show large vesicles by light microscopy. These vesicles sequester GSK3 and GSK3 substrates during Wnt signaling. From Albrecht *et al.*, 2018.

MVBs form during the normal progression of intracellular membrane traffic. Early endosomal vesicles pinch off the plasma membrane. In the case of Wnt, it was known that endocytosis was required for signaling (Blitzer and Nusse, 2006) and that components of the receptor complex and the cytosolic destruction complex accumulated in the cell membrane and early endosome (Bilic *et al.*, 2007). However, the decrease of GSK3 activity in the cytoplasm requires its sequestration inside the ILVs of MVBs. Once inside, the enzyme becomes separated from its cytosolic substrates by two membranes: the ILV membrane and the late endosome/lysosome limiting membrane (Taelman *et al.*, 2010) (Figure 3).

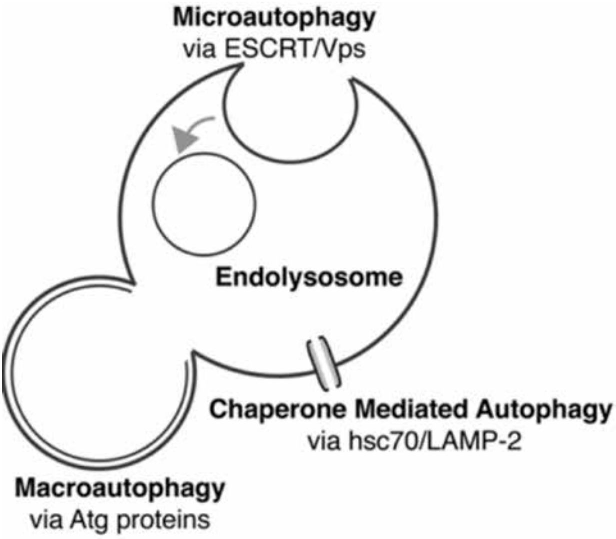

Figure 3. Cytosolic proteins can enter the lysosomal compartment in three different ways. Macroautophagy forms a double membrane via ATG proteins that encircles certain cytosolic regions and organelles that then fuse with lysosomes (Ohsumi, 2014). Chaperone-mediated endocytosis translocates proteins with a heat shock 70 protein recognition signal though a LAMP-2 channel (Cuervo, 2010). Microautophagy incorporates cytosolic proteins such as GSK3 and PRMT1 through the formation of intraluminal vesicles that require the ESCRT/Vps machinery.

The process of ILV formation is called microautophagy and results in the digestion of purely cytosolic proteins in lysosomes. The outside-inside formation of ILVs requires great effort by the cell (Piper and Katzmann, 2007). All eukaryotic cells contain an elaborate ESCRT machinery (Endosomal Sorting Complexes Required for Transport), sometimes called Vps (Vacuolar protein sorting) proteins that are necessary for membrane invagination into late endosomes.

All plasma membrane proteins must pass through the intraluminal vesicle step before they can enter the lysosome for degradation. Most growth factor receptors, such as the EGF receptor, use endolysosomes to downregulate receptor activity (Katzman *et al.*, 2002). The case of Wnt is different, because the sequestration of GSK3 and Axin constitutes the signal itself. Indeed, inhibiting the activity of the ESCRT proteins HRS/Vps27 or Vps4 blocks canonical Wnt/GSK3 signaling (Taelman *et al.*, 2010).

The main conclusion from these experiments is that Wnt signaling requires the sequestration of a cytosolic protein kinase, GSK3, inside endosomes.

2. Wnt regulates the stability of many proteins

2.1. How many proteins are regulated by Wnt/GSK3?

GSK3 is a very abundant protein kinase, and has the peculiarity of being constitutively active (Wu and Pan, 2010). Most other protein kinases require an activation step before they can add phosphates to proteins using ATP as substrate. GSK3 has many other substrates in addition to β-Catenin (Jope and Johnson, 2004; Kim *et al.*, 2009). This raised the question of how many proteins might be stabilized by Wnt/GSK3.

GSK3 has a preference for pre-phosphorylated substrates. The priming phosphorylation can be introduced by many different kinases such as MAPK, CK1, CDK or PKA. Once phosphorylated, the substrate is recognized by the priming phosphate site in GSK3. The enzyme scans the protein and if a serine or threonine is found in the fourth position upstream of the priming phosphate, another phosphorylation is introduced (Cohen and Frame, 2001). This is a processive mechanism, so that if another Ser/Thr site is found four amino acids upstream, an additional phosphate is introduced until a Ser/Thr is no longer found.

To investigate how many proteins might conceivably be regulated by Wnt/GSK3 we analyzed the human entire proteome. We found that 20% of human proteins contain three or more consecutive GSK3 sites. This is much more than what might be expected by chance alone. The complete list of these proteins is available at: http://www.hhmi.ucla.edu/derobertis/EDR_MS/GSK3%20Proteome/Table_1-full_table.xls

Determining whether a certain protein has possible GSK3 sites is a good predictor of whether it might be stabilized by Wnt signaling. We have investigated some such proteins and found that several are indeed regulated by Wnt addition. Examples include: MITF (Microphthalmia transcription factor, a key oncogene of melanocytes) (Ploper *et al.*, 2015); Tau (a microtubule-associated protein involved in Alzheimer's disease) (Dobrowolski *et al.*, 2012); HDAC4 (histone deacetylase 4) (Taelman *et al.*, 2010); Smad1 (a transcription factor activated by BMP signaling) (Fuentealba *et al.*, 2007); Smad4 (a transcription factor shared by the TGFβ and BMP pathways) (Demagny *et al.*, 2014).

We conclude that Wnt regulates the degradation of a plethora of other proteins in addition to β-Catenin.

2.2. Wnt signaling regulates total cellular protein stability

The effect of Wnt on protein stability is massive. In pulse-chase experiments with radioactive Methionine (30 minute pulse followed by chase in unlabeled medium containing a 5-fold excess of cold Methionine) the half-life of total cellular proteins in human 293 cells was extended by 25% (Taelman *et al*, 2010). This effect is so marked that it increased cell size measured by flow cytometry (Acebron *et al.*, 2014). We confirmed these observations and found that HeLa cells increase 14% in size after treating with Wnt for 48 hours and demonstrated that this increase requires the ESCRT machinery (Kim *et al.*, 2015).

This increase in protein stability has been designated Wnt-STabilization Of Proteins (Wnt/STOP) by Christof Niehrs (Acebron *et al.*, 2014). Wnt signaling is maximal during the G2/M phase of the cell cycle (Davidson *et al.*, 2009), leading to the interesting proposal that Wnt/STOP provides a means for cells to increase their volume by preventing protein degradation just prior to mitosis (Acebron *et al.*, 2014).

These experiments indicate that Wnt, through the sequestration of GSK3 in multivesicular endosomes, is a potent regulator of cellular protein degradation.

3. Wnt signaling translocates Lys48-linked polyubiquitinated proteins normally degraded in proteasomes into the lysosomal pathway

3.1. Microautophagy can translocated proteins targeted to proteasomes into lysosomes in the presence of Wnt

Since GSK3 should be inhibited by Wnt, we expected that during Wnt signaling there would be less protein polyubiquitination due to lower levels of GSK3 phosphodegrons. To our surprise, we found that total polyubiquitinylated proteins accumulated after one or two hours of Wnt signaling. This accumulation could be blocked by GSK3 inhibitors. Furthermore, the increase was particularly in Lys48-linked polyubiquitin, which is the form that normally targets proteins to the proteasome. Wnt did not affect proteasomal activity. Further investigation showed that these proteins are channeled by microautophagy into the lysosomal pathway by Wnt treatment (Kim *et al.*, 2015). Thus, proteins normally targeted to proteasomes are degraded in endolysosomes in the presence of Wnt (Figure 4).

The main finding from these investigations was that the proteasomal and lysosomal pathways are not independent of each other as previously thought. Remarkably, the physiological choice between proteasomal and lysosomal degradation is controlled by the Wnt extracellular signal.

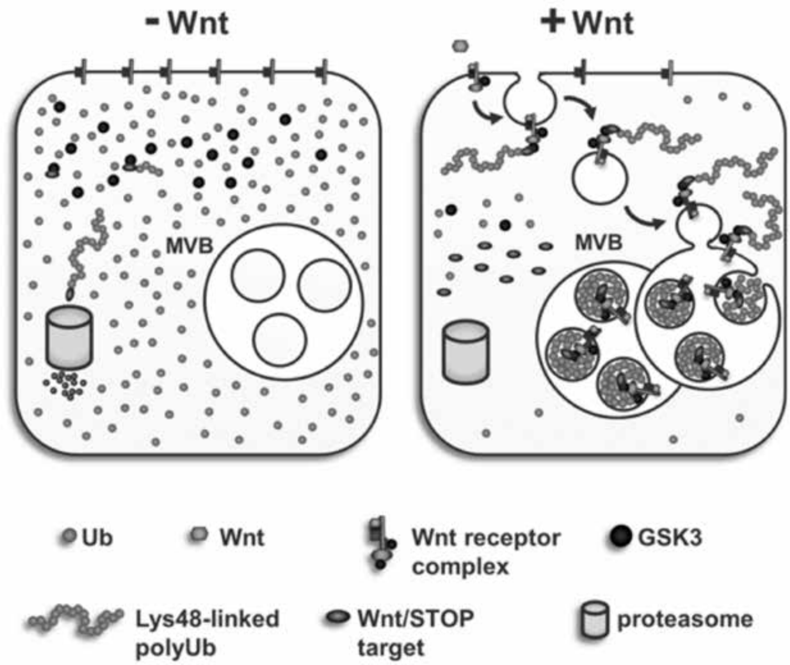

Figure 4. The lysosomal and proteasomal protein degradation systems crosstalk in a Wnt-regulated manner. During Wnt signaling Lys48-linked polyubiquitinated proteins, normally degraded in the proteasome, are translocated into MVB/lysosomes by microautophagy. The sequestration of polyubiquitin chains is so marked that it causes a reduction in free mono-ubiquitin, which is the substrate that marks proteins for degradation. The decrease in mono-ubiquitin results in generalized inhibition of protein degradation during the first two hours of Wnt signaling. From Kim *et al.* 2015.

4. Protein Arginine methylation is required for canonical Wnt signaling

4.1. An unexpected result

We observed that of the large number of putative GSK3 substrates, many have been shown to be also modified by a post-translational modification known as Arginine methylation. One report had shown that Arginine methylation is required to promote consecutive GSK3 phosphorylations on a cytoskeletal linker protein called Desmoplakin (Albrecht *et al.*, 2015). This suggested to us that Arginine methylation might play a role in regulating GSK3 signaling.

Arginine methylation is emerging as a fundamental protein modification as it is as prevalent as phosphorylation and occurs in both the nucleus and cytoplasm (Larsen *et al.*, 2016). Arginine methylation was previously thought to be irreversible. However, the discovery of the Jumonji demethylase enzymes marked a revolution in the field as it revealed that Arginine methylation can be switched on and off to dynamically regulate cell signaling (Chang *et al.*, 2007). Proteomic analyses revealed that 33% of Arginine methylation substrates contained GSK3 consensus motifs (Albrecht *et al.*, 2018). To test whether Arginine methylation was coordinated with Wnt signaling, cells were treated with Wnt protein and immunostained with methyl-Arginine specific antibodies. We found that Arginine methylated proteins were translocated from the cytosol into endosomal vesicles by Wnt signaling (Figure 5).

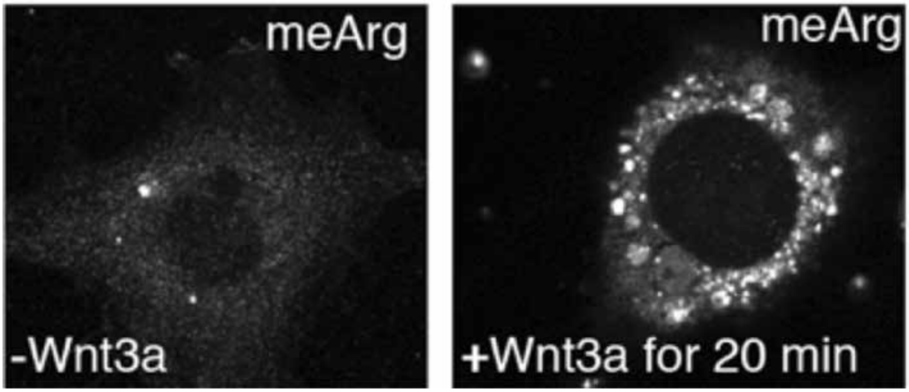

Figure 5. Arginine methylation (meArg) modified proteins rapidly accumulate inside endosomal vesicles after Wnt3a treatment. See Albrecht *et al.* 2018.

Arginine methylation is catalyzed by Protein Arginine Methyltransferase enzymes (PRMTs) (Bedford and Clarke, 2009). Of the eight PRMT enzymes, PRMT1 accounts for 85% of cellular methylation (Bedford and Clarke, 2009). In an important study, the group of R. Derynck found that PRMT1 initiates TGF-β and BMP growth factor receptor signaling (Xu *et al.*, 2013). We found that in the case of Wnt signaling cytosolic PRMT1 is rapidly sequestered into multivesicular bodies (Figure 6). In addition, GSK3 is translocated into the same vesicles as PRMT1 following Wnt protein addition (Figure 6) (Albrecht *et al.*, 2018). The results suggest that PRMT1 and GSK3 function coordinately during Wnt signaling.

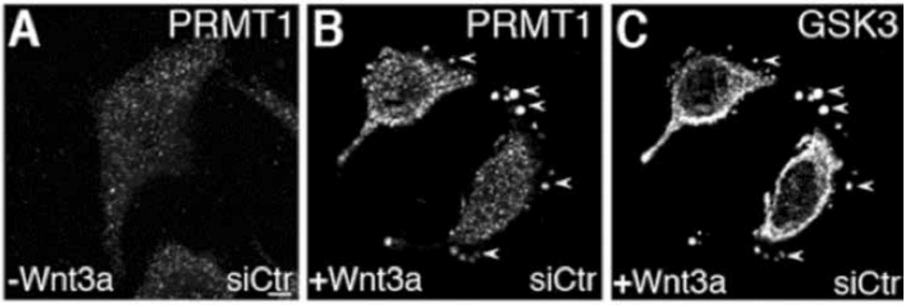

Figure 6. *In situ* proteinase K protection assays show that Wnt3a translocates the enzymes PRMT1 and GSK3, which are normally cytosolic, into endolysosomes (arrowheads) by the process of microautophagy. In these assays cells were permeabilized with Digitonin, a detergent that dissolves cholesterol patches present in the plasma membrane but not in internal membranes. When exogenous protease is added to cells still attached to the culture dish (on ice), cytosolic proteins are digested but proteins inside membrane-bounded organelles are protected from degradation. This method provides a very useful tool in cell biology. See Albrecht *et al.* 2018.

Conclusions

Organisms use a small number of cell signaling pathways for cell-cell communication. The study of cell signaling is very important in developmental and cancer biology. The Wnt pathway is particularly interesting because it is involved in the initiation of many tumors and also provides the first asymmetry during development of the amphibian embryo. The discovery that PRMT1 is sequestered into the same vesicles as GSK3 and is required for Wnt signaling could offer innovative therapeutic approaches to prevent the progression of cancers with an activated Wnt pathway (usually resulting from loss-of-functions mutations in APC or Axin proteins). This could be achieved by inhibiting Arginine methylation, endocytosis, or lysosomal activity. The studies discussed here are at the intersection of the cell biology of membrane trafficking, cell signaling and the regulation of cellular protein degradation. They revealed that the Wnt signaling pathway uses the normal membrane trafficking machinery of endocytosis to generate a signal that results from the sequestration of GSK3 and Axin inside multivesicular endosomes. The removal of GSK3 from cytosol stabilizes a multitude of proteins, leading to a marked increase in protein stability and cell size. GSK3 has many substrates within the Wnt receptor complex and is translocated together with it, as well as with many of its cytosolic substrates, inside the intraluminal vesicles of multivesicular endosomes. Many of these substrates will fall into a specialized cohort modified by both

Arginine methylation and GSK3 phosphorylation. Wnt causes a previously unsuspected switch of protein degradation from the proteasome to the lysosome, two pathways that were thought to be independent of each other.

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Dependence Receptors: Transforming an Original Mechanism for Cell Death Into a Novel Anti-Cancer Strategy in Patients with Advanced Cancers

Patrick Mehlen[1]

The discovery of the first dependence receptor (DR) in 1998 [1] challenged the general dogma on transmembrane receptors, active only in the presence of their ligand. Indeed, our team unveiled receptors functioning in an either/or context rather than as conventional on/off switches. In effect, ligand-bound receptors activate a so-called "positive" signaling (proliferation, survival, differentiation), while unbound receptors transmit a "negative" pro-apoptotic signal (Figure 1). Hence, cells expressing DRs on their surface are dependent on the ligand for their survival, and these receptors have accordingly been termed "dependence receptors". Currently, the DR family comprises around 20 members, homologous in their dual functionality. These known receptors may have one or several known ligands, and inversely a ligand may bind one or several receptors (Table 1).

All of the receptors described above, when engaged by their specific ligands, transduce different pathways leading to the induction of cell differentiation, migration, inter-cellular communication or cell survival. These "positive" signaling functions are generally well-described, several of which are briefly presented below (Table 2). However in the absence of ligand binding these DRs triggers caspase-dependent cell death through pro-apoptotic mechanisms that have been reviewed previously [20] (Figure 2).

Aside from their common dual functionality, DRs are all highly involved in embryonic development and tumorigenesis. Their expression in the latter case is generally a factor of good prognosis, and it is generally admitted that tumors have developed escape mechanisms to evade this pro-apop-

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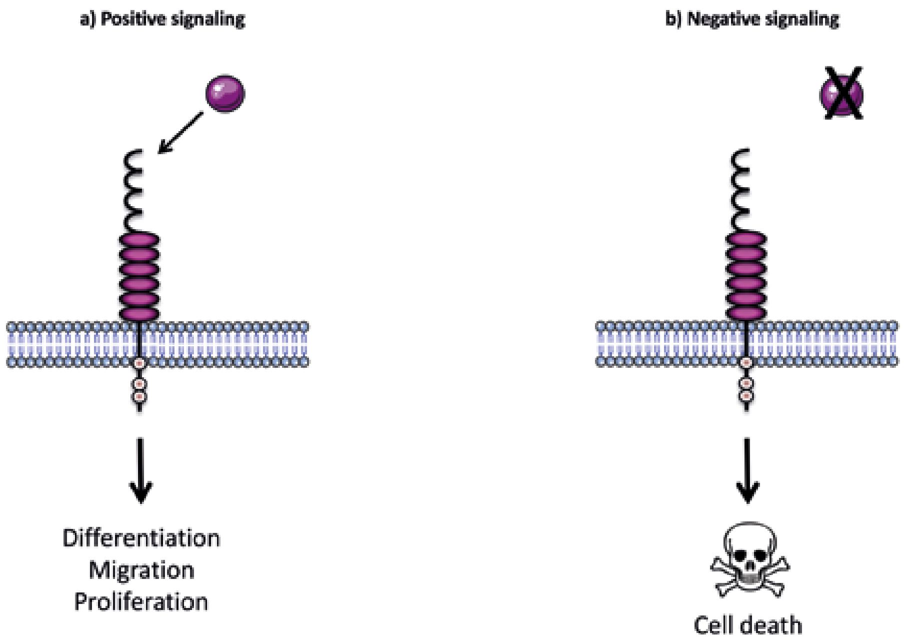

Figure 1. The Dependence receptor paradigm. a) Positive signaling. Ligand bound dependence receptor can trigger various survival signals such as differentiation, migration or proliferation. b) Negative signaling. In the absence of its ligand, the dependence receptor induces cell death in an active manner.

totic signaling either via a decrease in DR expression or an increase in ligand availability. Indeed, DRs limit tumor progression by eliminating supernumerary cells in a limited ligand environment, and thus constitute a natural mechanism to control cell growth [26]. As a consequence, tumor cells capable of counteracting it will have acquired a selective advantage. Two major mechanisms have so far been identified to bypass this control of cell death, namely the (i) silencing of the DR or its pro-apoptotic signaling pathway, and (ii) the autocrine production of the ligand (Figure 3).

This review will detail how tumors are able to develop by impacting either DRs or their ligands, and how such an interaction has become a target for personalized cancer therapies.

Table 1. Table of the known Dependence Receptors and their respective ligands.

Dependence Receptor	Ligand(s)	Reference
Deleted in colorectal cancer (DCC)	Netrin-1	[1]
Uncoordinated homologs (UNC5H1, 2, 3, 4 or UNC5A, B, C, D)	Netrin-1	[2,3]
Neogenin receptor	Netrin-1 Repulsive guidance molecule (RGM)	[4]
Neutrophin receptor p75 (p75NTR)	Nerve growth factor (NGF)	[5]
Patched-1 (PTCH-1)	Sonic hedgehog (SHH)	[6]
Cell-adhesion molecule-related/ Down-regulated by Oncogenes (CDON)	Sonic hedgehog (SHH)	[7]
Plexin-D1	Semaphorin-3E (Sema3E)	[8]
Rearranged during transfection (RET)	Glial cell line-derived neurotrophic factor (GDNF)	[9]
Tropomyosin receptor kinase (Trk) A	NGF	[10,11]
TrkB	brain-derived neurotrophic factor (BDNF)	[10,11]
TrkC	Neutrophine-3 (NT-3)	[10,11]
Ephrin type A receptor 4	Ephrin-B3 (EphB3)	[12]
MET or hepatocyte growth factor receptor (HGFR)	HGF	[13]
Insulin receptor (IR) and insulin growth factor 1 receptor (IGF-1R)	Insulin and insulin growth factor 1 (IGF1)	[14]
Anaplastic lymphoma kinase (ALK)	Jelly belly (Jeb)	[15]
Integrins α and β	2-{ethyl[(5-{[6-methyl-3-(1H-pyrazol-4-yl)imidazo[1,2-a]pyrazin-8-yl]amino}isothiazol-3-yl)methyl]amino}-2-methylpropan-1-ol (EML)	[16]
Kremen-1	Dickkopf 1 (DKK1)	[17]
Notch3	Jagged 1 (Jag-1)	[18]
Latrophilin	Contactin 6 (CNTN-6)	[19]

Table 2. Table of the known signaling triggered by DRs.

Receptor/ligand pair	Positive signaling induced	Reference
DCC or UNC5H/Netrin-1	PI3K and MAPK signaling pathway with a key role in axonal growth and orientation	[21] [22]
IR and IGF-1R/insulin and IGF-1	activate many pathways such as PI3K/Akt or Ras/MAPK required for glucose uptake, glycogen synthesis or proliferation	[23]
PlexinD1/Sema3E	Ras activation, critical for hippocampus formation during the embryonic stage	[24]
Notch3/Jagged1	Activation of notch3 on vascular smooth muscle cells (VSMC) is essential for VSMC maintenance and maturation via activation of a canonical pathway including Notch3 intracellular cleavage (NICD) and NICD-dependent transcription	[25]

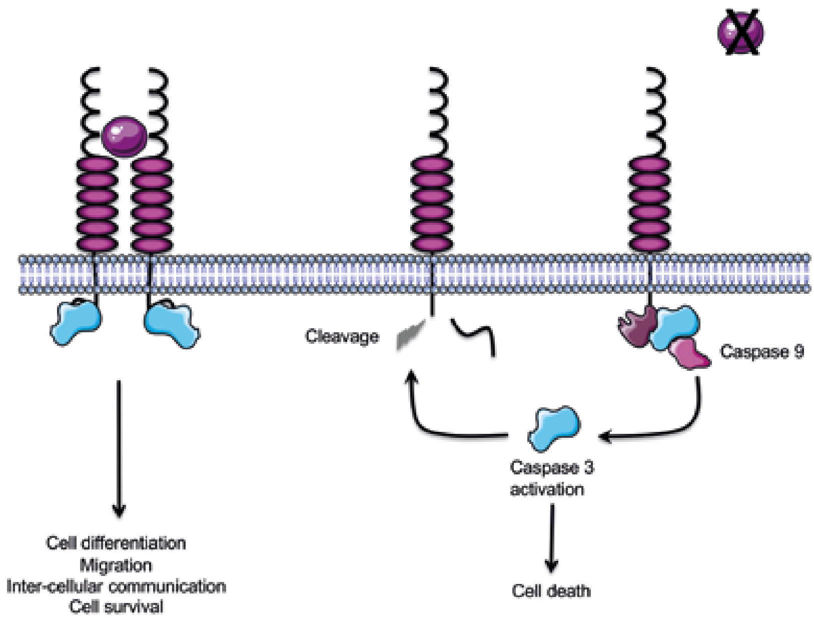

Figure 2. Signaling of cell death by dependence receptors. Simplified view of how DRs triggers caspase dependent cell death.

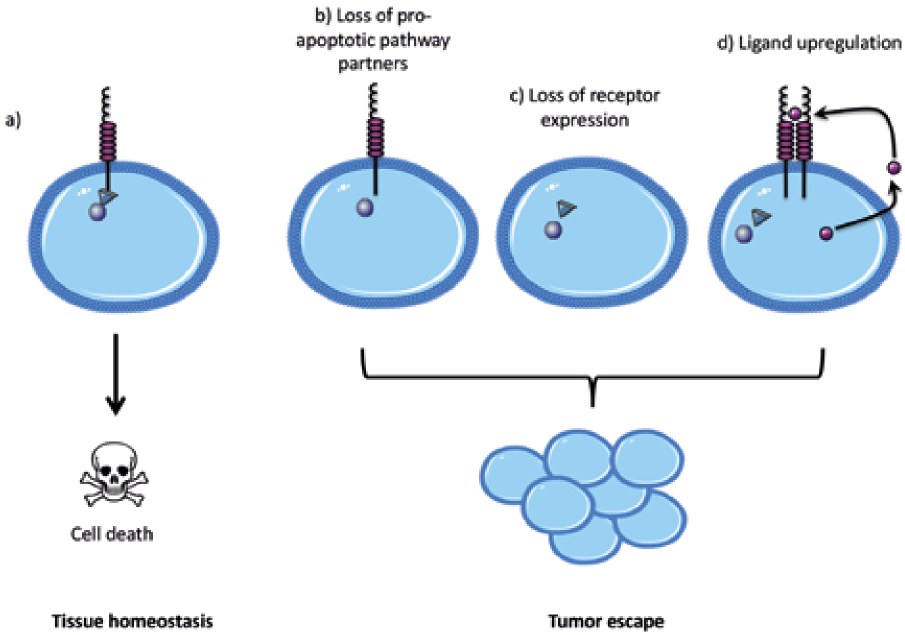

Figure 3. Escape of tumor cells by bypassing the survival dependence to dependence receptors. a) Tissue homeostasis. In a limited ligand environment, aberrant proliferation is controlled by dependence receptors, which induce cell death when unbound by their specific ligands. Tumor escape can be achieved by the silencing of pro-apoptotic pathways (b)), either by the loss of the dependence receptors at the cell membrane (c) or (d) by ligand upregulation in an autocrine (by the cell itself) or paracrine (by other surrounding cells) manners.

How to suppress a natural tumor suppressor

The prototypical DR, deleted in colorectal carcinoma (DCC), was originally identified in 1990 [27], and its gene located on chromosome 18q, a region prone to loss of heterozygosity (LOH), is frequently absent in colorectal cancers and more generally in a large fraction of cancers, resulting in the reduction or in the loss of DCC expression [27]. This LOH is mainly found in advanced stages of the disease, and its frequency increases with tumor progression [28-31], suggesting a role for DCC in cancer progression rather than initiation. Experiments seeking to restore DCC expression in tumor or metastatic lines demonstrated a reduction in ganglion invasion and prevention of metastatic spread of these cells to the lungs [32-35], arguing in favor of its role as a tumor suppressor in the late phases of tumor progression. The loss of DCC expression has been demonstrated in a variety of cancers [3,36,37], and results not only from a LOH but also through the hypermethylation of its promoter [3,38,39]. Although its rate of somatic mutation is relatively low in colon cancers (10-15%) [21], DCC is frequently mutated in sun-induced melanomas [40] and a single nucleotide polymorphism (SNP) in DCC has been identified in gallbladder cancer [37]. The role of DCC in cancer progression was first challenged in 1996 [21], prior to being associated with its DR function by our team in 1998 [1]. Mechanistically, we generated mice bearing a mutated DCC receptor with a non-functional pro-apoptotic activity. The absence of DCC-induced apoptosis was associated with the development of spontaneous intestinal tumors at low frequency and with increased adenocarcinoma when the DCC mutant mice were backcrossed with mice highly susceptible to spontaneous intestinal adenoma formation (APC mutant background) [41]. These DCC "death-dead" mutants displayed a tendency to develop both more colorectal cancers and lymphomas [42]. In another genetically-modified mouse model of mammary carcinoma based on the somatic inactivation of p53, the invalidation of DCC led to the appearance of metastases [43]. Hence, DCC, via its pro-apoptotic activity, is a strong tumor suppressor, and its mutation or suppression are highly advantageous for tumor cells.

Following the discovery of the role of this unique dual functioning DR in cancer progression, our team and others embarked in a research crusade to unveil other DRs potentially implicated in tumorigenesis. Uncoordinated homolog (UNC5H) receptors, in particular UNC5A, B and C, are often lost or greatly reduced in cancers [44,45]. The loss of expression of UNC5H in human primary tumors, as well as in cell lines, is mainly due to epigenetic mechanisms, such as the methylation of promoters [38,39,44,46]. Along this line, the promoter region of UNC5C is hypermethylated in nearly 80% of the colorectal tumors analyzed and its inactivation is associated with tumor aggressiveness [46]. In addition, invalidation of UNC5C is associated with intestinal tumor progression in mice [46]. Inversely, expression of UNC5A in various cancer cell lines, including colon cancer, reduces their ability to form colonies and induces apoptosis [47]. Moreover, UNC5A, B and D are p53 target genes, which participate in the pro-apoptotic activity of p53 [47,48,49].

Tropomyosin receptor kinase A was first identified as an oncogenic fusion protein [50–52], and this rearrangement is also found for TrkC in particular in congenital fibrosarcoma and acute myeloid leukemia [53,54]. Owing to their kinase activity, these receptors have been shown to play an important role in the biology of cancers, notably of neuronal or neuroendocrine origin. Surprisingly, despite their strong homology TrkA, B and C receptors behaved in a very dissimilar way. While TrkB is expressed in very aggressive tumors, the expression of TrkA and TrkC is associated with a good prognosis, at least in neuroblastoma and medulloblastoma [55,56]. These paradoxical findings are highly consistent with their dual functionality as DRs. Accordingly, as observed for netrin-1 receptors, TrkC is under-expressed in a large fraction of colorectal cancers in humans. This decreased expression is mainly due to promoter methylation [57]. However, to date, a functional demonstration that loss of TrkC or TrkA promotes tumor progression remains to be demonstrated mechanistically.

The Patched-1 receptor (PTCH-1), of the Sonic Hedgehog (SHH) morphogen, is a well-known tumor suppressor [58]. Loss of PTCH-1 expression, or mutations leading to its inactivation, has been observed in basal cell carcinomas and medulloblastomas [59]. It is generally accepted that the tumor suppressor activity of PTCH-1 is related to its repression of a canonical oncogenic pathway (Smoothened-Gli). However it was more recently shown to reduce the tumorigenicity via its DR activity [6]. However, there is currently no evidence *in vivo* that PTCH-1 functions as a tumor suppressor by its pro-apoptotic activity. This has nonetheless been demonstrated for another SHH receptor, namely the CDON receiver. High throughput sequencing has shown many false-sense mutations of CDON in human cancers (Sanger Institute Catalog for Somatic Mutations in Cancer web site, http://www.sanger.ac.uk/cosmic). In addition, loss of CDON expression has been observed in humans in tumors of the colon, kidney, lungs and breast [7]. Interestingly, the expression of CDON is inversely correlated with the tumor grade (according to the TNM classification) in colorectal cancers and mice mutated for CDON are prone to develop intestinal adenocarcinoma when backcrossed with APC mutant mice [7].

Among the other DRs, Kremen1, one of the latest to have been discovered, is down regulated in several cancers [17,60]. Mutations of Kremen1 in the domain responsible for the apoptotic activity induced by the receptor in the absence of its ligand DKK-1 were identified in cancer patients, supporting the view that these mutations confer a selective advantage for tumor cell survival [17]. Neurotrophin receptor p75 (p75NTR) is partially lost in the localized prostate tumor epithelium. This loss is inversely correlated with tumor grade (Gleason score) and total loss has been observed in metastatic prostate cancer lines [61,62]. Ephrin typr A receptor (EphA4) is down-regulated in invasive forms of breast cancer [99], in liver and kidney cancers [64] and in metastatic melanoma [65]. It has also been suggested that the expression of neogenin may be inversely correlated with malignancy in breast cancer [66]. Consistent with a tumor suppressor function, Notch3 is as also downregulated in breast cancer and this loss is associated with poor survival [67,68].

Overall, the association of these recently identified DRs with tumorigenesis is suspected, however, in most cases, animal models are lacking in order to demonstrate this role.

How to overwhelm tumor suppressors to foster cancer progression

Tumors have thus developed selective advantages to inactivate the natural tumor suppressive activity of DRs, and it was therefore speculated that tumor cells may also overwhelm DRs by producing larger amounts of ligand, conferring cancer cells with the ability to survive independently of ligand limitation and to increase "positive signaling". Consistently, a growing body of evidence indicates that this "gain of ligand" occurs in many tumors, and is more particularly described for netrin-1, NT-3, SHH, Sema-3E, DKK-1 and Jagged-1.

In line with the first discoveries on DCC and cancer progression, the confirmation that a gain of ligand is associated with tumor progression was first obtained with DCC's ligand netrin-1. Indeed, the ectopic expression of netrin-1 in the intestinal tract of mice was accompanied by a net decrease in epithelial apoptosis, and these mice had a significant increase in the development of spontaneous focal hyperplasia and adenomas. Moreover, when backcrossed with an APC mutant background, the mice developed more adenocarcinoma [69]. Netrin-1 is overexpressed in a large fraction of cancers [42,70-72], and this overexpression is associated with a poor prognosis in patients with poorly differentiated pancreatic adenocarcinoma [73]. In breast cancer, netrin-1 is correlated with the aggressiveness of the disease and especially with its metastatic potential. An experimental silencing of netrin-1 in various cancer cell lines showed that netrin-1 is associated with cell death *in vitro* and with tumor growth and metastasis inhibition in mice [74,75]. *In vitro* cell death and tumor growth inhibition *in vivo* were also observed when agents interfering the netrin-1/receptor binding were used [74-76], supporting the view that inhibition of netrin-1/DR interaction could be a promising therapeutic strategy. Mechanistically, the pathways underlying netrin-1 up-regulation remain largely unknown, though several studies have proposed diverse routes [76-81].

Neurotrophin-3 (NT-3), ligand of TrkC, is overexpressed in a large fraction of advanced neuroblastoma, and this overexpression blocks the pro-apoptotic activity of TrkC *in vitro* in human neuroblastoma cell lines [82]. In addition, NT-3 silencing or the inhibition of NT-3/TrkC interaction via an antibody inhibits tumor growth and metastatic spread of human neuroblastoma in xenograft models in chicken and mice [82].

Sonic Hedgehog (SHH) is up-regulated in many cancers in an autocrine and paracrine manner [83,84]. Initially this overexpression was associated with activation of the so-called canonical pathway involving the activation of Gli transcription factors via smoothened (Smo). Nevertheless, while a potent inhibitor of the canonical pathway, the Smo antagonist, GDC-0449, has shown a beneficial effect in patients with basal cell carcinomas or medulloblastomas presenting activating mutations of the PTCH-1-Smo-Gli pathway, this drug has no effect in other tested cancers, even though patients were stratified according to SHH expression. Hence, SHH signaling was suggested to be more complex, involving its DR(s), by blocking their pro-apoptotic activity (especially CDON) [7]. Preclinical models demonstrated that inhibition of SHH/CDON interaction by a SHH titration (SHH-TRAP) could efficiently engage CDON-induced tumor cell death and could potentially benefit patients with tumors expressing SHH [7].

Semaphorin 3E (Sema-3E), ligand of the PlexinD1 receptor, is overexpressed in a large number of cancers, and most often associated with tumor progression. The expression of Sema-3E is associated with the metastatic capacity of ovarian, colon and melanoma cancers, and is correlated with poor survival of patients with colorectal and pancreatic cancers [85-87]. Sema-3E was initially identified as a gene expressed in metastatic breast adenocarcinoma cell lines, whereas it was expressed in only 30% of non-metastatic cell lines [88,89]. The pro-tumoral function of Sema-3E in cancer is controversial, as its overexpression in some models resulted in a decrease in neo-angiogenesis and a reduction in tumor growth [86,87,90], but overexpression of the Sema-3E cleavage fragment by furins contributed to tumor invasion and distant metastasis formation [86,87,91,92]. Since unveiling PlexinD1 as a DR, novel insight into the role of Sema-3E/PlexinD1 in cancer has been gained. Indeed, the autocrine production of Sema-3E was shown to increase the survival of breast cancer cell lines by inhibiting PlexinD1-activated pro-apoptotic signaling. Consequently, the use in preclinical models of TRAP, blocking the Sema-3E/PlexinD1 interaction, led to inhibition of tumor growth and metastasis [8].

The Dickkopf-1 (DKK-1) ligand of Kremen-1 is up-regulated in a number of cancers [93] and this over expression is correlated with poor prognosis [94-100]. Moreover, DKK-1 expression is correlated with cancer aggressiveness in myeloma patients [101]. Paradoxically, this overexpression was perceived as counter-intuitive as up-regulation of DKK-1 should be associated with inhibition of the Wnt pathway, a pro-oncogenic pathway. Once again, its implication as a DR ligand clarified this paradoxical over-expression [17]. Of interest, although not in the context of its role as a DR ligand, DKK-1 inhibition by either knock down or anti-DKK-1 antibodies approaches was considered as a potential cancer therapeutic strategy in a large panel of cancers [93,102]. Sato et al. showed that interference with DKK-1 with an anti-DKK-1 antibody could limit lung tumor growth *in vivo* and this was accompanied by extensive cancer cell death [93]. Furthermore, the use of an anti-DKK-1 antibody inhibited metastasis of osteosarcoma or of hepatocellular carcinoma in xenograft mice models [102,103] or multiple myeloma dissemination in immunodeficient mice transplanted with relevant organs of the human immune system (SCID-hu mice) [104].

Transposing a recently discovered concept to treat patients with advanced solid cancer

Based on the findings presented above, our team dedicated a significant workforce to transfer our fundamental/preclinical results into a clinical application interfering with ligand/DR interaction, in our case netrin-1/receptors. In effect, an anti-netrin-1 antibody was generated and showed some interesting anti-cancer activities in pre-clinical models [81,105]. This antibody was humanized and has been through all the regulatory pre-clinical stages. A phase 1 clinical trial launched in 2017 encompassing 60 patients with advanced solid tumors is ongoing (https://clinicaltrials.gov/ct2/show/NCT02977195), and although it is too soon to conclude on the benefits of the anti-netrin-1 mAb, our preliminary data recently reported at ESMO (Cassier et al., Annal of Oncology, 2019) show an excellent safety profile with no dose-limiting toxicity and few adverse effects (i.e. mainly infusion-related reaction commonly seen for humanized antibodies). More importantly and even though next steps will be to explore more specifically target patients that may respond to the treatment, and to investigate whether combination treatments with standards-of-care such as chemotherapy and immunotherapy increase overall patient survival, we have seen some clear signs of clinical activity in patients with advanced cancers. It includes patients showing long-term disease stabilization (>18 months of treatment) or even objective response (shrinking of over 50% of tumoral lesions) (Figure 4). This supports the view that the dependence receptor concept may in the future provide promising solutions for the wellbeing of patients.

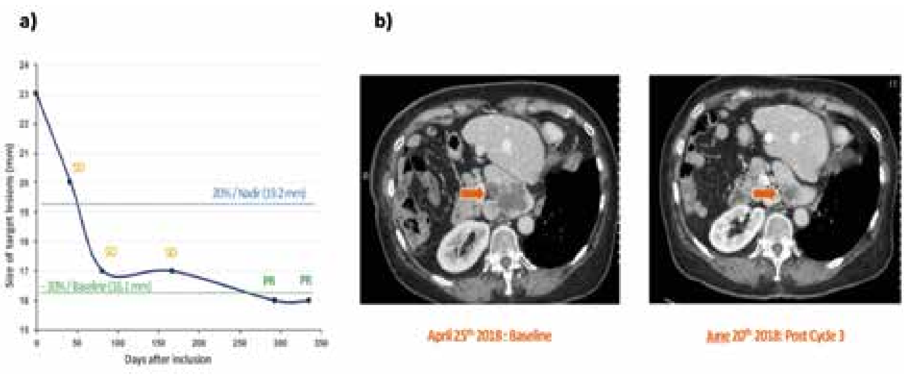

Figure 4. Preliminary data on the phase 1 trial assessing the anti-netrin-1 mAb. Efficacy of the netrin-1 mAb treatment in patients treated in the NP137 trial. a. Evolution of the RESIST (Response Evaluation Criteria in Solid Tumours) lesions in patient 01-10 (advanced cervical cancer) before (0) and upon treatment with NP137 (netrin-1 mAb), showing reduction of the target lesions. b. CT-scan before (Baseline) and after 2 cycles of treatment with the NP137 in patient 02-04 (endometrium adenocarcinoma).

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From Basic Research on Polymeric Protein Models to the Most Used Drug Against Multiple Sclerosis

Michael Sela

I would like first of all to make a couple of comments on the main topic of our deliberation, namely on "emerging basic science toward solutions for people's wellbeing". On the one hand, the drug we invented against multiple sclerosis (Copaxone) improved the health of many hundreds of thousands of patients and this helped their wellbeing and alleviated the worry of their families.

At the same time the drug, Copaxone, became the main export of Israel and definitely improved the economy of the country. Thus, what started as totally basic research ended in significant improvement of health and economic growth.

As shown previously, in continuation of our work on polymers of amino acids as models of proteins we were able to show immunological cross reactivity with proteins such as collagen or enzymes like lysozyme. We prepared a positively charged copolymer resembling to some extent the myelin basic protein in the brain. This copolymer, which we used to call copolymer 1 or Cop 1, and industry later named Copaxone or glatiramer acetate (GA), is now the most frequently used drug against the exacerbating-remitting stage of multiple sclerosis. Close to 400,000 patients in 50 countries are being treated by the drug, which is specific and does not act as a general immunosuppressive modality. Recent work on an animal model of multiple sclerosis (experimental autoimmune encephalomyelitis), suggests that Copaxone not only prevents demyelination but may even promote re-myelination in the brain.

In this study the purpose was curiosity-driven basic research. If the amino acid copolymers were meant as models of proteins, then we expect them to resemble proteins also immunologically. A copolymer meant to resemble this protein appeared to repair the damage done to mice by the original protein. Thus started the translational research that led to the drug against multiple sclerosis.

For most individuals, after many years of research, publication in an impressive journal seems the end of the road, but this is not true, certainly not in translational research, because the next step – the development of the fruits of research – is most important. The translation of research into products is important both for the individual and for humanity as a whole.

Nevertheless, in summary, while both achievements – health and economic – are significant, undoubtedly the greatest satisfaction for a scientist is the unexpected result in basic research.

Principles and Prospects of Cancer Immunotherapy

Thierry Boon-Falleur

The specific component of our immune system involves two types of lymphocytes: B cells and T cells. B cells produce antibodies and some T cells called T helper cells collaborate in this process. Other T cells destroy by a lytic process cells that are infected by viruses. They are named cytolytic T lymphocytes (CTL).

The presence on human tumors of tumor-specific antigens that can be recognized by CTL of the cancer patients was definitively demonstrated about 25 years ago. These tumor-specific antigens arise through two main mechanisms. The first is the occurrence in the genes of tumor cells of many point mutations that are not present in normal cells. Many of these mutations change the sequence of the protein produced by the mutated gene. This results in the production of a new short peptide which is presented on the surface of the tumor cell by specialized molecules called MHC class I molecules. These peptide-MHC complexes are recognized by CTL which can destroy the tumor cells. These CTL spare the normal cells of the body as these cells do not harbour the mutation and hence do not present the antigen. The second mechanism is the activation in tumor cells of the transcription of a number of genes that are not expressed in normal adult cells. The genes of this group, the first of which was named Mage, are usually located on the X chromosome. Their activation results from a demethylation process which activates the promoter of the gene. This demethylation occurs at random in tumor cells and not in normal cells with the exception of early germ cells. But these germ cells do not present the relevant antigen because they do not bear class I MHC molecules on their surface. Hence the tumor-specificity of the antigens encoded by these "cancer-germline" genes. In addition to these two main mechanisms, a host of anomalous transcription and translation processes found to occur only in tumor cells produce tumor-specific antigenic peptides.

The tumor-specific antigens resulting from mutations are highly individual for each patient. This made their exploitation for cancer immunotherapy nearly impossible in the early days. However recent considerable progress reducing both the time and the cost of the sequencing of human genomes is now beginning to make their exploitation practical. In contrast Mage-type antigens are shared by significant proportions of cancer patients but they may be less potent antigens than those resulting from mutations.

Almost two decades of trials involving immunization with tumor-specific antigens have not led to a medical breakthrough: responses were observed in only 10% of the patients, a percentage too low for medical use. In contrast, the use of antibodies that block inhibitory receptors of T lymphocytes has led to a much larger fraction of responding patients with many long-term responses. It is through this approach that immunotherapy is now having a considerable impact on cancer treatment. However, this procedure is activating all T lymphocytes and not just the anti-tumor lymphocytes. This results in a significant proportion of patients who undergo severe autoimmune side effects harming essential normal cells. But these side effects are better and better managed by the clinical cancer therapists.

I do hope that at one point an improved vaccination procedure will lead to a cancer therapy which is both highly effective and safe. Combining vaccination with a low dose of T lymphocyte activators represents an attractive possibility. We should bear in mind that our immune mechanisms which are quite successful in curing us from bacterial and viral diseases are rather clumsy, involving an enormous number of activating and inhibitory agents. Perhaps we should be prepared to be equally complex in our approaches by combining vaccination with several local and systemic agents adapted to the profile of the tumor.

At this point, I cannot avoid mentioning that the European authorities have promulgated regulations regarding clinical trials that are well adapted to guarantee the quality of the large phase-three trials, which are managed by pharmaceutical firms to obtain authorizations to market new drugs. Unfortunately, these regulations are totally unsuited for innovative exploratory trials involving a very small number of patients who should be extensively tested to understand the processes at play. This, in my opinion, has all but killed innovative clinical research pursued in European Universities, often increasing the delays by tenfold and the cost by hundredfold. Ill-conceived privacy regulations also prevent the collection of samples from patients at the time of relevant clinical observations. I can personally testify how the extensive analysis of blood and tumor samples of less than five patients provided 90% of the knowledge we have of tumor-specific antigens.

We know now that most metastatic cancer patients for whom we are trying to induce a strong anti-tumoral response have previously mounted a spontaneous response against their tumor. But extraordinarily, this response has stalled. It seems amazing that for such a vital issue, the immune system that is so effective at freeing us for viruses and bacteria that would otherwise kill us within a few days fails to achieve the apparently easy task of eliminating the relatively slow growing tumor cells. The explanation probably rests on the fact that defending young persons against bacteria and viruses had an enormous selective impact during human evolution. On the contrary, cancer kills mostly old people well past their reproductive age and there is therefore little selective value for resistance to cancer.

Finally, what about the consequences of improved cancer treatment for society? When faced, as we were until recently, with the imminent and inexorable death of women in their thirties leaving behind very young children, it is difficult to doubt the validity of one's purpose. I can understand the concern that cancer improvement will extend lives in a way that imposes a considerable burden to society, especially if little progress is made in the area of diseases such as Alzheimer's disease. However, I am confident that ways can be found to manage this situation, by combining technical progress and the pursuit of an inclusive society as, I believe, is occurring in Japan. I fear the prospect of having too many old people much less than I fear the continuous accumulation of a greater and greater share of mankind in monstrously large cities where most of the people live in conditions that are incompatible with human nature.

Block 3 |

Transformative Roles of Science in Societies

SESSION VIII – FUTURE SCIENCE POLICY – REFLECTIONS FROM REPRESENTATIVES OF SCIENCE ORGANIZATIONS, POLICY MAKERS, RELIGIOUS COMMUNITIES AND ACADEMICIANS

The European Research Council (ERC) – Science Ecosystem, Structural Impact, Interdisciplinarity

Jean-Pierre Bourguignon

Thank you very much for the invitation and the introduction. We are totally faithful to the idea that the ERC is funding research on the basis of scientific quality, welcoming initiatives taken by researchers, therefore following a strictly bottom-up approach.

If you allow me, I would like to make three points: the first one is that we, scientists, have to remember all the time that we are evolving in an ecosystem which has several components, and we have to ensure that the right balance exists between these components. So, of course, as President of the ERC, I very strongly make the case that the bottom-up part of the financing of research must be very significant and that the initiative has to be left to researchers for a number of things. Of course, we know that long-term planning for some specific activities requires developing more top-down instruments. So it is clear that a variety of approaches is needed. At the European level, this is why the so-called framework programme has three pillars, as they are usually called, going from research in different forms to innovation. This touches an issue already discussed briefly, namely how to transform scientific results into activities having, in the end, an economic or societal impact.

So, just to continue on the idea of an ecosystem, the other component of the ecosystem that is vital is, of course, the people, because research is, in the end, done by people. Therefore it is very important that researchers, in particular young ones, have a perspective that they might find support to develop their research and a career. As you know, this is not the case in a number of countries where, for various reasons, either positions are not available or they have become extremely unstable or even, in some cases, people feel that they are not welcome and actually better develop their activities by going elsewhere. So the need to offer a professional perspective for young people is something which, I think, has to have a high priority. Having the right ecosystem is not just the question of having enough money to distribute; it requires also an environment in which people feel comfortable to develop their work. So much for the ecosystem.

To obtain that the European Research Council be set up was the result of a long battle by the scientific community. Personally, the first time I heard about the possibility of having an ERC was in 1995. So it took twelve years to get it off the ground, and there were a number of times when scientists thought they were close to getting it and then far from it and then close again. It was quite a complicated process. Finally, the ERC became a reality and, if you look at the detailed history, there were actually interesting moments where some people played a key role. It is always interesting to consider these turning points, and to see that some of the people who made a difference were not scientists, but politicians or civil servants from the European Commission. I don't want to name anybody here, but actually some people changing their minds at the last minute made a big difference. The ERC has now been in existence for eleven years, and I think it has really been endorsed by the scientific community. Just to give one example, last year we celebrated ten years of ERC and we offered the possibility to all institutions to organise some kind of a celebration. Altogether there were 164 such celebrations in Europe, spontaneously organised. We didn't give any money to help them. I personally attended twenty-nine of them, and that was already a lot but a fantastic experience. It really shows the breadth of the endorsement.

Of course, the ERC is providing quite substantial amounts of money to its grantees. This year the ERC budget will pass the 2 billion Euro mark. It will sign more than 1000 new contracts. So it is a very substantial contribution to the support of research, but the point I want to make – actually my second point – is the fact that the ERC has, beyond the money distributed, a structural impact. I think this is extremely important for the ERC governing body, which, as you know, is its Scientific Council, which has the full responsibility of deciding how to spend the money and how to set up the evaluation.

What do I mean by structural impact? Of course, the ERC is very competitive, its success rate this year will be around 13%. We are fully aware that preparing an application requires a lot of work, but now people know that, in order to be successful, they have to come up with ambitious ideas and provide some evidence that they have the potential to achieve these ideas. For a number of young people, and I heard many testimonies to this effect, preparing an ERC application was the first instance ever where they had the opportunity to express what they really wanted to do in the coming five years. The ERC has lifted the ambition of European researchers.

From that point of view the ERC really gives to a number of people, not only young ones, an opportunity to devevlop a really ambitious objective. Actually, in some countries, the fact that young people are given such possibilities is structurally not so obvious as, there, young researchers have to do what their bosses tell them to do.

This is one of the impacts. There are also various mechanisms by which the ERC makes sure that researchers have really the control of things. One of them, that is sometimes misunderstood, is portability. What does that mean? Simply that a researcher who has won an ERC grant hosted at an institution can decide, for one reason or another, to move to another organisation. Actually, it is not so often used but it is some sort of a nuclear weapon in the hands of researchers. Indeed, if an ERC grantee tells his or her president, vice-chancellor or rector, *"Well, maybe I'm going to go elsewhere"*, because things are not going the way they should – sometimes because the institution abuses a little bit and refuses to address problems pointed out by the researcher – usually the problem gets solved. So it shows that portability empowers researchers, which I think is very important.

My third point has to do with interdisciplinarity, a topic about which we heard today how critical it is to achieve a number of results. Often, to really make things happen, you have to bring together people having competences in domains that are not so close to one another. From that point of view, most of the ERC panels are already pluridisciplinary, but we know that some progress can still be made. Indeed, people working in fields that are truly mixing two disciplines often do not get a fair evaluation. One initiative the ERC Scientific Council took to address this challenge was to create a new space for that in the form of a new type of grants. Ordinary ERC grants are given under the responsibility of one Principle Investigator, young or not so young. We decided to reinstate the so-called Synergy Grants which allow a group of two, three or four researchers to call for joint support to a common project. We did that in particular with the hope – and I think it is actually happening – that people coming from different backgrounds, different fields, will join forces in truly creative ways to deal with really major scientific problems. In doing that we stick to a strictly bottom-up approach. We need to make the scientific community ready, intellectually, to work across disciplines. To achieve that, it is very important to make sure there are institutions or programmes in which such an approach is welcome. And to show that this is not so easy I am coming again to my idea of an ecosystem. Pluridisciplinarity is actually not obvious at all because most of the academic life, I am sure you are all aware of that, tends to still be organized on the basis of departments and disciplines.

Promotions tend to be more difficult for people who have been working in several domains. The members of the ERC Scientific Council always have in mind the need to promote interdisciplinarity. We don't have any thematic priority but we work at welcoming and making it easy for people who want to practice research in this way to do it and to get support.

Thank you very much for your attention.

How Scholarship and Science Can Provide Advice to the Political Sphere

Georg Schütte

In modern high-income societies of the global north, we currently observe profound changes in the interaction among the scientific, the political and the social spheres. Expectations towards the science system have changed. They call for new modes to justify and legitimize scientific knowledge. This in turn alters to what extent and how science systems can provide knowledge and advice to the political sphere and to society at large.

The utilitarian challenge

Increasingly, politicians, business leaders, or interest groups confront science systems with the expectation to be useful and to prove their usefulness. This is not new. Already in 1939 Abraham Flexner had to argue in the United States for the "Usefulness of useless knowledge" and thereby for the support of curiosity-driven basic research. Moreover, it does not come as a surprise. For centuries, science had brought about new technologies that led to or contributed to increasing levels of wealth and welfare in these societies. What is new, however, is the expectation that science has to provide solutions instantaneously. The time span from problem definition to the delivery of solutions is shrinking. Digitization will put even more pressure on this process as the production of knowledge, its dissemination and absorption by the respective communities will happen almost simultaneously.

The complexity challenge

At the same time, the complexity of the modern world has increased tremendously. While the world population continues to rise, natural resources become scarce. Food security, clean water, the provision of health services and adequate education opportunities, the adaptation to and mitigation of climate change, to mention just a few, have become so-called "global challenges". The United Nations responded to these challenges by formulating the 17 Sustainable Development Goals (SDG) of the "UN Agenda 2030". While single academic disciplines can provide advice on how to address specific SDG-related questions, no single discipline can address the complex interplay of the various SDGs as a whole. There are conflicting ends as well as conflicting means. Therefore, answers cannot be easy and often require compromises.

The participatory challenge

In addition, science systems cannot develop solutions to these global challenges alone. Moreover, against the backdrop of rapid technological development and digitization some people are afraid of lagging behind and view science and scholarship as part of the problem. Thus, scholars and scientists have to collaborate and interact with those affected by the specific global changes. Therefore, those fields of science that aim at contributing applicable solutions have become – and need to be – partially participatory. Partially participatory means that they do not necessarily need to include those who are affected in the research process. Rather, it means that their perspectives, needs or fears are respected in the overall process of generating (applicable) knowledge and problem solutions. This has not been self-evident. Rather, it runs counter to decades and centuries of scientific expertise delivered ex cathedra. It is a learning process, which often juxtaposes scientific knowledge and indigenous knowledge and calls for new forms of mediation amongst these knowledge orders.

The communication challenge

Scientific knowledge is characterized by its universal nature. Within the science community, there is a shared understanding that there are universal standards of scientific practice. These standards lead to scientific knowledge that is robust, useful, adaptable to new situations, and open to many who can make use of it. At the same time, however, scientific knowledge is historical, transient. The latter makes it difficult for scientists to communicate easy answers at a time of increasing complexity. There is no universal truth that can be grasped by a single scientific discipline or scholarly expertise. Rather there tend to be insights and solutions that hold true for a specific situation at a specific time and for a specific time span. At the same time, the digital revolution has altered the way people in modern societies communicate. In online-based media of direct people-to-people communication, modes of discourse characterized by emotional exchanges and audio-visual modes of communication challenge the standard practice of scientific discourse, i.e. the rational exchange of ideas. These new modes of communication open up opportunities for political and societal actors who claim to provide easy and compelling answers. Populist notions of simplification challenge the scientific notion of complexity.

The deliberation challenge

As a result, scholars and scientists need to adapt the way they work and the way they communicate. Scientists and science organizations need to defend and stand up for their right and ability to self-organize their science system. In liberal, democratic societies, this right is very often constitutionally guaranteed or historically accepted. This freedom to organize itself comes along with the freedom to set out a research agenda, which is driven by inner-scientific reasoning and interests. At the same time, this freedom of research comes along with the responsibility of science systems to contribute to the societal good and to provide answers to pressing problems. This type of research needs to be inclusive. It needs to reach out to and include various groups of stakeholders. In addition, it needs to engage in deliberation. The answer to growing skepticism towards scientific and scholarly reasoning cannot be retreat and exclusion. Rather, scholars and scientists need to explore and to engage in new forms of debate and dialogue. At a time in which trust in public institutions including scholarship and science is eroding, these attempts at debate and deliberations might help to regain acknowledgement and trust. An ideal realm to explore these new forms of interaction is the agenda-setting process for large research agendas which will have a significant impact on society at large.

What does this mean for science advice to politics? In the light of the challenges sketched above, scientific advisors, be they individuals, groups of scientists and scholars, or scientific organizations like, e.g., academies of science, might consider the following recommendations.

Be aware of different logics

In liberal democracies, politicians represent their electorate and aim to respond to the needs of the people. They are part of a network of allegiances, are under public scrutiny and eventually strive for the power to shape and steer public action. Scholars and scientists strive for new knowledge. Some of it is useful for immediate or medium-term action. Some of their insights point to the need for long-term changes of public action. As publicly funded research, research agendas also have to respond to public needs and must be developed together with different stakeholders. The quality of scientific and scholarly work, however, primarily has to live up to the standards of the respective academic field. It cannot and should not be contested by a majority vote of laypersons. Thus, the logics of the political and the scientific sphere differ fundamentally. Whereas scientific and scholarly knowledge has to withstand the contestation of peers, political reasoning has to withhold public debate. In this debate, politicians and various audiences (or the public at large) express and reconcile short-term political interests and long-term convictions based on norms and values. In turn it is the task of scientists and scholars to develop an evidence-base, to present the facts and to rationalize the character of these debates.

Be as inclusive as possible

This does not mean that the scientific and scholarly sphere has to isolate itself. The challenges to our common physical environment and to the social fabric of many societies call for the best knowledge and profound efforts of the academic world. This effort needs to be embedded in society. Science needs to take into account the interests, perspectives and knowledge of different groups within society. For this reason, this part of the general scientific agenda calls for public engagement. Scientists and scholars have to include these knowledge realms and public interests in their reasoning. As a former German Minister of the Environment once remarked: Science and research do not have to restrict themselves to public demand. However, it would be helpful if researchers considered public demand when setting up their research agendas. In doing so they need to explore new modes of public participation in scientific agenda setting. This procedural change might lead to a qualitative change of research results. Many academic disciplines, for example, may address the challenges of adaptation to and mitigation of the effects of climate change. In addition, they may do so from many different angles. Bringing together the knowledge from various natural and social science perspectives might ease the uptake of this advice in the political realm.

Be humble

Science and scholarship is the endless attempt to question existing knowledge and build new knowledge. Thus, scientific and scholarly knowledge is transient. Scientific advice to politics has to take into account this transient and contingent nature. There is no absolute "truth" to be delivered by a single scientific discipline or scholarly expertise. Rather, scientists and scholars have to be self-reflexive. They have to convey and communicate the limitations of their findings, the uncertainties that are due to the limitations of the perspective they can show.

Be understandable

Despite the need to be self-reflexive, scientific advice needs to be as understandable as possible. At the same time, it has to be as complex as necessay. This is not an easy task. There might be inner-scientific reasoning, which might be of interest to scientists and scholars involved. However, the degree of relevance to a political or general public may be low. As one government science advisor once remarked, it might be interesting for the scientific community involved to know that some of the research was basic, and some was applied. For the larger public it sufficed to say that sound research was the basis of the findings.

Be trustworthy

Things move at the speed of trust. Therefore, the basic requirement of scientific advice is trust. Given the challenges mentioned above and the proposals made so far, it seems to be crucial to respect the different logics of the scientific and scholarly sphere on the one hand and the political sphere on the other. Scientific advice can offer options for action. For complex challenges, be it to our natural environment, our social fabric, or to both, there is usually more than one answer. This does not mean, for example, that the International Panel on Climate Change (IPCC) should not recommend a 2-degree temperature rise threshold. However, the way to reach the objective to stay within this corridor requires public debate and political reasoning. This might take longer than it seems appropriate from the scientific point of view. Would it help if science moralized its recommendations to underpin the sense of urgency? Given the many attempts to emotionalize public debates, it seems doubtful whether the voice of scholarship and science can make itself heard that way.

Be persistent

Given the complexity of the challenges we face in our world, the task of scientific and scholarly advice to politics remains to be an endeavor that constantly requires critical reflection by all parties involved. Nevertheless, it is worth trying, again and again, in order to maintain a sense of reason at times of emotional debate, and a commitment to persistence in order to address the fundamental changes ahead of us. Especially in times of fake news and manipulated communication, it is important that science and scholarship contribute to putting public discourse on a rational basis, to making the facts be heard and to enable a change of perspective that is based on evidence and sound research. By constantly applying critical reason, they can help to disclose the all-to-obvious populist simplifications of scientific challenges.

Promoting Inclusive Innovation in Latin America

Lino Barañao

Latin America shows high levels of inequality due to its productive matrix that still relies mainly on natural resources. This is in contrast with countries exporting knowledge-intensive products that show considerably lower levels of income inequality.

On the other hand, employment associated with routine activities is likely to decrease in the near future due to increased automation. This is already happening in industrial agriculture in the region, with the consequent displacement of rural population to the big cities.

It clear then that unless deliberate actions are implemented at the government level, political tension in the region will arise. Therefore, promoting inclusive innovation, understood as the development of value chains based in new technologies that create job opportunities even for those that cannot access to a better education, should be a priority for the region.

I will briefly summarize some of the actions that are being implemented in Argentina. This direction could be extrapolated to other countries of the region.

One of the main changes that we are witnessing is the digital revolution. In contrast with the industrial revolution that produced deep asymmetries in the distribution of wealth between countries, the digital revolution is horizontal and can reach populations that were heretofore not benefited by the previous technologies.

However, these benefits can only take place when proper training is provided and new value chains are developed that lead to an improvement in the number and quality of the job post.

As an example of the magnitude of the digital divide that we have in our country I can mention the case of a region in Mendoza, close to the Andes. We have there an antenna from the European Space Agency which is operated by five Argentinean engineers that can communicate with the Curiosity rover in Mars. A few kilometers from that station was a local community that had no electricity or telephones and therefore could only communicate with people within sight. Thanks to a special program promoted by the Ministry of Science that gathered scientists from different government institutions, this community was able develop a technology to manage guanacos (a South American Camelid) and produce fiber worth up to 600 USD per kg. They have since not only obtained electricity but also internet and access to an e-commerce platform that allows them to commercialize their products. In this context we are also promoting the use of blockchain for the certification of organic products by small producers in order to facilitate access to foreign markets.

On the other hand, Argentinean companies were able to export experimental nuclear reactors and we have just launched a satellite based on radar technology. Three of the Latin American Unicorns are Argentinean software companies. However, there is a shortage of about five thousand engineers and programmers. To provide training and attract youngsters to STEM careers we are teaching code and introduction to robotics in elementary schools and we run a 50-hectares science fair (Tecnopolis) in Buenos Aires, with smaller versions that travel throughout the different provinces. In addition, we run a TV channel called TECTV that airs locally produced documentaries and series showing the opportunities offered by the new technologies, from biotechnology to the development of videogames.

We are also developing value chains for organic and premium food that incorporate technologies such as freeze drying for conservation and blockchain for traceability and validation of environmental and fair trade certifications. The idea is also to associate these products with ancestral cultures, thus providing differential value to the so-called responsible consumer market.

Finally, it is necessary to start forming scientists in the region under a new paradigm. Until now, the norm in Latin American countries has been to send graduate students or postdocs to centers of excellence, usually in Europe or the US. This has been extremely satisfactory in terms of access to the forefront of science in the different areas of research. This strategy has also allowed continuous updating of the technologies used in their countries of origin, provided special conditions required for repatriation are implemented. Otherwise, this policy leads to a brain drain.

In Argentina, thanks to a special program called "RAICES" (which stands for "roots") which provides special contracts and grants to those professionals willing to return, we have succeeded in repatriating more than 1,300 Argentinean scientists. This program also maintains a network of five thousand Argentinean professionals working abroad; these investigators receive weekly information about events and programs taking place in our country. Moreover, we have established a special initiative providing for joint grants that link them with the local scientific community.

In spite of the above-mentioned benefits, education of the scientific labor force in developed countries has two pitfalls.

First, scientists in developed countries have production of knowledge as their sole responsibility. The conversion of this knowledge into wealth is carried out by a productive system that depends on innovation to maintain competitiveness. In those countries, for example in the US and Israel, governments and/or the private sector are also able to make an effective use of the resulting technologies.

However, in Latin America we need a different type of scientist. Like the Roman god Janus, they need to have two faces. One face should look outward to the frontiers of competitive science and the other should focus inwards, searching for means to improve their fellow citizens' quality of life. This latter insight is not usually learned in the centers of excellence of the Northern Hemisphere and is related to scientists' social responsibility.

In Argentina, the vast majority of scientists graduate from public universities which are State-funded and free. Therefore, although they do not have financial debts, they should have an ethical debt towards their community.

However, when students study abroad, they end up having professional and personal acquaintances with scientists from different countries, and less of a link to their community of origin. This, in turn, will make it more likely that potential future collaborations will not include other Latin American scientists. Of course, this also implies that the subject of such collaborations will most likely deal with the mainstream topics of a given field rather than with problems that are relevant to their country of origin.

On these bases we decided to create the Latin-American Centers for Interdisciplinary Formation (or CELFIs in Spanish). The idea behind the creation of these centers was to provide an environment in which young scientists from Latin America could bring problems with such complexity that could not be tackled by a single discipline. This common space should also provide opportunities for students and scientists to share experiences and to develop personal bonds that could be the basis of future collaborations. Thanks to the support from the Latin-American Development Bank we have provided fellowships to more than 1500 students and professors from 19 Latin-American Countries to participate in 270 different courses and research programs.

To conclude, it is clear that scientific and technological development is a necessary but not sufficient condition to promote economic growth. Specific actions are required in developing countries to produce wealth out of knowledge and promote inclusive innovation.

On Trust in Science, Resilience, Co-existence and Hope

Rev. Antje Jackelén

If we want to communicate science to a broader audience – which I think is part of the vocation of a scientist – we need to understand the dynamics of society. Obviously, this is important when we focus on transformative roles of science in society, but also if we want to understand the transformative roles that society can have on science. In my contribution to this panel, I would like to start with the issue of trust.

Trust

It has been said several times throughout this meeting that trust in science is decreasing. If that is true, at least Sweden seems to go against the tide. Swedish society still has high levels of trust in general. When it comes to research and researchers, Sweden last year displayed the highest levels since monitoring started 20 years ago.[1] 61% of Swedes have high or relatively high trust in universities and university colleges.

When it comes to disciplines, it turns out that we find the highest levels of trust in research in medicine. The Macchiarini affair at Karolinska Institute in 2016 entailed a dip, but the usually high levels of trust were quickly restored. Even technology and natural science enjoy high levels of trust; whereas the social sciences, education science and humanities rank significantly lower.

Highly educated and younger people show higher levels of trust than less educated and older people. The closer you live to a university or university college the more likely you are to have high trust. Hence there are notable differences between urban and rural populations.

When it comes to political interest the survey shows that Greens hold the highest levels of trust in research (83% have high trust). Right wing populists hold the lowest (45% have high, 14% little or very little trust).

Research in heart and lung disease and in the environment were deemed to be the most urgent. Least urgent were philosophy and space science.

[1] Survey from 2017. Based on 3,400 individuals aged 16-85 and living in Sweden. 55% responses. https://v-a.se/2018/06/varapport2018_3/

Nanotechnology scored highest on "no opinion" – possibly indicating that its applications are not so well known to the broader public.

One may interpret the results in general as follows: trust depends to a certain degree on proximity to a university or university college; moreover it is related to what one experiences as one's own concern or interest. There seems to be a "this-is-about-me factor" in rating heart and lung disease, as well as the environment, high, and space science low.

I would not say that it is some fuzzy irrationality or subjective feelings that are guiding principles when people think about their trust in science. Rather, it seems to be about perceived relevance and the possibility of getting involved. It may also be about the dynamics of "me-bubbles", amplified by the culture of social media. It seems likely that the scourge of "bubblification" (rather than publication) affects science as well.

In the results of the World Values Survey, we find Sweden almost off the charts – way up in the right corner of the diagram, indicating a maximum of secular-rational values and self-expression in Swedish society.[2] Nevertheless, the package of populist opinions has its vigorous supporters even in Sweden. It manifests itself in an unholy trinity of nationalism, climate scepticism and misogyny: anti-migrants, anti-climate and anti-gender justice. This package tends to be accompanied by "alternative facts" and anti-science attitudes. In social media, climate engagement can be portrayed as a kind of sectarian behaviour, based on blind faith rather than facts, and as oppression of alternative views. Even regarding public service media, claims are raised that supporters and deniers be provided with equal space – as if (climate) science were a sporting game between two teams, and as if questions of mitigation and adaptation were nothing but propaganda. Similar claims for equal treatment have surfaced in discussions around immunizations.

If the difference between science and pseudo-science disappears, the discussion and communication of scientific theories and data will be severely hindered. It is not just that data are trivialized by claiming that they represent subjective opinions rather than facts. It is also about the politicization of science "from outside". In light of the populist pattern of politicizing, science and theology find themselves in the same boat. As much as the scientific data that are disliked are said to be politics or a dubious expression of political correctness, as much are theological facts that do not fit the populist agenda declared to be politics, and not theology.

[2] http://www.worldvaluessurvey.org/WVSContents.jsp?CMSID=Findings

This can have dire consequences. Attention is effectively diverted from discussion of facts and from a shared informed view of reality. Initiative is successfully taken away from the proponents of science and theology. Mainstream media is picking up on the suspicion of politicization. And instead of being able to share facts and engage in discussions that may further development in society, scientists and theologians need to put their energy into defending themselves and their disciplines against fabricated allegations.

A conclusion that might be drawn from the data and ensuing reflections on trust: High levels of formal and theoretical trust in science do not necessarily translate into practical trust in the processes and results of scientific research. This impacts the communication of science and the transformative roles that science can have in society.

So what's the problem?

The problem is: The world is drunk

In all too many countries, people are constantly drinking from a cocktail made of five dangerous ingredients, five poisonous P's: polarization, populism, protectionism, post-truth and patriarchy. This poison affects science, religion and society. Polarization tears apart what should belong together and work together. Populism pits people and so-called elites against each other. Protectionism puts one's own country, one's own people and one's own interests first, at the expense of the common good. Post-truth is the contempt of truth that disfigures the vital triad of the true, the good and the beautiful, without which we cannot live. Patriarchy continues to deprive the world of the full flourishing of women and children, and in the end it dehumanizes women as well as men.

I do not know a panacea that will make this drunken world sober and whole. However, literacy certainly is a key element in countering the worst consequences. We need literacy in science, philosophy (hermeneutics!) and theology (factual knowledge as well as spiritual practice and experience). We know from history how much literacy has meant for the development of societies, especially the literacy of girls and women.[3] In his contribution to this session of the Pontifical Academy of Sciences, Professor Lutz spoke of the subspecies of *homo sapiens literata*. I would like to add that we need to think about the subspecies: *homo sapiens literata digitalis*. The digital

[3] Cf the paper by Professor Wolfgang Lutz, "World Population Trends and the Rise of *homo sapiens literata*", delivered at this session of the Pontifical Academy of Sciences.

revolution and digital literacy will change life and work dramatically for billions of people. What does it mean to work with digital natives? What are the implications of digital divides? What are the effects of digitalisation on human brains?

A second key requirement is that we appropriately attend to the basic and crosscutting dynamics of fear versus hope. The five P's are driven by fear. Behind them, the question of hope looms large. We need to acknowledge and understand the fears that are present in individuals as well as in communities and societies – be it fears of loss of security, of economic status or of cultural identity. What does permanent exposure to stressors, especially in small doses, do to collective nervous systems? At least two reactions stand out as reasonable. Either externalization in terms of scapegoating, with increasing polarization as a consequence. Or internalization, with the typical behaviour of a traumatized person of blaming oneself. Either way, the dynamics of sustained fear tends to make us defensive, opposed to change, prone to rigidity – a behaviour that directly feeds into a new loop of the five P's. We end up with a vicious circle. One might say that this requires trauma-sensitive communication.[4]

In dealing with a world drunk with the five P's, we need to foster the ability to engage constructively with alterity, complexity, empathy and accountability. This is a prerequisite for effective communication, also for science.

In doing so, we will be better off in our attempts to create a framework for effective and positive transformation of society, scientifically sound and with enlightened humanism. For this framework, I suggest three key terms:

Resilience, co-existence and hope

Because:

With a framework of resilience, we will be able to make sense of the fights of women and men for the health, wellbeing and future of their children. We will be able to make sense and meaning of necessary sacrifices. With a framework of resilience, we will be able to confront the trends and powers that impede our constructive engagement with the greatest challenges of our time. We will be able to confront polarization. We will be able to resist populism. We will be able to counteract protectionism. We will be able to fight against post-truth. And we will be able to overcome patriarchy.

[4] Cf Jennifer Baldwin, *Trauma-Sensitive Theology: Thinking Theologically in the Era of Trauma*. Eugene OR: Cascade. 2018.

With a framework of co-existence, we will be able to revisit some of the borders that are harmful to our working and living together. We will be able to foster more adequate views of nature and will listen to the groaning of creation and we will be in a much better position to address climate change in a holistic way. With a framework of co-existence, we will be more eager to hear the stories of those who are suffering and will be suffering from the degradation of their environments and livelihoods. We will be better at listening to the voices of indigenous peoples.

With a framework of hope, finally, there is reason to expect change. Hope is one of the theological virtues in Christian tradition and hence a theological category. It is more than optimism. Optimism extrapolates from that which is already known. Hope reaches farther than that: it looks for promise and builds up its strength in trusting in that which is not yet. Optimism rests on what the past has brought about, hope looks to what the future can bring. Hope energizes our desire for truth, love and justice. It has a sister in courage. Together, they insist that change must be possible.

Changing minds, *metanoia*, must still be possible! Both our own minds and those of others.[5] With a theology of hope, we will be able to counter narratives of hate and fear with narratives of love and hope. The world is crying out for credible words of hope and for the works of love that faith compels us to carry out, together with people of good will from many traditions.

[5] A point in case can be found in Matthew 15:21-28, the story of the Canaanite woman who asks Jesus for help for her sick daughter. He turns her down twice, even comparing her to a dog who is unworthy to receive help. Yet, she persisted and made Jesus change his mind. Jesus changes the sense of his own mission and hence the mission of the whole church. If one woman was able change Jesus's mind, changing minds, *metanoia* must still be possible!

Transformative Science? Transformative University?

Jürgen Mittelstraß

Reflection on science is now one formula richer: *transformative science*. Not long ago, the descriptions used here were "responsible science" and "citizen science". As responsible science, as it is said, science meets the requirement to ensure the integrity of the research process as well as to follow society's call to solve societal problems. As citizen science, as it is said, science compensates for the purported societal lack of participation in the research process. And now transformative science.

In fact, science, in a general sense, is always transformative, against itself – any scientific insight also alters scientific knowledge – and against society, if one thinks of the transformation of theoretical knowledge into practical, application-relevant knowledge. Where insights within science itself have evolved, they are referred to as scientific *progress*, in case of fundamental new insights as scientific *revolutions*,[1] where external effects of scientific insights are registered, they are referred to as *innovations*, i.e. technique-oriented applications of scientific knowledge with regard to societal aims. What, actually, is new when we today, mainly in connection with the call for *sustainability*, talk so strongly about transformative science? Is it a matter of substance, of the rediscovered nature of science, or is it a matter of rhetoric, i.e. science marketing? Science, so it seems, plays with its nature. A wakeup call.

Science connects *epistemic* structures, i.e. the way science understands the world, with (scientific) truth, and it connects *institutional* structures with (social) reality. Both structures form a complicated unity within science itself in which the distinction between internal and external elements, for example internal norms like logical consistency and external norms like applicability, threatens to become blurred. For science is both the particular form of knowledge formation as well as the institutional form of this knowledge formation itself, the university being the paradigm of such a connection. It is the institutional aspect which interests us here,

[1] See Th.S. Kuhn, *The Structure of Scientific Revolutions*, Chicago and London: University of Chicago Press 1962, 3rd edition 1996.

namely the concept of a transformative science, by which science is determined by social and environmental objectives. For example, in a proposal for the Cancun conference on climate change in 2010, calling it the *Great Transformation*, the principle of sustainability, a concept nowadays used in an almost inflationary way, is declared to be a comprehensive programme, based on a new social contract which includes science and the university.[2]

Under the title 'transformative university' with the objective of a *sustainable society*, diverse forms of obligation of the university are discussed today. They range, mostly on a systems-theory background, from a recollection that universities serve not only (scientific) truth, i.e. autonomously determined knowledge formation, but also the objectives and aims of a society which recognizes in science an essential basis of its progress, to a direct commissioning of the university according to social objectives, in this case the realization of a sustainable society. The university, as we know it, not only since Wilhelm von Humboldt, is becoming a *sustainable university*. Its definition runs as follows: "The sustainable university is one that through its guiding ethos, outlook and aspirations, governance, research, curriculum, community links, campus management, monitoring and *modus operandi* seeks explicitly to explore, develop, contribute to, embody and manifest – critically and reflexively – the kinds of values, concepts and ideas, challenges and approaches that are emerging from the growing global sustainability discourse".[3]

In this rather vague definition, the coordination of the system, university, which is part of the system of science among other systems like politics or economy, is succeeded by the subordination of the university to these systems. Reference is to a model, *Humboldt 2.0*, in which the search for (scientific) truth and knowledge no longer determines the pace of the university but rather service to society, here with respect to sustainable

[2] WBGU (Wissenschaftlicher Beirat der Bundesregierung Globale Umweltveränderungen) (ed.). *Welt im Wandel: Gesellschaftsvertrag für eine Große Transformation. Hauptgutachten*, Berlin: WBGU 2011.

[3] R.S. Sterling, "The sustainable university: challenge and response", in: R.S. Sterling *et al.* (Eds.), *The Sustainable University: Progress and prospects*, London and New York: Routledge 2013, p. 23. See also H. von Weenen, "Towards a vision of a sustainable university", *International Journal of Sustainability in Higher Education* 1 (2000), pp. 20-34; D. Fisher *et al.*, "Getting an empirical hold of the *sustainable university*: a comparative analysis of evaluation frameworks across 12 contemporary sustainability assessment tools", *Assessment & Evaluation in Higher Education* 40 (2015), pp. 785-800.

progress.[4] By the way, this task can also be found in concepts like a stakeholder university or an entrepreneurial university. Here, too, not scientific or academic interests guide the university, but rather social, particularly economic interests. Its self-conception in the old sense is then described in such a way that universities "provide research and teaching in return for public funding at a relatively high degree of institutional autonomy; under this contract, the universities, often supported through research-funding agencies, have been expected to generate fundamental knowledge for society, and to train the highly qualified manpower required by an advanced industrial society".[5] But what is wrong with this description? Certainly not that the university fulfils its obligations towards research and teaching. That it sticks to the image of linear process leading from university research to applied research? Indeed, this image is questionable, but for other reasons than those usually given. It is not the utilization of science and the university for a sustainable society, thus a social-theoretical argument, which speaks against a linear transfer model from basic research to applied research, but this distinction itself, thus a science-theoretical or epistemological argument.

As a matter of fact, basic research, applied research and development today form a *triangle of research*, often mutually supportive in concrete research programmes both in and outside the university. They interlock and intermingle when focusing on a problem. Pure basic research still exists only in very special research fields; application-oriented basic research is becoming more and more the norm. The archaic simplicity (sometimes simplemindedness) in research affairs has become a complex interlocking of interdependent research orientations. This means that the goals of science, in as much as these are expressed by such ideals as truth and knowledge, are more and more joined to the goals of a world that is less inclined to admire than to apply the results of science. Again, this is an inner-scientific, and also an inner-university development, nothing imposed by the society or by a paradigm shift turning the university into a transformative or sustainable university.

[4] U. Schneidewind and M. Singer-Brodowski, *Transformative Wissenschaft: Klimawandel im deutschen Wissenschafts- und Hochschulsystem*, Marburg: Metropolis Verlag 2013, pp. 102-103.

[5] M. Gibbons, "Science's new social contract with society", *Nature 402* (2 December 1999), C81.

All the same, it is said that it is society which started a transformation of science. With the catchword *mode 2* a fundamental change in the relation between science and society has been described,[6] meaning a shift from 'reliable knowledge' to what is now called 'socially robust' knowledge:[7] "The latter characterization is intended to embrace the process of contextualization. For 'socially robust' knowledge has three aspects. First, it is valid not only inside but also outside the laboratory. Second, this validity is achieved through involving an extended group of experts, including lay 'experts'. And third, because 'society' has participated in its genesis, such knowledge is less likely to be contested than that which is merely 'reliable'".[8] At the same time it is claimed that socially robust knowledge is superior to reliable knowledge "because it has been subject to more intensive testing and retesting in many more contexts – which is why it is 'robust' – and also because of its malleability and connective capability".[9] With this, science and the university are committed to a societal programme; research becomes programme research and is socially determined. Such a turn ignores the fact that autonomy is not an external property of research, and that the scientific community does not represent itself as an individual entity which can be controlled from outside. But what might be even more serious: here, it is not only the *status* of science that is changing (or is meant to be changed), but also, in a highly problematical sense, the *concept* of science. The new concept, one could say, is the concept of science studies, which is a sociological concept, not the concept of philosophy of science and science itself.

As far as the university and its redefinition as transformative (or even more: as a sustainable university) is concerned, this definition, taken by itself, is rather strange. After all, it is not the transformativity and sustainability of the university that is at stake, but rather its autonomy in research and teaching as well as its responsibility in dealing with problems which the world offers and with the future of society. The transformativity and sustainability of the university – if one really wants to talk this way – is, ironically, endangered only if the university should become obliged to ob-

[6] M. Gibbons *et al.*, *The New Production of Knowledge: The Dynamics of Science and Research in Contemporary Societies*, London etc.: Sage Publications 1994.

[7] H. Nowotny *et al.*, *Re-Thinking Science: Knowledge and the Public in an Age of Uncertainty*, Cambridge: Polity Press 2001.

[8] M. Gibbons, "Science's new social contract with society", C82.

[9] M. Gibbons, "Science's new social contract with society", C84.

tain the protection of transformativity and sustainability in the defined sense and, accordingly, if its autonomy were to be restricted.

In this situation, I plead for more modesty and a sense of proportion. The university does not solve the problems of the modern world, but it certainly can contribute to their solution. In the case of climate research, but also, for instance, in the case of energy and medical research, this is obvious. However, the best way for the university to serve society is to stick to its core missions – (basic) research and teaching that is close to it, care of fields and disciplines, training of young scientists – and thereby to develop a strong sense for the solution of practical problems as well. This is the (epistemological and, at the same time, moral) meaning of a *research imperative* or research commandment which can be formulated as follows: Let yourself be guided by the thirst for the new and the will to know what innermost holds the world together, but remember that it is no lesser goal to hold that world together with what you do in research and development.[10] Whoever follows this imperative, here in its meaning as a moral imperative, follows the right track anyway. He holds fast to the strengths of science and the university and does not deliberately put these strengths at risk in favour of a – always a bit trendy – transformativity and sustainability rhetoric. The strongest critic of science, also in these matters, is always science itself.

[10] See J. Mittelstraß, *Schöne neue Leonardo-Welt: Philosophische Betrachtungen*, Berlin: Berlin University Press 2013, p. 170.

El futuro ecológico de las grandes ciudades

Cardenal Lluís Martínez Sistach

Al hablar de ecología, como de la encíclica *Laudato si'* del Papa Francisco, podría parecernos que afecta a la naturaleza, a las zonas rurales y no a las grandes ciudades. Pero no es así, en absoluto, porque las grandes ciudades sufren las consecuencias negativas del deterioro de nuestro planeta y son causa también de este deterioro. Por ello, debe haber por parte de las grandes urbes, de sus ciudadanos y de sus autoridades un interés en velar y conseguir que las grandes concentraciones urbanas sean ecológicas. La encíclica lanza esta pregunta "¿qué tipo de mundo deseamos transmitir a los que vendrán después de nosotros, los niños que están creciendo?"[1]

El Papa Francisco en su encíclica sobre la ecología trata un tema muy suyo: las grandes ciudades. El Papa afirma que "hoy advertimos el crecimiento desmesurado y desordenado de muchas ciudades que se han hecho insalubres para vivir en ellas, a causa no solamente de la contaminación originada por las emisiones tóxicas, sino también del caos urbano, de los problemas del transporte y de la contaminación visual y acústica… No es propio de los habitantes de este planeta vivir cada vez más inundados de cemento, asfalto, vidrio y metales, privados del contacto físico con la naturaleza".[2]

La humanidad se convierte en urbanita. Actualmente el 54% de la población mundial vive ya en grandes ciudades y el año 2050 será el 75%, 6.000 millones. La ecología y las grandes ciudades es tema de primera actualidad y de mucho futuro. La Fundación que constituí en Barcelona, "Antoni Gaudí para las grandes ciudades", organizó en julio de 2017 un Congreso Internacional en Río de Janeiro sobre "*Laudato si'* y grandes ciudades". Tres temas centraron la atención que inciden en una ciudad sostenible y limpia: el agua potable, la calidad del aire y la solución a la abundancia de residuos.

El punto de partida de la encíclica es la escucha espiritual de los mejores resultados científicos disponibles hoy en materia ambiental para dejarse

[1] LS 160.
[2] LS 44.

tocar en profundidad y dar una base para concretar el itinerario ético y espiritual que hay que seguir.

Agua potable

El agua es el elemento esencial para el desarrollo de la vida. El acceso a cantidades suficientes de agua limpia es obligatoria para una vida sana, y tenemos actualmente la tecnología para proporcionar agua suficiente y limpia a todos los humanos. Aunque la situación del tratamiento y la disponibilidad de agua han mejorado en los últimos veinte años, el cambio climático y la presión creciente de la población sobre los recursos hídricos pueden poner en peligro este progreso.[3]

De hecho el agua potable no llega a todos. En la actualidad, no hay agua potable para 900 millones de personas (Banco Mundial, 2009) y no hay agua con saneamiento adecuado para 2000 millones (UNICEFF/OMS, 2004). El Papa Francisco ha afirmado que “en muchos países donde la población no tiene el agua potable no falta el suministro de armas y municiones que continúan deteriorando aún más la situación”.[4]

Hemos de tener presente que hay dos tipos de megaciudades. Algunas de ellas eran grandes hace mucho tiempo y tienen ya estructuras adecuadas que han ampliado y que sólo necesitan mantenimiento. Por ejemplo, Tokio, con 38 millones de habitantes y 27.000 Km de tuberías para la distribución del agua al 100% de la población. Las megaciudades nuevas han experimentado una vida rápida que a veces modifica el territorio y altera los flujos de agua preexistentes, creando así la necesidad de adaptar las infraestructuras de distribución. De hecho, en algunas ciudades, se anima a las personas a recolectar y usar el agua de la lluvia proveniente de su techo. Cuando la densidad de población es alta, las enfermedades transmitidas por el agua son más frecuentes.

El agua es un derecho humano básico y universal, relacionado con la dignidad humana, como lo destacó en 2010 el Consejo de Derechos Humanos de las Naciones Unidas. El Papa afirma que “el acceso al agua potable y segura es un derecho humano básico, fundamental y universal porque determina la supervivencia de las personas y, por tanto, es condi-

[3] Cf. J.O. Grimalt, *El agua y su depuración,* en LL. Martínez Sistach (comp.) Laudato si’ *y grandes ciudades. Propuestas de una ecología integral,* Madrid 2018, 66-67.

[4] Discurso al Congreso Internacional sobre la gestión de agua, Universidad Urbaniana de Roma, 8 de noviembre de 2018.

ción para el ejercicio de los otros derechos humanos".[5] Un principio ampliamente aceptado en teoría es que el precio del agua debe ser asequible a todos los ciudadanos, incluidos los más pobres. Además, cuando haya escasez, el agua debe distribuirse con imparcialidad. Como afirma el Papa San Juan Pablo II en su encíclica *Centesimus annus*: "Dios le dio la tierra a toda la raza humana para el sustento de todos sus miembros, sin excluir ni favorecer a nadie".[6]

En las últimas décadas ha habido una tendencia a confiar la distribución del agua y el tratamiento de aguas residuales a las empresas privadas. Se ha argumentado que las estructuras públicas son ineficientes a menudo, que el mantenimiento de las tuberías, para la distribución del agua requiere una tecnología moderna y, finalmente, que una empresa de agua también debería ocuparse del tratamiento de las aguas residuales, para lo que hace falta una tecnología compleja. Recientemente, sin embargo, las autoridades públicas han decidido revertir esta tendencia en muchos casos y asumir el control directo de las compañías de agua.[7]

Los mapas mundiales de los recursos hídricos revelan una situación de contraste entre regiones y países con gran abundancia de agua, con m^3 por habitante, como es el caso de Islandia, Congo, Brasil, etc. Y otros países con gran escasez como Kuwait, Franja de Gaza, Emiratos Árabes Unidos, etc. Esto indica que la solución a esta importante y vital problemática del agua no pasa sólo por la racionalidad técnico-operativa y científica, sino también por la racionalidad axiológica, en la que hay otros valores antropológicos, teológicos y culturales relacionados con los recursos hídricos. De ahí la importancia del enfoque ético. Francisco nos dice que la "cuestión ecológica" es también una cuestión moral. Ante el cosmos estamos sometidos a leyes no sólo biológicas, sino también éticas. La transgresión de las cuales no queda impune.[8] Francisco recuerda que "algunos estudios han alertado sobre la posibilidad de sufrir una escasez aguda de agua dentro de pocas décadas si no se actúa con urgencia".[9]

[5] LS 30.

[6] N. 31.

[7] Cf. M. Iaccarino, ¿Cómo *obtener agua de buena calidad en las ciudades en desarrollo?,* en LL. Martínez Sistach (comp.), Laudato si' *y grandes ciudades…*, o.c., 79.

[8] Cf. Ll. Martínez Sistach, Laudato si'*: una encíclica para la humanidad*, *en* LL. Martínez Sistach, Laudato si' *y grandes ciudades…,* o.c., 36.

[9] LS 31.

Hay un contravalor consistente en la visión objetivista y cuantitativa del agua, tratándola únicamente como un mero objeto de compraventa y sometiéndola a la lógica del mercado, vaciándola de su valor teleológico y de su dimensión socioambiental. Esta mercantilización del agua acaba convirtiéndola en un objeto de lucro.[10] El Papa Francisco ya advierte "que es previsible que el control del agua por parte de grandes empresas mundiales se convierta en una de las principales fuentes de conflictos en este siglo".[11]

La *Laudato si'* aborda estos aspectos importantes sobre el agua: 1) La importancia del agua potable para la vida humana y el sostenimiento de los ecosistemas; 2) La preocupación por el aumento de la escasez de los recursos hídricos sobre todo en las grandes ciudades, lo cual crea una problemática que alcanza la escala mundial, regional y local. Conviene recordar cuanto va a aumentar la gravedad de esta cuestión con el cambio climático; 3) En muchas partes del mundo la calidad del agua afecta directamente a los pobres, con altos índices de mortalidad infantil; 4) Dada la importancia de las aguas del subsuelo como reserva de futuro, hay que tener presente los peligros de la contaminación, las actividades agrícolas, el extractivismo, los residuos industriales; 5) Con el crecimiento en los últimos años de la explotación y el consumo de agua mineral, aparece el dilema ético de la privatización de este recurso, que es un bien universal y un derecho de las personas; 6) La consecuencia de la escasez del agua se refleja en el aumento del precio de los alimentos, lo que los convierte en menos accesibles para la mesa de los pobres.[12]

Contaminación del aire

Las ciudades no son precisamente lugares sanos. El denso tráfico, los escasos espacios verdes, la contaminación del aire, el ruido y la violencia contribuyen a deteriorar la salud. Muchas de nuestras grandes ciudades están asfixiadas por la contaminación. Muchas ciudades del mundo, incluso algunas de las más contaminadas, aún no recogen de forma sistemática la información sobre la calidad del aire ambiente.[13]

[10] Cf. J.C. de Siqueira, *Enfoque ético del agua,* en Ll. Martínez Sistach (comp.), Laudato si' *y grandes ciudades…*, o. c., 87.

[11] LS 31.

[12] Cf. Ibid, 86-88.

[13] Cf. M. Neira, *Prioridades en salud pública global,* en LL. Martínez Sistach (comp.), Laudato si' *y grandes ciudades…*, o.c., 117-119.

Las muertes por enfermedades no transmisibles que pueden atribuirse a la contaminación del aire han aumentado hasta la cifra de 6,5 millones anuales. Cuando dañamos la Tierra, dañamos nuestra propia salud. Los seres humanos somos tan vulnerables como cualquier otra especie.

Para reducir las repercusiones de la contaminación atmosférica urbana sobre la salud pública es preciso reducir las fuentes principales de contaminación, en particular la combustión de combustibles fósiles para el transporte motorizado y la generación de electricidad, y mejorar la eficiencia energética de los edificios y las fábricas. Las ciudades cuyas autoridades han invertido en la capacidad para monitorear y notificar regularmente las mediciones de la calidad del aire patentizan con ello el compromiso de afrontar los problemas de calidad del aire y la salud pública.

Cuando tratamos de estas cuestiones a veces damos la impresión de que toda la responsabilidad recae en los que mandan en la sociedad, como si los ciudadanos no tuviéramos nada que hacer. El Papa Francisco se refiere a muchas cosas que hemos de realizar los ciudadanos desde la manera de tratar los residuos que generamos hasta la utilización de los combustibles y de los medios de transporte.[14]

Aumento de los residuos

Narea afirma que "ningún problema ambiental en el mundo ha adquirido la importancia de los residuos sólidos, con la excepción del cambio climático en el siglo XXI".[15]

La verdad es que la basura no fue un problema hasta que el hombre empezó a vivir en ciudades. En 1896 un director de escuela de sanidad de Nueva York revolucionaría el mundo de la recolección de basura. Han transcurrido más de cien años y podemos seguir observando que los problemas de los residuos sólidos constituyen una de las preocupaciones de mayor envergadura en las ciudades. El medioambiente y la salud de la población demandan un tratamiento integral para alcanzar soluciones adecuadas desde el punto de vista ético, social y económico. Todo esto, en la actualidad exige un tratamiento sistémico de aspectos relacionados con la recolección, transporte, tratamiento y disposición final de los residuos domiciliarios.

[14] Cf. M. Barbarà, *Reflexiones éticas sobre el problema del aire,* en Ll. Martínez Sistach (comp.), Laudato si' *y grandes ciudades…*, o.c., 142.

[15] M.S. Narea, *Los residus urbanos en grandes ciudades e impactos ambientales y sociales,* en Ll. Martínez Sistach (comp.), Laudato si' *y grandes ciudades…,* o.c., 148.

Un interesante estudio, elaborando para el Banco Mundial, sobre la gestión de los residuos sólidos urbanos en el mundo, estima que en la actualidad los 3.000 millones de urbanitas generan 1,20 kilos de basuras por persona al día (1.300 millones de toneladas anuales). Hacia el 2025, cerca de 4.300 millones de ciudadanos producirán 1,42 kilos por persona y día (2.200 millones de toneladas anuales).[16]

Los desafíos que plantea esta expansión urbanizadora para la calidad de vida humana y la sostenibilidad medioambiental son incuestionables. El aumento demográfico en las ciudades y el cambio en sus patrones de producción y de consumo comienzan a chocar con los límites de algunos recursos naturales finitos. El Papa Francisco en su carta *Laudato si'* señala que "la humanidad está llamada a tomar conciencia de la necesidad de realizar cambios de estilos de vida, de producción y de consumo, para combatir este calentamiento o, al menos, las causas humanas que lo producen o acentúan".

El concepto de manejo integral de residuos sólidos está siendo adoptado por varios países de América Latina y el Caribe. Este manejo envuelve una serie de actividades coordinadas que abarcan desde la generación hasta la deposición final de los residuos, lo que incluye la reducción en la fuente, la separación, la reutilización, el reciclaje, el coprocesamiento, el tratamiento biológico, químico, físico o térmico, el acopio, el almacenamiento, el transporte y la deposición final de los residuos con el fin de lograr eficiencia sanitaria, ambiental, tecnológica, económica y social. Finalmente, en grandes ciudades se deberían incorporar la integración de los recicladores de base, la colaboración en el cierre de los cincuenta vertederos incontrolados más grandes del mundo próximo a las ciudades – propuesta efectuada por ISWA – y el esfuerzo para contener los vertederos incontrolados, reinsertándolos, por ejemplo, en un parque, como es el caso del antiguo vertedero La Feria, hoy parque Padre André Jarlan, en Santiago de Chile.[17]

Ciudades inteligentes por la sostenibilidad y el clima ecológico

Se constata que los avances de la ciencia y de la técnica no se han visto acompañados por un progreso ético y cultural. El Papa Francisco aboga por un pacto entre ciencia y conciencia, entre ciencia y sabiduría, y en esto las diversas culturas y las religiones tienen unas "reservas" humanas de mucho valor. La ecología es también un tema ecuménico e interreligioso. En la

[16] Cf. Ibid, 153.
[17] Cf. Ibid, 168-169.

pastoral de las grandes ciudades hay que tener muy presente los contenidos ecológicos que humanizan estas realidades. La crisis ecológica, afirma Francisco, pide una "conversión ecológica" también a los cristianos.[18] Y añade: "Es un bien para la humanidad y para el mundo que los creyentes reconozcan los compromisos ecológicos que brotan de sus convicciones religiosas".[19]

La Resolución aprobada por la Asamblea General de la ONU, de 25 de septiembre, recalca la necesidad de luchar todos contra el cambio climático, presenta un panorama sombrío sobre todo lo relacionado con la ecología integral en nuestro mundo, y establece 17 objetivos para conseguirlo. El objetivo onceavo se refiere a las ciudades con estos términos: "lograr que las ciudades y los asentamientos humanos sean inclusivos, seguros, resilientes y sostenibles", concretando lo siguiente: "De aquí a 2030, reducir el impacto ambiental negativo *per cápita* de las ciudades, incluso prestando especial atención a la calidad del aire y la gestión de los desechos municipales y de otro tipo" (11,6). A pesar de ello, el Papa Francisco, en julio de 2018, ha dicho "que todos los gobiernos deben esforzarse por cumplir los compromisos asumidos en París para evitar las peores consecuencias de la crisis climática… La reducción de los gases de efecto invernadero requiere honestidad, valentía y responsabilidad".

Las ciudades generan más de un 70% de las emisiones de gases de efecto invernadero, que son la causa del cambio climático, y éste es la amenaza más seria para nuestra supervivencia como especie. Hay que tener en cuenta que estas ciudades crecen en número y en habitantes constantemente al convertirse nuestro planeta en urbanita.

Pero hay grandes ciudades que ofrecen buenas perspectivas para evitar el cambio climático catastrófico y crear un futuro sostenible. Coincidiendo el 2005 en Londres, con la celebración del G-20, el alcalde de esta ciudad, Ken Livingstone, convocó una reunión de alcaldes de las mayores ciudades de los países del G-20 para debatir únicamente el cambio climático. A partir de aquella primera reunión, los alcaldes de grandes ciudades del planeta se han erigido en líderes en la lucha contra el cambio climático. Esta red de ciudades del C40, está formada por 91 ciudades, representando a 650 millones y un 25% del PIB mundial, y todas ellas están comprometidas con una acción climática urgente.

En diciembre de 2015, durante las negociaciones de la conferencia de París sobre el clima, más de 750 alcaldes asistieron a una cumbre en el

[18] Cf. LS 217.
[19] LS 64.

Ayuntamiento parisino para visibilizar el compromiso colectivo de las ciudades. Unos días más tarde, casi 190 firmaron el acuerdo de París sobre el cambio climático.

El objetivo del acuerdo de París es limitar el aumento de las temperaturas globales al 1,5 grados Celsius por encima de los niveles preindustriales. El C40 ha calculado que es lo que deben hacer para lograrlo las mayores ciudades del mundo, y la magnitud del desafío es formidable. Estos alcaldes están encabezando la revolución de lo sostenible y la disminución del uso del carbono en nuestras ciudades. Con medidas como el despliegue de flotas de autobús eléctricos en las ciudades chinas, los esfuerzos de las ciudades europeas, sudamericanas e indias para expulsar del centro el tráfico de los vehículos más contaminantes, la adopción de decenas de miles de edificios en las ciudades norteamericanas para conseguir una mayor eficacia energética y los barrios en bajo uso de carbono en las ciudades de todo el mundo. A finales de 2020 todas las ciudades del C40 tendrán un plan para garantizar que pueden cumplir con las obligaciones del acuerdo de París.

Hay que recordar que después de que Donald Trump retirara su país del acuerdo de París sobre el cambio climático, más de 300 alcaldes estadounidenses se han comprometido a "adoptar, cumplir y respaldar los objetivos del acuerdo". En octubre de 2017, un grupo pionero formado por 12 ciudades del C40 (Londres, París, Los Ángeles, Barcelona, Copenhague, Quito, Vancouver, México D.F., Milán, Seattle, Auckland y Ciudad del Cabo) se comprometieron a realizar la transición hacia unas calles libres de combustibles fósiles adquiriendo sólo autobuses con cero emisiones a partir de 2025 y asegurando que parte importante de esas ciudades sean cero emisiones para el 2030. Como afirma el texto de la declaración: "Como alcaldes y alcaldesas de las ciudades más importantes del mundo, nos comprometemos a transformarlas en lugares más verdes, saludables y prósperos para vivir. Nuestras calles deben ser seguras y accesibles para todos y el aire que respiramos debe ser limpio y libre de emisiones perjudiciales. De esta manera mejorará la calidad de vida de toda la ciudadanía y se ayudará a combatir la amenaza global para el cambio climático".

Un progreso similar se está realizando en todos los aspectos de la vida urbana desde el reciclado de basura, los edificios, la producción y el consumo energéticos, los alimentos y el agua.

Hoy se habla de las ciudades inteligentes que son el resultado de la necesidad cada vez más imperiosa de orientar nuestra vida hacia la sostenibilidad. Así, estas ciudades se sirven de infraestructuras, innovación y tecnología para disminuir los consumos energéticos y reducir las emisiones de combustibles fósiles.

El tipo de formaciones urbanas actuales en todo el mundo representan un considerable desafío a nuestra comprensión del orden mundial basado hasta ahora en la piedra fundamental del Estado, que en estos momentos ya se ha vuelto inestable ¿Estamos presenciando un reajuste en el tipo de relación entre ciudades globales y los Estados? Simon Curtis recuerda que las redes de gobernanza transnacional como el grupo C40, representan una agrupación política planetaria que supone un gran salto de escala y que vincula acciones locales con resultados de gobernanza global, todo al margen de las actividades estatales.[20] Los dirigentes de las ciudades globales se enfrentan hoy al desafío de preservar los beneficios de décadas recientes y al mismo tiempo abordar las injusticias. Tal es el desafío reconocido por la Nueva Agencia Urbana de la ONU-Habitat.

El problema del cambio climático es real y grave, pero se abren caminos tímidos para luchar contra este cambio y crear ciudades salubres para ofrecer a los ciudadanos una vida humana más sana y feliz.

[20] Cf. *Las ciudades globales y el futuro del orden mundial,* en Dossier La Vanguardia, enero-marzo 2018, 8-15.

Religions Must Act Together to Defend Human Dignity and the Planet

H.E. Msgr. Marcelo Sánchez Sorondo

What is the meaning of religion in our meeting? I am thinking of the great challenges that we are facing, which were indicated by Pope Francis in his address to the Academy yesterday, in particular climate change but also the nuclear menace. I think that we need to go back to the basic questions and basic values of science, as President Joachim von Braun says in his programme.

We can say that in the Christian religion – for there are only representatives of the Christian religion here today – we follow St Paul and St John, the most intellectual of the Apostles. The reasons we follow them are to be found in one of the most important Encyclicals of St John Paul II's pontificate, *Faith and Reason*. We need to follow faith and reason, because, like faith, reason too is a gift of God. Inspired by St Paul, it is traditional in the Church to follow philosophical reason. However, today this philosophical and humanistic reason also extends to scientific reason, and this is very clear in Pope Francis' Encyclical *Laudato Si'*, where he, of course, mentions the conclusions of theology while also adopting the conclusions of science. For example, in his theological vision he speaks about evolution in a central way, and this is a new thing. In order to assume the scientific notion of evolution he quotes St Thomas Aquinas but also Teilhard de Chardin, in line with St John Paul II during his famous address to the Pontifical Academy of Sciences when he spoke about evolution as a concept that could be accepted without denying the notion of creation. But Pope Francis goes beyond that and assumes the description of the situation of our planet from science.

Therefore, I think that the force of religion today is also to give a motivation to follow the conclusions of reason, not only philosophical reason, but also scientific reason and this is very important to the challenge of climate change but also to the problem of nuclear war and other questions, although these are maybe the most important ones.

In this sense, I think that the attitude of Pope Francis is a little different from the previous Magisterium. It is in line with the attitude of the Second Vatican Council, which created two new councils in the Church.

One for dialogue among Christians, which we call Ecumenism, on the things that we have in common with the other Christian religions, and one for Interreligious Dialogue, which was created especially to dialogue on the contents of other religions. Both have as their focus a dialogue on the contents of religion. Today, however, the most important question is to work together to defend human dignity, the planet, peace, justice and all the values that we need to include in our society to create that civilization of love that St Paul VI speaks about. Even though it is not always easy to pray together with the other religions, saving human dignity, our planet and peace we are obliged to overcome our religious differences and work and act together, because our ideas for saving human dignity and the planet do not differ.

For this reason I am very happy that, maybe for the first time, our President Joachim von Braun has invited some very important representatives of the humanistic and scientific questions but also some religious representatives to improve our understanding of the problem and to give new motivations to this programme that comes from the sciences. And the sciences also need to be clearer in their solutions, as Pope Francis said in the speech he gave us the other day.

SESSION IX – TRANSFORMATIVE ROLES OF SCIENCE, PEOPLE AND EDUCATION

EDUCATION FOR A SUSTAINABLE DIGITAL ENVIRONMENT

ANTONIO M. BATTRO

Introduction

The celebrated Encyclical *Laudato Si'. On care for our common home* by Pope Francis (2015) declares the need to help the media in the digital world "to become sources of new cultural progress for humanity and not a threat to our deepest riches".[1] This is our great responsibility as educators towards the construction of a sustainable digital environment. We must learn and teach the *care of our digital environment* as we should do for the care of our common home, our *natural environment*. In fact, the great novelty for humanity is that we have constructed a *new home* on top of the natural one, and both need our constant care, because they interact in a great variety of ways. The natural environment has been given to us, the digital environment, instead, is a human construct with new properties in permanent and accelerated evolution that we cannot find in nature. The increasing interaction between the two environments exceeds our imagination; the Internet of Things is one impressive example of this trend. And this interaction should be improved and protected by a *sustainable digital*

[1] Encyclical Letter *Laudato Si'* of the Holy Father Francis on care for our common home (24 May 2015) "47. *Furthermore, when media and the digital world become omnipresent, their influence can stop people from learning how to live wisely, to think deeply and to love generously.* In this context, the great sages of the past run the risk of going unheard amid the noise and distractions of an information overload. *Efforts need to be made to help these media become sources of new cultural progress for humanity and not a threat to our deepest riches.* True wisdom, as the fruit of self-examination, dialogue and generous encounter between persons, is not acquired by a mere accumulation of data which eventually leads to overload and confusion, a sort of mental pollution. Real relationships with others, with all the challenges they entail, now tend to be replaced by a type of internet communication which enables us to choose or eliminate relationships at whim, thus giving rise to a new type of contrived emotion which has more to do with devices and displays than with other people and with nature. *Today's media do enable us to communicate and to share our knowledge and affections.* Yet at times they also shield us from direct contact with the pain, the fears and the joys of others and the complexity of their personal experiences. For this reason, we should be concerned that, alongside the exciting possibilities offered by these media, a deep and melancholic dissatisfaction with interpersonal relations, or a harmful sense of isolation, can also arise".

and ecological education.[2] This is essentially an ethical engagement, not only a technological one.

This new ecosystem must support a "healthy internet" to keep our digital environment in good shape and provide the necessary means to face the increasing dangers of all kind of crimes that are taking place everywhere in our connected world: aggression, violence, bullying, grooming, sexting, sexual abuse, commercial exploitation, etc. Many organizations, public and private are dedicated to controlling, eradicating and punishing the multiple perversions that are corrupting the digital world. Hundreds of digital initiatives around the world are today working to protect the most fragile sectors of the population, children and families in the first place. It is a moral engagement on human dignity. We can mention some international initiatives such as UNICEF *We protect: Global alliance against child abuse online. Worldwide cooperation to stop the crime of online sexual abuse and exploitation* (77 countries); *IWF Internet Watch Foundation; UNICEF: Child online protection project; UNHCR: United Nations Refugee Agency.*

The Final Statement from the Conference organized in Rome by the Pontifical Academy of Sciences and the Foundation for World Wide Cooperation (October 10, 2017) on *Internet Connectivity as a Human Right*, stressed the fact that "It is necessary to reaffirm the role of the internet as the primary means to enable inclusion, efficiency and promote innovation in different economic sectors as such as healthcare, agriculture, the environment, jobs, gender equity, and mutual understanding… Education is the clearest example that the internet is a human right. Even in the 21st century, hundreds of millions of children have no access to school or leave school unable to read. With internet connectivity, they could improve learning capacity. This is of vital importance for the poorest children of the planet".[3]

Moreover, as Pope Francis recently declared to the participants of the congress on *Child Dignity in the Digital World* (2017), "we have to keep our eyes open and not hide an unpleasant truth we would rather not see. In fact, the net also has a secret dimension (the "dark net"), where evil finds

[2] Battro, A.M., Léna, P. von Braun, J., Sánchez Sorondo, M. (Eds). (2017). *Children and Sustainable Development. Ecological Education in a Globalized World*. Springer & Pontifical Academy of Sciences.

[3] Final Statement of the Workshop on *Connectivity as a Human Right*, Casina Pio IV, 10 October 2017, Vatican City http://www.pas.va/content/accademia/en/events/2017/connectivity/statement.html

ever new, effective and pervasive ways to act and to expand".[4] A sustainable digital environment must become a place of justice and peace for all. And the main path to reach this goal for humanity is education.

Talents and handicaps

The digital environment expands our cognitive capacities in the most diverse situations, giving unique opportunities to develop our talents and to overcome many limitations. It is in *the margins of society* where the impact of the digital environment is most needed. In particular, I will give some examples in special education and rehabilitation, in the social inclusion of refugees and immigrants, and in remote places without schools.

In other studies I have shown that the *click option* is a basic unit of behavior. In the case of humans, the possibility to use the click option since the first months of life is key to many neurocognitive developmental studies. In fact "to click or not to click" is a universal proposition of enormous importance. It can be represented by the elementary lattice of 4 nodes of a Boolean algebra. Moreover with Percival Denham we have proposed the click option as the "core" of a new kind of intelligence, a *Digital Intelligence*, that could be included in Howard Gardner's taxonomy of Multiple Intelligences (MI). A most useful property of the click option is that it can be recorded by a precise neuronal activation at the cortical level as a *covert mental* event that can be detected by brain imaging techniques while the *overt behavioral response* is expressed by pressing a key, for example.[5]

[4] Address of His Holiness Pope Francis to the Participants in the Congress on *Child Dignity in the Digital World, 6 October 2017* http://w2.vatican.va/content/francesco/en/speeches/2017/october/documents/papa-francesco_20171006_congresso-child-dignity-digitalworld.html

[5] Battro, A.M. (2002). The computer in the school: A tool for the brain. In *The Challenges of Science: Education for the Twenty-First Century*. Scripta Varia 104, Pontifical Academy of Sciences: Vatican City. Available online at http://www.pas.va/content/dam/accademia/pdf/sv104/sv104-battro.pdf; Battro, A.M. (2004). Digital skills. globalization and education. In M. Suárez-Orozco, D. Baolian Qin-Hilliard, Eds. *Globalization: Culture and Education in the New Millennium*. California University Press: San Francisco; Battro, A.M. & Denham, P.J. (2007). *Hacia una inteligencia digital*. Academia Nacional de Educación: Buenos Aires; Battro, A.M. (2007). Homo Educabilis, A neurocognitive approach. In M. Sánchez Sorondo, Ed. *What is Our Real Knowledge About the Human Being?* Scripta Varia 109. Pontifical Academy of Sciences: Vatican City. Available online at http://www.pas.va/content/dam/accademia/pdf/sv109/sv109-battro.pdf; Battro, A.M. (2009). Digital Intelligence: the evolution of a new human capacity. *Scientific Insights Into the Evolution of the Universe and of Life*. W. Arber, N. Cabibbo & M. Sánchez Sorondo, Eds. Acta

It is interesting to remember that among the first attempts to deploy a digital environment in education several decades ago many disabled children were those who were leading the new field. For example, deaf children started to use computer networks for communication at the very beginning of the whole movement, in the early 80s, well before most of the hearing students of their generation. Today, the use of powerful neuroprostheses as cochlear implants, also based on digital technologies, have changed radically the education of the deaf and have become a remarkable feat of a sustainable digital environment. A similar approach is now implemented with the promising new retinal implants. There are also several neurotechnologies known as "neuromodulation prosthetics" that try to overcome the burdens of many disabilities in the motor system, via Deep Brain Stimulation (DBS). A most remarkable advance in movement restoration is being produced by Brain Computer Interfaces (BCI), that bypass damaged brain structures. We are still in the first stages of the implementation of these neuroprostheses that may even improve some cognitive abilities by interfacing with Artificial Intelligence procedures, but, as John Donoghue clearly affirms: "Changing brain circuits raises ethical issues" because they can affect personality or behavior. We need to protect human dignity in all the digital environments we are creating.[6]

Today the number of disabled people that have significantly improved their life with the help of the digital technologies is increasing in the whole world and their success becomes a continuous source of inspiration to expand a sustainable digital environment for all. Our dear colleague Stephen Hawking gave us a remarkable example of a whole life of impressive scientific achievements and social interactions with his exceptional courage and his ability to overcome the extreme restraints of a severe lateral amyotrophic sclerosis with a clever use of the digital environment.[7]

20, Pontifical Academy of Sciences: Vatican City. Available online at http://www.pas.va/content/dam/accademia/pdf/acta20/acta20-battro.pdf; Battro, A.M. (2009) Multiple intelligences and constructionism in the digital era. *Multiple Intelligences Around the World*, (J-Q Chen, S. Moran & H. Gardner Eds) Jossey-Bass/Wiley: San Francisco.

[6] Donoghue. J.P. "Neurotechnology for human benefit and the impact of AI" in S. Dehaene and A.M. Battro (Eds) (2017). *Power and Limits of Artificial Intelligence*. Scripta Varia 12. Pontifical Academy of Sciences. Available at http://www.pas.va/content/accademia/en/publications/scriptavaria/artificial_intelligence/donoghue.html; For the retinal implants see: www.youtube.com/watch?v=DTiVKvs_IXg

[7] Battro, A.M. (2018). Stephen Hawking, ejemplo de vida dedicada a la ciencia, y a los demás. *Criterio.* Buenos Aires. Available online at http://www.revistacriterio.com.

In my experience of several decades working in the rehabilitation of disabled people with the help of ICT I have recollected many moving and suggestive experiences. I will never forget the quadriplegic architect who learned to draw buildings on his computer with his voice, well before internet, who told me "I need a voice for the winter", the digital environment has no seasons... I had also the privilege to follow for some twenty years the remarkable development of Nico, a boy who was submitted to a right hemispherectomy when he was 3 years old, because of intractable epilepsy. He started to use a computer in the first grade of school and loved to program digital artwork. He has now become an accomplished painter and a national champion in fencing and is a truly remarkable example of the amazing capabilities of human neuroplasticity. Even if artificial neurons, "neuromorphic neurons", can compute faster than those of the human brain and fire up to one billion times per second, current robots cannot yet work with only half of their hardware or software, but Nico is thriving with a half brain. Similar cases of neuroplasticity have been described after a left hemispherectomy. A sustainable digital environment is crucial for disabled people and we must take special care to promote and enhance digital accessibility to all of them.[8]

The role of elders in supporting the sustainability of the digital environment

We should also reflect on the impact of the digital inclusion of senior adults in our globalized society and in the ways they can support the sustainable status of today's digital environment. Indeed, the profound changes in the world's population distribution, the significant and constant increase in the number of elderly people, is having a great impact on society and is transforming the future of humanity. Some studies estimate that by 2020 about 1 billion people will be over 65 years old (the so called 65+). At the

ar/bloginst_new/2018/03/16/stephen-hawking-ejemplo-de-vida/

[8] Battro, A.M. (2000). *Half a brain is enough. The story of Nico*. Cambridge, UK: Cambridge University Press; Vargha-Khadem, F. (2011). Extent and limits of speech and language organization after early left hemisphere injury. In *Human Neuroplasticity and Education*. A.M. Battro, S. Dehaene & W.J. Singer, Eds. Pontifical Academy of Sciences. Scripta Varia 117. Vatican City. Available at http://www.pas.va/content/dam/accademia/pdf/sv117/sv117-vargha.pdf; Battro, A.M. (2014). The art of fencing and painting with a half brain. In *Mind, Work and Life: A Festchrift on the occasion of Howard Gardner's 70th birthday*. (M.L. Kornhaber and E. Winner Eds. Cambridge, MA); Schneider, M.L. *et al. Sci. Adv.* 4, e1701329 (2018) National Institute of Standards Technology, Boulder, CO 80305, USA.

same time in some developed countries people over 75 show a healthier status and a better use of neurocognitive skills than those of the same age some 20 years ago. In a sense "old age is getting younger". Our dear colleague and Nobel laureate Rita Levi Montalcini dedicated a whole book to the significant cognitive resources of old leaders in the arts, sciences and politics, and famously said on her 100th birthday anniversary that "the brain doesn't go into retirement".[9]

As for a permanent education for the ageing population there are hundreds of academic initiatives in the world, including the programs of lifelong learning by UNESCO, University of the Third Age (U3A), Open University, etc. These developments show the emergence of a new field of research: *Gerontechnology*,[10] which pursues the practical aim of designing technologies and environments for independent living and social participation of older persons towards a better health, comfort and safety.

As an example, we can mention the success of Uruguay with the *Ibirapitá* program, which is giving 400,000 tablets to those retired citizens over 65 who do not work and receive a monthly pension of less than 800 US$ per month.[11] Ibirapitá was launched by the government of Uruguay in May 2015 to reduce the digital gap in the third age, when only a 4% was using a computer. The program was an immediate success and was supported by a network of national institutions, the Ministry of Education (Centros MEC), the telephone company (ANTEL), the University for Senior Adults (UNI3), the Plan Ceibal (aprender tod@s) and private initiatives. A recent initiative is a collaboration between *Ibirapitá* and AGESIC, the national organization that implements a Digital Government for citizenship inclusion. *Ibirapitá* is thus actively promoting the unfolding of new talents, the "late bloomers" of the digital environment. This new population of retired people is joining the community of all teachers (40,000) and students of public primary, secondary and technical schools (some 700,000 today), who already have tablets or laptops connected to the Internet by the Ceibal program.[12] Today we can see how grandparents are spontaneously helping to

[9] Levi Montalcini, R. (1998). *L'asso nella manica a brandelli.* Baldini & Castoldi: Milano. Center for Lifespan Psychology, Max Planck, Berlin: Lindenberger, U. (2014). Human cognitive aging: Corriger la fortune? *Science, 346.* Available online at www.mpib-berlin.mpg.de/en/research/lifespan-psychology

[10] Gerontechnology http://www.gerontechnology.org

[11] Ibirapita https://ibirapita.org.uy

[12] Galenson, D. (2010). *Late bloomers in the arts and sciences.* NBER, Nacional Bureau of Economic Research. Working Paper No. 15838, March. http://www.nber.org/pa-

educate their grandchildren in the *good use* of the digital environment they all share. It is certainly moving to observe the unfolding of those new links without borders among generations. A modest household in Uruguay today is an example of a sustainable digital environment where several laptops and tablets connect the whole family for a variety of purposes. The development of this new kind of *connected family* via portable tools (smartphones are starting to be included in increasing numbers) also provides a new hope of reinforcing a sustainable digital environment where the "digital family" has new rights and duties that must be taught and respected. The dialogue between generations is essential for our society, as Pope Francis always recalls, and the expanding digital environment is now becoming a suitable place for this exchange in the most diverse situations.

Immigrants and refugees in a digital environment

A joint meeting of the Pontifical Academy of Sciences and the Pontifical Academy of Social Sciences *on Humanism and Mass Migration*[13] recognized that the "forced displacement of millions of human beings represents an existential crisis of our times, causing suffering in others that we should consider as ourselves. Millions of forcefully displaced, of refugees, of asylum seekers, of unauthorized and irregular migrants – our brothers and sisters – are placed in barbaric conditions that rob them of their human dignity and their inherent capacity to flourish. The catastrophic migrations of the 21st Century are most unforgiving to millions of children".

The recent report from *UNICEF, State of the world's children 2017 – Children in a digital world 2017* makes clear the enormous importance of ICT in the social and cultural inclusion of millions of displaced persons.[14] For

pers/w15838.pdf; https://www.ceibal.edu.uy/es; Battro, A.M. and De La Paz, C. (2014). Sustainable education: Uruguay's Plan Ceibal. In *Sustainable Humanity, Sustainable Nature: Our Responsibility.* Pontifical Academy of Sciences, Extra Series 41: Vatican City. Available online at http://www.pas.va/content/dam/accademia/pdf/es41/es41-battro.pdf; Battro, A.M. & Nogueira, A. (2016). Digital generations: children and grandparents. In *Science and Sustainability. Impacts of Scientific Knowledge and Technology on Human Society and its Environment.* Pontifical Academy of Sciences, Acta 24. Vatican City.

[13] Final Statement of the Workshop on Humanism and Mass Migration, Pontifical Academy of Sciences & Pontifical Academy Social Sciences, UCLA, 18-19 January 2017, available online at http://www.pass.va/content/scienzesociali/en/events/2014-18/migration_ucla.html

[14] UNICEF, *State of the world's children 2017. Children in a digital world 2017.* Available online at https://www.unicef.org/publications/files/SOWC_2017_ENG_WEB.pdf; www.voicesofyouth.org/en/sections/content/pages/sowc-2017

the same purpose a letter from the Permanent Observer of the Holy See, Msgr. Bernardito Auza to the UN Secretary-General encouraged States "with significant labour migrant inflows to adopt national policies which protect against exploitation, forced labour, or trafficking". Some examples would be: "Enact national policies which allow migrants, asylum seekers and refugees to access and use telecommunications, such as the Internet or SIM cards for mobile telephones, without burdensome procedures or fees".[15] Most of them are in desperate need of communication with their families and friends. The digital environment can clearly become a second home for immigrants and refugees.

This humanitarian recommendation to provide connectivity to all is a central issue for migrants and refugees: to remain in contact among them and with family and friends they left behind, and of course to deal with the challenges of being a stranger in their host society, frequently with a different culture and language. Belonging to a digital environment means for them to feel, in some sense, at home again. This digital access is an enormous asset to help their inclusion in the new society. Computers, laptops, tablets, smartphones, are bridges of freedom and support. Many can now enjoy all kinds of apps to improve their new life, automatic translation of voice and texts, access to public services, transportation, health, online education, etc.

A decade ago with Dean Marcelo Suárez Orozco we imagined providing free digital tools to immigrant children to maintain and enhance the communication with their family and friends remaining in their native country. This proposal was very difficult to enforce at the time but now we are pleased to verify that it works in places where the digital environment is already available to all students and teachers in public schools. This is the case of Plan Ceibal in Uruguay where all immigrant children attending public schools are equipped with a tablet or laptop connected to internet. We must also stress the increasing role of smartphones in the hands of children and adolescents and the new opportunities and challenges this ubiquitous technology is creating around the world. A recent book has been dedicated to analysing the multiple types of inclusion of the ITC in Latin America.[16]

[15] Letter dated 6 October 2017 from the Permanent Observer of the Holy See to the United Nations: Responding to refugees and migrants: 20 action points. II. To protect: ensuring migrants' and refugees' rights and dignity.

[16] Cobo, C; Cortesi, S; Brossi, L; Doccetti, S; Lombana, A; Remolina, N; Winocur, R,

With Marcelo Suárez Orozco and Sebastián Lipina, we organized in October 2018 the 13th course of the International School on Mind, Brain and Education, at the Ettore Majorana Foundation and Centre for Scientific Culture, on *Migration and education*, to discuss the fact that "worldwide, civil and ethnic wars, structural violence, unchecked climate change, environmental cataclysms, and poverty are behind the largest displacement of people since World War II. Today there are over 65 million forcefully displaced and 22.5 million formal refugees of whom half are children and youth. We shall endeavor to cultivate and disseminate high quality data and conceptual work, relevant policy interventions, and best practices as a way to shape new practices and inform change". We published a statement online to consider *Mass migrations as a planetary emergency* and many colleagues around the world are now signing this declaration.[17]

One crucial issue in the social inclusion of immigrants and refugees in the host country is the urgent acquisition of a second language. This requirement demands a profound neurocognitive transformation that can be greatly supported by a digital environment. In fact, several countries have deployed special initiatives to facilitate the new linguistic skills using digital tools. Among them smartphones became a first choice.[18]

Digital schooling without schools

Advances in communication and information technologies are so impressive and several implementations that were impossible to imagine even a few years ago are now provoking substantial changes in extreme cases in remote places without schools.

The current example of the first testing of the *Global Learning X Prize* in Tanzania, reveals how much a child can learn by himself – and by peer learning – with the help of connected tablets that are distributed in small illiterate and isolated communities without adult support. Children can learn and teach each other when they have access to a connected tablet using special apps designed for learning arithmetic, reading and writing.[19]

y Zucchetti, A. (Eds.). (2018). *Jóvenes, transformación digital y formas de inclusión en América Latina*. Montevideo, Uruguay: Penguin Random House.

[17] www.mbe-erice.org

[18] Final Statement of the Workshop on Humanism and Mass Migration, Pontifical Academy of Sciences & Pontifical Academy Social Sciences, UCLA, 18-19 January 2017, available online at http://www.pass.va/content/scienzesociali/en/events/2014-18/migration_ucla.html

[19] https://learning.xprize.org

This is only a first but encouraging step towards education that will help to build a sustainable digital environment for all in developing countries.

Conclusions

We have sufficient evidence today that the digital environment is experiencing exponential growth in the most diverse situations around the world. We must take care to make it sustainable and capable of dignifying the human person during his or her entire lifespan. Education is the best instrument to provide such a delicate balance between the rights and duties of the individual and society. As Ghandi said: "On the River Ganges of human rights there rise the Himalayas of human duties".

Science Education and Climate Change

Yves Quéré and Pierre Léna

Climate Change has an obvious relation to people's wellbeing and it would be a definite misconduct to ignore it in our educational programmes for the years to come. Children of today will be those adults directly impacted by the consequences of climate change in future decades and we have to prepare them to it, especially to the understanding – in simple terms – of the science behind those changes, but also to the action they may carry, wherever they are.

The question then arises of how to adapt a proper way of teaching science to the new and interdisciplinary theme of climate change.

A proper way of teaching science to children

There is presently a worldwide consensus about the necessity to introduce the concept of *inquiry* in the way to teach science: children and youngsters will be required to try to solve a problem of science (physics, botany...) as if they were detectives using their sense of observation, their experimental skill, their intuition and their intelligence to find the solution to the problem. Needless to say, the help of the teacher is required, preventing them from wasting their time on wrong paths. Also needless to say, a number of scientific data (classification of plants, astronomical concepts...) can be presented to them only in a classical, directive, way. A proper balance between these two ways of teaching, *Inquiry Based Science Education* (IBSE) and *Directive Pedagogy* (DP) has to be found by the teacher (G. Charpak, P. Léna, Y. Quéré, 2005).

It is obvious – considering the time devoted to experimental work – that IBSE, as compared to DP, will allow less scientific scores to be recorded by children than DP; but altogether will enhance their understanding of what science is, how it proceeds and what can be expected from it. This is exactly what has been confirmed in the last PISA (*Programme for International Student Assessment*) 2015 Science Test.

A number of high level scientists have devoted themselves to the dissemination of IBSE, including Bruce Alberts in the US, Wei Yu in China, Nobel Laureates Georges Charpak, Leon Ledermann, Mario Molina, and Lee Yuan Tseh, not forgetting Marie Curie, building a brand new bridge between the world of scientists and that of school teachers. They essentially agree on the fact that IBSE:

i) Stimulates both curiosity, a word (latin *cura*) related to the empathy by which we 'take care' of what is around us, a word which then carries a flavour of ecology; and imagination (that is, the faculty to create i*mages* of what is hidden behind the wall);
ii) Introduces us to the difficult concept of truth in a world invaded by a spineless relativism (*Tout est relatif ! A chacun sa vérité,* etc.);
iii) Tells us that we do not know everything, the founding sentence of science being "I do not know" (to which we have to add "...but I would like to know"), which implies a hue of modesty in our behaviour and also, possibly, for the student, a desire to search and to become a scientist;
iv) Introduces the student – *à propos* simple objects like a pendulum – to the essential problem of the separation of parameters of a complex problem like those which he/she, as an adult, will frequently encounter (conflicts, decisions to be taken...);
v) Finally, tends – together with mathematics – to create logic and rational thinking in our brain, and in particular in our language.

E-learning

It is easy to foresee that all fields of education will be, in the 21st Century, more and more influenced, not to say invaded, by e-processes. This opens a mostly positive perspective in the dissemination of knowledge – and possibly culture – in large areas of the world's population. In this 'digital age', new strategies will certainly be developed which will multiply the possibilities and modify the procedures in global education.

The benefits of it will possibly be huge, but an immediate *caveat* should be introduced in the debates about future education: the risk does exist of an increased abstraction, screens replacing little by little not only the dialogue with a 'real' teacher, his/her voice, convictions, passion, empathy, sense of humour... in brief his/her human density; but also destroying the physical contact of children with the reality of nature and of man-made objects.

Natural sciences are on the battlefront of this possible conflict between the concrete nature of the world and the virtual nature of images (and discourses) supposed to represent it. Paradoxically, it might be said that the more e-learning will grow, the more science should be taught to children in a concrete way in order to counterbalance a possible, if not likely, extension of a virtual vision of nature. This means a necessity to develop as much as possible the teaching of science (at least to young students) most concretely, as this is encouraged in IBSE.

Climate Change and Education

The huge problem of climate change has been more and more evoked by scientists, and concretely (and most often bitterly) experienced by populations, in the last 2 or 3 decades. In the recent past, IPCC has delivered its 5th Assessment Report, 2014, and the special Report *1.5°C*, giving rise to the Paris COP 21, 2015. It prepares presently the special Reports on *Cryosphere/Hydrosphere* (2019), on *Land use* (2019), and on *Cities* (2020), before the Sixth Assessment Report (2022).

The voice of *Laudato Si'* joins in the warnings of the scientists:

> Climate change is a global problem with grave implications: environmental, social, economic, political and for the distribution of goods. It represents one of the principal challenges facing humanity in our day [...].Sadly, there is widespread indifference to such suffering, which is even now taking place throughout our world. Our lack of response to these tragedies involving our brothers and sisters points to the loss of that sense of responsibility for our fellow men and women upon which all civil society is founded. (§ 25)

This disturbing 'lack of response' requires a reaction from us, which should first be expressed through our educational systems. Following a workshop at the PAS here, in this room, 2016, on *Children and Sustainable Development: a Challenge for Education*, the Assembly of the Academies of sciences worldwide, the IAP, issued in 2017 a *Statement on Climate Change & Education* insisting on the necessity:

- To develop a *Climate Change Education*, building "a critical mind and an hopeful heart";
- To act in primary, secondary and higher education;
- To help teachers to develop inter-disciplinarity, including social sciences and ethics;
- To mobilize scientists and engineers for local support.

These recommendations are highly justified considering the low level of public concern about these questions. For instance a measurement in France (ADEME, 2017) of the weight of various 'points of concern' (for adults) gave, to the item: *Environment, greenhouse effect and climate warming*, the following incredibly low and incredibly stable answers, from 2011 to 2017: in %, 7, 6, 7, 2, 4, 5, 6, as compared to *Employment*: 26, 30, 37, 35, 37, 30, 29. Contrariwise, children are much more motivated: in 2018, in France, 59% of school students and 57% of higher education graduates place environment as n° 1 of causes they would like to work for. Attending an IPCC on Climate and Cities in Edmonton, young students gathered from many countries considered (2018) that the biggest barriers to addressing Climate Change are (in order): Lack of awareness, Government, Finance, and 'Not my responsibility'. They pleaded for a proper preparation of their teachers.

Concrete actions

Implementing the IAP Statement, a number of concrete initiatives have recently emerged. Let us mention:

In California: Universities: *Bending the curve* (V. Ramanathan)
Schools: California Global Education Project
State: California Blueprint for Environmental Literacy.

In India: *Trans-disciplinary Research-oriented Pedagogy for improving Climate Studies and Understanding* (TROPICSU), born with ICSU.

In France: Creation (2018) of the *Office for Climate Education* (OCE): creation of Tools and Resources for Teachers, in phase with the IPCC Reports.

The OCE, a significant initiative, was launched in France by the *Fondation 'La main à la pâte'* with various NGOs and private partner organizations, especially in Germany, combining an Executive Secretariat, with a small team in Paris, and a network of Partners in various parts of the world. It is funded by public and private funds essentially – but not only – from France and Germany (P. Léna and D. Wilgenbus, 2018).

The ambition of OCE is to accompany IPCC reports with the publication of resources that may help teachers and education systems to implement Climate Change Education; and to stimulate and coordinate a large network of partners to enhance their actions in this field. This must take into account both a global view considering the Earth as a whole, and more local impacts of climate change differing from place to place: desertification, glacier melting, sea level rise etc., implying local actions.

The predictable invasion, in the next decades, of e-processes in the educational systems worldwide should give rise – at least in the field of Climate Change education – to a definite counterbalance of *hands-on* and *investigation* practices in schools. The problems raised by Climate Change are of immediate and concrete influence on everyday life. Consequently they should be addressed in schools through a proper alloy of e-teaching, presenting globally to children the huge complexity of the problems raised all around the planet and their interconnection; and of IBSE-teaching by which children are induced to create and study, 'on the table', simple models of the physical, or chemical, or mechanical processes involved.

The OCE has already undertaken training sessions in South-East Asia, and is planning new ones in Benin, Tunisia and Chile. It also contributes to the organization of high-level regional conferences gathering educational authorities and scientists like the one with ISTIC in Kuala Lumpur, May 2018, on *Climate Change Education* with a large attendance from the South East region. The production of resources for teachers is continued in the format of *La main à la pâte* documents for teachers (e. g. M. Hirtzig, D. Wilgenbus, G. Zimmermann, 2015), including class activities, simulators, games, participative science and documentation. This is open to comments and proposals from teachers and schools anywhere.

As a conclusion

Climate change and, more generally, the health of our Earth have become such a (highly deserved) concern for humankind that it must be included in our educational systems, with a double purpose: 1. Children should at least be informed of, and possibly understand, the main scientific concepts, results and laws governing the functioning of our planet taken as a physical system; 2. They should be ready to become actors of a drastic change of mankind behaviour concerning their planet taken as their natural common house.

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Self-Presentation of New Academicians

Helen M. Blau

I am a stem cell biologist, I was born in London, England and grew up in Europe, in Germany, in France and in England. I came to the United States to pursue doctoral studies with a scholarship to Harvard University. I received my PhD with Professor Fotis Kafatos, whose death we are sadly commemorating at this meeting. With Fotis, I learned how to perform rigorous experiments. After studying insect eggshell morphogenesis as a model system, I wanted to work on topics more closely related to human health, and I moved to the University of California, in San Francisco, to pursue post-doctoral studies with Charles Epstein in medical genetics, where I became a genetic counsellor and studied heritable diseases in the context of the whole person, their socio-economic background, education, ethnic background and genetics. At that time I began my work on muscle gene expression in the context of disease.

I then joined the faculty at Stanford Medical School in California, and was one of the first women to be hired on the tenure track in basic science there. I've been privileged to spend my entire academic career at this centre of technology, research and medicine. I am the Donald E. and Delia B. Baxter Foundation Professor and the director of the Baxter Laboratory for stem cell biology. I am an elected fellow of the American Association for the Advancement of Sciences, a member of the American Academy of Arts and Sciences, the National Academy of Inventors, the National Academy of Medicine, and the National Academy of Sciences. I have had the honour of serving as President of the American Society for Developmental Biology and President of the International Society of Differentiation. I served as an advisor on the Council of the National Institutes of Aging, of the NIH, and on the Harvard board of overseers among others, and I've had the opportunity to forge international collaborations as a Rolf-Sammet Fonds visiting professor at the University of Frankfurt, and Fulbright Senior Specialist Scholar at the Institut Pasteur and as a Mayent Rothschild Visiting Professor at the Institute Curie in Paris. I have been honoured with honorary doctorates from the University of Nijmegen in Holland and the University of York in England.

As an assistant professor I set out to challenge the dogma that the differentiated state is fixed and irreversible. At the time it was believed that a liver cell or a skin cell were irreversibly destined for that fate. I devised a cell fusion system to test this, whereby I created heterokaryons, stable fusion products of an excess of mouse muscle cells fused with human liver cells. Using species-specific markers, I showed that silent muscle genes in the liver cell could be activated and expressed evidence for nuclear reprogramming in mammalian cells. This body of work showed the plasticity of which specialised cells are capable given the appropriate milieu and has been credited for setting the stage for the derivation of pluripotent cells by an abundance of transcription factors by Shinya Yamanaka years later, a member of this Academy as well.

I have since used induced pluripotent cells to model heritable human heart failure, providing the first evidence that such diseases are accompanied by premature telomere shortening of precocious aging. Further I have capitalised on the stem cells that reside in muscle tissues to restore muscle function and have identified mechanisms that lead to their dysfunction with aging, and ways to circumvent and rejuvenate the population, to augment regeneration and restore muscle mass and strength. While I love the basic science, I am working now to translate these findings as therapies for patients suffering from muscle atrophy due to immobilisation or following injury. Chancellor – who I admire so much – it is a particular honour to receive this award from you.

Robert Eric Betzig

I was born in a middle class family in Ann Arbor, Michigan in 1960. For as long as I remember I wanted to be an astronaut, so that immediately led to an interest in science and technology and eventually my enrolment in Caltech where I became a Physics major. One time in a sophomore Fluid Mechanics lab I realised that I had an actual affinity and a love for doing experimental work with practical applications that I could do with my own hands, and that's what really guided my career ever since. Eventually, therefore, when I graduated from Caltech, I decided to go to the Department of Applied and Engineering Physics at Cornell. And I knew when I went there that I wanted to do something transformative, as opposed to something incremental. And I had my chance when I met my advisors Mike Isaacson and Aaron Lewis, who had an idea for making an optical microscope to look at living cells with the resolution of an electron microscope. Today that is known as near-field optics.

So I worked on that for six years, first in graduate school and then another six years on my own at AT&T Bell Labs. Bell Labs is by far the most exciting place I have ever worked. It really matured me as a scientist and it really formed a lot of my own current opinions about how science should be done. I am, however, very saddened to see – and I think it has been a great loss for science – the decline of the industrial research labs that has occurred in the United Stated during the course of my career, and so while the near-field technique that I developed there had a number of successes, it also had a number of fundamental limitations that made it clear, eventually, that I was never going to meet my dream of being able to look at living cells with high resolutions. I also became increasingly disenchanted as a whole as I watched the level of scholarship decline and the level of hyperbole increase as more and more people entered the field, so I became quite discouraged and I quit Bell Labs and I basically stayed at home while my wife continued to work.

And then one day, while I was pushing my daughter around in a stroller, I realised that you could make a different way of trying to get to this molecular resolution microscope if you could somehow isolate individual fluorescent molecules, and then find their positions to sub-wavelength precision. Unfortunately at that time there was no good way of isolating molecules at the densities that exist inside of cells, so I just published the idea and left it at that. And so, in the end, I and my family moved back to Michigan where I grew up. A few years earlier my father had started a machine tool company which was successful, so I worked for him. And I came up with an idea for what I believed was a revolutionary new machine tool technology that would greatly reduce the cost of parts for the auto industry. I spent four years developing that technology and three years selling it. In the end, I sold exactly two machines, so it was a complete disaster, so I apologised to my father for burning a million dollars of his money and I resigned. And so now I was unemployed again for the second time with no idea what I was going to do next.

Nevertheless, I did something smart in that I reconnected with my best friend from Bell Labs, Harald Hess, and Harald had also left Bell as it shrunk and went to work in a company in San Diego, so we started to meet at various national parks around the country because he was facing the same sort of mid-life crisis I was about what do we really want to do. We decided that whilst we never felt we would be happy in a normal academic environment, we both very much missed being able to work with our own hands and do curiosity-driven science, so we started to look around for ideas. One day we went to Florida State University where we heard of a new kind of fluorescent molecule that could be turned on at will, and that was the key into the lock which made the idea that I had pitched ten years earlier to be suddenly practical. We were fortunate that Harald was able to keep a lot of his equipment when he left Bell, so we took that out of the storage shed and we built the microscope on his living room floor in three months and we then had a collaboration with some people at NIH. In another three months we had all the data that was in our original paper and nine years later that's what got me the Nobel Prize, so to this day, after all those years of disappointment and frustration, I still consider myself incredibly lucky to have come out of the wilderness, so to speak, and finally have something that would work. I was also very fortunate in that same year in that I got hired by Howard Hughes Medical Institute as the first group leader at their new research facility, Janelia Research Campus, which was consciously modelled after Bell Labs.

And so for the last decade I've been there and I worked for the first couple of years on extending our super resolution technique, but eventually realised it had its own limitations as well, but now fortunately I was a little older and hopefully a little wiser and instead of quitting instantly, I instead used those limitation to figure out other types of microscopes that would work in other ways that would be better. So now we have microscopes that optimise resolution or optimise speed or optimise gentleness to the sample or optimise how deep we can image and they all have roles, and I feel like the most productive time of my career has been in that sort of rebirth of that Bell Labs model at Janelia for the last decade.

So all of that is fine, but for family reasons I've just recently moved to Berkley, and I'm trying to use this opportunity. Now I feel microscopy is fairly matured, it's a big field; I've learned I don't like to be on a bandwagon, I like to build a bandwagon and so I think it is time for me to bow out of that field. So now it's my third mid-life crisis again, figuring out what I am going to do for the last stage of my career and the one thing that I've decided is that there are very few people in the world that have now as much professional security as I have, between tenure at Berkley, a Nobel Prize in my pocket, and HH in my funding and so I think, as a consequence, it's my responsibility to try to come up with something, to take a very big risk that potentially could have a very big payoff. I'm trying to take the blinders off now and trying to figure out what that would be. That was part of my motivation for coming to this conference, but what my heart tells me to do is to work on nuclear deep space propulsion, but I need to find the time to work in isolation again as I have done before, for a year or two, to learn, to contemplate, to think, and see if I can convince my head if that is a wise course of action or a foolhardy one.

Thank you very much.

Steven Chu

I grew up as a middle child of three brothers in a suburb of New York City and in this family education was not merely emphasised, it was the reason for our existence. Firstly, all the aunts and uncles and parents had PhDs in Science or Engineering and it was really taken for granted that I would have to become a scientist. My older brother has a PhD in Physics, an MD PhD in Molecular Biology. My younger has a PhD and two advanced law degrees, and I could only manage a single advanced degree, so this inferiority complex motivated me to become a scientist for many, many, decades.

I was a very inefficient student, and would often go astray, and during my PhD studies I started several projects, abandoned them, got interested in something else, and finally settled on an experiment to test the unification of electricity and magnetism with the weak nuclear forces. I was somewhat lacklustre in that, it took me many years to complete it, in fact I begged my advisor to give me a PhD and I would stay, and after two more years I barely got a result. But despite that performance they made me assistant professor at Berkeley, which to this day I don't fully understand because I had no scientific publication when they made me the offer.

In any case, I immediately spent my start up money, but they also said I could take a leave of absence and I jumped at the chance to go to Bell Laboratories, and I share Eric Betzig's view of Bell Laboratories, it was a marvellous place. I did a number of experiments there in many different fields, atomic physics, laser spectroscopy, condensed matter physics. And it was there that I demonstrated the laser cooling of atoms and its optical trapping, which was later recognised with a Nobel Prize. I should also mention that the original idea of laser cooling was introduced by Ted Hänsch and Art Schawlow, ten years before I did the work.

So in 1987 I moved to Stanford, and became the first science professor of Asian descent outside of the medical school in the history of the university. That was in 1987. And whilst at Stanford we invented methods to split atoms apart quantum mechanically, using the wave-like nature to bring them together, and we showed how to measure how atoms fall in gravity with a precision of 11 decimal places. The irony of this work is that today NASA is designing a space mission to use that very same technique to measure climate change and how glaciers are melting due to atom interferometry measurements of changes in glacial ice mass.

At Bell Laboratories I also worked with Art Ashkin and he showed, during the same time we were working on atom traps, that one can hold on to single bacteria with these so-called optical traps, which we called optical tweezers, and the irony is that he had come up with the idea eight years earlier but never bothered to try it, and it wasn't until we were trying it with atoms that he said, maybe we should try it with particles in water. Now that work was just recognised this year with another Nobel Prize, which I am very happy about, but when I left Bell Laboratories, I said, "alright Art, you showed us how to hold on to bacteria, we can hold on to atoms", and at Stanford I immediately started to work on how to hold on to individual bio molecules like DNA, with Jim Spudich and Bob Simmons, actin-myosin systems.

That started what I would call a deep scientific promiscuity, in the sense that I was willing to become intimate with any field of science, and so in addition to biophysics, I went into polymer physics and biology, and more recently, since stepping down from the Department of Energy, have been doing nano-particle synthesis, which is now allowing us to probe molecular transport in neurons, which we think will have some influence on trying to understand the root cause of diseases like Alzheimer's. That remains to be seen but we are now collaborating with two groups in order to explore this.

Now, as a concerned citizen I became interested in climate change, began to read about it and began to think that maybe there is some truth in these early warning signs, and this is around the year 1998-2000, and as a result of that, in 2004, I was asked to become Director of Lawrence Berkeley National Laboratory. I said no twice, and it turns out you have to say no three times. Biblically that is the tradition, and the third time they asked me, I said "well maybe I'll show up for an interview" and I took the job. The reason was I began to talk about climate change several years before that, and I thought, if I'm talking about it, but not willing to vote with my feet, then why am I talking about it? So I did join Berkeley Lab with the intent of trying to inspire people to think of what science they are doing and what expertise they have and could it lend to new science and discoveries that could give us better solutions. And no deed goes unpunished and two weeks after the election of 2008, I got a phone call and was asked to meet with the President Elect who then asked me to be the next

US Secretary of Energy. I was the first scientist to hold a cabinet position in the history of the United States which may seem a little surprising, so I'm the Jackie Robinson of scientists, but as a practising scientist, I was able to recruit a number of personal friends to join the department who would not have thought of working for the government, and that was a real joy in working below the radar, to do this work.

Now, in addition to the Nobel Prize, I'm going to spare you the other awards. I am a member of a number of honorific societies, I'll just mention a few: the National Academy of Sciences, foreign member of the Royal Society, foreign member of the Royal Academy of Engineering, the Chinese Academy of Sciences, the Korean Academy of Sciences and Technology and, actually, the National Academy of Belarus.

Now in addition, I am the President Elect of the American Association for the Advancement of Science, and become President this coming February. Now I say that because the AAAS was founded in 1848 and it is the largest general science organisation in the world, and its mission is, and I quote 'to advance science, engineering and innovation throughout the world for the benefit of all people', this discussion at this meeting is particularly relevant to the mission of the AAAS. Now, in closing, I will add that although I have only one real PhD degree, I've at long last caught up with my brothers: I do have 32 honorary degrees.

Rev. Guy Joseph Consolmagno SJ

Like Dr Betzig, I'm also from Michigan, eight years older, also grew up in the Detroit area and went to the Jesuit High School. Now, everybody of my generation who was male was going to be a scientist, and that was because of the space race, and sadly girls weren't going to be scientists, just boys in those days, a terrible, terrible thing. So I had this interest in astronomy, and we had the chemistry set in the basement with all these sorts of things, and like Dr Chu, I had a family that was very well educated. Both my parents were college educated, my grandfather who had come from Italy as a child had gone to Boston University and become a lawyer. My Dad was a journalist. I was torn between science and journalism. When I went to the Jesuit High School in Detroit, they told me all the smart kids did Latin and Greek, and I wanted to be a smart kid, so I left science behind. I did the Classics major and then went on to Boston College to be a History major, but at the same time, my best friend from High School was a freshman at MIT and while I'd visit him at the weekend I found that MIT had tunnels you could explore, and pinball machines, and weekend movies, and most importantly, the world's largest collection of science fiction. In order to read science fiction, I figured out a way to transfer to MIT, but I had to declare a major, and I knew I was not going to be an engineer because the only thing I can make with a hammer is noise. And I knew I wasn't going to be a Physics major because I had a classics background, I was a historian, but I found on the list of majors, Earth and Planetary Science, and I thought, planets, people have adventures on planets, so I checked that off. They let me in. To this day I don't know why. After I arrived, I discovered I had signed up for the geology department, and I could not imagine anything more boring than looking at rocks. What are you going to do? There's a rock, there's another rock, what's to study? But there was a professor there, a fellow called John Lewis, who had been a student of Harold Urey, who had been a student of G.N. Lewis, so he was well connected, and he taught a class about meteorites, and meteorites are rocks but they have fallen from outer space. They are pieces of space that you could hold in your hands. And he was a tremendously dynamic teacher and I got so excited that I would wake up every Tuesday and Thursday and jump out of bed eager to get to class to hear more about meteorites. I stayed on and actually did a completely theoretical-based thesis on ice and rock together, and what happens if you have a moon made of ice and rock, and is there going to be enough radioactive material in the rock to melt the ice, and in the process, at the end of my Master's thesis, I had predicted in 1975 everything that Voyager discovered when it got to the icy moons of Jupiter in 1979, and all the bases of where my calculations came from were totally wrong. I had underestimated the heat input by a factor of 10, and underestimated the heat output by a factor of 10, but I came up with the right number, and at least gave them the right idea of what to look for. I also in the thesis ended by saying, 'I will not go as far as to predict life in these oceans under the ice crusts of Europa, I will leave that for others, more experienced in such speculations', making fun of Carl Sagan. This is, as far as I know, the first time in the literature anyone mentioned life in an icy moon in Jupiter, except I'm not the first person to predict it, I'm the first person to go out of my way not to predict it.

I was enjoying this so much that I was encouraged to join a brand new department at the University of Arizona in Planetary Sciences. I went there in 1975, worked with a few different professors, and eventually got a degree with a fellow named Randy Jokipii who worked in cosmic rays, on the electromagnetism in the early solar nebula and what are its effects – hardly any that we could find – but it took a thesis to work that out.

My real goal was to go back to Boston. I loved being in Boston; I loved being at MIT, so I was two years as a post-doc at Harvard, and then three more years as a post-doc at MIT, at which point I realised that five years as a post-doc meant that you're not going to get a job. I was turning 30, and that Jesuit training came back to haunt me, "Why am I doing astronomy when there are people starving in the world?" And I couldn't answer it, I'm busy trying to write theoretical papers that five people in the world will read and two of them are my enemies, why am I doing this? So I quit science and I joined the US Peace Corps, and I said "I will go anywhere you want me to go, do anything you want me to do, let me be useful". They sent me to Kenya and within three months I was at the best high school in Nairobi, Starehe Boys Centre, that had laser labs and computer labs in 1982, and I was there for one term, and then they sent me to the university, where I was teaching graduate students astrophysics, and I thought, people are starving. The kids I was teaching all had jobs waiting at the Kenya Science Teachers' College to teach the teachers to teach, to help development, that was the logic. But that wasn't why they wanted to know astronomy. Every weekend I would go up country with a little telescope and everybody in the village would come and look through the telescope and they'd see the rings of Saturn and they'd go 'Wow', and of course everybody back in Michigan when they see the rings of Saturn they go 'Wow', and has anybody here ever seen the rings of Saturn in a small telescope and not gone 'Wow'? Because this is what human beings do. Because this is what separates us from well-fed cows, because this is the meaning of 'We do not live by bread alone'. You also have to feed your soul, and that's why you do astronomy, when people are starving in the world they are starving for more than just something to fill their stomach.

Thrilled by this, I went back to America, got a teaching job at Lafayette College, a wonderful little school, broke up with the girl I was dating, which was the happiest day in both of our lives, because we were really not right for each other, she was a wonderful person but it wouldn't have worked. And at that point, with my two MIT degrees, I did a mathematical calculation: if I met the perfect woman tomorrow, by the time we had a family I'd be 40, by the time those kids were teenagers I'd be 65. Way too old. What's plan B?

Well I had this Jesuit background, if I joined the Jesuits I could teach at a Jesuit school and never have to worry about tenure – not true, but I didn't know that. So I joined the Jesuits and I discovered that plan B was really plan A: for the first time in my life I was content, I knew where I belonged, and when I was telling somebody the story of turning 40 and a family, they said, 'Guy, 40 plus 15 is 55, not 65', so the reason I became a Jesuit is that I don't know how to add. Also, they didn't let me teach at a Jesuit college, like I expected. Under obedience, they forced me, they ordered me without asking, to go to Rome, eat that terrible food we've been having, look at that horrible scenery, and, oh yes, live in the Pope's summer palace, and my instructions upon arriving at the Vatican Observatory were 'Do good science'.

Incidentally, we happen to have a collection of a thousand meteorites. Remember meteorites? Remember how excited I was with meteorites? What do you do with a collector's collection of a thousand meteorites? We didn't have the equipment to break them up, but I knew from my theoretical work that no one had actually measured their physical properties, the density, the porosity, the magnetic properties, the thermal properties, so knowing that it might take twenty years to do it, but also knowing I wasn't under the pressures of a three-year grant cycle, or tenure, I had twenty years, so that's what I've been doing for the last twenty years, and then the last five years turned it over to Bob Macke, who is a younger Jesuit brother who does the same thing I do, only better. And the collection, any data that you see in the literature now about the physical properties of space material, probably comes out of our lab.

Three years ago Pope Francis assigned me to be the director of the Vatican Observatory. It's a five-year term renewable until I get sick of it, so I'm in year three of it but I'm enjoying myself too much, so I expect to be in for a while. It has been my joy to continue to do, and to tell the new people what I had been told, "your job is to do good science, and you have as much time and as many resources as you need", and the science I do, physical data collection, may not get me the Nobel Prize, but it is data that will still be true one hundred years from now, which is probably more than you theorists can do. Thank you very much.

Mohamed H.A. Hassan

Three episodes shaped my research and professional careers.

First Episode

1. 1974: I returned to Sudan after obtaining my Doctorate degree in mathematics from Oxford University and joined the University of Khartoum as a young Lecturer.

2. I did my research in theoretical Plasma Physics, which was a very exciting field of research at that time, because of its application to controlled thermonuclear fusion which promises unlimited supply of clean energy. My research resulted in formulating and solving a complex system of nonlinear partial differential equations and the derivation of simple diffusion equations that have been used to study transport processes in fusion experiments.
3. Upon my return from Oxford, however, I soon felt a discouraging sense of isolation. Without access to current journals and with no scientist working in my area of research to speak to, my research output started to increasingly wither.
4. At the same time my father, who was a successful businessman, wanted me to help him to expand his business and he asked me to travel to Italy to purchase machinery for his new soap factory. I was pleased to do that as it also gave me the opportunity to do a detour and visit the ICTP in Trieste.
5. There I met Abdus Salam, the founding Director of the Center, for the first time. I explained to him the research challenges that I faced in Sudan and my intentions to move away from research and work with my father. He appeared deeply concerned and in order to help me remain in science and not be lost to the business world, he offered me the associate membership of the ICTP, which I gladly accepted.
6. Being appointed an ICTP Associate enabled me to travel to Trieste several times over the course of the next few years, breaking my isolation at home and actively resuming my research work in theoretical plasma physics.
7. I also started to develop interest in the physics of wind-blown sand and dust in the Sahara, a phenomenon that is rampant in most African countries, including my own. Together with my colleagues we developed physical and mathematical models that improved our understanding of the movement and impact of wind-blown soil particles and the resulting formations of complex surface features in deserts. The models also found useful applications in snowdrifts studies.

Second Episode

1. 1982: Salam informed me about the meeting he had with a group of eight eminent scientists from Developing Countries present at the 1981 PAS Plenary Session here in the Vatican. It was at that meeting that the idea to establish the Third World Academy of Sciences (TWAS) was

first discussed and unanimously endorsed by the participants. Salam was asked to turn the idea into reality. He then surprised me by asking if I would be interested in helping him launch the Academy. Obviously, l could not say no to a man whose intervention saved my research carrier.

2. The following year (1983) I was invited to visit the ICTP to help organize the foundation meeting of TWAS. The meeting was a great success, but there was no money available to run programs. The truth is that many advocates and funders of international science at that time did not see the need for an organization like TWAS.
3. It was in 1985, shortly after spending a year at Laurence Livermore Lab on a Fulbright Scholarship, that Salam informed me that the Italian Minister of Foreign Affaires, Giulio Andreotti, had decided to provide $1.5 million to officially inaugurate TWAS and launch its programs. He requested me to come back to Trieste for three months to help. Little did I realize that this three-month stay would turn into a commitment spanning nearly 25 years during which I served as TWAS founding Executive Director. During that period, thanks to the continued support of the Italian Government, TWAS witnessed substantial growth in its membership, programs and international recognition, resulting in the Academy becoming a leading voice of excellence in science in the Developing World.
4. In 1988 TWAS organized a major conference on women in science in developing countries, which resulted in the establishment of the Organization for Women in Science (OWSD) based in Trieste under the management of TWAS. OWSD currently has over 7,000 members, making it the largest women's organization in the world.
5. In 2000, at their general assembly in Tokyo, Academy Members of the InterAcademy Panel (IAP) decided to transfer the secretariat of IAP from London to Trieste to be hosted by TWAS. Shortly afterwards, Yves Quéré and Edwardo Kreiger were elected IAP Co-Chairs. In 2003 the Italian Government approved a law to fund both TWAS and IAP on an annual basis. And in 2003 the InterAcademy Medical Panel (IAMP) also decided to transfer its secretariat from Washington to Trieste.
6. These four organizations (TWAS, OWSD, IAP and IAMP) together with the ICTP and the ICGEB make Trieste a unique place for international collaboration in STI and in global science policy debates. I was privileged to be able to contribute to the development and growth of this unique system of international organizations, the so-called "Sistema Trieste".

Third Episode

1. 1985, at the inauguration of TWAS in Trieste, when the African scientists present, under the leadership of Thomas Odhiambo, met and decided to establish the African Academy of Sciences (AAS). I worked closely with Tom to develop AAS during its formative years and later succeeded him as President from 2001-2011. AAS is modeled on TWAS with a specific focus on developing capacities and promoting excellence in science and education for sustainable development in Africa. It is based in Nairobi.
2. As Executive Director of TWAS and President of AAS at the same time I was in a privileged position to promote synergies between the activities of the two organizations, especially those that relate to building capacities, supporting young scientists and science-based development in Africa.
3. At the beginning of my AAS Presidency in 2001, I was concerned about the status of national merit-based Academies in the continent. There were only 7 merit-based Academies at the time among the 53 African nations and all, with the exception of ASSAF, were pretty inactive. The seven Academies met in 2001 in Nairobi and decided to form a network (NASAC) under the management of AAS and I was elected President of NASAC.
4. With the support of IAP, TWAS and NAS a major program to strengthen the 7 Academies and to establish new ones was launched, resulting in the establishment of 19 new academies in the following years. NASAC now has 26 members and is one of the four powerful IAP affiliated regional networks of academies.
5. Although both AAS and NASAC have developed and implemented important programs to support excellence in scientific research and education in Africa, compelling challenges stand in the way of progress towards achieving the SDGs in the continent. Addressing these challenges needs the full engagement of the African scientific communities and their academies of science, to assist in developing STI-based implementation strategies for the SDGs. This will require organizing regional and global forums that bring together leadership from the scientific, development, finance and diplomatic communities to discuss and implement common actions. The Pontifical Academy of Sciences will be an effective partner in this effort.

Commemorations of Deceased Academicians

Günter Blobel († 18.II.2018)

Günter Blobel was a cell biologist born 81 years ago in Silesia, eastern Germany, now part of Poland. He had a colourful life. He had an idyllic childhood during the Second World War – his village was untouched by the war – and had to move ahead of the Red Army at the age of 8. For the first time he saw his first large city in Dresden, where he greatly admired the architecture of the Frauenkirche, the Church of the Virgin, and a few days later, staying with relatives thirty kilometres away, he saw the sky light up with fire during the fire bombing of Dresden, so clearly you could read the newspaper under the fire of Dresden. Impressed by this, he later used his Nobel Prize in 1999 as the seed money for a foundation for the reconstruction of the Dresden Frauenkirche and the synagogue there. That's the colourful part.

The most interesting part of Blobel's life is his science, because it provides an example of the epistemology of biology, how we do biology. In the 19th century, French physiologist Claude Bernard published a book on the introduction to experimental medicine. I once gave a whole talk here on that, and how, in experimental biology, we construct an idea in our minds, and then we test it by experiments. So Blobel, who studied medicine in West Germany and then did a PhD in Wisconsin, ended up in the laboratory of George Palade, who was a member of this Academy, at Rockefeller. And Palade had discovered that secreted proteins go to the endoplasmic reticulum to be secreted, while other proteins do not, and so he wanted to know, how is it that some proteins go to the secreted pathway and others do not. And there, in the lab of Palade, he teamed up with a young assistant professor called David Sabatini and they produced a hypothesis of how this might work, in their own minds. David Sabatini was a graduate student of my father in Argentina, and now we have his son, sitting right there. So they came up with an idea without any proof, so this was very much resistant, and their idea was the signal hypothesis. They said maybe the way the proteins go into the endoplasmic reticulum is because there is something in the messenger RNA, in the protein, a signal in the beginning of the protein that is going to tell the ribosome using a signal recognition particle, so the beginning of the protein will have a signal that will bind it to the membrane of the endoplasmic reticulum so that it can be secreted in the microsomes. So ribosomes have a small sub-unit and a large sub-unit so this one starts first, and they actually produced this, there will be a signal in the beginning of the protein that will put it out of the endoplasmic reticulum.

This was in 1971 but they had no evidence for this. Sabatini had discovered that there was a channel in the large sub-unit of the ribosome that protected the nascent peptide from degradation, and then he had also found that the large sub-unit binds first to the membranes. Except for that there was no evidence, so this was very much resisted and criticised, and Blobel kept on working on this until in 1975 he could publish two papers with Dobberstein, reconstructing the system in-vitro by adding ribosomes and membranes and messenger RNA and showing that it is the property of the messenger RNA which will lead the protein inside the membranes and make it resistant to protease.

Now this is an example of how you can come up with an idea and prove it only five years later, and it proved to be correct, and so this is the famous signal hypothesis, and in recognition of this he got the Nobel Prize in 1999. He was a great cell biologist in the school of Palade, who was here in this Academy too.

EDWARD M. DE ROBERTIS

Stephen W. Hawking († 14.III.2018)

Soon after I enrolled as a graduate student at Cambridge, I encountered a fellow student, who seemed unsteady on his feet and spoke with difficulty. I learnt that he'd arrived two years before me – from Oxford, where he'd been, by all accounts, a 'laid back' but brilliant undergraduate. He'd recently been diagnosed with a degenerative disease, and told he might not survive to finish his PhD. After this diagnosis, his expectations dropped to zero. He later said that everything that happened afterwards was a bonus. And what a triumph his life has been.

Astronomers are used to big numbers. But few could be as big as the odds I'd have given, back then in 1964, against witnessing his amazing crescendo of achievement spanning more than 50 years.

By the late 1960s he was wheelchair-bound. But in other respects fortune had favoured him. He married Jane, who provided a supportive home life for him and their children, Robert, Lucy and Tim.

And in those years astronomy was on a roll – we realized that black holes actually existed, and that our universe expanded from a mysterious big bang. Stephen gave us insights into black holes. And, with Roger Penrose, he discovered a new mystery: that deep inside them, and in the big bang, there lurked 'singularities' – where conditions transcended all known physics.

For acclaimed findings like these, he was elected to the Royal Society in 1972, when only 32. And he was proud to receive the Pius XI Medal from this academy the following year.

He was by then so frail that many suspected that he could scale no further heights. But, for Stephen, this was still just the beginning. Within a year he came up with his best-ever idea – encapsulated in the equation on his memorial stone.

His 'eureka moment' revealed the first firm link between the two overarching 20th century theories: the quantum theory, describing the very small, and Einstein's relativity, describing gravity and the cosmos. He showed that, because of quantum effects, black holes weren't completely black but emitted what's now called 'Hawking radiation'. This discovery surprised all the experts – 40 years later, its ramifications still, in a colleague's words, cause 'more sleepless nights than any physics paper in history'.

Stephen was always based in Cambridge, and became a familiar figure navigating his wheelchair around the city's streets. In 1979 the University elevated him to the Lucasian Professorship, once held by Newton and Dirac.

In 1985 he contracted pneumonia. He underwent a tracheotomy, which removed even the limited powers of speech he then possessed. But he was saved by technology. A computer, controlled by a single lever, allowed him to spell out sentences. These were then declaimed by a speech synthesiser, with the androidal American accent that became his trademark. And this machine enabled him to finish a long-planned book.

The feature film *The Theory of Everything* portrayed the human story behind his career – and did this so well that the main characters were themselves happy with their portrayal. But it chronicled only half of his adult life, concluding when the massive global sales of *A Brief History of Time* catapulted Stephen to stardom.

From then on he was idolised worldwide – in the White House, the Great Hall of the People, and here in the Vatican too – and made countless media appearances. The concept of the imprisoned mind roaming the cosmos had global resonance.

Stephen was far from being the archetype nerdish scientist – his personality remained amazingly unwarped by his frustrations and handicaps. He revelled in his travels – and enjoyed theatre and opera. He had robust common sense, and forceful political opinions. He promoted many causes. Above all, we should acclaim his lifelong support for disabled people; and his campaign for Britain's NHS – to which he acknowledged he owed so much.

In academia, it's a common custom to honour colleagues when they reach 60. In 2002, scientists came from all over the world for Stephen's 60th. But his celebrations weren't just scientific – that wouldn't have been his style. He was surrounded by children and grandchildren; there was singing and dancing; there were 'celebrities' in attendance. When the week's events were over, he took a trip in a hot air balloon.

And he later had a spin in the NASA aircraft that allows passengers to experience weightlessness – pictures show him manifestly overjoyed to escape, albeit briefly, the clutches of the gravitational force he understood so well. As, year by year, he weakened, his supportive network expanded. And his communication – to his immense frustration – became even slower. He learnt to economise with words. His comments were aphoristic or oracular, but often witty too.

But his pre-prepared lectures – accompanied by clever visuals – were still inspirational. He reached his largest-ever global audience when he starred at the opening of the 2012 London Paralympics. His mantra was: "Look up at the stars and not down at your feet. Try to make sense of what you see, and wonder about what makes the universe exist. Be curious".

Right until the end, despite the campaigns, the razzmatazz, and his fragility, he continued to probe grand questions. What equations describe the bedrock of physical reality? What 'breathes fire' into those equations? Most challenging of all, he strove, with many colleagues, to understand how our vast and complex universe might have evolved from something microscopically small – a mind-blowing cosmic analogue of Charles Darwin's realization that all life evolved from a 'simple beginning'.

Stephen described his own scientific quest as learning 'the mind of God'. But this was a metaphor. He resonated with the agnosticism of Charles Darwin, who wrote. 'I feel most deeply that [religion] is too profound for the human intellect. A dog might as well speculate on the mind of Newton. Let each man hope and believe as he can'.

But it is fitting that Stephen Hawking is now commemorated in Westminster Abbey, our national shrine, alongside Darwin, Newton, Dirac, and other great scientific and cultural figures.

Stephen's name will live in the annals of science: nobody else since Einstein has done more to deepen our understanding of space, time, and gravity. Millions have had their cosmic horizons widened by his books and lectures; and even more, worldwide, have been inspired by a unique example of achievement against all the odds.

Martin J. Rees

Fotis C. Kafatos († 18.XI.2017)

Fotis Kafatos, the distinguished Greek biologist, passed away on November 18, 2017, in Heraklion, at the age of 77, after a long illness. He had a brilliant academic carrier in both the United States and in Europe where he became the founding President of a very important institution, the European Research Council, which had a remarkably positive influence on the development of Science on our continent.

Fotis was born in Heraklion. His father was an agricultural engineer. He graduated from the Lyceum Korais, in that city, and had the chance of moving to the United States thanks to a scholarship generously provided by a rich French philanthropist, Anne Gruner-Schlumberger, patron of arts and science, who was fond of Greece. He was also assisted by the Fulbright Programme and first studied at Cornell University. He earned his PhD at Harvard in 1965 and, at 29 years of age, became the youngest professor appointed at this University. Throughout his career, Fotis was one of the most prominent figures in biological sciences, through numerous important discoveries that had a huge impact on both fundamental and applied biology.

He started by working on the mechanisms of cellular differentiation leading to the formation of the eggs in insects. Later, his contributions concerned the field of genetics and genomics. He was one of the first to introduce molecular biology to the study of development by his discoveries on gene families such as the chorion gene families in both the silk moth and the fruit fly. He had a critical role in establishing complementary DNA ("cDNA") cloning, a technique that has been essential to modern molecular biology. His team was the first to clone an entire mammalian gene and to demonstrate that gene regulation sequences were the same in evolutionary distant animals. Later on, he became a key figure in insect genome sequencing programmes. He launched genome projects for the fruit fly and malaria-carrying mosquitos, a manifestation of his desire to link basic science and practical application.

His studies opened new horizons in developmental and evolutionary biology. Notable is Fotis Kafatos' involvement in bioinformatics, as early as the 1980s, long before it became common practice in the scientific community. In addition to a constant dedication to his research, Fotis held several influential positions in European research and will be remembered as a remarkable science administrator at the European Molecular Biology Laboratory (EMBL) in Heidelberg (Germany).

Kafatos is considered as the driving force behind the creation of the European Research Council (ERC) in Brussels of which he was the founding President. He was also the founder of the University of Crete where he created and directed the Institute of Molecular Biology and Biotechnology.

Although he spent most time of his life away from Greece, the state of science in his native country remained one of his lifelong concerns. He had, for a while, part time chairs in Athens and later at the university of Crete.

At the end of his career, he became Professor of Immunogenetics at the Imperial College in London, where he was still focusing on the genomes of the insects vectors of malaria.

Fotis Kafatos was a visionary who was able to make his visions come true.

Nicole M. Le Douarin

Félix Malu wa Kalenga († 22.IV.2011)

Professor Félix Malu wa Kalenga died in April 2011 at the age of 74 years. He was born on September 1936 in Boma, province of Congo. From the very beginning he was a brilliant student and concluded his undergraduate studies in 1960, going to the United States and getting his Master's of Science from the University of California, Berkley in 1963. From 1970 to 2000 he occupied the position of professor at Faculté Polytechnique de l'Université de Kinshasa and turned into an emeritus professor after 2000. He was a scientist in the field of Nuclear Physics, and principal player on the project for the construction of the nuclear reactor Mark II for the Centre Régional d'Études Nucléaires de Kinshasa. He was a great enthusiast for the development and use of atomic energy in Africa. He was also a spokesman for new sources of renewable energy, producing one of the first studies about the energy demand for the development of Africa.

He published many papers, mainly on the promotion for the use of nuclear energy for progress and not destruction. He was also quite active in the investigation of nuclear forces. He received many prizes in recognition of his work, Silver medal for Civic Merit Africa, and Gold Medal for Scientific Achievement, also from Africa. Chevalier de la Ordre de la

Francophonie et du Dialogue des Cultures, officer de l'Ordre National du Léopard, and he also received a prize from the Global Energy Society for Eradication of Poverty and Hunger that was given in Ohio, USA. He was one of the founding members of the Third World Academy of Science (TWAS), based in Trieste, Italy.

He occupied many positions in Africa, including the General Commission for Atomic Energy.

A few things call my attention in his work. In 1965 he wrote a text about the necessity to combine science, technology and social problems, or social needs, for the success and solutions for the continent of Africa. He also wrote about the paradigm of quantum physics and biological science in the late 1980s. He wrote a book in 1999 called *Science and Technology in Africa*, in French, with a chapter that discussed Science for the Development of Africa, the Big Challenge.

For him, Africa was not a land for exploration only, but also a continent full of opportunities, and contributions to humanity. With the correct attitude and investment in science, the problems of Africa could naturally be solved, leaving behind a good balance of benefits for the whole world. He was proud of being a member of the Pontifical Academy of Sciences since 1983, and today the Pontifical Academy of Sciences is proud to pay a small tribute to a good scientist and a great man, Félix Malu wa Kalenga.

Vanderlei S. Bagnato

Vera Rubin († 25.XII.2016)

Vera Rubin was one of those who revolutionized our understanding of galaxies and cosmic structure by confirming the existence of dark matter. She died on Christmas Day 2016 at the age of 88. Vera had a lifelong love of the cosmos. "How could you possibly live on this Earth and not want to study the universe?" she wondered. Vera was a devoted champion of women in science and a role model to generations of astronomers.

Vera's pivotal work in the 1970s established that the orbital speeds of stars in the outer parts of galaxies remain constant to large distances (known as "flat rotation curves"), rather than decline as expected from Newton's law. As an analogy, it was as though we had found that Neptune was moving around the Sun as fast at the Earth was. We'd have had to infer a shell of invisible matter outside the Earth's orbit but inside Neptune's. In our galaxy, this excess mass wasn't in stars or gas. Vera's observations provided crucial and convincing evidence for the existence of this excess "dark matter", a suggestion first made by astronomer Fritz Zwicky in 1933 based, similarly, on large velocities observed in clusters of galaxies. Vera's flat rotation curves implied that galaxies are embedded in large dark matter halos; we now know that these halos contain most of the mass in the universe.

Vera's observations were carried out in close collaboration with her colleague Kent Ford, who built the sophisticated spectrograph needed for these precise measurements. Their first results, in 1970, were for our nearby Andromeda galaxy. At that time, rotation curves were also being observed with radio telescopes, tracing the rotation of the neutral hydrogen gas disks that surround spiral galaxies; these observations, carried out by Morton Roberts and others using the 21-centimeter line of neutral hydrogen, found that the speed of the orbiting hydrogen clouds gas didn't fall off at larger distances from the galaxy. Vera and Ford's observations of the stellar rotations, using optical telescopes, were an important supplement to the radio data. Both sets of observations ultimately revealed the need for dark matter extending far outside the main visible part of the galactic discs, Rubin and Ford's observations of a large sample of galaxies in 1978, all showing the same remarkable constant rotation speed out to large distances. This evidence was crucial in confirming the ubiquity of dark matter and the large dark halos around galaxies.

We now know that most of the mass in the universe, 85%, is dark matter; it profoundly affects the evolution of the universe and the formation of structure. The dark matter is believed to be a new, exotic, yet undetected nonbaryonic particle, not the familiar atomic elements that make up stars, gas, planets, and people. We don't yet know what these particles are. Many experiments have been searching for these particles; detecting and understanding their nature is one of the most important open quests in science. When asked what she thought of a theoretical suggestion that dark matter may not exist but instead a change in Newton's gravity law was needed, Vera was open minded: "I don't know if we have dark matter or need a change in gravity or need something else; we know so little about our universe. It is a strange and mysterious universe. But that's fun".

Vera was born in Philadelphia in 1928; her family moved to Washington, DC when she was 10. She was fascinated by astronomy from an early age, watching the stars wheel past her bedroom window or wondering why the Moon always followed her wherever she travelled. She graduated from Vassar College in 1948, continued to Cornell for her Masters in astronomy, then received a doctorate from Georgetown University in 1954, working with the famous physicist George Gamow. Vera's thesis showed that the distribution of galaxies in the universe was clumped rather than uniformly distributed in space, a novel and important result at that time. Vera joined Carnegie's Department of Terrestrial Magnetism in Washington, DC, in 1965. There she carried out her groundbreaking research with Kent Ford and meticulously mentored generations of young scientists studying galaxy dynamics and dark matter.

Early challenges as a woman in science never deterred Vera. She tells her personal story in a nice autobiographical article. A college interviewer, who dismissed her interest in doing research in astronomy, asked if Vera would consider instead a career painting astronomical objects. A department chairman suggested that he should present her research paper at an upcoming American Astronomical Society conference, instead of her, because she was pregnant. Replied young Vera: "That's OK; I'll do it". She was denied observing on the Hale telescope at Palomar because women were not allowed until the 1960s. "Don't let anyone keep you down for silly reasons", she liked to say. Vera passionately supported women scientists, always encouraging, inspiring, helping pave their way, saying "worldwide, half of all brains are in women," and "there is no problem in science that can be solved by a man that cannot be solved by a woman".

Cheerful, enthusiastic, and positive, Vera was a kind, caring, and fun-loving person. She had a loving family, consisting of her husband Bob Rubin, also a scientist, who pre-deceased her, and four children who all became scientists themselves.

Vera's accomplishments were recognized by numerous awards, including the US National Medal of Science, the Gold Medal of the Royal Astronomical Society, the Gruber Cosmology Prize, the Watson Medal of the National Academy of Sciences, and many honorary degrees. Her role as the "mother" of flat rotation curves and dark matter will be forever honoured, as will her legacy as a mentor and role model of generations of scientists, men and women. Through their work her star will continue to shine.

MARTIN J. REES

The Pius XI Medal Award

NOBLE EPHRAIM BANADDA, Ph.D.

Noble Banadda is a professor and the Chair of the Department of Agricultural and Biosystems Engineering, Makerere University (Uganda). Noble holds a Ph.D. in Chemical Engineering (2006) of the Katholieke Universiteit Leuven (Belgium). In 2007, Noble won the Cochran Fellowship to do postdoctoral studies in the Department of Chemical Engineering at Massachusetts Institute of Technology (USA).

Other Appointments

– Adjunct Professor, Department of Agricultural and Biological Engineering, Iowa State University (USA)
– Senator, Makerere University, Kampala (Uganda)

Awards

– Next Einstein Fellow Laureate, Class of 2015-2016, March 2016
– Honored Young Scientist, Annual Meeting of New Champions 2015, World Economic Forum, Dalian, People's Republic of China, 9-11 September 2015
– President, National Young Academy, Uganda, 11 October 2015-Present
– Honored Young Scientist, Annual Meeting of New Champions 2014, World Economic Forum, Tianjin, People's Republic of China, 10-12 September 2014
– First Full Professor, Department of Agricultural and Bio-Systems Engineering, Makerere University, Uganda, August 2012-Present
– Prolific Author, The Inter-University Council for East Africa, August 2012

Key Publications

Prosper Achaw Owusu, Noble Banadda, Ahmed Zziwa, Jeffrey Seay and Nicholas Kiggundu. Reverse engineering of plastic waste into useful fuel products. *Journal of Analytical and Applied Pyrolysis*, 130: 285-293, 2018. https://doi.org/10.1016/j.jaap.2017.12.020

S.G. Arhin, N. Banadda, A.J. Komakech and S.J. Marks. Pilot field-scale application of hybrid coagulation-ultrafiltration process for decentralized water treatment in low income settings: A case study in Kampala, Uganda. *Water Science and Technology: Water Supply*, ws2017159, 2017. In Press. DOI: 10.2166/ws.2017.159

Nora J. Sadik, Sital R. Uprety, Amina Nalweysio, Noble Banadda, Joanna Shisler, Patrick Degnan and Thanh H. Nguyen.

Quantification of multiple waterborne pathogens in drinking water, drainage channels, and surface water in Kampala, Uganda during seasonal variation. *Environmental Health Perspectives*, 1(6): 258-269, 2017

D. Aboagye, Noble Banadda, R. Kambugu, J. Seay, N. Kiggundu, A. Zziwa and I. Kabenge. Glucose recovery from different corn stover fractions using dilute acid and alkaline pretreatment techniques. *Journal of Ecology and Environment*, 41:26-37, 2017

D. Aboagye, N. Banadda and N. Kiggundu. A review on the potential of Ghana to convert orange peel fibres into bio-oil using fast pyrolysis. *Renewable and Sustainability Review Journal*, Vol. 70:814-821, 2017

Experience of Building a Low Cost Tractor in a Developing Country Context: A Case of Uganda

Mutesasira Samuel, Nsubuga Denis, Tibaku-Zira Ernest, Miito Gilbert, Banadda Noble, Kiggundu Nicholas, Zziwa Ahamada, Muyonga Herbert, Kabenge Isa, Wanyama Joshua and Kambugu Robert[1]

Introduction

Most developing countries have an economy strongly dominated by the agriculture sector (Intarakumnerd, Chairatana, & Tangchitpiboon, 2002). Agriculture generates up to 50% of gross domestic product, contributing more than 80% of trade in value and more than 50% of raw materials to industries (Joshi, Gulati, Birthal, & Tewari, 2004). In Uganda, Agriculture and forestry contributes 14.6% of GDP (Fan, Mogues, & Benin, 2009; Kiddugavu *et al.*, 2003; UBOS, 2014), employing about 80% of the population. Despite its domination, agriculture is grossly underdeveloped in most African countries (Mrema, Baker, & Kahan, 2008). Furthermore, 30-40% of agricultural produce is lost owing to poor post-harvest handling, storage and processing methods (Salami, Kamara, & Brixiova, 2010). Studies have shown that 99.4% of smallholder farmers use traditional, rudimentary and obsolete technologies and methodologies for post-harvest operations with devastating effects of high post-harvest losses and low market value. Therefore, there is high potential for expansion of the agriculture sector at all levels (Aksoy & Beghin, 2004). The low level of engineering technology inputs in agriculture has been cited as one of the main constraints hindering the modernization of agriculture and food production systems in Africa.

In Sub-Saharan Africa (SSA), land productivity is among the lowest in the world (Böttinger, Doluschitz, Klaus, Jenane, & Samarakoon, 2013), and Agricultural Mechanization has stagnated in recent years. In SSA countries, over 88.6% of farm power is still provided by people's muscles, mostly from women, the elderly and children, 10.2% of farm power is provided by drudge animals and less than 1.2% of mechanization services

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are provided by engine power (Kienzle, Ashburner, & Sims, 2013). These methods place severe limitations on the amount of land that can be cultivated per family. They reduce the timeliness of farm operations and limit the efficacy of essential operations such as cultivation and weeding, thereby reducing crop yields. Reliable and affordable transportation is vital to economic growth. Transportation connects products to markets, people to education, and supplies to businesses and farms. However, Sub-Saharan Africa (SSA) generally has poor road infrastructure (Tiffen, 2003). As such 90% of the transportation of agricultural produce from field to home and/or local markets is done on the heads of women and children (Boserup & Kanji, 2007).

Africa has enormous potential, not only to feed itself and eliminate hunger and food insecurity (Clover, 2003), but also to be a major player in global food markets, agriculture as a sector can therefore contribute towards major continental priorities, such as eradicating poverty and hunger. Despite a slight increase in production in Sub-Saharan Africa, agricultural growth in SSA is generally achieved by cultivating more land and by mobilizing a larger agricultural labor force (Diao, Hazell, Resnick, & Thurlow, 2007), but there has been very little improvement in yields and barely any change in production techniques. Farm power in African agriculture, especially SSA, relies to an overwhelming extent on human muscle power, based on operations that depend on the hoe and other hand tools. Such tools have implicit limitations in terms of energy and operational output in a tropical environment

Current statistics indicate that there are about 470,000 tractors in Africa (Houssou, Diao, & Kolavalli, 2014). The total number of working tractors would have to be about 3.5 million (7 times more) to put Africa on a par with other regions. There are 0.175 tractors per 1,000 people in Uganda compared to Slovenia which is the highest in the world with 54.2 tractors per 1,000 people. In SSA the general average number of tractors is about 28 tractors per 1000 ha whereas it is about 241 tractors in other regions. Many areas of the developing world lack affordable transportation. Inhabitants spend a significant percentage of their time transporting agricultural products and water manually, over rough terrain and long distances, and it can be difficult to get fresh produce to markets where it can be sold before spoilage occurs. In Sub-Saharan rural Africa, Lumkes (2012) found that transportation problems cannot be solved simply by improving the roads.

To address the problems of SSA by providing affordable transportation of agricultural produce while offering portable power options for agricultural mechanization, water pumping, food processing, and electrical power generation, a team from Makerere University embarked on a project to develop a basic utility vehicle (BUV) that is low-cost, durable, adaptable and easily manufactured, which was a modification of the existing BUV from Purdue University (Lumkes, 2015). A multi-purpose tractor dubbed the MV Mulimi was designed and fabricated at the Makerere University Agricultural Research Institute Kabanyolo under the sponsorship of the Presidential Initiative on Science and Technology. The tractor was intended for the vast majority of Uganda's farmers who cultivate on 10 acres or less, who may not be in a position to buy large-scale agricultural equipment given their incomes and farm sizes. With a body made out of a combination of wood and steel, the three-wheel vehicle 13-horsepower five-speed engine does not only plough fields, it also transports produce, threshes maize, pumps water for irrigation and can charge phones. It has a pump that pumps water from depths of up to seven meters to a height of 33 meters. The tractor comes with a three-disc plough. This will save farmers from the laborious task of using a hand hoe. This attempts to solve farmers' problems at the source. This paper seeks to show the experience of constructing a BUV in a developing country.

Design Considerations

A multi-purpose tractor dubbed the MV Mulimi was to be manufactured at the Makerere University Agricultural Research Institute Kabanyolo under the sponsorship of the Presidential Initiative on Science and Technology. The tractor is intended for the vast majority of Uganda's farmers who cultivate on 10 acres or less. These may not be in position to buy large scale agricultural equipment given their incomes and farm sizes, yet they still need labor to run their operations. A body is made out of a combination of wood and steel (made from locally available materials), a three-wheel vehicle 13-horsepower five-speed engine which does not only plough fields, but also transports produce, threshes maize, pumps water for irrigation and can charge phones would be fabricated. The tractor was to have a provision for mounting a three-disc plough.

Tractor & Engine Configuration

The selected configuration is a full-time rear-wheel drive with a Chinese 186F engine situated longitudinally besides the control foot pedals in line with the front wheel linked with the clutch through the sprockets-chain combination reduction system. From the clutch rotary power is transmitted to the five-speed gearbox to the propeller shaft, differential and drive axles and finally to the hubs where the agricultural tires are mounted.

Construction Procedures

The first week was spent laying out a fabrication plan, purchasing all the required tools, and clearing the work area inside the shop. A working table was made by screwing a steel plate onto a wood table and leveling it using spirit levels, after which purchase of the steel was done. There are many different steel suppliers in Kampala (Figure 1) and the steel comes from a variety of sources. Much of the steel was manufactured in Uganda or in other East African countries with some being imported from China, India, and South Africa. The market is flooded with very poor quality steel and supplies seem to be rather inconsistent with a short time on the shelf. Because of this, it was crucial to buy steel in bulk for small-scale vehicle production to ensure quality and consistency. Once the steel was purchased, the shop was equipped, the frame fabrication went on smoothly (Figure 2), although there were challenges of power outages in the shop. It is important to note is that manufacturing of the BUV was done using only local skills and tools.

Procurement Process

Procurement of vehicle parts was a slow process for the tractor because a middleman was used to locate the parts needed, which led to a limitation in terms of price negotiations to reduce costs for the vehicle. There was,

Figure 1. During purchase of steel.

Figure 2. During frame fabrication.

however, an abundance of rear axles (Figure 3) and front strut assemblies as most of the cars in the country were four-wheel drives, but rear-wheel drive transmissions were hard to find. A supplier was later found to supply transmissions, clutch assemblies, flywheels, and crankshafts.

For the sake of battery charging with the vehicle, the BUV required an alternator but one-cylinder diesel and petrol engines with in-built alternators and key-start were not easily available in Kampala. Agricultural tires were needed for the rear wheels, but small agriculture tires were not easily available in Kampala. These were purchased from Nairobi along with sprockets and chain, as they were more readily available than in Kampala.

The wood for the vehicle was locally purchased, machined to the precise size and cut into the required dimensioned pieces (Figure 4). The

Figure 3. Rear wheel axle.

Figure 4. Fixed wooden carriage.

crankshaft hub was also cut and machined at a machine shop in town before being pressed on the shaft, balanced, then welded in place.

The electrical components were mostly taken from used cars with the taillights coming from motorcycles and the purchase of new headlights. The electrical system was installed (Figure 5) and tested, a plough provision was incorporated using a 2-disc plow from a walk-behind-tractor. Used lower links and an upper link from small tractors were purchased and then modified and a winch was added for raising and lowering the plow to save on materials.

Once the plough was complete (Figure 6), a threshing machine was purchased from one of the local government organizations that specialize in fabricating custom agricultural equipment and post-harvest processing machinery. The thresher was relatively large but could process up to 700 kg/hour and was easily mounted to the side of the vehicle allowing the operator to feed from the bed.

Figure 5. Electrical system assembly.

Figure 6. The completed BUV.

Functional Capabilities

The MV Mulimi after its completion could accomplish five major tasks: ploughing agricultural fields, transportation of agricultural produce and/or workers up to 1 ton, pumping water up to a head of 33 m, providing electrical power for lighting and phone charging with output port built on the dash-board and, finally, availing rotary power to run stationary agro-processing equipment, for example, a maize thresher.

Performance-Related Challenges and Design Improvements

Since the machine design is new in the country, the plough and maize thresher which were used on the machine were not compatible. Some effort was made to modify the maize thresher in order to match the vehicle performance during testing, but more is still needed where one graduate student will have to come up with the best design. Ploughing was also tested and found not working effectively. Therefore, research will be done centering on the hitching system to maximize the ploughing capability of the multipurpose vehicle.

Conclusions

Despite the success of the project, this does not guarantee future success and sustainability of the project. There are still aspects of the project that are being learned and could lead to problems in the near future or even failure of the project if not considered. In particular, a project management strategy should be developed before beginning the planned small-scale production. The project is in need of a solid marketing strategy to integrate ICT in its operations. It is also necessary to mention that waste plastics are melted into liquid fuels that run this vehicle. Smallholder agriculture that represents the vast majority of farmers on the African continent is in dire need of technologies that work and are multi-purpose.

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Other Appointments

- Howard Hughes Medical Institute Investigator, 2008-present
- Broad Institute, Cambridge, MA Senior Associate Member, 2004-present
- Koch Institute for Integrative Cancer Research at MIT, Member, 2004-present

Awards

- Switzer Prize, 2018
- Dickson Prize in Medicine, 2017
- Lurie Prize in Biomedical Sciences, 2017
- National Academy of Sciences, Member, 2016
- National Academy of Sciences, Award in Molecular Biology, 2014
- Howard Hughes Medical Institute, HHMI Investigator, 2008

Key Publications

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Regulation of Growth by the Nutrient-sensing mTORC1 Pathway

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The mechanisms that regulate organismal growth (mass accumulation) and coordinate it with the availability of nutrients were unknown until two decades ago. We now appreciate that one pathway – the mTOR pathway – is the major nutrient-sensitive regulator of growth in animals and plays a central role in physiology, metabolism, the aging process, and common diseases (reviewed in (Saxton and Sabatini 2017)). The mTOR protein kinase is the target of the drug rapamycin and the catalytic subunit of two multi-protein complexes, mTORC1 and mTORC2, that control distinct branches of the pathway. Rapamycin is a very interesting small molecule that was first isolated from bacteria collected on Easter Island, an island in the South Pacific which is also known as RapaNui.

We now appreciate that mTOR Complex 1 (mTORC1) pathway is one of the central signaling systems of mammals and is a major regulator of growth at the cell, organ, and whole body levels. It balances the activities of anabolic and catabolic systems, such as protein, lipid, and nucleotide synthesis versus autophagy. In addition, it is deregulated in many common human diseases, such as cancer and neurological disorders like epilepsy and also plays a key role in the aging process (Saxton and Sabatini 2017). Because of the potential of mTORC1 inhibitors to ameliorate aging-related diseases, there is great interest in developing small molecule inhibitors that are truly specific for mTORC1 and do not also inhibit mTORC2, which the best-known mTORC1 inhibitor (rapamycin) can also target (Sarbassov, Ali et al. 2006, Lamming, Ye et al. 2012).

A fascinating aspect of the mTORC1 pathway is that it senses many diverse stimuli, including growth factors, nutrients, and various forms of stress. A major focus of our laboratory has been to elucidate the mechanisms through which mTORC1 senses nutrients, amino acids in particular. In my presentation at the Pontifical Academy of Sciences I focused on our work on nutrient sensing.

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Nutrient Sensing Pathway Components

We now appreciate that nutrients, including amino acids, activate mTORC1 by promoting its translocation to the lysosomal surface where Rheb, its activator, is located (see summary diagram in Figure 1). Rheb is a small GTP binding protein that directly interacts with mTORC1 and strongly stimulates its kinase activity. The translocation process depends on a second set of GTP binding proteins, the heterodimeric Rag GTPases. The Rag GTPases in turn are regulated by a large set of lysosomally-localized protein complexes, including GATOR1, GATOR2, Ragulator, KICSTOR, FLCN-FNIP. GATOR1, a negative regulator of the cytosolic branch of the nutrient-sensing pathway, has three subunits: Depdc5, Nprl2, and Nprl3, and is a GTPase Activating Protein (GAP) for RagA. We used site-directed mutagenesis, GTP hydrolysis assays, co-immunoprecipitation experiments, and structural analyses and identified Arg-78 on Nprl2 as the arginine finger that carries out the GATOR1 GAP function. Substitutions of this arginine render mTORC1 signaling insensitive to nutrient starvation and are found in cancers such as glioblastoma. None of the GATOR1 components have sequence homology to other proteins and so in a long-standing collaboration with Dr. Zhiheng Yu (HHMI Janelia Farms) we used Cryo-EM to solve two structures: GATOR1 and GATOR1 bound to the Rag GTPases. GATOR1 adopts an extended architecture with a cavity in the middle. Nprl2 is as a link between Depdc5 and Nprl3, and Depdc5. Biochemical analyses revealed that two binding modes must exist between the Rag GTPases and GATOR1.

KICSTOR is composed of four proteins, KPTN, ITFG2, C12orf66 and SZT2, and is required for nutrient deficiency to inhibit mTORC1 in human cells. KICSTOR localizes to lysosomes, binds and recruits GATOR1 to the lysosomal surface, and is necessary for the interaction of GATOR1 with its substrates, the Rag GTPases. In mice lacking SZT2, mTORC1 signaling is increased in several tissues, including in the brain. Just like for GATOR1 components, several KICSTOR components are mutated in neurological diseases like epilepsy.

We recently found that Ragulator and SLC38A9 are each unique guanine exchange factors (GEFs) that collectively push the Rag GTPases toward the active state. Ragulator triggers GTP release from RagC, thus resolving the locked inactivated state of the Rag GTPases. Upon arginine binding, SLC38A9 converts RagA from the GDP- to the GTP-loaded state, and therefore activates the Rag GTPase heterodimer.

Because mTORC1 senses lysosomal amino acids in addition to cytosolic ones, we became interested in developing methods to measure metabolite levels in organelles. We first developed the MitoIP method for the mitochondrial matrix and more recently an analogous method (LysoIP) for lysosomes. We are using these methods to understand how electron transport chain inhibition affects matrix metabolites, how mTORC1 regulates lysosomal amino acid efflux, and to de-orphan the function of lysosomal storage disease genes. In unpublished work we generated mice expressing the transgenes necessary to implement the methods and we are beginning to validate conclusions in vivo that we first made in cultured cells.

We used the LysoIP approach to measure the metabolite content of lysosomes from cells lacking SLC38A9 and uncovered an unexpectedly central role for it in amino acid homeostasis. SLC38A9 mediates the transport, in an arginine-regulated fashion, of many essential amino acids out of lysosomes, including leucine, which mTORC1 senses through cytosolic Sestrin2. SLC38A9 is necessary for leucine generated via lysosomal proteolysis to exit lysosomes and activate mTORC1. Pancreatic cancer cells, which use macropinocytosed protein as a nutrient source, require SLC38A9 to form tumors. Thus, through SLC38A9, arginine serves as a lysosomal messenger that couples mTORC1 activation to the lysosomal release of the amino acids needed for cell growth.

Lastly, in work that is under review, we used Cryo-EM to solve the structure of mTORC1 bound to the complex of the Rag GTPases with Ragulator, which comprise the docking site for mTORC1 on the lysosomal surface. Using it, we generated a model for how mTORC1 docks on the lysosome, revealing what we believe to be its active state. Using structure-guided mutagenesis, we defined the key residues mediating the interaction between Rag-Ragulator and Raptor, the subunit of mTORC1 that directly binds to them. Mutants that disrupt the interaction inhibit mTORC1 and prevent its lysosomal localization. It is very gratifying for us to see the structure of a complex that we have worked on for so many years.

Nutrient Sensors

The GATOR1, GATOR2, and Ragulator complexes interact with a number of direct sensors of individual amino acids and metabolites in the cytosol. The Sestrin family of proteins (Sestrin1, Sestrin2, and Sestrin3) directly sense leucine in the cytosol while the CASTOR family of proteins (CASTOR1, CASTOR2) directly sense cytosolic arginine. SAMTOR senses methionine but does so indirectly as it binds to S-adenosyl-methionine, a product of methionine catabolism that is used in hundreds of methylation reactions. Lastly, SLC38A9 senses arginine in the lysosome ((Sancak, Peterson et al. 2008, Sancak, Bar-Peled et al. 2010, Zoncu, Bar-Peled et al. 2011, Bar-Peled, Schweitzer et al. 2012, Bar-Peled, Chantranupong et al. 2013, Petit, Roczniak-Ferguson et al. 2013, Tsun, Bar-Peled et al. 2013, Chantranupong, Wolfson et al. 2014, Jung, Genau et al. 2015, Rebsamen, Pochini et al. 2015, Wang, Tsun et al. 2015, Chantranupong, Scaria et al. 2016, Saxton, Chantranupong et al. 2016, Saxton, Knockenhauer et al. 2016, Wolfson, Chantranupong et al. 2016, Castellano, Thelen et al. 2017, Gu, Orozco et al. 2017, Peng, Yin et al. 2017, Wolfson, Chantranupong et al. 2017, Wyant, Abu-Remaileh et al. 2017). Our recent works suggest that SLC38A9 senses lysosomal arginine as an indication that ribosomes, which are very high in arginine content, are being degraded in lysosomes and can serve as a source of nucleotides under periods of starvation. These nucleotides are released from the lysosome and recycled into RNA in the cytosol.

Our identification of nutrient-sensors upstream of mTORC1 revealed a novel group of targets amenable to therapeutic intervention (Chantranupong, Wolfson et al. 2014, Wang, Tsun et al. 2015, Chantranupong, Scaria et al. 2016, Wolfson, Chantranupong et al. 2016, Gu, Orozco et al. 2017, Wyant, Abu-Remaileh et al. 2017). We solved the structures of two of these and defined their nutrient-binding pockets, which enables a rational approach to developing a novel class of mTORC1 pathway inhibitors (Saxton, Chantranupong et al. 2016, Saxton, Knockenhauer et al. 2016, Saxton, Knockenhauer et al. 2016). Gratifyingly, a small molecule activator of mTORC1 (NVP-5138) that acts by mimicking the action of leucine on Sestrin1/2 (Kato, Pothula et al. 2019, Sengupta, Giaime et al. 2019) recently entered clinical testing (clinicaltrials.gov) for treatment-resistant depression, in which there is substantial evidence that depressed neuronal mTORC1 signaling plays a pathogenic role (Li, Lee et al. 2010, Jernigan, Goswami et al. 2011, Koike, Iijima et al. 2011, Li, Liu et al. 2011, Dwyer, Lepack et al. 2012, Chandran, Iyo et al. 2013, Voleti, Navarria et al. 2013, Yang, Hu et al. 2013, Yu, Zhang et al. 2013, Ota, Liu et al. 2014, Zhou, Wang et al. 2014, Dwyer, Maldonado-Aviles et al. 2015).

We have also made some progress in understanding what happens to animals when we deregulate its capacity to sense the absence of nutrients in vivo. We have generated mice in which mTORC1 is no longer inhibited when we starve the animals for nutrients but under the fed condition is not hyperactive. As far as we can tell, these animals are fine as long as they are in nutrient replete conditions. Upon starvation their fitness drops very quickly, most likely because they cannot induce autophagy to liberate nutrients from their internal stores. We can rescue their fitness defect by inhibiting mTORC1 with rapamycin or simply injecting glucose into the animals as it appears to be the nutrient that becomes limiting first. In fact, the mice perish when glucose in the blood becomes undetectable using a clinical-grade glucometer. We find equivalent results when we perform these experiments when the animals are neonates or young adults. In addition, the adult animals appear to suffer seizures, which are very similar to those caused by mutations in GATOR1, the Rag negative regulator, in people.

Future Directions

While we have made progress in understanding how mTORC1 senses nutrients, several major questions remain unanswered, many of which revolve around the GATOR2 complex. This complex has emerged as *the* central integrator of cytosolic nutrient signals to mTORC1 and acts upstream of GATOR1, which negatively regulates RagA/B by acting as a GTPase Activating Protein (GAP) for them. Despite its importance, GATOR2 remains very mysterious. First, we do not understand its biochemical activity, how it signals to other pathway components, nor its structure. Second, we know little about how its regulation by nutrient sensors like Sestrin2 impacts organ physiology in vivo. Third, while our previous work has helped elucidate how amino acids signal to mTORC1, we still have almost no mechanistic insight into how glucose regulates the GATOR1-GATOR2 axis to control mTORC1 activity. In unpublished work, we find that mTORC1 does not directly sense glucose but rather an intermediate in glycolysis. We are currently trying to identify the sensor for this intermediate.

In addition, we are currently generating mice in which we are eliminating each nutrient sensor one by one or introducing mutations into them that prevent their capacity to bind a particular amino acid. In preliminary data we find that these animals have a fitness defect when placed on diets lacking the cognate nutrient for the sensor. Fortunately, the mTORC1 pathway still contains many mysteries for us to solve.

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Other Appointments

- Advisory Board, Shanghai Institute of Microsystem and Information Technology, since 2016
- Agence Nationale de la Recherce (ANR, France), International evaluator of research projects, ANRAAP générique 2016 - CES24, since 2016

Awards

- 37° International Prize Guido Dorso – Research – Senate of the Italian Republic, 2016
- ERC Consolidator Grant 2015
- Early Career Achievement Award – SPIE International Society for Optics and Photonics 2015
- "Sergio Panizza" Optoelectronic and Photonic Award – Italian Physical Society 2012
- International Scientific Authors Award International Conference on Intersubband Transitions in Quantum Wells (USA)
- Young Scientist Award 2005, International Conference on Matter, Materials and Devices, Genova, Italy
- INFM Prize for Young Authors 2004

Key Research Achievements

Invention of THz wire lasers with record performances (*Nature Communications* 2018)

Invention of flexible THz saturable absorbers from liquid phase exfoliation of graphite (*Nature Communications* 2017)

Invention of the first THz near field probe for coherent phase/amplitude imaging with deeply sub-wavelenght spatial resolution (*Nature – Scientific Reports* 2017)

Ultrafast optical switched for THz waves based on interface polaritons in black-phosphorus (*Nature Nanotechnology* 2017)

Invention of the first THz device exploiting van der Waals heterostr. (*Advanced Materials* 2016)

First experimental demonstration of an active photonic device exploiting topological insulator surface states (*Nano Letters* 2016); 3 invited talks

Invention of black phosphorus THz photodetectors (*Advanced Materials* 2015, *Scientific Reports* 2016); 7 invited talks

Demonstration of coherent perfect absorption of photons (*Nature Phys.* 2014)

Invention of quasi-crystal THz lasers (*Nature Communications* 2014); 6 invited talks

[1] *Presentation available at:* http://www.pas.va/content/accademia/en/publications/acta/acta25/vitiello.html