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Edited by

Joachim von Braun, Peter K.A. Turkson, Chien-Jen Chen,
Ewine van Dishoeck, Fabiola Gianotti, Mohamed H.A. Hassan,
Jürgen Mittelstraß, Veerabhadran Ramanathan, Edward M. De Robertis

Basic Science for Human Development, Peace, and Planetary Health

Proceedings of the Plenary Session
Casina Pio IV, Vatican City, 8-10 September 2022

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"In this Plenary Session, you emphasize 'basic science,' which makes available a great deal of new knowledge about the Earth, the universe and the place of human beings within it. I congratulate you because you maintain the goal of connecting basic science with resolving current challenges, of connecting astronomy, physics, mathematics, biochemistry and climate sciences with philosophy in the service of human development, peace and the health of our planet. This interconnected approach is very important because, as scientific achievements increase our awe at the beauty and complexity of nature, there is a growing need for interdisciplinary studies, linked to philosophical reflection, that can lead to new syntheses. This interdisciplinary vision, if it also takes stock of Revelation and theology, can help provide answers to humanity's ultimate questions, which are also being asked by new, and sometimes disoriented, generations. ... Dear Members of the Academy, at this moment in history, I ask you to promote knowledge with the aim of building peace. After two tragic world wars, it seemed that the world had learned to move progressively towards respect for human rights, international law and various forms of cooperation. Unfortunately, history shows signs of regression. Not only are anachronistic conflicts intensifying, but instances of a myopic, extremist, resentful and aggressive nationalism are re-emerging (cf. *Fratelli Tutti*, 11), and new wars of domination, affecting civilians, the elderly, children and the sick are causing destruction everywhere."

Pope Francis addressing the Pontifical Academy of Sciences. 2022, 10 September


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Address of His Holiness Pope Francis to the Pontifical Academy of Sciences

10 September 2022, Clementine Hall

Your Eminences,
Dear Brother Bishops,
Distinguished Ladies and Gentlemen!

I welcome you on this occasion of the Plenary Session of the Pontifical Academy of Sciences. I thank your President, Professor Joachim von Braun, for his kind words. I likewise express my gratitude to Archbishop Marcelo Sánchez Sorondo, who has worked very hard as Chancellor in service of this Academy and that of the Social Sciences. May the Lord reward him and bestow upon him many blessings. We send him good wishes for his eightieth birthday and for a happy retirement! Now others can take charge. We also welcome the new Chancellor, Cardinal Peter Turkson: thank you for accepting, Your Eminence!

The theme of your Plenary Session, "Basic Science for Human Development, Peace, and Planetary Health", underlines the key issues facing our human family at this moment in history.

Yet first, I would like to answer a question that not a few people are asking: Why did the popes, beginning in 1603, wish to have an Academy of Sciences? As far as I am aware, no other religious institution has such an academy, and many religious leaders have expressed an interest in establishing one. Leaving historical hypotheses to others, I would interpret this decision today in the context of love and care for the common home that God has given us. The Church embraces and encourages a passion for scientific research as an expression of love for the truth and for knowledge about the world on both the macro and microcosmic levels, and about life in all its symphonic splendour. Saint Thomas Aquinas states that "the end of the whole universe is truth" (Summa contra Gentiles, I,1). As part of this universe, we ourselves have a unique responsibility, which stems from our ability to wonder and ask "why?" when faced with reality as it is. At the heart of this, then, lies a contemplative attitude, and the complementary task of caring for creation. Dear friends, the theme of your Plenary Session is situated in this same perspective.

Looking back on recent years, I gratefully recall PAS's declarations in the face of various emergencies, whether concerning food crises and the fight against hunger – in cooperation with the UN Food Summit – or to do with the health of the oceans and seas, or indeed with strengthening the resilience of the poor in the case of climate shocks. Important too were your efforts to help rebuild poor neighbourhoods in a sustainable way making use of the bioeconomy, as well as an equitable response to health problems caused by the Covid pandemic. No less relevant is the work to establish international standards for organ donation and organ transplants in the fight against human trafficking, as well as undertakings to promote a new science of medical rehabilitation for the elderly and the poor. Moreover, I particularly appreciate your efforts to engage science and politics in order to prevent nuclear war and war crimes against civilian populations. I congratulate all those who have actively participated in this, especially you, Professor von Braun, for the wisdom and commitment with which you have brought fresh ideas into the life of the Academy. You have taken up today's challenges as concrete scientific opportunities, in order to address them by working with scientists who can help to resolve problems.

In this Plenary Session, you emphasize "basic science," which makes available a great deal of new knowledge about the Earth, the universe and the place of human beings within it. I congratulate you because you maintain the goal of connecting basic science with resolving current challenges, of connecting astronomy, physics, mathematics, biochemistry and climate sciences with philosophy in the service of human development, peace and the health of our planet. This interconnected approach is very important because, as scientific achievements increase our awe at the beauty and complexity of nature, there is a growing need for interdisciplinary studies, linked to philosophical reflection, that can lead to new syntheses. This interdisciplinary vision, if it also takes stock of Revelation and theology, can help provide answers to humanity's ultimate questions, which are also being asked by new, and sometimes disoriented, generations.

Indeed, this century's scientific achievements must always be directed to the needs of fraternity, justice and peace, and help meet the great challenges facing our human family and our environment. In this sense, too, the Pontifical Academy of Sciences has a unique structure, composition and set of goals, which are always aimed at sharing the benefits of science and technology with the greatest number of people, especially those most disadvantaged and in need. In this way, it also strives to liberate people from various forms of slavery, such as forced labour, prostitution and organ trafficking. These crimes against humanity, which go hand in hand with poverty, also occur in developed countries, in our own cities. The human body, whether in part or in its entirety, can never be an object of trade! I am pleased that PAS is actively engaged in supporting these goals, and I trust it will continue to do so with ever greater intensity commensurate with growing needs.

In short, the positive results of science in the twenty-first century will depend, to a great extent, on the ability of scientists to seek the truth and apply discoveries in a way that develops in tandem with the search for what is right, noble, good and beautiful. I look forward to the results of your work, which will also be important for educational institutions and younger generations.

Dear Members of the Academy, at this moment in history, I ask you to promote knowledge with the aim of building peace. After two tragic world wars, it seemed that the world had learned to move progressively towards respect for human rights, international law and various forms of cooperation. Unfortunately, history shows signs of regression. Not only are anachronistic conflicts intensifying, but instances of a myopic, extremist, resentful and aggressive nationalism are re-emerging (cf. *Fratelli Tutti*, 11), and new wars of domination, affecting civilians, the elderly, children and the sick are causing destruction everywhere. The many ongoing armed conflicts are of serious concern. I have said that it was a third world war being fought "piecemeal" – perhaps we can now say that it is "all out" – putting people and the planet at ever greater risk. Saint John Paul II gave thanks to God that, through Mary's intercession, the world had been preserved from atomic war. Unfortunately, we must continue to pray for protection against this danger, which should have been averted long ago.

All knowledge based on science and experience must be utilized to avoid wars and overcome suffering, poverty and new forms of slavery. By rejecting research that in the past has been destined for deadly ends, scientists around the world can unite in a common readiness to disarm science and thus become a force for peace. In the name of God, who created all human beings for a common destiny of happiness, we are called today to bear witness to our fraternal vocation to freedom, justice, dialogue, mutual encounter, love and peace, and avoid nurturing hatred, resentment, division, violence and war. In the name of the God, who gave us the planet to safeguard and develop, we are called today to ecological conversion, to save our common home and life, and that of future generations, rather than increasing inequality, exploitation and destruction.

Dear Members of the Academy, dear friends, I encourage you to continue working for truth, freedom, dialogue, justice and peace. Today more than ever – also thanks to you! – the Catholic Church is an ally of scientists who follow this aspiration. I assure you of my prayers and, respecting each one's beliefs, I invoke upon you God's blessing. And please, in your own way, also pray for me. Thank you!

Statement by Joachim von Braun, President of the Pontifical Academy of Sciences

At the Papal Audience on September 10th, 2022 on the Occasion of the Plenary Conference "Basic science for human development, peace, and planetary health"

Dear Holy Father,

We are most grateful to You for welcoming us on the occasion of the Plenary Conference of the Pontifical Academy of Sciences.

Today we have an historic audience with You, because of the following two reasons:

1. Our esteemed and beloved former Chancellor, H.E. Bishop Marcelo Sánchez Sorondo, has just retired. Yesterday we recognized his tremendous achievements building the Academy for a quarter century with a special session on "Science in Philosophical and Religious Perspectives".
2. We warmly welcomed H.Em. Cardinal Peter Turkson as our new Chancellor. We are grateful to him for now serving the Academy, and grateful to you for this distinguished appointment, which demonstrates your esteem and support of our Academy.

I am pleased to inform you that today, we have eleven new members of the Academy to introduce to you, who are leaders in diverse fields of science from many different countries. We also gave the Pius XI Medal to two distinguished young scientists for their excellent research.

The members of the Academy consider it an honor to offer their precious time to your Academy. They do so because our Academy has an excellent reputation for commitment to scientific truth and its liberating benefits that are open to all people, especially those most in need. PAS also appeals to us because of the autonomy in research that you guard and respect, as well as the international composition of its membership and their excellence in scientific disciplines.

The Academy has an increasing reach and impact through You, especially on issues of climate, protection of human and planetary health, and equity, as demonstrated, inter alia, by the Encyclical *Laudato Si'*.

Our agenda at this Plenary conference was "Basic science for human development, peace, and planetary health". Basic science is essential to improve human welfare, for example by means of improved medicine, food systems, and energy for the poor. Moreover, basic science offers deeper understanding, knowledge of causes and enables a wisdom that is able to respond to the challenges of our time.

We addressed topics at the frontiers of sciences in key areas that change world views and have the potentials to improve human development, peace, and planetary health. We discussed, for example,

1. Climate and atmospheric science and resilience of People and Ecosystems under Climate Stress
2. Reconstructing cities, incl. slums
3. Health of the oceans
4. Life Sciences and Medical science, on healing cancer, and regenerating cells
5. Covid-19 and actions to address the pandemics
6. Mathematics and Artificial Intelligence, using AI to accelerate scientific discovery
7. Astronomy, exploring how our Milky Way was formed.

The fact that important discoveries come about because of curiosity as a result of wonder and admiration of nature raises philosophical, ethical, religious, as well as policy questions. We also integrate philosophy and theology in our work, drawing for instance on Aristotle, Thomas Aquinas and contemporary thinkers that we invite to our meetings. Marcelo has helped us a lot in that over the years, and we also hope to draw on his wisdom also in the future. Our workshop on "Symbols, Myths and Religious Sense" of early humans hundreds of thousands of years ago is an example.

Dear Holy Father,

Basic sciences are at risk of being marginalized or misused by the strong powers of the day. This is especially true when economic crises, wars, and growing risks trouble people, as is currently the case. Therefore, it is ever more important for science to have peace as a goal. A few months ago, the Pontifical Academy of Sciences did again call attention to the threats of nuclear war, and wars against civilian populations. We also emphasized the fundamental drivers of conflicts: divisiveness, discord, hatred, greed, exploitation, human trafficking and racism, which undermine both peace and planetary health.

In order to address neglect of science-informed rational arguments, the Church can help the understanding of science, for instance through science education in school and university curricula.

We stress that, in view of the well-known powerful contributions of basic science, related knowledge and good practice need to be shared more widely, especially with low-income regions of the world. Otherwise the benefits for human development, peace, and planetary health will not come about. Our Academy therefore is also actively reaching out to scientists in Africa, Latin America and Asia and we are expanding our membership in these hemispheres.

Dear Holy Father,

Thank you for the most thoughtful statements with which you accompany our work, and encourage us. While promoting the freedom of scientific research, you also foster fruitful reflections among science and faith which are important for our work that aims at human development, peace, and planetary health.

We thank you for your prayers, and pray for you.

Best wishes and God bless you.

Concept Note

The Pontifical Academy of Sciences has held conferences and issued science-based statements urging to address, among others, the massive health problems caused by the pandemic and by inadequate health systems, the large-scale destruction of nature and the climate crises, artificial intelligence, rising inequalities, hunger and poverty, and increasing local and global conflicts. We identified specific science opportunities to address each of these problems.

The Academy has a strong track record of seeking scientific solutions and engaging with political and societal actors to implement innovative actions to overcome the most serious problems facing humanity.[1] The 2022 Plenary does not abandon this perspective. Actually, the emphasis on basic science in this conference with a thought-perspective "from basic science to problem solving", is in the long run not in contradiction to the perspective "from noting problem to search for science". Both perspectives serve human advancement and our planet, yet the former is at risk of being somewhat marginalized. This is especially true when crises, wars, and growing risks trouble people and planet, as is currently the case.

There are, for instance, key areas where basic science is going to improve human welfare, such as medicine, food systems, and energy and more. Many of the main disciplines of science are involved in those areas. The progress and prospects of basic science relating to those areas are hugely important and clearly timely. Moreover, basic science is of intrinsic value. Obtained insights lead to deeper understanding, knowledge and possibly wisdom.

While keeping human development, peace and planetary health problems in perspective, the 2022 Biannual Plenary of the Pontifical Academy of Sciences aims to explore and highlight the driving forces and opportunities relating to basic science for human development, peace and planetary health. We will be addressing the following questions:

– What are new and emerging breakthroughs in sciences?
– How did science breakthroughs come about? And then ask

[1] See events and conferences at https://www.pas.va/en/events/plenary-session.html and https://www.pas.va/en/events/workshop.html

– How can they influence new, better and more effective ways to reduce the threats and problems for people, peace, and planet?

The first two questions are fundamental to science processes. The third one is a challenge which we must engage in, too.

It is ever more important for science to have peace as a goal. The Pontifical Academy of Sciences has actively engaged in support of this goal at critical junctures before, such as addressing threats of nuclear war,[2] and more recently, opportunities and risks of Artificial Intelligence and robotics[3]. The many ongoing armed conflicts are of grave concern to us. The accelerated and even global risks that emerge from threatened or actual attacks by powerful countries on neighbors are putting political order and human civilization at risk. At a time, when science is so dominant in culture, all science disciplines should consider their potential contributions to peace. Peace is a precondition for sustainable development. Divisiveness, for instance related to race – not just absence of war – undermines both peace and planetary health.

The time horizon of science for certain issues such as climate, biodiversity, genetics, robotics must be very long term, even decades or centuries. Emphasis on basic sciences with a humanity and planetary health perspective is very much in line with the Academy's Statute, "The aim of the Pontifical Academy of Sciences is to promote the progress of the mathematical, physical and natural sciences and the study of epistemological problems related thereto" and PAS "... promote(s) the progress of sciences and the solution of important scientific-technical problems, which are fundamental for the development of mankind". When taking long-term views philosophical questions and epistemological problems must also be considered. An obvious one may be the ambit of science, what can be known, and how many problems there are beyond its consideration.

This PAS Plenary Session features a session in honor of H.E. Msgr. Marcelo Sánchez Sorondo, our admired and esteemed former Chancellor, on the occasion of his 80th birthday. We can relate to Aristotle, who at the beginning of his Metaphysics, said "It is through wonder (τὸ θαυμάζειν) that men now begin and originally began to philosophize; wondering in the first place at obvious perplexities, and then by gradual progression raising questions about the greater matters too, e.g. about the changes of

[2] https://www.pas.va/en/events/2022/preventing_nuclear_war.html
[3] https://link.springer.com/book/10.1007/978-3-030-54173-6

the moon and of the sun, about the stars and about the origin of the universe". (Aristot. Met. 1.982b 11-20). The fact that important discoveries didn't come about because of a goal, but because of curiosity as a result of wonder and admiration, raises philosophical, ethical, religious, as well as science policy questions. And Aristotle points out another essential attribute of disinterested knowledge which is that of being free: "Clearly then it is for no extrinsic advantage that we seek this knowledge; for just as we call a man free (ἐλεύθερος) who exists for himself and not for another, so we call this the only free science, since it alone exists for itself" (Aristot. Met. 1.982b 28-30).

This Plenary is driven by the expectation that strong support for curiosity-driven science has huge payoffs that often come about in unpredictable ways, mostly in the long term, but increasingly even in the short term. A fine example of what basic science can achieve, as it happened, is the rapid development of the COVID vaccine thanks to developments in the decade-long studies of messenger RNA, which were planned for completely different purposes. Moving beyond anecdotes we want to explore systematic patterns in the progress of basic science insights in different disciplines and their interdisciplinary linkages. The conference discourse shall include voices of scientists about the challenges they faced, in order to understand the very basic aspects of the problem regarding, for instance, cutting-edge science like CRISPR-cas, Quantum Physics, Laser innovations, atmospheric science, mathematical algorithm innovations or Astrophysics. The theme of the 2022 PAS Plenary is timely also in view of the United Nations' "International Year of Basic Sciences for Sustainable Development" that will be developed on the basis of themes identified as priorities by UNESCO and the United Nations.

The Pontifical Academy of Sciences had already addressed issues of beliefs and science skepticism in the public at large, and the ability to adhere to false beliefs instead of rational arguments. These issues have further emerged in recent years. It is thus necessary to further consider at the Plenary 2022 the determinants of these tendencies, the role that religion may play in both adherence to science skepticism and openness to science, and the opportunities of science education to make a difference. Science discourse at PAS is transparent to the global public.

The narratives on basic sciences among PAS Academicians are of interest to a broad community to see how science is done, and what can come out of it, not neglecting risks of misuse of science. Scientists should feel encouraged to speak from the bottom of their hearts about all aspect of curiosity-driven science, which has at times ended up unintentionally changing the world, and share their diverse narrative on what brought them to the invention and how curiosity and great efforts drove their work, but also how they connect to the big issues of human development, peace, and planetary health.

Joachim von Braun

Conclusions on “Basic science for human development, peace, and planetary health”

Statement of the 2022 Plenary Session

PAS President, PAS Chancellor, with Academicians and Participants in the Plenary Session

Abstract

The 2022 Plenary of the Pontifical Academy of Sciences explored and highlighted the driving forces and opportunities related not just to basic science per se, but to basic science for human development, peace and planetary health. The topic is also timely in view of the United Nations’ “International Year of Basic Sciences for Sustainable Development”.

There are certain key areas where basic science is going to improve human welfare directly, such as medicine, food systems, energy and more. Progress is also happening in interdisciplinary science building on strong basic science, such as: Mathematics and AI; Astronomy; Physics and Biophysics; Climate Science; Chemistry/Bio-Chemistry; Life Sciences and Medical Science.

The fact that important discoveries do not come about because of a goal, but because of curiosity and imagination as a result of wonder and admiration, raises philosophical, ethical, religious, and science policy questions. We thus noted the importance and benefits of long-term perspectives in science, and called for society – including faith-based communities – and policy to recognize and more strongly support basic sciences.

We emphasize that it is ever more important for science to have peace as a goal. As scientists, we must neither neglect the fundamental drivers of conflicts, nor ignore the role of science.

The Pontifical Academy of Sciences remains concerned about neglect or ignorance of science-informed rational arguments and science skepticism in parts of the general public and in conventional and social media.

The abovementioned powerful contributions of basic science and its related capacities need to be shared more equitably – especially by the rich nations – with low-income regions of the world.

1. First of all, let us clarify the concepts embedded in the Plenary topic *"Basic science for human development, peace, and planetary health"*:

- *Human development* is understood here as the process of enhancing people's and communities' freedoms, capabilities, and opportunities, improving their physical, mental, and social well-being, so to achieve their aspirations.
- *Peace* is, first and foremost, the absence of wars and violent conflicts, but there is more to it: it includes overcoming divisiveness, racism, nationalism, and growing inequalities often combined with crime, human trafficking, and marginalization. Promoting justice, cooperation and peace in the world requires a science that seeks the truth, considers potential misuses, and is free from ideologies.
- *Planetary health* means the health of human civilization and the state of the natural systems which sustain it, recognizing that all life, not just human life, depends on the state of the biosphere and geosphere and their interdependence. Examples of disequilibria are self-destructive lifestyles, pandemics, climate change, loss of biodiversity, devastation of ecosystems and of natural beauty.
- *Basic research* advances fundamental knowledge and is a source of new scientific ideas and ways of thinking. It is often curiosity-driven, truth-seeking and questioning of established theories.

At first glance, the three goals – human development, peace, and planetary health – and the values underpinning them, do not seem related to basic science, because that type of science is driven by epistemic interest rather than the need to solve practical problems. Yet, in the long term, basic sciences often become the foundation for applied science and technological innovations. Moreover, there are indications that the transformation of new basic knowledge to societal applications has been progressing more rapidly in recent years.

2. The 2022 Plenary of the Pontifical Academy of Sciences explored and highlighted the driving forces and opportunities related to *basic science for human development, peace and planetary health* by addressing the following questions: What are the new and emerging breakthroughs in the sciences? How did these science breakthroughs come about? How can these discoveries instruct new, better and more effective ways to reduce the threats and problems for people, peace, and planet? The first two questions address processes intrinsic to science. The third concerns the translation of knowledge, which is a major challenge that we must also engage in. Emphasis on basic sciences with a human and planetary health perspective is very much in line with the Academy's Statute, "The aim of the Pontifical Academy of Sciences (PAS) is to promote the progress of the mathematical, physical and natural sciences and the study of epistemological problems related thereto", and the PAS "…promote(s) the progress of sciences and the solution of important scientific-technical problems, which are fundamental for the development of mankind".

3. The theme of the 2022 PAS Plenary, "Basic science for human development, peace, and planetary health", is timely in view of the United Nations' "International Year of Basic Sciences for Sustainable Development" that has just started on the basis of topics identified as priorities by UNESCO and the United Nations. The PAS is committed to continuing its close cooperation with the UN in fields of science and related policy consultations, as we have done in the recent past on climate, food, biodiversity, pandemic, universal health care, and other issues.

4. There are certain key areas where basic science is going to improve human welfare directly, such as medicine, food systems, energy and more. Many of the main disciplines of science are involved in those areas. The progress and prospects of basic science related to those areas are crucial and clearly timely. Moreover, basic science is of intrinsic value. Its insights lead to deeper understanding, knowledge and possibly wisdom. Science's search for the truth remains fundamentally important. The PAS has held conferences and published science-informed statements urging to address issues such as the massive health problems caused by the pandemic and by inadequate health systems, the large-scale destruction of nature and the loss of biodiversity, the climate crisis, the opportunities and risks of artificial intelligence, rising inequalities, hunger and poverty, and increasing local and global conflicts. We were able to identify specific science opportunities to address these problem areas, emphasizing the opportunities of advancing the sciences in each of these fields, as well as the need to expand interdisciplinary research.

5. We explored patterns in the progress of basic science insights in different disciplines and interdisciplinary linkages. The conference discourse included voices of scientists on the challenges they faced in order to understand the very basic aspects of a given problem. Examples came from cutting-edge science like genetic modification (CRISPR-cas), quantum and laser physics, atmospheric science, mathematics (new algorithms) and astrophysics. The PAS Plenary 2022 addressed topics at the forefront of science in key areas that change world views and have the *potential to improve human development, peace, and planetary health.* The following are some of these highlights that should not be seen in isolation, but as a growing opportunity for cooperation among disciplines:

- **Mathematics and AI** addresses intrinsic insights from mathematics as well as the opportunities for new applications, e.g. mathematics of AI, and using AI to accelerate scientific discovery. DeepMind's AlphaFold algorithm has already had a disruptive effect on disciplines that are dependent on protein structure and it will likely have similar transformational effects in diverse fields including weather and climate forecasting, but also on behavioral science. If used responsibly, AI has the potential to help with all of the aims of this Plenary Session – human development, peace, and planetary health. Teaching of mathematics and basic sciences in education systems needs to be intensified to tap into these opportunities.
- **Astronomy** seeks to provide insights into the origin and evolution of stars, planets, galaxies (e.g. via galaxy archeology) and even the Universe itself. As Immanuel Kant wrote: "Two things fill the mind with ever new and increasing admiration and awe, the more often and longer the reflection occupies itself with it: the starry sky above me, and the moral law within me".
  Where do we come from? Are we alone? What is the future of our Sun and its solar system, and of the Milky Way, the galaxy of which we are part, which we now know has a supermassive black hole at its center? Do the known laws of physics hold under extreme conditions? These are some of the biggest questions that humankind can ask, appealing to deep cultural and philosophical yearnings. Society has advanced through the development of new technologies driven in part by astronomy. Because of its broad appeal, astronomy is a gateway science that nurtures inquisitiveness and curiosity in children and students of all ages. The collective body of data sets, often openly accessible to the entire world for study purposes, trains scientists in the use of innovative big data and AI techniques that have their applications elsewhere in society. Astronomers also raise awareness and take actions to protect the dark and quiet skies, important

for human culture, heritage and health, which are currently being threatened by urban artificial light pollution and swarms of satellites in space. Being able to view the pristine spectacle of the starry night sky is of fundamental value for every human being. We need technological developments that can serve both night light and satellite services on the one hand, and provide access to the view of the night sky on the other.

– The **Physics and Biophysics** science on the agenda considered both the large and the small. We saw how large-scale phenomena such as solar activity and its impact on earth need attention in areas such as climate, human health and infrastructure (e.g. electricity grid). As for the small, we examined how microscopy at molecular-scale resolution in fluorescence provides insights into molecules in living cells, offering new ways of disease detection; and we reviewed new pathways from protein folding to understanding viruses such as Covid-19 and designing new types of vaccines. Physics and biophysics have much to add to the understanding of biology and medicine through tools to observe and mechanically perturb molecular systems and, secondly, by developing new theoretical models and simulations for a more quantitative and predictive understanding of these processes.

– **Climate Science** critically relies on atmospheric, planetary, and ecological sciences. We also highlight the growing need to address adaptation and resilience to climate change in conjunction with mitigation, and with integral attention to loss of biodiversity and growing inequalities that make ever larger shares of the population vulnerable to climate stress and related health and food crises. Two of the solutions that came up were nature-based and climate-sensitive: for example, the building sector should adopt nature-positive materials as part of a circular bioeconomy approach; and urban designers should plan for climate change and pay close attention to transforming slum areas.

– **Chemistry / Bio-Chemistry** for human development, peace, and planetary health highlight innovation by evolution, bringing new chemistry to life, such as in food systems; brain organoids, that are stem-cell derived 3D cell culture models for human brain development, offer treatment of neurological disorders. The case of Uruguay exemplifies how science can and did make a huge difference during the pandemic by adopting science-informed approaches and cooperative engagement by health policy. Horizontal gene transfer in the context of a rich biodiversity as part of evolution was explained, in particular in relation to bacteria modification enzymes.

– **Life Sciences and Medical Science** are showcasing new opportunities for regenerating and rejuvenating aged tissues. Organ transplantation remains crucial for many diseases and is enhanced by scientific advances in immunology, organ repair before transplantation, and the emerging use of modified pig organs. Of similar importance are new insights into the causes of dementia from prion strains.

6. The fact that important discoveries do not come about because of a goal, but because of curiosity and imagination as a result of wonder and admiration, raises philosophical, ethical, religious, and science policy questions. Emphasizing these perspectives, this PAS Plenary Session featured a session in honor of H.E. Msgr. Marcelo Sánchez Sorondo, our esteemed former Chancellor, on the occasion of his shift to Emeritus, under the theme of science from a philosophical and religious perspective. We can relate to Aristotle, who said "It is through wonder that men now begin and originally began to philosophize; wondering in the first place at obvious perplexities, and then by gradual progression raising questions about the greater matters too, e.g. about the changes of the Moon and of the Sun, about the stars and about the origin of the universe". "… therefore, if it was to escape ignorance that men studied philosophy, it is obvious that they pursued science for the sake of knowledge, and not for any practical utility" (Aristot. Met. 1.982 b 11-20). Aristotle pointed out another essential attribute of disinterested knowledge which is freedom: "Clearly then it is for no extrinsic advantage that we seek this knowledge; for just as we call a man free who exists for himself and not for another, so we call this the only free science, since it alone exists for itself" (Aristot. Met. 1.982b 28-30). The deliberations emphasized the key concepts of hope and the responsibility of the scientist. For sciences to flourish, scientists must enjoy scientific freedom: freedom of association, movement, and expression. This freedom is accompanied by responsibilities: to act with integrity; to uphold the values of science; to combat threats to science and scientific freedom; and to use scientific knowledge to benefit society. This is where ethical consultations between science and faith can be particularly valuable.

7. We recognize the importance and benefits of long-term perspectives in science, and call for society, including faith-based communities, and policy to recognize and more strongly support basic sciences. When emphasizing the importance of basic science, we are aware that there are also reasons to criticize the results of curiosity-driven investigations. And science must be transparent to the public at large: for example, it must be explained how it contributes to problem solving. Basic sciences are always at risk of being marginalized when crises, wars, and growing insecurity occupy people's minds and divert resources to the mitigation of day-to-day problems, as is currently the case. However, science operates on long time scales and requires continuity. Certain issues such as climate, biodiversity, genetics, medicine, astrophysics and the analysis of intelligent systems, both natural and artificial, can only be pursued on time scales of decades, if not centuries. Still, science-informed actions on some of these challenges need to be taken now. We realize that the search for solutions to these existential societal challenges can come from advances in science. Therefore, paradoxically, curiosity-driven basic science needs to develop a stronger sense of urgency: we need more opportunity for inquisitiveness in the younger generation, fostered by vibrant educational systems that stimulate imagination. We note that strong support for curiosity-driven science has huge payoffs that often come about in unpredictable ways, mostly in the long term, but increasingly even in the short term. A fine example of what basic science can achieve is the rapid development of the COVID vaccine thanks to developments in the decade-long studies of messenger RNA, which were planned for completely different purposes.

8. It is ever more important for science to have peace as a goal. The PAS had already actively engaged in support of this goal at critical junctures in the past, such as addressing threats of nuclear war and, more recently, risks of artificial intelligence and robotics in warfare. The many ongoing armed conflicts, such as the Russian attack on Ukraine, wars in Tigray/Ethiopia and in Yemen and Syria, as well as many other armed conflicts inside and between countries, are of grave concern to us because they cause great suffering for civilian populations, particularly for women and children. We condemn all atrocities against civilians, war crimes and crimes against humanity, and we call for accountability and independent investigations into these crimes. We also call for unfettered humanitarian aid, access to basic services to civilians and lifting of sieges. As scientists, we must not neglect the fundamental drivers of conflicts, and not ignore the role of science in the arms race. We thus take this opportunity to re-emphasize our recent statement on "Preventing Nuclear War and War Against Civilian Populations: Also a Task for the Sciences".[1] The accelerated – and even global – risks that emerge from threats or actual attacks by powerful countries on their neighbors are putting political order and human civilization at risk. At a time when science is so dominant in culture, all scientific disciplines should consider their potential contributions to peace. Peace is a precondition for human development. Divisiveness, for instance related to ethnicity and race – not just absence of war – undermines both peace and planetary health. This is part of the rationale of our theme "Basic science for human development, peace, and planetary health".

9. The Pontifical Academy of Sciences remains concerned about neglect of science-informed rational arguments and science skepticism in parts of the general public, and in conventional and social media.[2] These issues have escalated in recent years. During the 2022 Plenary it became necessary to re-examine the determinants of these tendencies, and the role that religion may play in both adherence to science skepticism and openness to science. The Academy would like to emphasize the importance of science education in the pursuit of truth and in better understanding societal developments. We note, however, that there is also well-informed, important skepticism about sometimes overlooked disconnections between science, technology, and their real-world impact, such as rebound effects of innovations and externalities. These require more attention in the research process. The PAS adheres to transparent science discourse open to the general public, and follows established science ethics. Indeed, PAS Academicians and their narratives on basic sciences can appeal to a broad audience, to show how science is done and what can come out of it, without neglecting risks of misuse. PAS Academicians are encouraged to do more in sharing their diverse narratives on what brought them to a certain invention, what their discovery means, and how curiosity, imagination, and efforts drove their work, including how they connect to the broad issues mentioned above, i.e. human development, peace, and planetary health. Science skepticism can also be channeled into productive discourse by engagement of science with ethicists over the introduction of

[1] 8 April 2022 https://www.pas.va/en/events/2022/preventing_nuclear_war.html
[2] https://www.pas.va/en/publications/acta/acta25pas.html

new technologies. In that context and in general, scientists must work hard on a language that is understood and identified by most of the population to communicate the goods that science delivers.

10. The abovementioned powerful contributions of basic science and its related capacities need to be shared more equitably – especially by the rich nations – with low-income regions of the world. Otherwise, the benefits for human development, peace, and planetary health will not come about. Scientific institutions, including Academies of Sciences, need to further strengthen their mechanisms of sharing and engaging with political and societal actors worldwide.[3] Transcending countries, cooperation in science is not only important to facilitate large-scale science programs, but also in terms of inclusiveness: it allows us to understand and welcome cultural differences that are important for peace. Two-way consultations with society are beneficial, for instance between science and faith-based organizations, embracing value and moral issues, as we practice in the PAS.[4]

[3] See events and conferences at https://www.pas.va/en/events/plenary-session.html and https://www.pas.va/en/events/workshop.html

[4] See addresses by the Popes from Pope Benedict XV to Pope Francis 1914-2022 at https://www.pas.va/en/magisterium/francis/2020-7-october.html. And cf. *Papal Addresses to the Pontifical Academy of Sciences 1917-2000 and the Pontifical Academy of Social Sciences 1994-2000*, ed. Marcelo Sánchez Sorondo, PAS, Vatican City 2003; https://www.pas.va/en/publications/scripta-varia/sv100pas.html

SESSION I – ASTRONOMY FOR HUMAN DEVELOPMENT, PEACE, AND PLANETARY HEALTH

The Black Hole at the Center of our Galaxy

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Proving that massive black holes do exist in the Universe has been a stepwise process. As compared to forty years ago, measurements have pushed the 'size' of the 4 million solar mass concentration in the Galactic Center downward by a factor of almost 10^6, and its density up by 10^18. Looking ahead toward the future, the question is probably no longer whether SgrA★ must be a massive black hole, but rather whether general relativity is correct on the scales of the event horizon, whether space-time is described by the Kerr metric and whether the 'no hair theorem' holds. Further improvements in technology, most notably of the European Southern Observatory VLT interferometer GRAVITY (to GRAVITY+) and the next generation 25-40m telescopes (the ESO-ELT, the TMT and the GMT), promise further progress. A test of the no hair theorem in the Galactic Center might come from combining the stellar dynamics with EHT measurements of the photon ring of SgrA★.

The full text of this forty-year journey can be found in my Nobel lecture posted at https://arxiv.org/ftp/arxiv/papers/2102/2102.13000.pdf

Testing Relativistic Gravity with Radio Astronomy

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Abstract

Radio astronomy allows a number of experiments that can confront theories of gravity with unique experiments. These include observations of radio pulsars or imaging observations of black holes. General relativity has passed all these tests with flying colours. Nevertheless, continued tests are necessary, for scientific and societal reasons. However, commercial pressure on the sky above us and the frequency spectrum around us threatens humankind's ability to explore the Universe and its fundamental laws.

1 Introduction

As astronomers we try to infer the fundamental laws of physics by watching the sky. Our experiments cannot be controlled, but we can only watch the results of physics unfolding. To quote Richard Feynman from his Lectures on Physics (Vol. I, lecture 2), *"We do not know what the rules of the game are; all we are allowed to do is to watch the playing. Of course, if we watch long enough, we may eventually catch on to a few of the rules. The rules of the game are what we mean by fundamental physics."* [1]. For millennia, before the telescope was invented, humans could only use their naked eyes. Then, for several hundreds of years, observations with a telescope were restricted to only optical wavelengths. It is only in the last 100 years or so, that we have learnt to follow the game using also other sources of information. Radio astronomy was one of the first new such techniques; nowadays we gather information not only across the whole electromagnetic spectrum but also via neutrinos or gravitational waves, outside the electromagnetic spectrum.

Radio astronomy is an especially powerful tool to provide insight into fundamental physics that is otherwise not obtainable: while the observed photons are of low energy, they often result from the most energetic particles in the cosmos. With their properties (including polarisation and arrival times), they carry information about the most extreme objects in the Universe (neutron stars, black holes). As such, radio photons provide unique insight into Nature's only two fundamental long-range forces, electromagnetism and gravity. With this information we explore the nature of gravity, cosmic magnetism and the fundamental properties of matter. We search for extreme binary systems and transient radio signals to exploit them in our understanding of physics. We conduct experiments to explore the properties of black holes and especially aim to study the supermassive black holes with millions and billions of solar masses, via images, such as obtained by the "Event Horizon Telescope Collaboration", or via "Pulsar Timing Arrays" (PTAs). We determine the properties of gravitational waves via precision pulsar timing and the direct detection of low-frequency gravitational waves using PTAs.

In this contribution, I give examples, how radio astronomy can be used as an ideal tool to study gravity. I will explain, why it is still important to confront relativistic gravity with new experiments – for scientific as well as societal reasons. Finally, I will conclude by raising awareness of a threat to radio astronomy - and astronomy as a whole - that may prevent our children and generations of future astronomers to look into the sky in order to understand the fundamental laws of the game called Universe. Indeed, man-made technologies literally block our view to the sky, with grave consequences if we do not find ways of co-existence for astronomers on one hand, and technological advances on the other.

2 General relativity

The general theory of relativity, or General Relativity (GR) [2], has passed its experimental tests with flying colours, so far. In these tests, it has been confronted with experiments using techniques and objects that were not even known when Einstein conceived his theory (see e.g. [3]). As a revolutionary new scientific idea, driven by Einstein's curiosity, GR changed the way how physicists thought about gravity, questioning Newton's gravity that was established centuries before. GR is also a most beautiful example of a modern theory with enormous predictive power, born out of *Gedankenexperimente*. It is a beautiful example for the topic of this conference.

Despite its successes, GR may not be our final answer in describing gravity on a macroscopic scale. There is a range of parameter space, from the quasi-stationary weak-field regime of the solar system to the strong-field regime of compact objects like neutron stars and black holes, in all of which one may encounter an experiment, where the theory could be falsified [4]. It is therefore important to test different aspects of the predictions of GR and alternative theories with different methods. For instance, observations with gravitational-wave detectors are able to test the highly dynamical strong-field regime and radiative aspects of gravity, but they are not able to test aspects of light-propagation in strong fields. This, on the other hand, and other aspects can be tested with binary pulsars [5].

3 Pulsars

Pulsars are natural and extraordinarily stable fly-wheel clocks. After their discovery [6] they were soon identified as rotating NSs, exceedingly dense and compact stellar remnants formed in supernova explosions of massive stars at the end of their life [7, 8]. Most known pulsars are located within our Galaxy, they typically have a mass of about 1.4 times the mass of the Sun ($M_\odot$) but a radius of only about 12 km. They are observed to spin very rapidly, up to ~ 700 times every second [9], thereby acting as a cosmic lighthouse that will emit a radio beacon with a period equal to its rotational period. The period is slightly increasing (with rates from 10^{-21} s/s to 10^{-12} s/s). Precise timing of pulse arrival times at the Earth shows that pulsars can have a rotational stability comparable to that of the best atomic clocks [10].

About 10% of all known pulsars are in a binary orbit with another star, mostly with white dwarfs but also - much rarer - with other neutron stars. The pulsars' great timing stability enables us to locate them to within 30 metres in their orbit. Tiny deviations from an expected arrival time allows tests of gravitational theories describing how pulsars move or how photons propagate in strong gravitaional fields, and investigations of many other physical phenomena (see Figure 1 adapted from [5]).

3.1 Testing GR with pulsar timing

The equations of GR, and indeed of alternative theories of gravity, are non-linear and must be approximated for comparison with binary pulsar data. Damour & Deruelle [11, 12] provided a leading-order pulsar timing model which includes the effects expected in GR, such as the advance of periastron and Shapiro delay, but which was parameterized in a way that did not assume the validity of GR or any other theory of gravity. Once measured, these "Post-Keplerian" (PK) parameters can be used to determine masses (based on an assumed theory) and perform self-consistency tests of theories; this was the approach subsequently taken in timing the Nobel-Prize winning Hulse-Taylor

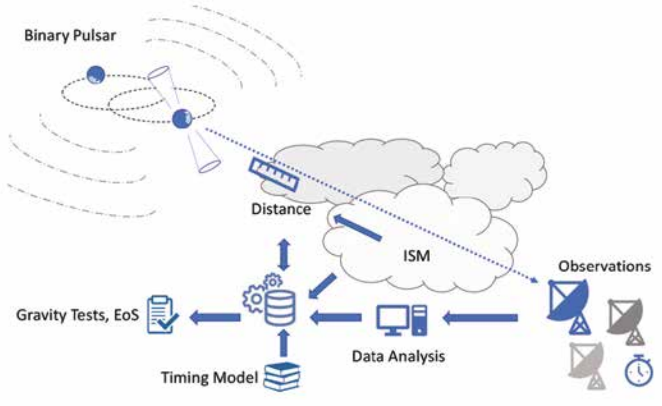

Fig. 1 A typical timing experiment binary pulsars. Adapted from Ref. [5].

pulsar [13] and other systems [5]. Damour & Taylor [14] expanded the formalism to include PK parameters based on the pulse profile changes expected in relativistic spin precession.

In this framework, any given relativistic theory of gravity provides a description of the PK parameters as functions of the measured Keplerian parameters and the two a priori unknown masses of the binary system. Measuring n PK parameters, where $n > 2$, over-determines this system of equations, providing $n - 2$ independent tests of the studied theory.

The recent study of the unique Double Pulsar system demonstrates this method by providing the most precise tests of relativistic gravity under strong-field conditions [5]. The Double Pulsar system, also known as PSR J0737−3039A/B [15] is a system with two orbiting active radio pulsars [16]. The system consists of a "recycled" 23-ms pulsar ("A") and the second-born 2.8-s pulsar ("B"). Probably after being "dead" or at least undetectable for a few million years, the A pulsar was spun up and restored to detectability as its companion star, the progenitor of pulsar B, evolved and transferred matter and angular momentum to it. Subsequently, the progenitor of B exploded, leading to two NSs in the highly-relativistic, slightly eccentric 2.45-hour orbit that we observe today. With its latest study [5] we have reached a juncture in the application of binary pulsars to tests of gravitational physics in many respects. From now on we have to consider a number of effects that could be neglected in the past, but now require attention and the application of new methods.

The Double Pulsar allows us to measure seven PK parameters in this system, more than for any other known binary pulsar. These PK parameters result from different relativistic effects that are simultaneously observed in this single system: a) a precession of the orbit, measured as a change in the periastron position, i.e. the orbital phase when the pulsars have their closest approach.

This effect had been observed for the first time in Mercury, presenting Einstein with the first test of his theory. In the Double Pulsar, this effect is many orders of magnitude larger; b) time dilation effects (i.e. gravitational redshift and second-order Doppler effects) as the orbital separation changes due to the slightly eccentric orbit; c) a relativistic deformation of the orbit; d) gravitational wave damping and e) light propagation in strong gravitational fields which are currently not testable by any other method, a so called "Shapiro effect". In particular, we observe the effects of retardation and aberrational light-bending that allow determination of the spin direction of the pulsar. For some of these effects, the measurement precision is now so high that for the first time we have to take higher-order contributions into account. These include the contribution of the A pulsar's effective mass loss (due to spin-down) to the observed orbital period decay, and the effects of the equation of state of super-dense matter on the observed PK parameters via relativistic spin-orbit coupling. The decay of the orbit due to the emission of gravitational orbits is confirmed with the currently most precise test of GR's quadrupolar description of gravitational waves, validating the prediction of GR at a level of 1.3×10^{-4} with 95% confidence (see Figure 2, adapted from [5]).

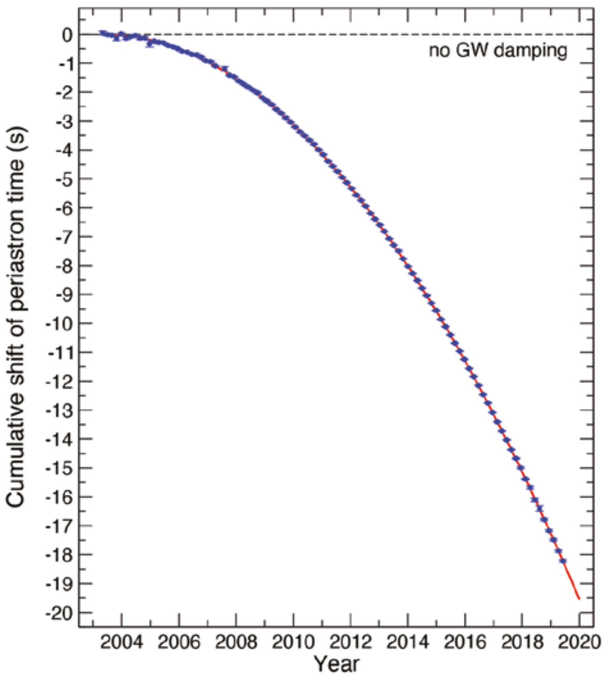

Fig. 2 Cumulative shift of the times of periastron passage relative to a model where gravitational waves do not exist. Each data point covers a time span of 60 days. The red curve is the GR prediction. Adapted from [5].

3.2 Testing GR with pulse structure measurements

A gyroscope freely falling in curved spacetime suffers a precession with respect to a distant observer. Experiments made in Solar System provide precise weak-field tests and confirm it. This effect also happens in a binary pulsar system, with the pulsar also being a gyroscope. This resulting relativistic spin-precession causes the pulsar to precess about the total angular momentum. As a result, the relative orientation of the pulsar towards Earth changes with potentially observable consequences as predicted by Damour & Ruffini in Ref. [17] even before the publication of the discovery of the Hulse-Taylor binary pulsar[18]. We note that the orbital angular momentum is expected to be much larger than that of a pulsar in the system, so that the orbital spin practically represents a fixed direction in space. Hence, effectively the pulsar precesses about the orbital angular momentum. The precession rate, $\Omega_{\rm SO}$, is another PK as introduced above. The effect of relativistic sin precession on pulsar timing is in principle measurable due to a change in the aberration parameters with time [14]. Much more obvious, and hence easier to measure, are the consequences of the changing line-of-sight as the pulsar precesses. We expect changes in the pulse shape (e.g. in simply the measured width, but also more dramatic changes) and especially in the measured linearly polarised emission which is a sensitive probe of the pulsar geometry [17, 19]. Such measurements have indeed enabled the detection of spin precession in a number of relativistic binaries. After the first detection in the Hulse-Taylor pulsar B1913+16 [20, 21] and later in PSR B1534+12 [22, 23], it is now possible to convert long-term observations in precise quantitative tests of spin precession and, hence, test of the "effacement" property of a spinning body.

A prime example to study relativistic spin precession is, again, the Double Pulsar. Here, we have two active pulsars, both of which could, in principle show the effects of precession. However, it turns out that due to the evolution of the system, the spin of pulsar A is aligned with the total angular momentum vector and profile changes for A are neither expected nor detected [24, 25]. In contrast, secular changes in the pulse shape of pulsar B were observed soon after its discovery [26], providing early evidence for spin precession of B. Around 2008, the pulsar temporarily vanished from our view when our line-of-sight moved out of the emission beam [27]. B will eventually re-appear. Meanwhile, it has been possible to track the orientation of the spin axis of pulsar B using the time evolution of the ~ 30-s long eclipses of A that are caused by the blocking rotating magnetosphere of B at superior conjunction. This absorption of the background emission, presumably by synchrotron self-absorption[28], is not complete, but because of the torus-shaped dipolar magnetosphere the light from the background pulsar A is visible every half-turn or full-turn of pulsar B, depending on the orientation of the spin-axis. Applying a simple but successful geometrical model [28], we are able to explain the observed modulation of A's lightcurve during the eclipse phase in great detail. The measured precession rate of $\Omega_{\rm SO,B} = 4.77^{+0.66}_{-0.65}{}^{\circ}\ {\rm yr}^{-1}$ is in very good agreement with GR [29].

The best test of spin precession is currently given by PSR J1906+0746, which is the young, non-recycled component in a compact relativistic double neutron star system [30, 31]. The spin-vector of the pulsar is inclined to the total angular momentum vector by $104° \pm 9°$, which is measured to precess about the total angular momentum vector with a measured rate of $2.17° \pm 0.11°$ per year, which agrees perfectly with the prediction of GR [32]. The observations do not only provide a test of GR, but they also allow us to study a fundamental aspect of pulsar radio emission: the properties of the emission beam. The precession changes our viewing geometry and moves the line of sight across the pulsar beam, providing a "tomography" of the emission beam. As the pulsar's magnetic axis has a fortunate nearly orthogonal orientation relative to the spin axis, our line-of-sight actually intersects the beam above both magnetic poles. The observations provide evidence that there is no symmetry between the two poles as the inferred beam patterns are clearly different. The beams are less extended in the longitudinal direction [32].

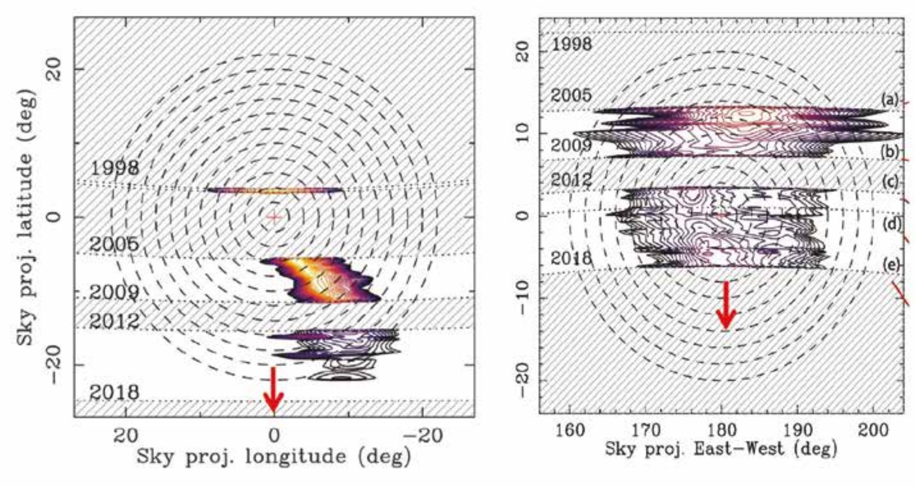

Fig. 3 Beam pattern of the two magnetic poles of PSR J1906+0746 as projected on the sky and observed by [32]. The beams are sampled via the line-of-sight moving due to relativistic spin precession. During the observations, the line-of-sight moves in the direction indicated by the arrow and crossed the magnetic pole on the right.

4 Shadows of black holes

In the previously described experiments, we have utilise the advantage of radio astronomy to obtain a large number of photons, which allow observations at the highest *time* resolutions. Another great advantage of radio astronomy is the unprecedented *spatial* resolution that can be obtained via Very Long Baseline Interferometry (VLBI). In such experiments, telescopes separated by distances of an Earth diameter (or more!) observe the same source simultaneously. By correlating the recorded voltage-phase data, one can construct an image with a resolution of a telescope that has a diameter of the largest separation between two telescopes during the experiment. Moving simultaneously to shorter wavelengths, the spatial resolution becomes the best across all astronomical methods. This led eventually to the idea to resolve the supermassive black hole in the centre of our Galaxy [33]. Even though the black hole does not emit any light, it is detectable via its "shadow". Embedded in some hot plasma, radio photons that would otherwise reach a distant observer, are absorbed by the black hole, so that the observer sees a paucity of light towards the black hole. Additional light-bending effects cause an image that is expected to show a bright ring around the shadow, whereas the size of ring and shadow depends directly on the mass of the black hole.

In April 2019, the so-called "Event Horizon Telescope" collaboration (EHTC) presented the first results of such an experiment [34]. The obtained image resolved the central compact radio source in the galaxy M87 as an asymmetric bright emission ring with a diameter of $42 \pm 3\mu$s, which is circular and encompasses a central depression. Overall, the observed image is consistent with expectations for the shadow of a spinning black hole as predicted by GR. An observed asymmetry in brightness in the ring can be explained in terms of relativistic beaming of the emission from a plasma rotating close to the speed of light around a black hole. The size of the ring indicated a central mass of $M = (6.4 \pm 0.8) \times 10^9 M_\odot$, which agrees with mass determinations based on stellar dynamics but is in contrast with a lower mass established from the gas dynamics in M87.

In May 2022, the ETHC presented also images of the super-massive black hole in the centre of our Galaxy, Sgr A* [35]. The images look quite similar to that of M87, with a ring diameter of $51.8 \pm 2.3\mu$s. Unlike in the case of M87, for Sgr A* we can use the exquisite prior constraints on the mass-to-distance ratio for Sgr A* based on stellar dynamics ([36], see the contribution by Reinhard Genzel at this meeting) to show that the observed image size is within 10% of the Kerr predictions. The hope is to eventually find a pulsar orbiting Sgr A*, so that the information from the pulsar orbit can be combined with the knowledge obtained from the stars and the image to test, for instance, the so-called "no-hair theorem" [37].

5 Putting things together

Radio astronomy allows a number of unique experiments to test relativistic gravity. The results are highly complementary to other methods, such as observations with gravitational wave detectors detectors or orbits of stars [36], or experiments in the solar system. Figure 4 demonstrates one way of using a two-parameter space to illustrate the complementary of different gravity experiments. The first parameter is the potential of the gravitational interaction Φ. This is typically the (external) potential probed by a photon or a mass (e.g. a pulsar) in the gravitational field of another mass. As a second parameter, one can use the maximum spacetime curvature in the system, $\xi_{\max}$ [5]. For BHs the maximum spacetime curvature (causally connected to its environment) is the one at the event horizon, which is a measure for the size and mass of the BH ($\xi_{\max} \propto M_{\mathrm{BH}}^{-2}$, for a non-rotating BH). Figure 4 illustrates how the Double Pulsar with its strongly self-gravitating components probes the mildly-relativistic strong field regime. The Double Pulsar appears twice in Fig. 4, once for the experiments related to orbital dynamics, like gravitational Wave damping and periastron precession, and a second entry (with label "Shapiro") for the test related to photon propagation. It is evident that, in terms of coupling between gravitational and electromagnetic fields, the Shapiro delay is the precision timing experiment which probes the strongest spacetime curvature. When comparing the different gravity experiments in the parameter space of Fig. 4 , one has to keep in mind the qualitative difference between them, for instance BHs vs. material bodies, stationary vs. dynamical/radiative situations, etc..

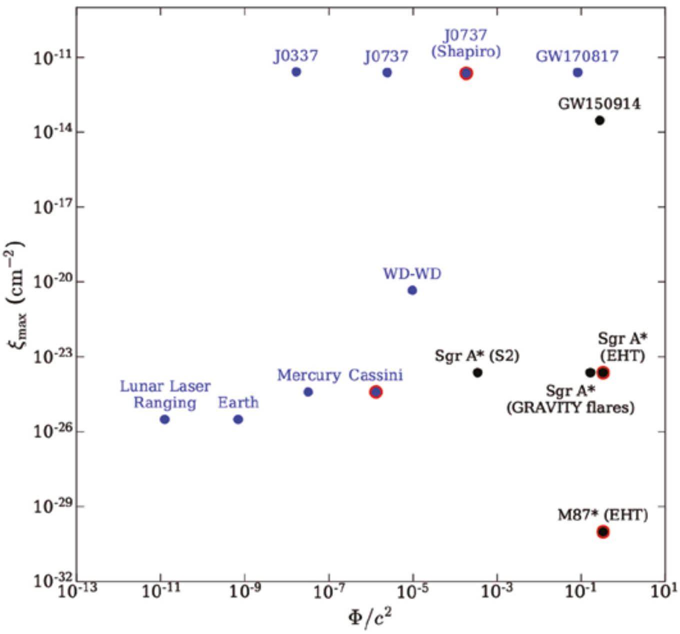

Fig. 4 Parameter space for comparing different gravity experiments. Φ is the potential of the gravitational interaction, and $\xi_{\max}$ is the maximum spacetime curvature in the system. Experiments involving BHs are indicated by black filled circles, whereas other experiments are reported in blue. For pulsar experiments we show the Double Pulsar ('J0737' and 'J0737 (Shapiro)') and the universality-of-free-fall test with the triple system pulsar ('J0337'). Besides these, the following experiments are shown: solar system, LIGO/Virgo mergers, experiments with the supermassive BHs Sgr A* and M87*, and compact double white dwarf systems ('WD-WD'). Experiments that probe the propagation of photons in curved spacetime are highlighted by red circles. See Ref. [5] for details.

6 Duty & Threats

Given that GR has passed all our experimental tests with flying colours, one is often asked whether it is still useful to continuing our tests of gravity. The scientific reason for continuing is clear: the incompatibility of GR with quantum mechanics urges us to expect that GR is not the final theory of gravity. The question is whether it breaks down above or below the Planck scale, and whether we can detect deviations on macroscopic scales. If we do, we have learnt a lot about the rules of the game. If we do not, we may not have found the right cosmic laboratory yet. Besides, we will never be able to *confirm* GR (or any other theory) - we can only *falsify* it.

But there are other reasons to continue. As it is surely familiar to everyone working on tests of gravity, nearly no week or month passes, when one does not receive an email, a letter or a phone call, where someone reports that (s)he has found a mistake in GR or in our experiments and that everything is wrong! It does not matter, whether those claims contradict our data. And it is true that quite often, the caller may not have a full education in experimental or theoretical physics, so that the basic principles of modern scientific work may not be known to him/her. But I believe that it is our duty to explain to these persons how we conduct our experiments and how we derive our conclusions. The claim that GR is "all wrong" may be more complicated to discuss, but the underlying attitude is the same: obvious scientific data are often ignored, and the conduct and integrity of established researchers is doubted, because the "other explanation" is simpler or much more appealing for some reason. This does not only apply to GR, but also to such obvious cases, whether the Earth is flat or not, or whether the Apollo astronauts really landed on the Moon. Having said this, I do agree with those people that it is important to question established theories, to find new ways of thinking, but we must also accept the lessons revealed by experimental data. Whatever the data tell us, we need to be open for the conclusions.

Getting these data may, however, be getting more and more difficult. Our view into the sky is threatend more and more. In the optical, light pollution and especially the threat of tens of thousands of satellites orbiting the Earth as "mega-constellation" endanger our ability to explore the cosmos. Light reflection (and pollution) is only one aspect. The danger of collisions and the creation of more irremovable space debris is also clearly there. At radio frequencies, the available band is smaller and smaller, due to the commercial pressure by telecommunication companies to have more and more bandwidth. The sum of the protected frequencies is a very small fraction of the spectrum and in many cases we are already "blind". We need to ask the question whether commercial pressure, or our convenience (e.g. to have satellite internet everywhere - also where it is not needed!) can justify that we cause irreparable damage to our access of the Universe. I think the answer is a resounding 'no'.

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How Was our Milky Way formed?

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Having grown up in Argentina and not too far from rural areas, I had the chance to enjoy the magnificent night sky in its full splendor. The vast majority of the stars that we can see with the naked eye are in our own galaxy, the Milky Way. The Galaxy is a system constituted by planets, stars, gas, dust and the mysterious dark matter, which are held together by the action of gravity. Its flattened, disk-like shape projected on the sky (seen in Figure 1) is what has given rise to its name. Understanding how the Milky Way has formed is thus closely related to "understanding how Nature put together the night sky".[1]

The Milky Way is one of many billions of galaxies in the Universe, and it is the one we know best. We can measure the properties of its stars in exquisite detail, something that is currently not possible for other (more distant) galaxies. The Milky Way turns out to be fairly average in terms of its mass, size, brightness and shape (2/3 of the large galaxies in the Universe are disks and are star forming). Because it is so typical it can be used to understand in general terms how galaxies form and evolve, what different physical processes are at play in the Universe and also to learn about what the Universe is made of, for example about the nature of dark matter.[2] But the Milky Way is also our home, and hence a big motivation to unravel how the Milky Way has formed stems from the human curiosity to understand our origin.

The current paradigm of structure formation in the Universe rather successfully describes the global properties of the galaxy population. It predicts that structure grows hierarchically, from tiny density fluctuations present in the early Universe, the seeds of all the structures we see today. The first galaxies to have formed were thus small, and through the action of gravity, they merged assembling larger galaxies like our Milky Way. The big question is, of course, whether this is really how the Galaxy formed. To be able to disentangle Galactic history we need measurements of the positions of stars (informing us of the current location), of their motions (which tell us where the stars came from), of their chemical properties (as their atmospheres reflect the conditions of the environment in which they formed), and of their ages (because these inform us about when they formed).

Figure 1. The Milky Way and Gaia. The background image of the sky is compiled from data from more than 1.8 billion stars collected by the Gaia mission (shown in the bottom left). *Credits*: Spacecraft: ESA/ATG medialab; Milky Way: ESA/Gaia/DPAC; CC BY-SA 3.0 IGO; A. Moitinho.

Galactic Archaeology

Stars, therefore, retain memory of their origin and can be used as fossils as it were. The subfield of Astronomy that exploits this approach has taken off dramatically in the past 15 years and is now known as Galactic Archaeology. This was a consequence of maturity of the models and the availability of new datasets, particularly of large surveys.

The Milky Way has various components, and the stars associated to each of these components have different characteristics. Clearly the majority of the stars in our Galaxy are in a thin disk-like structure, and they move in an orderly fashion on circular orbits around the centre of the Galaxy. Most stars in the disk (including our Sun) formed there, and there are new stars being born at a rate of roughly 1 sun/year. On the other hand, the most pristine stars, i.e. the oldest and those with the lowest chemical abundances,[3] are located in the Galactic halo. They have rather elongated trajectories and formed very early on; some stars appear to be as old as the Universe itself, as far as we can measure. These ancient stars have therefore effectively witnessed how the Galaxy was put together and can help us reconstruct its history.

The Galactic halo is in fact the natural repository of merger debris. According to theories of galaxy formation, halo stars must have formed in other small galaxies and were accreted a long time ago. Establishing the relative importance of accretion and mergers as a formation channel is one of the goals of Galactic archaeology. Another important goal is to reconstruct the family tree of our Galaxy, that is, to find the progenitors of our Galaxy, i.e. the galaxies that merged together and shaped the Milky Way. The characterization of their properties directly links to understanding the early Universe, since these are the leftovers or the local counterparts of the small galaxies that are now (barely) accessible with JWST.

How do we find merger debris? To this end, we need to have access to precise measurements of the motions of millions of stars, preferably in the halo of the Galaxy. Stars with the same origin move together through space, defining stellar streams as shown in Figure 2. This implies that one

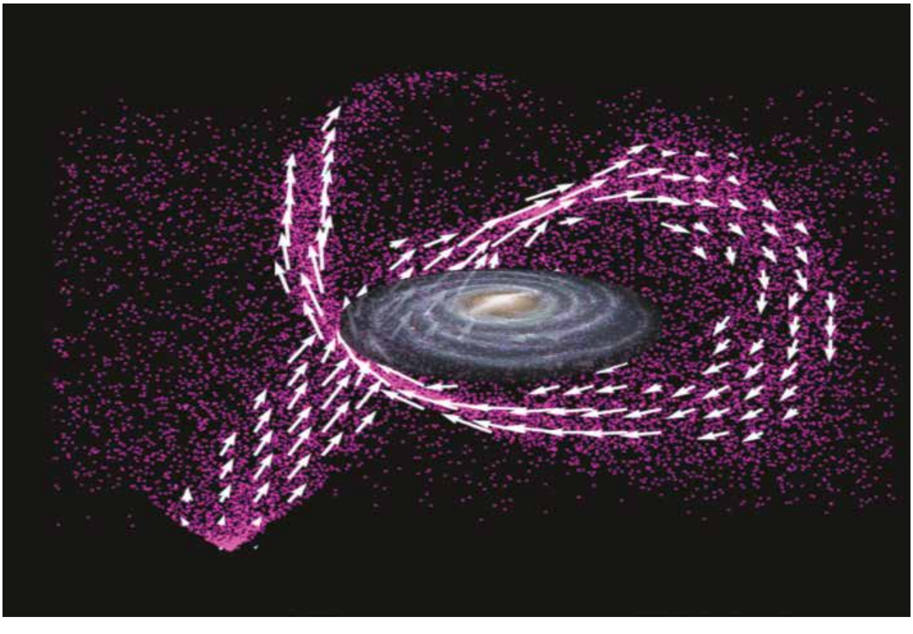

Figure 2. Star streams around the Milky Way. Image obtained from a numerical simulation of the accretion of a small galaxy by the Milky Way. The debris from the cannibilised system (in magenta) is distributed smoothly across the Galaxy, but moves coherently through space defining stellar streams. *Credits*: J. Veljanoski, M. Breddels and A. Helmi.

way to identify merger debris is to find groups of stars with similar velocities. Another useful space to identify merger debris is that of "dynamically conserved quantities". These are physical quantities, such as angular momenta or total energy, which do not change (much) in time. Stars from the same accreted galaxy shared initially the same spatial location and velocity (they were clumped in phase-space), and this implies they also had very similar angular momenta and energy (kinetic and potential, i.e., that associated with their motions and with the gravitational potential of the Milky Way respectively). Since these quantities are, under certain conditions, conserved in time as stars orbit around the Milky Way, this implies that the initial clumping should be present also today. Models predict that if the Milky Way halo formed via mergers, there should be 500 stellar streams in the halo crossing our immediate galactic vicinity. These streams would originate in a handful of large galaxies, and very many small ones if the model predictions are correct. To test these requires samples of at least 5,000 stars, but preferably 50,000 stars, in the halo near the Sun with full velocity information, and with exquisite precision.

The *Gaia* space mission

Assembling such a dataset is not trivial particularly because access to the full velocity vector of a star implies the ability to measure both its motion along the line of sight (from spectra using the Doppler shift), as well as transversal to it, i.e., on the sky. The projected motion of a star on the sky is inversely proportional to its distance (we know from daily experience that the farther away an object is, the more difficult it is to establish if it moves), and typically very small. For example, a halo star in the vicinity of the Sun might move with a velocity of a few 100 km/s, but its projected motion can be as small as 1 milliarcsecond per year. This cannot be done from the ground because of atmospheric blurring, and hence requires a space mission. This is *Gaia*.

The *Gaia* satellite[4] was built by the European Space Agency, adopted in the year 2000 and launched in December 2013. Since then, it has been scanning the sky to measure very accurately the positions of all objects on the sky brighter than a given magnitude, their fluxes in different wavelengths, and for a subset of the brightest objects it also obtains their spectra. By visiting the same sky location multiple times, the satellite determines the variation in the position of an object in time, from which it is possible to infer both its distance as well as its proper motion. Information on the intrinsic properties of the stars, such as their temperature, gravity or even their metallicity,[3] can

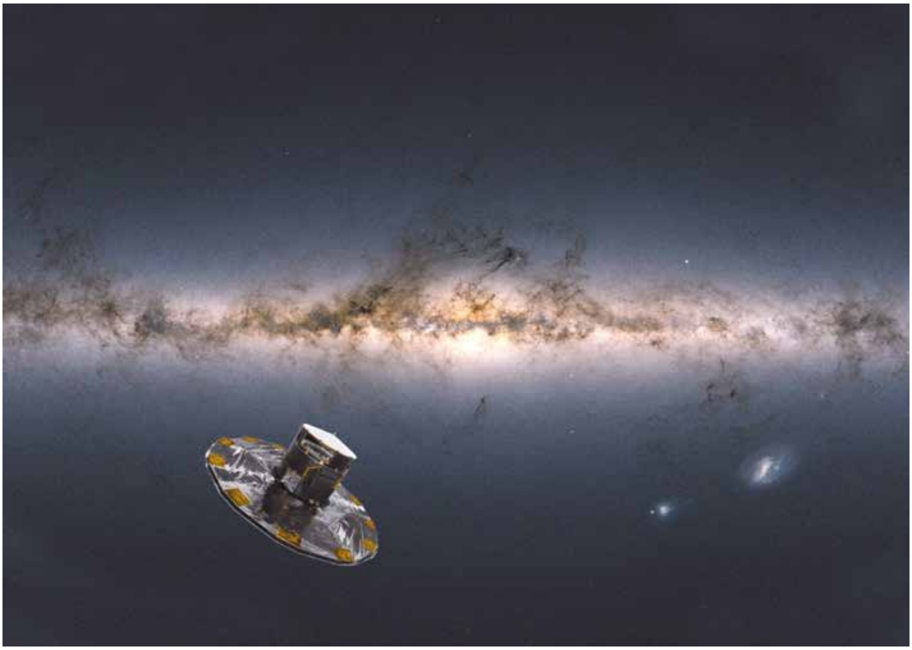

Figure 3. Illustration of the vast content of the latest data release from the Gaia mission. *Credits*: ESA/Gaia/DPAC.

be derived from the measured fluxes. Similarly, whether a star's brightness varies in time, which could be due to it being eclipsed by another star or a planet, or simply due to intrinsic oscillations which are useful to derive its internal structure. The stellar spectra obtained allow us to measure the velocity away or towards us as well as the chemical composition.

Thus far there have been four *Gaia* data releases (DR1, DR2, EDR3, DR3), with the latest one in June 2022. The vast amount of high-quality data, of measurements never done before, has triggered a revolution in Astronomy. A nice summary of the contents of *Gaia* DR3 is given in Figure 3.

New views on the Galaxy

The *Gaia* mission has enabled many discoveries, from our immediate cosmic neighborhood, i.e., the Solar System, where asteroids are present in families which have similar composition, to the realms of the Universe, where a hitherto unknown population of very distant double quasars has been uncovered.[5] In terms of Galactic evolution, some highlights include

1 – The discovery of the last big merger that the Milky Way experienced some 10-11 billion years ago;[6] this was a true milestone in Galactic history. Several other smaller accretion events have been uncovered thanks to *Gaia* data.

2 – The discovery that the Milky Way is still evolving dynamically,[7] implying that traditional (static) models to infer its mass distribution are fundamentally flawed. This is particularly important for inferences on its dark matter content.

3 – Many narrow streams leftover from accretion events, unexpectedly show a rather complex morphology.[8] The cause of this could be the presence of dark-matter clumps in the Milky Way halo, which would be expected for certain types of dark matter.

I will elaborate here on the first of these highlights and refer the interested reader to the reference list. Using Gaia DR2 data in combination with the APOGEE survey, we analyzed the motions, chemistry, age and spatial distribution of stars in a relatively large volume around the Sun. We discovered that almost half of the stars in the inner halo are part of a large kinematic structure whose average motion is in the opposite sense than the vast majority of stars in our Galaxy (including the Sun). These stars also have their own characteristic age distribution and they follow a separate sequence in chemical abundance space indicating that they formed elsewhere, in an accreted galaxy. We thus demonstrated that the inner halo is dominated by debris from a relatively large object (similar in size to the Magellanic Clouds). We named this long-gone galaxy *Gaia*-Enceladus. We estimated that at the time of accretion, roughly 10 billion years ago (for reference the Sun was born 4.5 billion years ago), *Gaia*-Enceladus had a mass of approximately 25% of that of the Milky Way at the time. As a result of the violence of the merger, the disk present at the time was shaken and heated dynamically, which explains the presence of large numbers of stars with very elongated trajectories but thick disk kinematics. The merger with *Gaia*-Enceladus not only led to the assembly of the inner halo, but also contributed to the formation of the Galactic thick disk component. Later work has also shown that significant star formation was triggered during the event. We may thus confidently state that the last big merger experienced by the Milky Way was a true milestone in Galactic history.

Debris from slightly more than a handful of small galaxies has also been uncovered in the Galactic halo near the Sun using the *Gaia* dataset through the application of clustering algorithms and statistical analyses. All in all, these findings are in line with the predictions from galaxy formation models.

The next steps in the field of Galactic Archaeology are the identification of merger debris beyond the Solar vicinity as well as the characterization of the accreted systems (their masses, star formation and chemical evolution history, time of accretion, etc.). This will be possible with new Gaia data releases in combination with data from ground-based spectroscopic surveys such as WEAVE and 4MOST which provide complementary information, for example, very detailed chemical abundance patterns that track the "DNA" of a star. This could be particularly useful for the identification of merger events that took place even earlier on in the history of our Galaxy.

Some general considerations

These wonderful discoveries were made possible by technological advances. For example, the ability to measure the tiny projected motions of stars on the sky effectively can be translated into a requirement to measure the diameter of a human hair at a distance of 1000 km. This puts strong constraints on basically all parts of the satellite, such as requiring an ultra-high stability of the platform over large periods of time and different temperatures, the ability to correct its position with a precise micropropulsion system (now also used for Euclid, the next large space mission of ESA) and very precise monitoring devices.

Gaia is undoubtedly a Big Data project. The ability to work with large datasets, to explore them efficiently and to identify the features one is after required the use of machine learning tools, which we typically validated on numerical simulations to understand their limitations. Clustering algorithms were used for the identification of clusters of stars with similar origin but it was as important to develop tools to establish whether a certain cluster is of high statistical significance.

For the analysis of the *Gaia* data, it was key to have software that could run fast, to perform quick data inspections through visualization tools without having to load all of the data. Postdocs in my research group developed a program namedVaex,[9] a tool that can plot a dataset with a billion entries using your standard laptop in less than 1 second! This tool, as well as 3D explorer (ipyvolume), are now being used also for non-astronomical applications, even for the restoration of Rembrandt's *Night watch* painting.

The night sky has always been a source of inspiration and awe for humanity. Astronomy will undoubtedly continue to inspire and attract new generations to science. However, a particular point of concern is the light pollution on Earth as well as from satellites that are being launched in large constellations to provide internet access across the whole world. As the motto of the 100 years of the International Astronomical Union states, "We are all under one sky". The sky belongs to humanity, to each one of us. Let's make sure this continues to be the case and protect together the heritage of dark and quiet skies.

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[1] Paraphrasing Prof. G. Gilmore.

[2] There is approximately 6 times more dark matter than normal matter (i.e., that which interacts electromagnetically and emits light; this is also known as baryonic matter). The presence of large amounts of such non-luminous matter (hence its naming) is revealed by the motions of stars in galaxies and of galaxies in the Universe, which move much faster than expected from the mass associated to the luminous matter. It is generally believed dark matter is constituted by elementary particles yet to be detected on Earth. However, an alternative is that our description of the gravitational interactions is not fully correct, and a modification of Gravity would be necessary.

[3] During the Big Bang only hydrogen and helium, as well as a small amount of lithium, were produced. All other chemical elements have been synthesized in stars, and astronomers refer to their total abundance with respect to hydrogen as their metallicity. The abundance of chemical elements other than hydrogen has thus increased with time as subsequent generations of stars explode (or through stellar winds) and enrich the interstellar medium around them, from which new stars are born. This means that, for example, stars with very low metallicity were born in very pristine environments, possibly very early on in the history of the Universe.

[4] https://www.cosmos.esa.int/web/gaia/home

[5] Gaia Collaboration: Galluccio and 446 colleagues 2022. Gaia Data Release 3: Reflectance spectra of Solar System small bodies. arXiv220612174G (A&A in press); Shen, Y. and 8 colleagues 2021. A hidden population of high-redshift double quasars unveiled by astrometry. *Nature Astronomy* 5, 569-574. doi:10.1038/s41550-021-01323-1.

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[9] https://vaex.io/

How to Make a Habitable Planet

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Motivation

The development of the human mind begins in wonder, and few things elicit wonder as readily as the beauty of the night sky. It is deeply regretful that access to the stars has become a luxury, and protecting dark skies where they remain should be as much of a priority as protecting beautiful monuments down on Earth. It is not only the beauty of the stars that makes them wondrous, however. We now know that almost all stars are worlds of their own, exo-Suns surrounded by their own extra-solar systems. One cannot help but wonder if one of these worlds are looking back at us. This possibility is one motivation for why we have been exploring what it takes to make a habitable planet and how likely such habitable planets are in our Galaxy.

A second motivation is our desire to understand our own history, and therefore the origins of our own planet, including the physical and chemical processes that conspired to make the Earth a habitable planet, and eventually an inhabited one. Combining these two puzzles – the likelihood of habitable planets outside of the Solar System and the origin of the Earth – enables us to better understand who we are as a planetary species, and how we fit into the galactic ecosystem.

I do not think it is by chance that grasping at these scientific truths has been a source of revelation of the beauty of our Galaxy. Through the development of new telescopes operating at wavelengths both shorter and longer than the human eye can see, engineers and astronomers have together unveiled the previously unseen beauty of interstellar clouds, protostars and planet-forming disks where new solar systems are currently assembling. These images seem to universally attract us, and through them astronomers are perhaps providing a source of peace, and a small compensation for the night sky that so many of us have lost. This paper is about how we use such astronomical observations to explore how to make a habitable planet.

What is a Habitable Planet?

There is no consensus on how to define a habitable planet [e.g. 7]. Most definitions of habitability, however, presume life to be water-based, as it is here on Earth. It is difficult to imagine the development of a complex enough chemistry to generate an origins of life without having access to a solvent, a liquid within which chemical reactions can take place and more complex chemical products can accumulate. Water is a unique solvent in its ability to dissolve a large range of inorganic and organic compounds. Therefore, while acknowledging that water is not the only conceivable solvent for organic chemistry, in this contribution we will consider access to water one of the criteria of habitability. This criterion has two parts: 1) that the planet has the right temperature to maintain liquid water, and 2) that there is liquid water present. In the Solar System this currently applies to the Earth and some of the moons in the outer Solar System, while in the past it likely applied to Venus and Mars as well.

A second criterion for planetary habitability is access to organic and inorganic building blocks of biomolecules, i.e., the dissolution of such building blocks in the planet's water reservoir. This criterion presumes that life in the Universe builds on organic chemistry, which is motivated by the chemical complexity enabled by carbon bond formation. There is evidence in the Solar System record [e.g. 2] that several planets and moons accreted a considerable organic reservoir, and would fulfill this criteria as well.

A third, and more controversial, criterion is that only planets with access to dry continents and reasonably transparent atmospheres are hospitable to origins of life. These criteria are based on origins of life scenarios that make use of UV chemistry in surface water [10], and would reduce the set of habitable planets to those that are truly Earth-like, that is, rocky planets with some, but not too much water, orbiting UV-luminous stars like our own. It would exclude so-called water worlds, moons and planets with subterranean oceans, and planets around cool stars that do not emit substantial amounts of UV. In this paper we are mostly agnostic to the particular origins of life scenario, and will focus on how often planets form with access to water and organics.

Planet Formation

The formation of a planetary system begins with the collapse of an interstellar cloud that consists of gas and dust [13]. Most of the collapsing cloud goes into forming a protostar. Due to preservation of angular momentum, the collapse also produces a rotating disk around the young star. In the disk, planet formation begins by the coagulation of small dust grains to form pebbles and boulders. These then combine to form planetesimals, comet and asteroid-sized bodies, which collide to build up the planet core. The composition of the dust grains therefore determines the chemical composition of the solid part of a planet. These solids are mainly composed of metals and rock-like material in the inner part of the disk, which is hot due to the proximity to the star, and of a combination of metals, rock and ice in the outer cooler disk. Earth-like planets form from dry dust grains, while gas and ice giants, and comets form from ice-rich grains. Once the planet core is formed, the planet can obtain water and organics through accretion from the disk gas, outgassing from the rocky core, and delivery from comet and volatile-rich asteroid impacts. This all presumes that the disk does indeed contain water and organics, which we have not yet established.

During the past few years we have been able to obtain images of planetary systems in the making. Such images reveal young stars surrounded by disks of dust and gas in which planets are assembling. While we can rarely detect the planets directly, the forming planets leave their clear marks on the disk in the form of dark lanes where they have accreted the dust and gas in their orbits. Importantly for this paper, planetary systems are currently being made, which means that it is, in theory, possible to answer how often they are being made conducive to habitability. In other words, do planets typically form with access to water?

Water in Planet-Forming Disks

The conceptually most straightforward path to explore whether planets typically form in the vicinity of water would be to use one of our telescopes to observe water in planet-forming disks. This is, however, technically challenging due the presence of water in the Earth's atmosphere. Instead, much of our evidence for water in these disks is indirect and takes into account the environment within which these planet-forming disks assemble.

Astronomical observations of interstellar clouds and protostars have revealed that water is one of the most common molecules present during the early stages of solar system formation. This should perhaps not be surprising since it is made out of hydrogen, the most abundant element in the Universe, and oxygen, the third most abundant element. Still, it is far from obvious that the exotic chemistry that characterizes the very cold and low-density interstellar clouds should conspire to produce this familiar molecule. It turns out that cold gas-phase chemistry is quite inefficient at producing water, and it is only because of the presence of interstellar grains and the associated grain-surface chemistry that large amounts of water are produced at the onset of star formation [14].

There are several pieces of evidence that this water becomes incorporated into the disk and further into forming planets, and that Earth's water is interstellar. In the Solar System, all water contains an excess of heavy water compared to what is expected from the cosmological abundance of deuterium. This kind of deuterium enrichment is a tell-tale sign of low-temperature (typically <30 K) water formation in interstellar clouds [5]. The inference that the Solar System planets formed in a water-rich environment due to inheritance of water from the molecular cloud phase makes it exceedingly likely that other disks also inherited water from their birth cloud and therefore that planets generally form in water-rich environments.

This inference is confirmed by the Spitzer Space Telescope's observations of water vapor in the innermost regions of many planet-forming disks [4, 11], close to where habitable planets may form. Furthermore, water ice has also been detected towards a handful of disks, with the special geometry required for ice absorption spectroscopy [1]. The typical water abundance in these disks is currently not well constrained, but the newly deployed James Webb Space Telescope (JWST) has the sensitivity and instrumentation to achieve exactly this, and we are currently eagerly analyzing the first data from JWST.

In conclusion, all evidence is currently pointing towards that planets form in water-rich environments and hence likely form with substantial water inventories. This is good news, since for a planet to be habitable it needs sufficient amounts of water to sustain a water-based chemistry. However, it is probably preferable to not have so much water that there is no dry land, i.e., to avoid it being a water world. This entails that an Earth-like planet needs to primarily form from dry dust grains that, at most, contain small amounts of water – on Earth the ocean contributes less than a permille of the total Earth mass. Whether this fine-tuning of water delivery is common or not remains to be seen, and can probably only be demonstrated by direct observations of the atmospheres of Earth-like planets.

Organic Chemistry During Planet Formation

Given that Earth-like planets regularly have access to water during their formation, do they also acquire the right kinds of organic and inorganic material to be chemically habitable? Molecular clouds do contain many of the organic molecules that are considered precursors to biomolecules, including nitriles, alcohols, aldehydes, and organic acids [e.g. 6]. There is some evidence from Solar System studies that these organics, analogous to water, survive disk formation. Our strongest evidence for the nature of the organic environment within which planets assemble comes from direct astronomical observations of organics in protoplanetary disks, however. Infrared spectroscopy has detected hot organic gas in the innermost disk regions, revealing a disk gas rich in nitriles and acetylene, just interior or terrestrial planet formation [4, 12]. It is currently unclear if this organic gas is also present in the terrestrial planet-forming region and therefore whether terrestrial planets accrete primary atmospheres that are rich in reactive organic molecules, and future observations with JWST and other telescopes are needed to explore this. If confirmed, this would imply that young Earth-like planets generally obtain a substantial organic inventory from birth.

A second source of organics for terrestrial planets is delivery from impacting planetesimals from the outer disk, where organic solids are abundant due to either inheritance from the interstellar medium or organic chemistry in the disk. The outer disk organic chemistry can be observed at millimeter wavelengths, which probes rotational transitions from colder molecules. These observations have demonstrated that there is indeed survival of interstellar organics and that we therefore should expect planetesimals assembling in outer disk regions to generally be rich in the same organics (generally oxygen rich) that are common in the interstellar medium [3].

Inheritance is not the only contributor to the organic inventory in the outer comet-forming parts of disks, however. Millimeter observations have also revealed large abundances of nitriles and other reduced forms of carbon that are implicated in origins of life chemistry [9]. These form through gas and grain surface chemistry in disks once most of the oxygen has become locked up in water ice and oxygen-rich organic ices. This oxygen-poor organic chemistry can become directly swept up in the atmospheres of planets forming in the outer parts of disks, but more importantly for the formation of habitable planets, they can freeze-out on grains and become incorporated in comets. These comets can then deliver a combination of oxygen-rich organic acids and alcohols, and oxygen-poor nitriles and carbon chains to young terrestrial planets, seeding their surfaces with a range of prebiotically interesting organics [8].

Concluding Remarks

The key ingredients to make a habitable planet are water and organics, and based on astronomical observations both are commonly available to planets as they are forming. We should therefore expect to find that many extra-solar planetary systems contain chemically habitable planets.

Whether all or any have gone from habitable to inhabited is a much bigger question that hopefully future astrophysical, chemical, and biological research will answer; even if potentially habitable planets are common, planets where life has been realized may be quite rare. Our own habitable planet made that step from habitable to inhabited about 3.5–4 billion years ago, resulting in an incredibly beautiful world, and if there is anything that can compete with the stars in elicit wonder, it is turning our gaze back on the Earth and realize how contingent its beauty is, and how many things had to go right to make this habitable planet of ours.

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Short Communication

Didier Queloz
Jacksonian Professor of Natural Philosophy
at the University of Cambridge, Nobel Laureate in Physics

After this series of great talks, I hope we all understand that the Universe is an amazing lab for physicist to test the limits of our knowledge on fundamental concepts such as time, space and matter, as well as to discover new physical elements like "dark energy" for example.

In this short communication, I would like to share with you that, recently, we have just started a new research avenue that is looking like some sort of 21st century extension of the Copernicus revolution: The origin and prevalence of life in the Universe!

What are the conditions for life to start and to evolve? What exactly happened on Earth, and is it happening elsewhere? Why does the Universe produce life? What does it mean to be alive? Is life massively present in the Universe or is it just a unique episode of sheer luck doomed to disappear when our Sun, exhausting its Hydrogen fuel, expands and engulf us? We all have to admit that these are amongst the greatest existential questions, so challenging that we don't have much of an answer yet.

We are living – I believe – in an extraordinary moment in our history where a couple of spectacular scientific breakthroughs in different directions are bringing us an optimistic and fresh perspective that modern science is within reach to deliver answers about "why do we have life on Earth and is that unique?"

Following my colleague Karin Öberg's talk it is pretty clear that Astrophysics is detecting and characterising an increasing number of exoplanets, bringing more and more information on their physics and chemistry and the surface conditions of some of them.

Planetary science is exploring in detail solar system objects, bringing pristine samples back to Earth. With the exception of some interplanetary dust from comets, the last time in human history we did this was 50 years ago, from the Moon.

Then, in the dawn of our century, organic biochemistry has made fascinating progress on the reverse engineering of the origin of life on Earth, and you may have a better glimpse of it in the following days.

But let's face it bluntly: individual progress in each of these disciplines does not guarantee we shall solve the core problem. A growing number of scientists, working at the forefront of this field from different perspectives, are becoming increasingly aware of the intrinsic difficulties to develop a deeper overall understanding without broadening our knowledge baseline with a step-change in our collaboration model.

Various groups of scholars and institutions are responding to this challenge and are developing new structural efforts to deal with its interdisciplinary challenges and to create functional bridges with other fields. They all share a simple idea that different disciplines, looking from different perspectives, can creatively operate together, filling critical knowledge sitting in boundaries to enable a better exploitation of opportunities. Similar lines of thought are being developed to address complex multidisciplinary challenges such as global warming and AI revolution.

I humbly recognise that the question of the nature and significance of life transcends the traditional boundaries of natural sciences. For this purpose, at Cambridge for example, in collaboration with the Center of Theological Inquiry in Princeton, we included Arts and Humanities studies in the core activity of the recently established Leverhulm Centre for life in the Universe. Our goal will be to encourage philosophy, literature and theology to actively engage and challenge concepts as well as to bring in a philosophical perspective.

I am not hiding that it is a broad and extremely ambitious agenda but significant prestigious research and teaching institutions in the world have responded to the challenge and are establishing Centres with similar purposes.

We are all convinced that collectively we are establishing not only a new knowledge but also a legacy by cultivating a new generation of researchers increasingly familiar with operating in a more flexible and interdisciplinary environment, with the strategical vision to establish a long-lasting pathway that will eventually lift the veil on one of the greatest mysteries of the Universe.

Thank you for your attention.

SESSION II – PHYSICS AND BIOPHYSICS FOR HUMAN DEVELOPMENT, PEACE, AND PLANETARY HEALTH

Solar Activity and Earth's Phenomena

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Abstract

Solar activities are the natural phenomena occurring within the outer atmosphere of the Sun. Studying solar activities is very crucial, as it has a lot to do with Earth's environment and its climate. Also, the magnetic field of the Earth is affected by some of these solar activities. Furthermore, solar flares produce high energy particles and radiation that is very dangerous to living organisms. Hence, the importance of studying solar activities and Earth's phenomena cannot be overemphasized.

This paper will x-ray the solar activity; Earth and its environment, equally explore Earth's various phenomena and solar terrestrial interaction. The effects of solar activity on Earth will be grossly handled. The relationship between solar activity and Earth's climate as well as climate change (CC) will be discussed because climate change is affecting the world globally. Results from previous researchers will be discussed, then inferences and conclusions will be drawn from this paper.

Keywords: solar activity, Earth's phenomena, solar flare, solar terrestrial interaction, geomagnetic storm.

Introduction

The Sun powers life on Earth; it helps to keep the planet warm enough for us to survive. It also influences Earth's climate: We know that changes in Earth's orbit around the Sun are responsible for the existence of the past ice ages. It has been found that extreme solar activity drastically compresses the magnetosphere and modifies the composition of ions in near-Earth space.

Most of the energetic particles produced at the Sun in flares rarely get to the Earth. Even when they do, the Earth's magnetic field prevents most of them from reaching the Earth's surface. The small number of these high energy particles that get to the Earth's surface does not significantly increase the level of radiation that we experience daily.

The most serious recorded effects on human activity occur during major geomagnetic storms which are induced by coronal mass ejections (CMEs). These various solar activities will be discussed as they are relevant to us.

Solar Activity

Solar activity is a natural phenomenon occurring within the outer atmosphere of the Sun. It includes: solar wind, coronal mass ejections, solar flare (SF), solar cosmic rays and sunspots.

Solar Cosmic Rays (Solar Energetic Particles) are high-energy particles coming from the Sun.

Solar Wind is a stream of charged particles released from the upper atmosphere of the Sun (corona). This plasma consists mostly of electrons, protons and alpha particles with KE between 0.5 and 10 KeV ejected into and through interplanetary space.

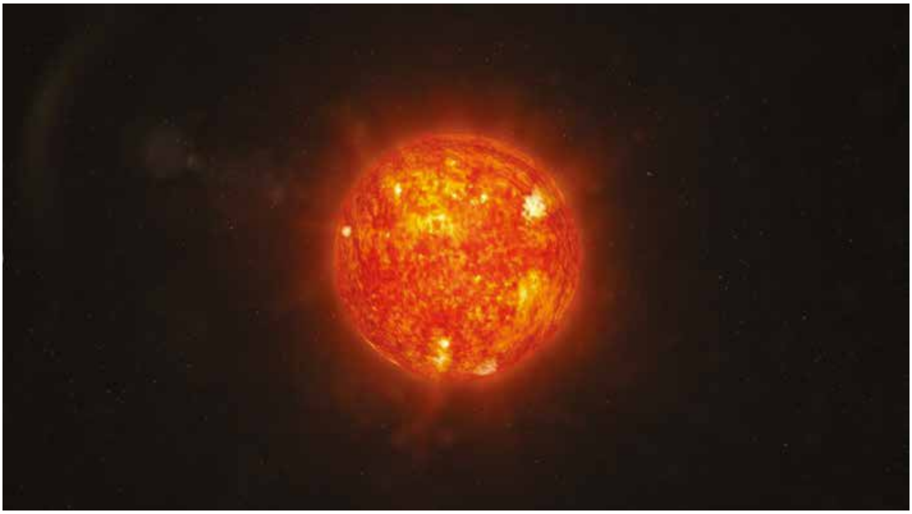


Figure 1. Solar Wind Animation. Source: https://www.youtube.com/watch?v=GX5FbXX-hks

Solar Flare is an intense localized eruption of electromagnetic radiation in the Sun's atmosphere. Solar Flares occur in active regions and are often, but not always, accompanied by CMEs, Solar Particle Events (SPEs) and other solar phenomena. The occurrence of SFs varies with the 11-year solar cycle.

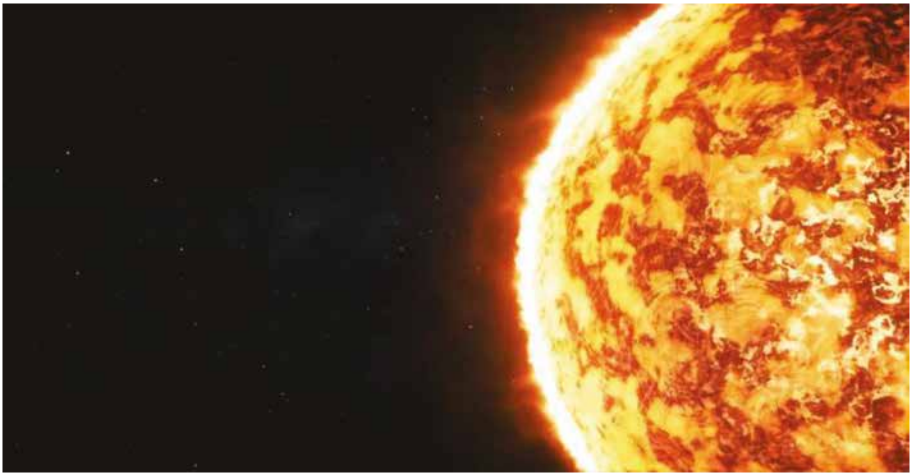


Figure 2. Solar Flare. Source: https://www.youtube.com/watch?v=t2UbmZfrGDM

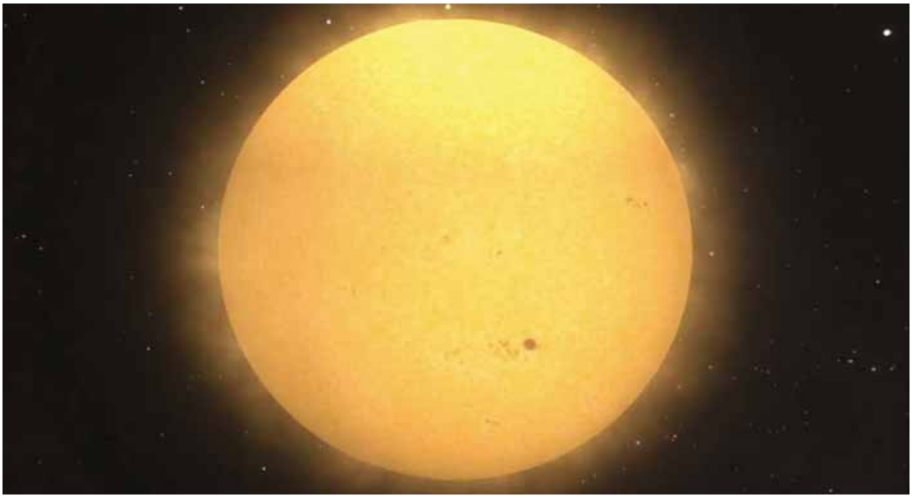


Figure 3. Coronal Mass Ejection. Source: https://www.youtube.com/watch?v=si4L6p7Clqo

Coronal Mass Ejection (CME) is a significant release of plasma and accompanying magnetic field from the Sun's corona into solar wind. CMEs are often associated with Solar Flares and other forms of solar activity.

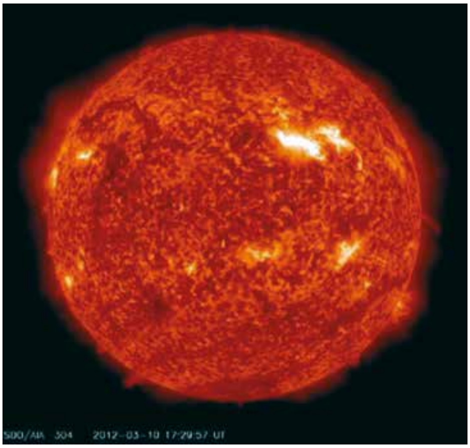


Figure 4. Sunspot. Source: this image was captured by the Solar Dynamics Observatory on March 10, 2012, at 12:29 P.M. est in the 304 Angstrom Wavelength. https://www.eurekalert.org/multimedia/719738

Sunspots are phenomena on the Sun's photosphere that appear as temporary spots that are darker than the surrounding areas. We note that if sunspots are active more solar flares will result, leading to an increase in geomagnetic storm activity for the Earth.

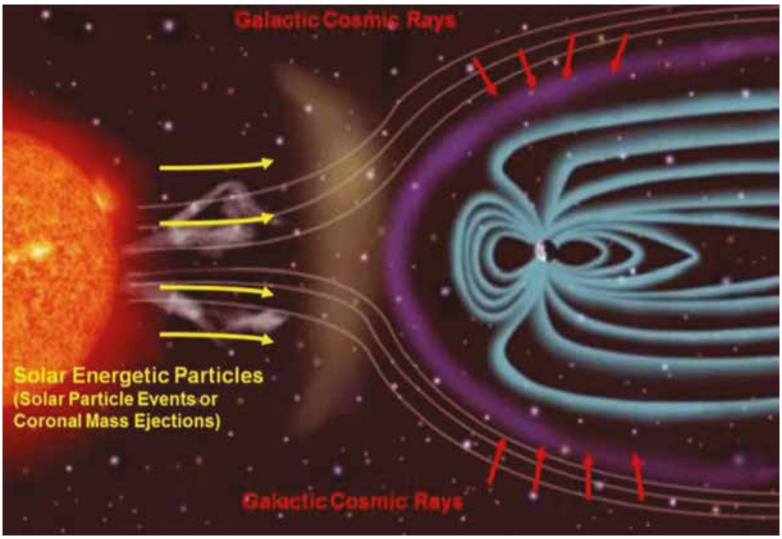


Figure 5. Galactic Cosmic Rays. Source: https://en.wikipedia.org/wiki/Cosmic_ray

Galactic Cosmic Rays are phenomena on the Sun's photosphere that appear as temporary spots that are darker than the surrounding areas. We note that if sunspots are active, more solar flares will result, leading to an increase in geomagnetic storm activity for the Earth.

Vertical Structure of the Atmosphere:

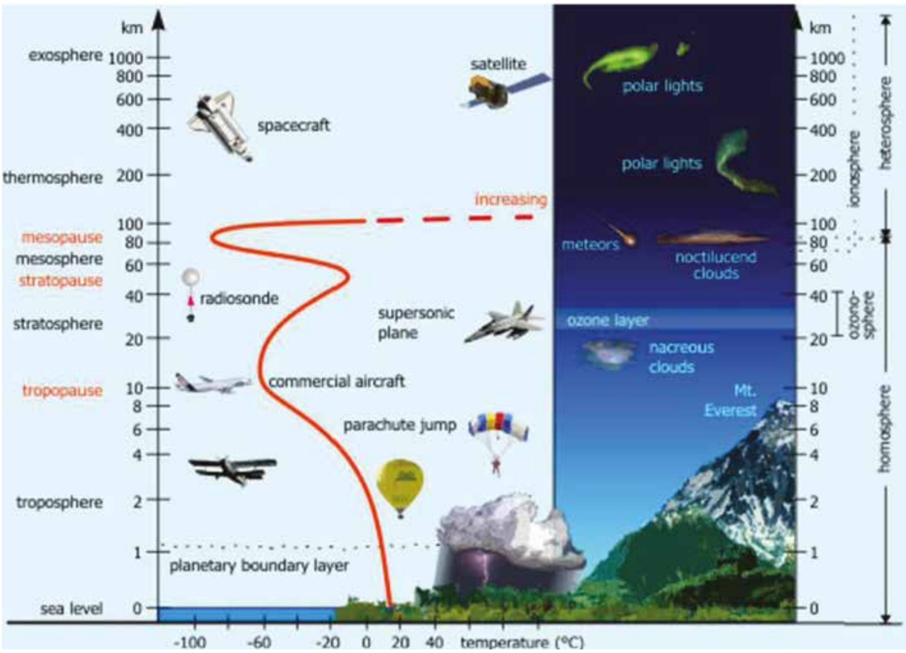


Figure 6. Vertical Structure of the Atmosphere. Source: https://www.sciencelearn.org.nz

Earth's Atmosphere: This consists of the following:

Troposphere: a layer that supports life and of principal weather activity-intense convection and cloud.

Stratosphere: it lies from 18km to 50km and is remarkable for stratospheric ozone layer-absorption of UV radiation.

Mesosphere: 50km to 80km. Temperature decreases with height.

Ionosphere: from 60km to 1000km, where free electrons are sufficient to influence transmission of electromagnetic waves (EM) at radio frequency.

Some Atmospheric Phenomena

Storm/Tropical Storm: These result from the whirling of large organized cloud masses of all sizes and shapes, and include tropical storms.

Figure 7. Tropical storms. Source: https://www.shutterstock.com

Hurricanes, cyclones and typhoons are all types of tropical storm, natural disasters that have very great impact in our atmosphere. A tropical storm is a hazard that brings heavy rainfall, strong winds and other related hazards such as mudslides and floods. Hurricanes are tropical storms that form over the North Atlantic Ocean, and Northeast Pacific Cyclones are formed over the South Pacific and Indian Ocean. Typhoons are formed over the Northwest Pacific Ocean.

Figure 8. Volcanic Eruption in Iceland generates aerosols (Dugdale). Source: https://www.washingtonpost.com

Aerosols

Many studies have shown that volcanic eruption releases volcanic ash and gases into the atmosphere (Figs 8 & 9), that alter atmospheric chemistry and consequently generate aerosols that lead to climate change.

Figure 9. Volcanic Eruption Giving Rise to Volcanic Aerosols (Stock/Julian). Source: https://www.usgs.gov

Geomagnetic Storms:

These, as part of atmospheric physics phenomena impact on our environment significantly. GMSs enhance the ionospheric currents and induce voltage on telegraph lines; hence information/signals are distorted. GMSs upset high frequency (HF) radio waves. The impact of high-speed particles has corrosive effects on satellites, charge buildup results. Electrical discharges can circle across spacecraft component thereby causing damage. During storm-time, the changes in thermospheric wind and density modify the drag on satellites.

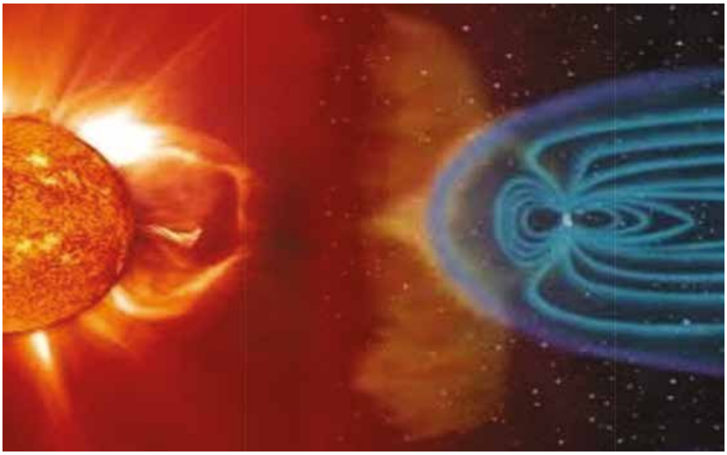


Figure 10. Geomagnetic storm. Source: https://images.app.goo.gl/fgBXafb1D9FWxHQK6

Results from Some Researchers

In a Danish study by Mads Faurschou and Peter Riisager (2009), their results suggested that the Earth's climate has been significantly affected by the planet's magnetic field. They equally found a strong correlation between the strength of the Earth's magnetic field and the amount of precipitation in the tropics.

Again, the study's results support the controversial theory published by Danish astrophysicist Svensmark, that climate was highly influenced by galactic cosmic rays (GCR).

Svensmark's theory (1998) involved a link between the Earth's magnetic field and climate, since that field helps to regulate the number of GCR particles that reach the Earth's atmosphere. He noted that cosmic rays have influence on Earth's climate. Henrik, Svensmark, et al. (2007) discovered experimental evidence for the role of ions in particle nucleation under atmospheric condition.

A very interesting result was observed from the documentary by Danish Director Lars Oxfeldt Mortensen, who explored the theory by Danish scientists, including Henrik Svensmark, on how galactic cosmic rays and solar activity affects cloud cover and how this influences the Earth's climate.

Hanson and Okeke (2020), from their study of 'Variability of Rainfall and Surface Air Temperature in Nigeria', found there are connections with sunspot number and Galactic Cosmic Rays. These findings summarize the fact that GCRs, the Earth's magnetic field, have influence on atmospheric parameters, invariably on climate change. Equally, Hanson and Okeke (2021), in their study of 'Impacts of sunspot number and Geomagnetic aa-index on climate of West Zone, West Africa', during solar cycles 22-24, found that the variability of SAT and Rainfall in Wet Zone West Africa could not be attributed to SSN and Geomagnetic aa-index. We therefore conclude that climate variability in Wet Zone West Africa is most probably not driven by solar magnetic activity, but could be attributed to anthropogenic activities.

Solar Terrestrial Interaction

Solar energetic particles, when magnetically connected to the Earth, enter the magnetosphere and potentially the high and mid latitude ionosphere. They cause a rapid increase in the ionization of the neutral atmosphere, dayside auroras and ozone destruction (Olga, et al. 2008).

The Earth's atmosphere blocks out the X-ray and most of the ultra violet radiation (UV). It protects inhabitants from the harmful effects of the radiation and particles that stream out of the Sun. These molecules of the Earth's atmosphere absorb the X-ray and UV photons and become ionized.

Earth's magnetic field protects living organisms from charged particles that reach the Earth. If the path of the particles is parallel to the field, it travels without deflection; if it travels across the field lines it will be deflected into a circular path by Lorentz force.

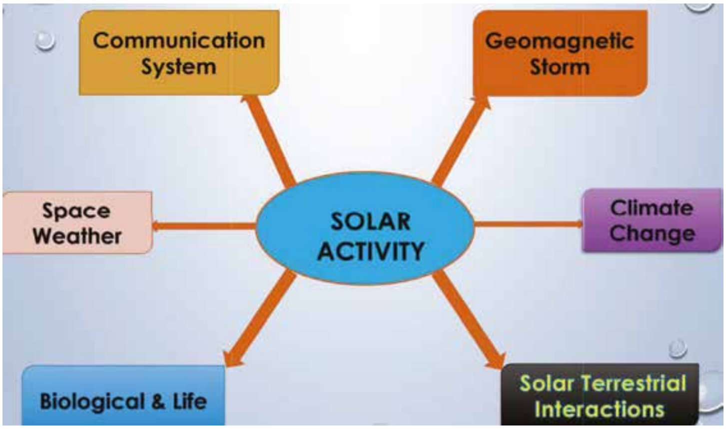
Solar Activity, Earth and Climate Change

Climate change can be caused by natural phenomena like volcanic eruption. This releases volcanic ash and gases into the atmosphere that alter atmospheric chemistry and climate.

Plate tectonic etc. could be caused by changes people have made and are still making to land and/or atmosphere.

Many factors, both natural and human, can cause changes in Earth's energy balance, which invariably amount to climate change. These changes could come from variations in the Sun's energy reaching the Earth or changes in the greenhouse effect that affects the quantity of heat which the Earth's atmosphere retains. Cosmic rays have been discovered to correlate highly with precipitation, one of the prominent parameters of climate change. On the other hand, cosmic rays are modified by Earth's magnetic field. Invariably, Earth's magnetic field has a lot to do with climate change.

Summary Chart



Conclusion

The most striking feature is the reconnection/coupling of the Sun's magnetic field with the Earth's magnetic field, via solar wind. If none of these exist, then, there will definitely be no research in most related fields.

It is impressive to note that its applications extend from induced currents, communications, satellites, biology and life to space weather. More interesting is the fact that solar activity, Earth's geomagnetic storm, is all related to Earth's climate change. The results from some researchers have shown that climate change is not only caused by human activities, but by some solar and geomagnetic activities.

Correlation of observable phenomena with effects on Earth and construction of models for solar-terrestrial environment requires three domains (the Sun, interplanetary medium and geomagnetosphere).

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Galactic Cosmic Rays. Source: https://en.wikipedia.org/wiki/Cosmic_ray

Geomagnetic Storm. Source: https://images.app.goo.gl/fgBXafb1D9FWxHQK6

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Solar Wind Animation. Source: https://www.youtube.com/watch?v=GX5F-bXX-hks

Solar Flare. Source: https://www.youtube.com/watch?v=t2UbmZfrGDM

Sunspot. Source: this image was captured by the Solar Dynamics Observatory on March 10, 2012, at 12:29 P.M. est in the 304 Angstrom Wavelength. https://www.eurekalert.org/multimedia/719738.

Tropical Storms. Source: https://www.shutterstock.com

Vertical Structure of the Atmosphere. Source: https://www.sciencelearn.org.nz

Volcanic Eruption in Iceland generates aerosols (Dugdale). Source: https://www.washingtonpost.com

Volcanic Eruption Giving Rise to Volcanic Aerosols (Stock/Julian). Source: https://www.usgs.gov

Molecular-Scale Resolution in Fluorescence Microscopy

Stefan W. Hell
Director, Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany & Director, Max Planck Institute for Medical Research, Heidelberg, Germany. Nobel Laureate in Chemistry

Optical microscopy has become nanoscopy: The MINFLUX and MINSTED concepts provide truly molecule-size resolution

Following 20th-century textbook wisdom, the resolution of light microscopy is limited by optical diffraction to about half the wavelength of light, which is why conventional light microscopes fail to distinguish object details that are closer together than about 200 nanometers.

Breaking this century-old diffraction barrier appeared as a far-out, perhaps entirely unrealistic goal. And yet, since the early 1990s, physical concepts were put forward and later demonstrated in practice, which resulted in novel fluorescence microscopes featuring diffraction-unlimited spatial resolution (Hell, 2007). The work of my research group laid the foundation of a new scientific field: superresolution fluorescence microscopy, also called fluorescence nanoscopy. The novel superresolution methods are destined to become primary tools for imaging living biological samples ranging from cells and tissues to small animals, with the potential to transform the life sciences.

Prominent methods implementing the first viable concepts to overcome the resolution barrier include STED and RESOLFT microscopy, which were complemented a few years later by the PALM/STORM concept, initially demonstrated with fluorescent proteins switching by a related mechanism. All these methods utilize reversible transitions or switching of fluorescent labels between a bright and a dark state. Since these superresolution concepts fundamentally rely on transitions between molecular states, novel labels are required that can be optically prepared in at least two different states. Consequently, my research groups in Göttingen and Heidelberg also pioneer the chemical synthesis and application of new labeling methods and techniques to improve the performance of the labels' switching behavior to separate close-by molecules.

Now, in the early 2020s, the outlook for this field is truly exciting. We continue to push the performance of nano-optical molecular imaging in (living) cells and tissues. As the Nobel foundation had put it on their widely distributed posters, "[the 2014 Chemistry laureates] had crossed the [resolution] threshold". And yet the actual holy grail of the superresolution field, molecule-size resolution, had remained outstanding until recently: With resolution at the ~1-nm scale, MINFLUX was the first concept to push the resolution of fluorescence microscopy to truly molecular dimensions (Balzarotti et al., 2017).

Of all the nanoscopy or super-resolution advances of the last decade, MINFLUX stands out, because it contains a radically new idea for localizing individual fluorophores. In PALM/STORM imaging with typical resolutions of 20-30 nm, the localization of a molecule is based on maximizing the number of detected fluorescence photons on a camera, which is inevitably limited by photobleaching. By contrast, in MINFLUX the molecule is actively localized by probing the molecule's position in the vicinity of the intensity zero of the donut-shaped excitation beam (Fig. 1). By iteratively refining the probing steps, the molecule's position ultimately coincides with the position of the donut at which fluorescence emission is minimal. Under ideal conditions, the MINFLUX localization precision doubles with every five photons. By abolishing a strict dependence just on the photon count, MINFLUX releases the 'square root brake' – which traditionally makes higher resolutions increasingly more difficult to achieve. The exponential dependence thus makes single nanometer resolutions and below now realistically achievable, including in cellular fluorescence microscopy (Fig. 2).

By fundamentally reducing the required number of fluorescence photons, MINFLUX is able to detect molecular positions and movements of a few nanometers, at temporal sampling speeds of hundreds of microseconds, while maintaining ~2-nm precision (Eilers et al., 2018). MINFLUX has thus opened the door to low-light level optical analysis of tiny objects at true molecular scale resolution (1-5 nm). And lens-based fluorescence microscopy has reached the ultimate resolution limit: the size of the fluorescent molecule itself. For practical biological purposes, the ultimate resolution limit is now merely set by the size and orientation of the molecular tag consisting of the fluorophore plus its specific molecular linker. Moreover, the resolution is attained at relatively high speed, at least 10 times faster than in PALM/STORM.

Further progress in implementations and applications of the concept has been achieved, including nanometer resolution in three dimensions, in living cells and multiple color channels (Gwosch et al., 2020), multicolor-3D imaging of densely packed mitochondrial proteins (Pape et al., 2020), MINSTED – a new super-resolution concept related to the same

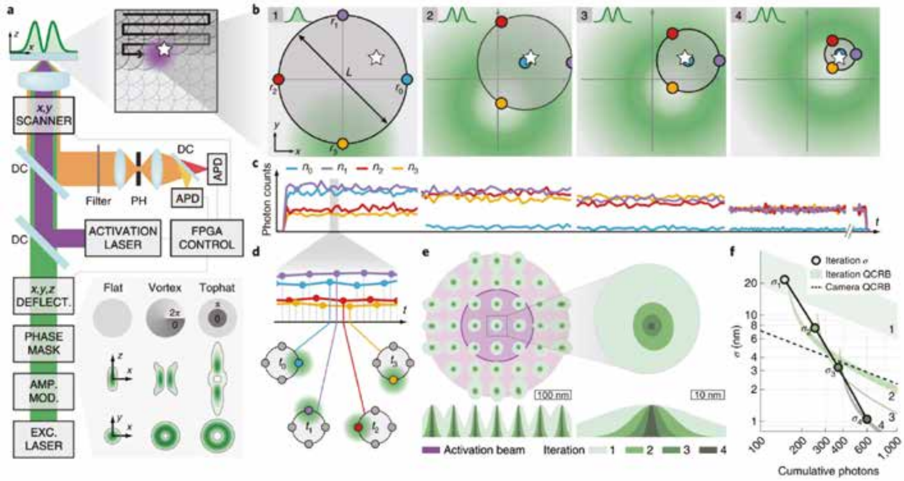

Figure 1. Iterative MINFLUX setup and localization. a, Setup. An excitation beam (green) is amplitude- and phase-modulated (bottom right inset; flat (regular focus), vortex (2D donut), tophat (3D donut)), electro-optically deflected in *x*,*y*,*z*, overlapped with a photoactivation beam (purple) and focused into the sample after passing a piezo-actuated mirror for coarse *xy* scanning (top right inset; white star, activated molecule position). Fluorescence is descanned, deflected by a dichroic mirror (DC), filtered by a confocal pinhole (PH), split in two spectral ranges by another dichroic mirror and detected by photon-counting avalanche photodiodes. **b**, Iterative *xy* localization by targeting the beam to four designated coordinates constituting the targeted coordinate pattern (TCP) (blue, purple, red, yellow and beam on yellow position in green). Step 1, regular focus; steps 2–4, 2D donut. The TCP is recentered and zoomed-in on the fluorophore (white star) in steps 2–4. **c**, Typical fluorescence counts for each iteration with the color indicating the targeted coordinate. **d**, Representation of the interleaved TCP measurement. **e**, Convergence of iterative localizations for molecules within the activation area (purple, 200 nm FWHM, 50% single molecule activation probability; pink, 2·FWHM, 95% activation probability). The covariance of each iteration (green shades) is represented as an ellipse of $e^{-1/2}$ level. **f**, Progression of the spatially averaged localization precision σ1 – σ4 for each iteration (green dots) with the corresponding Cramér Rao bounds (CRBs, green shades) and the CRB for standard camera-based localization (dashed line). **e**,**f**, Photons, $N_1 = 150$, $N_2 = 100$, $N_3 = 120$ and $N_4 = 230$, total $N_t = 600$; TCPs, $L_{1,reg} = 300$ nm, $L_{2,donut} = 150$ nm, $L_{3,donut} = 90$ nm and $L_{4,donut} = 40$ nm. Figure from (Gwosch et al., 2020).

powerful idea of "optical coordinate injection" as MINFLUX (Weber et al., 2021, see below). We also contributed to the realization of MINFLUX on a conventional microscope stand (Schmidt et al., 2021). The fundamentally strong localization properties of the so-called 4Pi arrangement, collecting and recombining fluorescence emissions from both sides of the sample, continue to be of great interest. This approach, which historically led to the first substantial axial resolution improvements, features a sharp

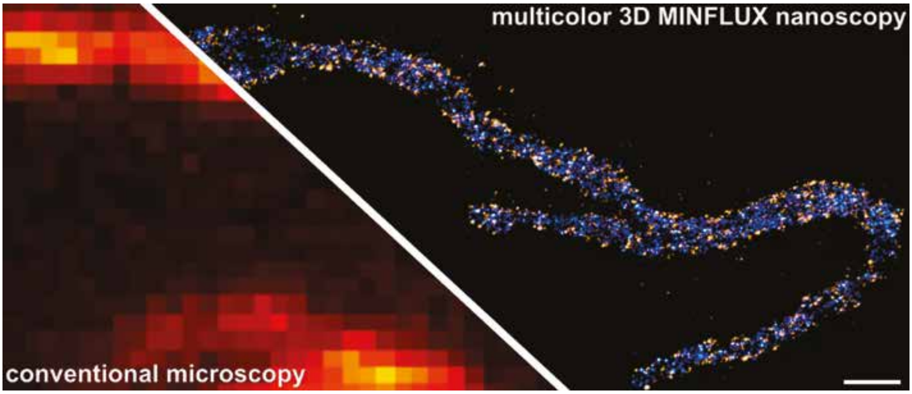

Figure 2. Dual-color MINFLUX imaging with 3D localization precision of ~5 nm: Distribution of Mic60 in mitochondria of human U-2 OS cells. Multi-color 3D MINFLUX nanoscopy visualizes the cellular distribution and relative position of proteins that are only a few nanometers apart. Resolution comparison Mitochondrion from a human skin cell in which two proteins in the inner mitochondrial membrane have been stained: A subunit of the MICOS complex (Mic60) colored in orange, and a subunit of the mitochondrial ATP synthase (ATPB) colored in blue. Scale bar: 500 nm. Data from (Pape et al., 2020).

signal modulation along the optical axis due to interference, and the 4Pi illumination and detection principle's fundamental benefits for MINFLUX are also the subject of ongoing explorations to push molecular imaging and tracking capabilities in 3D to new heights.

To highlight the novel spatiotemporal capabilities created, some of the initial work focused on tracking the movements of various protein complexes. In early tracking experiments, sub-millisecond position sampling had been demonstrated (Balzarotti et al., 2017). In the last couple of years, we improved on this work by advancing the measurement principle to an unprecedented spatiotemporal resolution of 5×10^{-10} m$\times$s^{-1} with as few as 40 photons per localization. Current work focuses on tracking the stepping behavior of the molecular motor Kinesin-1. Kinesin-1 moves along microtubules at a rate of approximately 400 nm per second under physiological conditions with a step distance of 16 nm and a sub-step distance of 8 nm, which is an ideal model system for displaying the capabilities of MINFLUX. To date we can track Kinesin with single digit nanometer precision at a temporal resolution below 1 ms (Fig. 3), which allows us to clarify open questions regarding the stepping mechanism of Kinesin-1 (Wolff et al., 2022). In particular, MINFLUX all-optical tracking also ex-

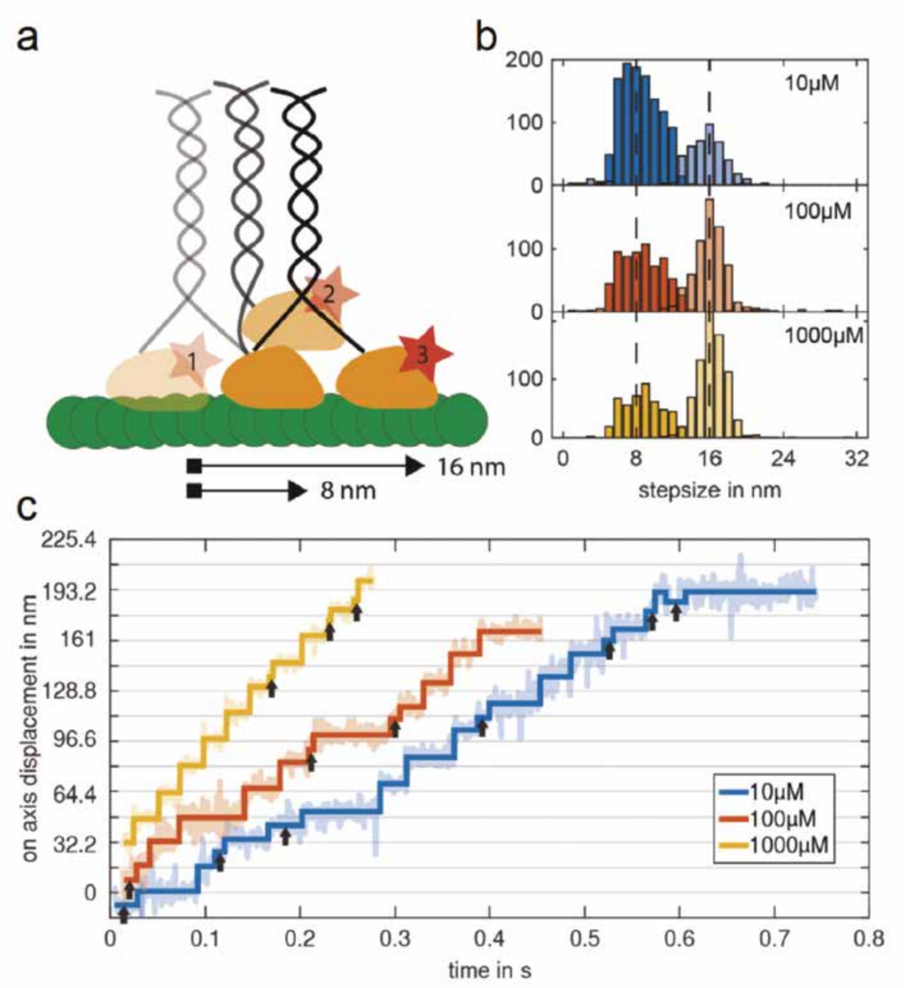

Figure 3. MINFLUX tracking of single-molecule-labeled Kinesin-1. (a) Schematic drawing of the in vitro system investigated. The position of the fluorescent label attached to the trailing head is shifted by 16 nm as this head detaches from and rebinds to the microtubule (positions 1 to 3). In the one-head-bound state (position 2, sub-step), the labeled head is found to be located approximately in the center of these positions. (b) Histogram of detected step sizes for varying ATP concentrations. For all concentrations, the full 16 nm step between two microtubule binding sites and the 8 nm sub-step, entering and leaving the one-head-bound state, can be clearly identified in the track data. For low ATP concentrations, sub-steps are detected more frequently compared to higher ATP concentrations, implying on average longer one-head-bound states with decreasing ATP concentration, which is strong evidence for ATP binding in the one-head-bound state. (c) Examples of MINFLUX traces of Kinesin-1 walking along a microtubule for different ATP concentrations. Detected plateaus of the intermediate waiting state are highlighted by the black arrows (Wolff et al., 2022).

tends into the regime of physiological ATP concentration, without the need for a bulky bead marker. Longstanding controversies such as whether ATP binding takes place in the one-head-bound or the two-head-bound state can now be answered with MINFLUX.

MINSTED: back to the roots for maximal precision

Considerations of the underlying principles – the paradigm shift that enabled the jump from typically 10s of nanometers to single-digit and even ~1-nm precision – came with the conviction that MINFLUX would not remain the only molecular resolution method, but rather would represent the first member of a new family of techniques with this level of detail. As the name suggests, MINSTED localization and nanoscopy (Figs. 4 and 5) relies on the original STED principle even more than MINFLUX. Like MINFLUX, it achieves molecular resolution, but the resolution can in fact be adjusted almost continuously from confocal-spot dimensions of 200-300 nanometers down to the molecular size.

In conventional STED imaging, only the molecules in the middle of the donut-shaped beam can fluoresce. Thus, the experiment always “knows” where the emitting molecules are. STED microscopy does not typically achieve molecular resolution because in practice the donut-shaped fluorescence inhibition beam cannot be made so strong that only a single fluorophore can fit into the central intensity minimum. For this reason, in MINSTED (Weber et al., 2021 and Weber et al., 2022), the fluorophores are initially isolated by randomly switching them on through an independent photochemical switching process. The fluorescence-preventing STED donut beam is then used to locate the fluorescent molecules individually. Its minimum, the intensity zero, serves as an ‘optically injected’ reference point. If the minimum coincides with the fluorophore, the fluorophore emits most strongly and one can find out precisely where it is, because the exact position of the STED donut beam is always known. The MINSTED experiment therefore gradually approaches the fluorophores in a targeted fashion based on direct feedback from every photon detection event with the donut beam (Fig. 4) and can thus locate the fluorescent molecules with precision and accuracy of 1 to 3 nanometers. In connection with the photochemical on and off switching which samples the ensemble of fluorophores over time and provides them in the on-state one-by-one, the resolution becomes molecular-scale.

An important aspect in practice, the STED light – applied to inhibit spontaneous emission peripheral to the scan coordinate – ensures that any

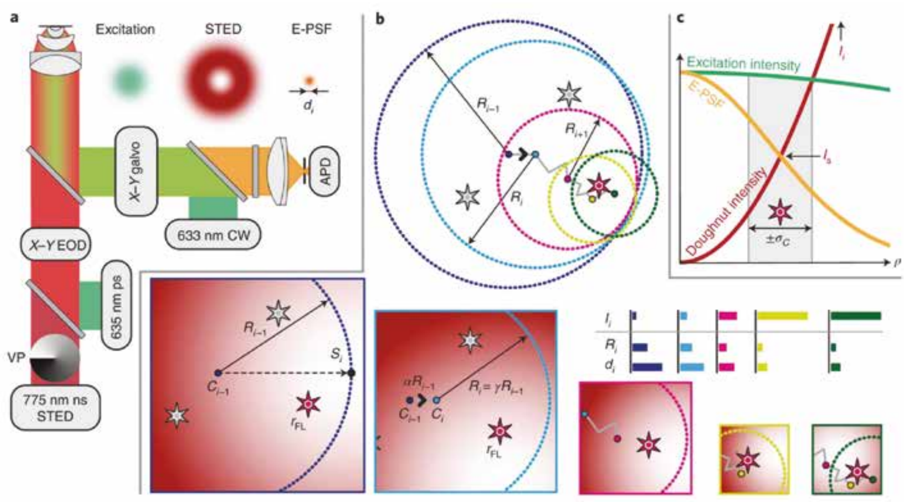

Figure 4. Principles of MINSTED localization. a, STED setup with co-aligned pulsed lasers for excitation and STED at 635 and 775 nm, respectively, and a vortex phase plate (VP) for helical phase modulation converting the STED beam into a doughnut; the inserts sketch the excitation and STED probability in the lens focal plane, along with that of the fluorescence (E-PSF). The 633 nm CW laser was used for fluorophore pre-identification in the focal plane, while the *X*–*Y* galvo unit also maintained the optical conjugation of the confocal avalanche photodiode (APD) detector to the center C_i of the circular scan performed by the electro-optical lateral deflector (*X*–*Y* EOD). **b**, The active fluorophore (red among grey stars), located at unknown position r_{FL}, was localized by circular *X*–*Y* scans. For each photon detection *i*, the centre C_i was shifted by a fraction α of the radius R_i toward the doughnut minimum S_i. Simultaneously, R_i and the FWHM d_i of the E-PSF were scaled by $\gamma < 1$. The centre C_i thus converges to the fluorophore position (grey line) as indicated in the lower panels that also sketch relevant parts of the doughnut for some detections during the homing-in process. Once a minimum radius R_{min} (yellow) is reached, only C_i is updated and the localization terminated after the fluorophore becomes inactive (*N* detections). The column diagrams illustrate the decrease of R_i and of d_i with increasing doughnut intensity I_i. **c**, Normalized probability of excitation (green) and fluorescence detection (E-PSF, yellow) as a function of radial distance ρ from the focal point, along with a non-normalized intensity profile of the STED beam doughnut (red). Although I_i is constantly increased during the localization to sharpen the E-PSF, the intensity experienced by the fluorophore remains about I_s within the $\pm\sigma_C$ position range of the center positions C_i highlighted in grey. Figure from (Weber et al., 2021).

additional fluorophore or fluorophores that happen to be activated inadvertently in the vicinity of the probed position are kept off. The result is a substantial reduction in background noise contributions to the MINSTED single-molecule registrations, and improved signal-to-background ratio in many situations compared to MINFLUX, where the excitation donut excites the fluorescence from all active fluorophores, including peripheral ones that should be avoided.

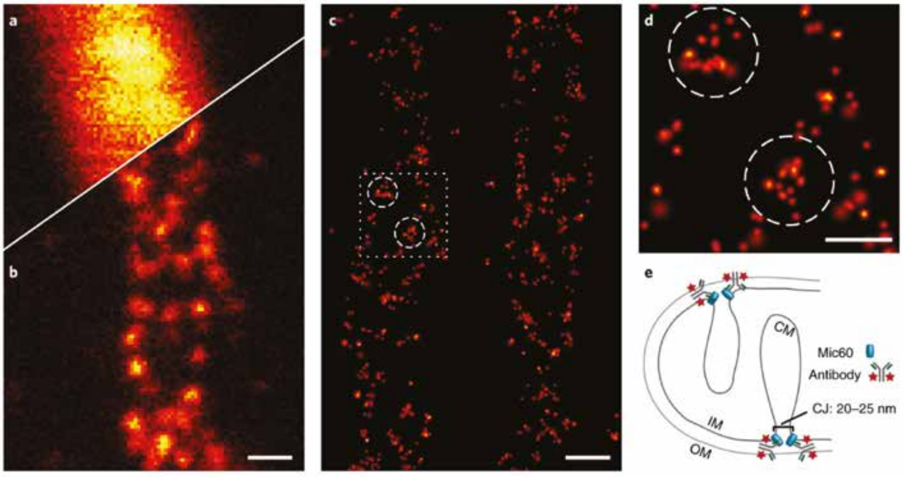

Fig. 5. MINSTED nanoscopy of mitochondrial protein Mic60. a,b Confocal (a) and STED (b) images with $d \approx 60$ nm of the same mitochondrion taken after simultaneous activation of all fluorophores. c, MINSTED nanoscopy image of similar mitochondria resolving the Mic60 clusters. **d**, Excerpts of data as indicated in c. e, Schematic of the presumed localization of Mic60 in the mitochondrial inner membrane. IM, inner membrane; OM, outer membrane; CM, crista membrane; CJ, crista junction. Scale bars: a–c, 200 nm; **d**, 100 nm. Figure from (Weber et al., 2021).

Entering the Ångström-level localization regime

The exciting developments seem to know virtually no bounds: In recent experiments with a blue-shifted MINSTED implementation, our analysis showed that if 10,000 emissions can be detected from the fluorophore under the same practical background and stability conditions, the precision is estimated to $\sigma = 2.3$ Å, a value that is in fact about 8 times smaller than the size of the fluorophore itself (Weber et al., 2022).

Microscopy on the molecular scale is here to stay. It is to be expected that MINSTED and MINFLUX will become widely used in the life sciences. The inherent confocality of MINFLUX, MINSTED and related concepts should also provide a critical advantage when considering imaging in more dense and three-dimensional specimens, such as brain slices and in-vivo imaging scenarios. With further development of other aspects, including field of view enlargement, etc., MINFLUX and MINSTED are bound to transform the limits of what can be observed in cells and molecular assemblies with light. This should most probably impact cell and neurobiology and possibly also structural biology. Moreover, it should be a great tool for studying molecular interactions and dynamics in a range that has not been accessible so far.

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Using Physics to Improve Human Health: From Protein Folding to Understanding Covid-19 and Designing New Vaccines

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Abstract

We explore how, utilizing a theoretical framework coming from the physical sciences, we can quantitatively understand the underlying mechanisms governing biological processes with applications to medicine. Here we specifically focus on how a virus may infect cells with emphasis on COVID-19. We discuss how the spike protein has to go through a major structural rearrangement during cell invasion. We also describe how a combined theoretical and experimental effort is used to propose a possible new vaccine for COVID-19 utilizing a phage display-based approach. Such a spray-based vaccine is cost-effective, needle-free, and can be stored at room temperature.

1. Introduction – A physical mechanism for virus infection

Viral infection is a serious public health issue contributing significantly to morbidity and mortality in society. Understanding the mechanisms by which a virus may infect cells should provide us with the needed understanding to develop new therapies. Several viruses have developed a fusion mechanism that utilize proteins involved in merging the host and viral membranes [1,2], a process by which the viral genetic material to invades the cell and begin the process of replication. During this invasion, these proteins undergo a large and global structural rearrangement. Understanding these major conformational changes is central to fully comprehend viral cell invasion and the associated infection.

In this presentation, we focus on the currently most serious viral disease, SARS-CoV-2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly contagious, and its transmission involves a series of processes that may be targeted by vaccines and therapeutics. The host cell invasion involves a large conformational change of the Spike protein that leads to membrane fusion between the host cell and the virus. This fusion creates transmembrane pores through which the viral genome infects the host cell.

2. Understanding COVID-19 cell invasion – a physical model

This physical mechanism is a based on a global transformation of the spike protein. The invasion starts when the Spike 1 (S1) domain that covers the spike 2 (S2) head identifies the receptor ACE2. ACE2 is located on the surface of many cells in the respiratory track. When S1 recognizes this receptor, the S1 dissociates and S2 starts a configurational transformation toward the viral capsid. During this process, S2 releases the fusion peptides that bind to the host cell. This binding process is followed by a zippering of S2 and the associated membrane fusion, the mechanism by which invasion becomes possible. S2 is covered by sugars called glycans. These glycans slow the conformational transition, providing the fusion peptides sufficient time for the fusion peptides bind before the free energy is released, allowing for the fusion of the membranes. If the glycans are not bound to the Spike protein, this free energy is released too early before the invasion could take place.

Removing the glycans from S2 probably makes the virus ineffective. Possible therapies may be inspired on this principle. Understanding this rearrangement, therefore, provides several other possibilities that can be potentially targeted to deal with this disease. These simulations start to provide enough understanding to generate new ways to defeat the SARS-CoV-2 virus.

2.a A physical mechanism for cell invasion

To investigate the pre-to-post membrane fusion rearrangement, simulations were performed employing an all-atom structure-based model [3,4]. To obtain the physical mechanism governing the transition between the pre-to-post rearrangement, this structure-based model was utilized to perform thousands of simulations between these two states [5]. A physical mechanism and associated intermediates were identified and are described in the schematic representation shown in figure 1.

From figure 1E, it can be noticed that the intermediate states are required to be sufficiently long-lived to allow for the fusion peptides to have sufficient time to capture the cell membrane. This is achieved by creating a sufficiently long-lived sterically-caged intermediate of the Spike protein during the conformational change. This is achieved by the steric presence

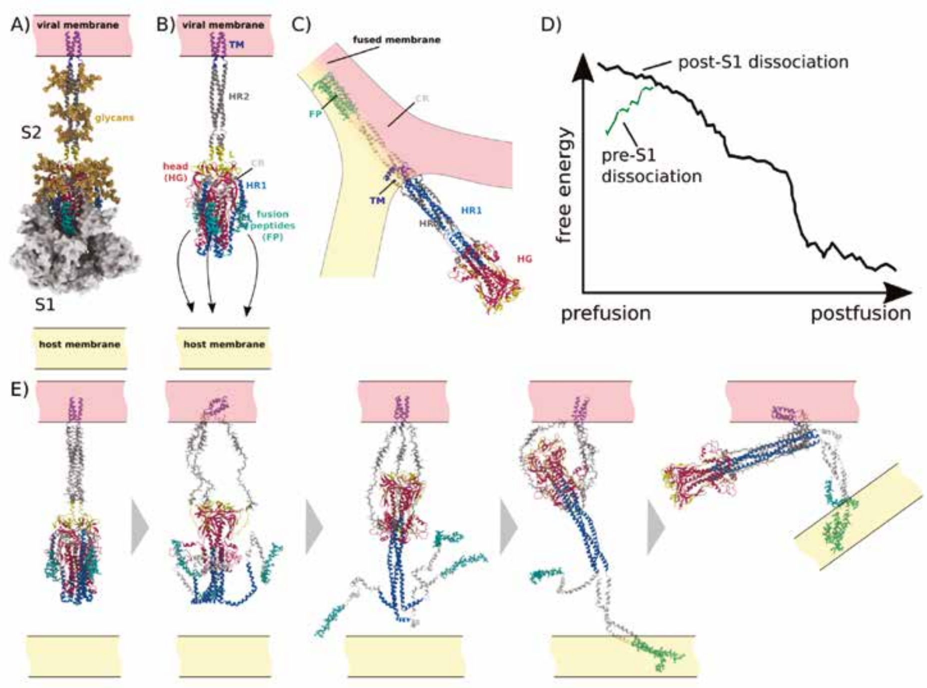

Figure 1. A) Active Spike proteins are composed of two subunits: S1 (white surface) and S2 (cartoon representation) [6]. (B) The S1 subunit dissociated during the recognition of the host cells. (C) The release of S1 allows the fusion peptides to associate with and recruit the host membrane which leads to fusion of the host and viral membranes. D) This transition was modeled by defining the postfusion configuration as the global potential energy minimum. The pre-cleavage state (green) is assumed to be stable, whereas cleavage and release of S1 leads to an unstable prefusion configuration (black). E) A sample transition between the pre-fusion and post-fusion configuration of the S2 subunit resulting in membrane fusion.

of glycans which may substantially increase the life of this intermediate. This glycan-induced delay is essential to provide the opportunity for the fusion peptides to capture the host cell. Therefore, the absence of glycans makes it much more difficult for the viral genome to enter the host cell. These results suggest a possible mechanism by which the glycosylation state may regulate infectivity [7].

Understanding this mechanism creates opportunities for searching new therapies inspired in this invasion mechanism which may help to reduce the negative impact of SARS-CoV-2 in society.

3. Creating new COVID-19 vaccines

In view of creating new COVID-19 vaccines, we have proposed a strategy that employs modified bacteriophages which can be inhaled to deliver protection via the lungs to the immune system. Exploring the unique features of phage (a bacterial virus), we are trying to develop phage display-based vaccine candidates against COVID-19. This will be achieved by utilizing engineered ligand-directed phage particles displaying structurally defined epitopes of the Spike protein.

The phages are engineered with an epitope from the SARS-CoV-2 spike protein, along with a small ligand peptide that helps the phage cross from the lungs into the patient's bloodstream. Once absorbed, they activated the immune system to defend against COVID-19. To facilitate the selection of these epitopes, the part of the antigen molecules that bind to specific biological targets, simulations were performed to determine their effectiveness in producing protecting antibodies [8]. The initial results are presented in figure 2.

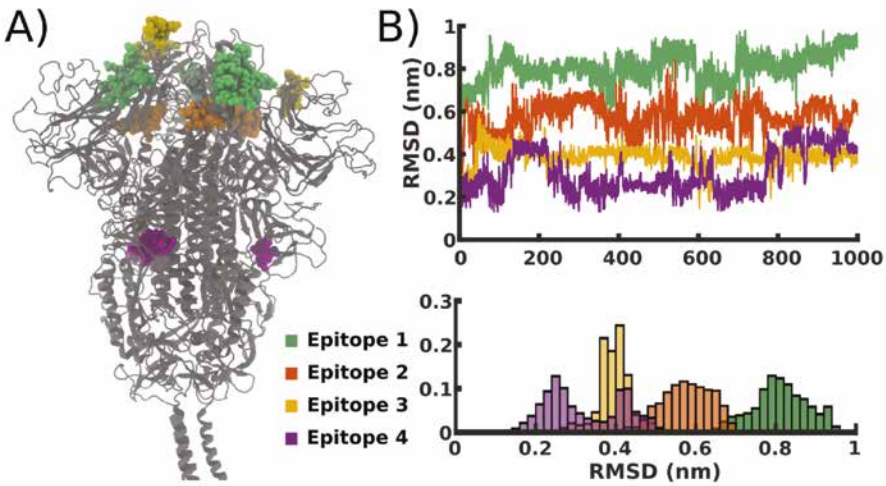

Figure 2. A) Four epitopes spanning the SARS-CoV-2 S protein were selected based on their ability to be introduced into phage-type virus coating proteins. Then, altered phages with the epitopes included were used to trigger an immune response against SARS-COV-2 virus in mice. Only epitope four was able to trigger a significant immune response. B) Explicit solvent simulations of the epitopes in an exposed environment, show that epitope 4 is the most stable ranging low values of RMSD (‹4A) when comparing it with the SARS-COV-2 structure. Then, it was hypothesized that working epitopes for this immunization strategy would require stable epitopes in exposed environments.

Experimental studies determining of the immunogenicity of the Spike protein epitopes demonstrated that epitope 4 is the most immunogenic among the selected epitopes [8]. Therefore, it provides strong support to our hypothesis that epitopes that display their native conformation when transferred to the phage will produce stronger specific immune response as predicted by the theoretical studies.

The success of these early results now provides a combined theoretical and experimental strategy towards the development of new SARS-CoV-2 vaccines. These phage vaccines have the potential of become powerful tools against this deadly disease.

4. Conclusion – The synergy of physical models and biological experiments as a transformative approach to medical science

The two examples in this presentation, 1) the mechanism for viral infection and 2) the development of phage vaccines, describe how approaches coming from theoretical and computational physical modeling can be used synergistically with biological and medical experiments to address challenges of current diseases affecting society. The complexity of these problems requires a combined multi-disciplinary approach in order to achieve successes and the physical sciences are becoming more and more part of the solution.

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SESSION III – MATHEMATICS AND AI FOR HUMAN DEVELOPMENT, PEACE, AND PLANETARY HEALTH

Using AI to Accelerate Scientific Discovery

Demis Hassabis

Founder and CEO of DeepMind

https://youtu.be/8QLoyueoaEc

On Platonism in Mathematics

Peter Scholze

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Abstract. There is an ancient philosophical debate on the epistomological nature of the objects of mathematical inquiry. Are they merely abstractions created by the human mind, or are they objects of their own world, independent of space and time, and amenable to empirical study? I will explain my personal thoughts on the matter.

It was only recently that I learned the etymological meaning of the word "mathematics"; some imperfect translations would be "die Lehre des Gelernten", or "that which is learnt".[1] This came as a revelation to me, as I had long struggled to articulate what mathematics really is, but I think this is an excellent description: It is the science of those most basic things that we have, beyond any reasonable doubt, learned. Not learned about the world we live in, but learned, period. Learned about what, then?[2]

There are two strong sources for the development of mathematics. The first source, I would argue, are numbers, likely originating from the idea of counting any kind of (suitably "discrete") objects, thereby coining the concept of the natural numbers $1, 2, 3, 4, \ldots$; historical artifacts of written representations of numbers – in the form of a corresponding number of lines, say – date back many millenia. Natural operations one can perform with objects naturally lead to the idea that one can add, and multiply, natural numbers; and that these operations on numbers make sense independently of how a natural number might be embodied as a number of objects in our surrounding world. It is here that I have the clearest sense that we are dealing with an entity that exists in and of itself. Note that a serious obstacle for handling natural numbers is precisely that they are not objects of our world: To manipulate them, we first had to invent some means of naming them, and writing them down (such as by Roman or Arabic numerals), and it is clear that this naming is arbitrary, and an imperfect approximation to the actual idea of natural numbers.

It turns out that there is a whole lot to learn just about the natural numbers. One ancient observation arises from noting that the natural numbers behave very differently with respect to addition and with respect to multiplication: While one can reach any natural number by starting with 1 and repeatedly adding 1 – relatedly, any natural number bigger than 1 can be decomposed as the sum of two smaller natural numbers – the same is not true for multiplication. Here, there are natural numbers bigger than 1 that cannot be decomposed as a product of two smaller natural numbers: These are the so-called prime numbers $2, 3, 5, 7, 11, 13, \ldots$.[3] This question, of dividing an integer into smaller pieces, is certainly something that may come up in daily life when it comes to distributing a number of items among a number of people, say, although it is harder to argue that the concept of prime numbers is something that is directly embodied in our surrounding world. A first nontrivial theorem about the natural numbers is the result that any natural number can be uniquely decomposed (up to reordering) into a product of primes, e.g.

$$4 = 2 \cdot 2, 6 = 2 \cdot 3, 8 = 2 \cdot 2 \cdot 2, 9 = 3 \cdot 3, \ldots, 2022 = 2 \cdot 3 \cdot 337, \ldots .$$

[1]The Dutch word "Wiskunde" is quite a literal translation.

[2]Disclaimer: In this note, I am talking about many things that I have no expertise in, and I want to make no claims to any (historical or otherwise) accuracy here.

[3]The start of this sequence (Is 1 prime? Is 2 prime?) has been subject to some historical changes, but there are now very strong arguments for starting the sequence with 2.

This so-called Fundamental Theorem of Arithmetic is nontrivial, but essentially goes back to Euclid's Elements. In any case it is very likely that this was first empirically observed, by decomposing small natural numbers into prime factors. But if it was empirically observed, what was it an empirical observation of? Again, I could only say that it is an empirical observation of that platonic world of numbers.

The second strong source for the development of mathematics has been the study of natural phenomena. This is very prominent in the development of analysis by Leibniz and Newton, which was directly inspired by describing the movement of natural objects in terms of their position, speed, and acceleration. More classically, one can argue that the whole development of geometry, such as the plane geometry of lines, triangles, and circles (as in Euclid's Elements), is an abstraction of those things that we can perceive with our eyes. In the case of geometry, one may again have made empirical observations, but this time in terms of actual lines and circles drawn on paper. In this case, it is clear how to denote these objects on paper, while it turns out that it is very nontrivial to give a rigorous mathematical foundation – it took until the late 19th century before the real numbers were properly formalized. So in this case, the formalization may be seen as an imperfect approximation to the ideal world of geometry. Later, the development of non-euclidean geometry, or geometry on curved objects, also came with an impetus from Gauß' cartographic work in the Hannover area, before Riemann's generalization became central in Einstein's General Relativity.

To this day, I think it is fair to say that most of mathematics can trace its roots to the study of numbers, or to the study of natural phenomena. Critically, as I argued above, both sources lend themselves to empirical study! I would thus object to the general sentiment that mathematics is a non-empirical science.

To me, the concept of natural number feels so basic that hardly any other concept could be formulated without presupposing natural numbers, if only to enumerate a list. Geometry, on the other hand, is much more contingent on the human experience of the world we live in, and how we perceive it. Below, I will however argue that there also seems to be a more elusive kind of geometry that arises from nothing but the natural numbers themselves – a platonic world created by nothing, but the natural numbers themselves?

Indeed, what I want to convey in this note is the rich world that reveals itself by studying the platonic world of numbers. The properties of this world are found by doing experiments with the natural numbers, for example by studying whether some equations are solvable in natural numbers. As a concrete example, let us study a simple quadratic equation. For a given prime number p and natural number n, one could try to solve the quadratic equation

$$x^2 = yp + n$$

for natural numbers x and y. A mathematician would say that in this case n is a square modulo p, as the square number x^2 leaves residue n upon division by p. Let us for concreteness choose $n = 5$, and study whether this has a solution for varying primes p (excluding 2 and 5 in order for the pattern to emerge more clearly). In this case, one empirically finds that

$p = 3$	no solution
$p = 7$	no solution
$p = 11$	$4^2 = 1 \cdot 11 + 5$
$p = 13$	no solution
$p = 17$	no solution
$p = 19$	$9^2 = 4 \cdot 19 + 5$
$p = 23$	no solution
$p = 29$	$11^2 = 4 \cdot 29 + 5$
$p = 31$	$6^2 = 1 \cdot 31 + 5$

$p = 37$	no solution
$p = 41$	$13^2 = 4\dot{4}1 + 5$
$p = 43$	no solution
$p = 47$	no solution
$p = 53$	no solution
$p = 59$	$8^2 = 1 \cdot 59 + 5$
$p = 61$	$26^2 = 11 \cdot 61 + 5$
$p = 67$	no solution

A close look at this table suggests that a solution exists exactly when the prime number ends with 1 or 9, and this pattern indeed continutes. Equivalently (as it is odd and hence cannot end in 4 or 6) this means that p leaves residue 1 or 4 when divided by 5. But these are precisely the square numbers modulo 5! In other words:

Theorem (Gauß' Quadratic Reciprocity for 5). *The number 5 is a square number modulo a prime number p if and only if p is a square number modulo 5.*

A similar (but not exactly the same) assertion holds with 5 replaced by any prime number. This theorem is by no means trivial, although by now hundreds of different proofs are known; Gauß himself collected many. Again, it is a phenomenon that was first empirically observed.

Much of number theory in the 19th and early 20th century was concerned with direct generalizations of Quadratic Reciprocity (dealing with Cubic Reciprocity laws etc.), culminating in what is known as Class Field Theory. What is most striking is that eventually, Quadratic Reciprocity came to be seen a reflection of a certain geometric structure, denoted $\mathrm{Spec}(\mathbb{Z})$ (here $\mathbb{Z}$ stands for the integers, which besides the natural numbers also includes 0 and negative numbers), that was understood to behave much like a 3-dimensional manifold (completely incidentally thus, of the same dimension as the space surrounding us), with quadratic reciprocity a reflection of a general geometric result. Inside this 3-dimensional object $\mathrm{Spec}(\mathbb{Z})$, there are subspaces $\mathrm{Spec}(\mathbb{F}_p)$ for each prime number p, with those behaving much like circles. There is thus a picture emerging of a 3-dimensional space together with infinitely many embedded circles. Of course, those circles may be nontrivially linked with each other, like two conjoined rings in the 3-dimensional world surrounding us; and in fact under this analogy this linking directly corresponds to whether or not one prime is a square modulo the other prime! This picture then gives a clear geometric reason for quadratic reciprocity, as "being linked" is a symmetric relation of the two circles.

Let us pause to describe one reason that the set of integers modulo a prime p, $\mathbb{F}_p = \{0, 1, \ldots, p-1\}$, should correspond to a space $\mathrm{Spec}(\mathbb{F}_p)$ that looks like a circle. The reason is that under this analogy, finite extensions of $\mathbb{F}_p$ should correspond to finite covers of the space $\mathrm{Spec}(\mathbb{F}_p)$. But a central theorem in algebra is that for any integer $n \geq 1$, there is a unique extension of $\mathbb{F}_p$ of degree n (known as a Galois field, in honour of Évariste Galois, 1832), and similarly in topology one has the result that for any $n \geq 1$ there is a unique n-fold covering of the circle (given by a circle that is winding itself n times around the original circle). Thus, subtle properties of the integers, or here of the integers modulo p, reveal geometric properties of the elusive space $\mathrm{Spec}(\mathbb{F}_p)$, itself a subset of the elusive space $\mathrm{Spec}(\mathbb{Z})$.

There are further relations between number theory, and geometry. When studying the solvability in natural numbers of a diophantine equation as above, it is helpful to first study the solvability in the real numbers, or modulo a prime number p. These questions are much easier: Solvability over the real numbers can often be analyzed by a direct graphic inspection, while solvability modulo a prime number p is a finite amount of work (for any given p). One can also ask for solutions modulo higher powers p^n of a given prime number p, leading to the question of solvability in the p-adic integers $\mathbb{Z}_p$. Thus, number theorists are led to "complete" the integers $\mathbb{Z}$ into either the real numbers $\mathbb{R}$ or the p-adic numbers $\mathbb{Z}_p$.

The following two theorems indicate the power, and unavoidability, of this passage from $\mathbb{Z}$ to $\mathbb{Z}_p$ or $\mathbb{R}$; they are given in slightly imprecise form, but we hope the reader forgives us.

Theorem (Ostrowski, 1916). *These are the only ways to complete $\mathbb{Z}$.*

Theorem (Minkowski[4], 1890). *Quadratic equations are solvable in $\mathbb{Z}$ if and only if they are solvable in the p-adic numbers $\mathbb{Z}_p$ for all p, and in $\mathbb{R}$.*[5]

Thus, number theorists are led to study the p-adic integers $\mathbb{Z}_p$ for any prime p, as well as the real numbers $\mathbb{R}$. In particular, the real numbers $\mathbb{R}$ describing the world surrounding us so well, arise as one of infinitely many possible completions of the integers. In this sense, to a number theorist, our $\mathbb{R}$eal world is just one of an infinite number of possibilities! (In fact, to a number theorist, $\mathbb{R}$ is the strange outlier – while the p-adic numbers $\mathbb{Z}_p$ behave somewhat similarly for any p, the real numbers $\mathbb{R}$ are often more peculiar.)

These completions also have a geometric meaning in terms of this elusive 3-dimensional space $\mathrm{Spec}(\mathbb{Z})$. Recall that any prime p gives rise to an elusive circle $\mathrm{Spec}(\mathbb{F}_p)$ inside $\mathrm{Spec}(\mathbb{Z})$. One could then imagine taking a small neighborhood of this circle, giving rise to some kind of doughnut – this would be $\mathrm{Spec}(\mathbb{Z}_p)$, itself a subset of $\mathrm{Spec}(\mathbb{Z})$.

The picture for the real numbers is a bit different: A good analogy here is to imagine the subset $\mathrm{Spec}(\mathbb{R})$ of $\mathrm{Spec}(\mathbb{Z})$ as analogous to the subset of points "very far away" in the 3-dimensional space $\mathbb{R}^3$. In stereographic coordinates, these form a space of the form $S^2 \times \mathbb{R}_{>C}$ for some large C, where S^2 denotes a 2-dimensional sphere. In fact, one gets an even better analogy with $\mathrm{Spec}(\mathbb{R})$ if one identifies points that are antipodal; this way, one arrives at the space $\mathbb{RP}^2 \times \mathbb{R}_{>C}$, where $\mathbb{RP}^2$ is the space obtained by identifying antipodal points on the 2-dimensional sphere S^2. Recall that for $\mathbb{F}_p$, I explained that there should be a correspondence between field extensions and covering spaces. The real numbers $\mathbb{R}$ famously admit the extension into the complex numbers $\mathbb{C}$ (but no further extension, as $\mathbb{C}$ is algebraically closed by the Fundamental Theorem of Algebra). Thus, there is a unique extension $\mathbb{C}$ of $\mathbb{R}$, of degree 2. Similarly, there is a unique covering of $\mathbb{RP}^2$, namely S^2, of degree 2.

It should be stressed that so far noone has been able to give a definition of $\mathrm{Spec}(\mathbb{R})$ that would explain in which way it is related to $\mathbb{RP}^2$ or $\mathbb{RP}^2 \times \mathbb{R}_{>C}$, but current investigations in number theory and representation theory (in particular, in relation to the Langlands program) as well as in geometry (in Hodge theory and its variant known as twistor theory) give very strong indications that there is such a relation. There is a p-adic version of this story, in which $\mathrm{Spec}(\mathbb{Z}_p)$ has been given a distinct geometric structure, known as the Fargues–Fontaine curve, that has been used with great success for various number-theoretic investigations.

Thus, in my life as a researcher in number theory, it feels to me like I am learning things about those most basic objects of inquiry, the natural numbers. And by doing so, a whole geometric world reveals itself! Not having any direct sensory access to the world of natural numbers, progress is naturally slow and contingent, but it seems steady, and pointing in a clear direction. And it certainly feels like uncovering a platonic world of itself.

Let me end this note with a puzzling coincidence. As I just said, the elusive space $\mathrm{Spec}(\mathbb{R})$, itself a subset of the elusive 3-dimensional space $\mathrm{Spec}(\mathbb{Z})$, seems to be closely related to $\mathbb{RP}^2$, which we can think of as the celestial sphere (the points very far away in the surrounding 3-dimensional space $\mathbb{R}^3$), up to the antipodal map. This has become known as the twistor space, and it arises out of purely mathematical considerations, for example within Hodge theory in the work of Simpson and Mochizuki. On the other hand, this same space arises also in Penrose's twistor reformulation of Einstein's theory of relativity, precisely in its interpretation as the celestial sphere; and it can also

[4] Incidentally, the same Minkowski known for the Minkowski space of special relativity, and teacher of Einstein.

[5] This is slightly false, one has to allow denominators.

usefully be applied in the formulation of quantum mechanics, in order to describe spinors. In all of these questions, it is critical that $\mathbb{RP}^2$ has some extra structure, namely a conformal structure. The symmetry group $\mathrm{SO}(3,1)^+$ of relativity is in fact precisely the group of conformal symmetries of $\mathbb{RP}^2$! The same $\mathbb{RP}^2$ that ought to capture the elusive space $\mathrm{Spec}(\mathbb{R})$, which indeed should also be endowed with this conformal structure.

How can it be that by studying just the natural numbers, one is led to feel that one is secretly studying a 3-dimensional space $\mathrm{Spec}(\mathbb{Z})$ that contains a "real part" $\mathrm{Spec}(\mathbb{R})$ whose geometry seems directly linked to some of the deepest properties of the universe surrounding us?

⋆ ⋆ ⋆

President Joachim von Braun presents the 2020 Pius XI Medal to Prof. Peter Scholze.

Africa's Brightest Young Minds: The African Institute for Mathematical Sciences (AIMS) and its Impact on Development on the Continent

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1. The context

The importance of education as a foundational building block for socio-economic development is well understood and acknowledged, as is evident for example in its inclusion as one of the 17 Sustainable Development Goals, and through its cross-cutting relevance to many of the others. Populations with a significant number of highly skilled graduates are well placed to work innovatively towards growth and to address major social and economic challenges. The converse is a stark one: lack of access, or poor access, to higher education constitutes a major barrier to development, and leads to deepening of inequalities, and marginalization.

Africa faces some of the world's toughest development challenges in health, agriculture and food security, education, communication infrastructure, the reduction of poverty levels, and in access to basic resources.

Advances in science and technology offer extraordinary opportunities and are the key to progress in socio-economic development. The onus is on Africa to respond to these opportunities by building a pool of scientific and technical talent that would lead the way to achieving such progress. There can be no more effective investment in Africa's future than in education which empowers young people. And in this age of rapid scientific and technological development, it is higher or tertiary education that holds the key to fostering growth and combating poverty and inequality.

The sustainability of a robust science system, well connected to similar systems and communities around the world, depends on the existence of a critical mass of graduates at masters and doctoral levels: graduates who are able to contribute to scientific advances, who would form the core of university teachers and researchers, and who possess the skills to build on solid foundations in adapting and contributing to the rapid developments in nanotechnology, artificial intelligence and robotics, biotechnology, energy, materials and other sciences, with substantial benefits in areas as diverse as manufacturing, health, agriculture and food security.

The challenge of expanding access to education at this level is, particularly among low-income countries, a substantial one. For example, Sub-Saharan Africa has the lowest regional tertiary enrolment rate in the world: only 9% of the traditional aged cohort continues from secondary to tertiary education [1].

Major planning and policy documents such as the Science, Technology and Innovation Strategy for Africa (STISA2024) [2] recognize the urgency with which to address these challenges, and are clear about their extent. For example, in 2018 Sub-Saharan Africa had 124 FTE Researchers per million of population, compared to 3372 for Europe, 4432 for North America, 593 for Latin America, and 1307 for China [3].

While there is some progress at national level and continentally – for example strong growth in enrolments at centres of excellence and in numbers of researchers [4] – the reality is that the G20 countries account for nine-tenths of researchers (88.8%), research spending (93.2%) and scientific publications (90.6%) globally.

2. The first steps: AIMS South Africa

Mathematics is central to the sciences and technology and there is a dearth of mathematically trained graduates in Africa. A specific response to this challenge begins with the conviction that the talent and commitment to succeed exists plentifully in Africa, and that it is possible to make a significant contribution towards the development of Africa by allowing such talent to flourish. This was the essence of the thinking behind the creation of AIMS, the African Institute for Mathematical Sciences (AIMS): the brainchild of Neil Turok, an outstanding mathematical physicist, born in South Africa to parents who were activists in South Africa's liberation movement, and who subsequently went into political exile with their children.

Bearing in mind the particular needs in the sciences, particularly mathematics, at the advanced levels, the vision was of an institute to provide Africa's brightest young minds with a high-quality, innovative education at the graduate level, equipping them to contribute to Africa's scientific development. "Mathematics is the cheapest of disciplines and provides the invisible plumbing underlying modern society" [5]. With considerable skill, determination and passion, Turok was able to generate support for the vision and reality of AIMS in academia, among policymakers, and philanthropic organisations internationally [5].

The key idea was to mount a residential Master's programme with students recruited from across the African continent. The Master's course would serve as a feeder programme for more advanced study, for example at doctoral level, and would provide a strong background for students proceeding to careers in education, government, and the private sector.

Given the intended location of AIMS in Cape Town, South Africa, it was essential to have the three institutions in the broader Cape Town area – the Universities of Cape Town, the Western Cape, and Stellenbosch – on board. Rather than seek registration as a degree-granting institution, agreement was reached with these three partners that students would be formally registered at their universities in equal numbers, but would be accommodated, supported, and would engage in academic activities at the AIMS campus. The three local universities were joined by the Universities of Cambridge, Oxford, and Paris-Sud to form the team of university partners. This group of universities – leaders, deans, faculty members – has played a pivotal role in getting AIMS on to its feet, working to address many threats, and in ensuring its many successes.

The idea of a dedicated campus or location for AIMS, central to the overall vision, became a reality with the donation to the Institute of an art deco building in Muizenberg, a coastal suburb of Cape Town, by the Turok family. This became and remains the hub, engine room, and locus for teaching and learning and social activities, with students (and many visiting lecturers) living there, taking their meals there, and attending lectures in this building, which had to undergo significant renovation to repurpose it from its previous incarnation as a home for the aged, to a modern, innovative educational institute and home for young people.

Finding the students would not be a problem, as became clear following the extensive numbers of enquiries and applications which followed the call. It was clear during the planning stages that the step from application to a positive offer to arrival would depend on the ability of AIMS to guarantee funding, given the essentially zero access to funds available to potential students. A key task of the AIMS Council and Trustees therefore was that of securing funding that would cover operational costs including that of the academic programme, as well as the students' accommodation and living and other costs related to their studies. In this regard AIMS was fortunate to be able to secure substantial funding support from a range of international donors, together with dedicated allocations from South Africa's departments of higher education and of science and technology.

Starting effectively with a blank sheet, the goal was to mount a one-year graduate programme in the mathematical sciences, which would provide a broad set of skills through a curriculum attuned to contemporary developments. Independent thinking and problem-solving in the context of individual and small-group work would be core to the approach. Furthermore, the mathematical sciences would be interpreted broadly, making for multi-disciplinary thinking and activity in a natural way.

The curriculum, then and now, comprises three phases: the first, referred to as the skills phase, provides foundational material, English language lessons (if necessary), acquaintance with open-source mathematical software packages, and addresses mathematical gaps in students' backgrounds. The second, review phase comprises an array of elective courses providing an overview and introduction to topics at a somewhat more advanced level. The review courses on offer in any academic year are selected from proposals solicited from academics internationally. The teaching mode both for the foundational and review material is an intensive one with courses presented in three-week blocks of around 30 contact hours. A further significant feature of the programme is that assessments are conducted orally and through project work. Lecturers are in residence during the period of their courses, during which time they are supported by tutors in residence. Students and faculty members and staff have their meals together and are able easily to interact socially and in the course of the students' work. During the third phase all students undertake a three-month long project during which they work on a topic under the supervision of a faculty member, usually from a South African university. The curriculum structure, mode of teaching and learning, and the highly inclusive manner in which the institute functions, all make for a warm, productive, energetic, culturally diverse and thriving academic environment.

Review courses offered over the years include topics as diverse as topology and geometry, number theory, astrophysics and cosmology, probability theory and statistical inference, fluid mechanics, stochastic calculus with applications to control and finance, epidemiological modelling, and wavelets.

The inaugural student cohort of 30 students, from 11 African countries, arrived in September 2003. These numbers would grow to a steady state in excess of 50 students annually, giving a total to date of around 900 AIMS South Africa alumni from 41 countries. Listening to the stories of these bright young minds, it was clear then and it remains the case that students and their families will have made huge sacrifices in order for them to leave home and study further at AIMS.

3. AIMS becomes a network

In due course it became natural, given the success of AIMS South Africa, to broaden the original vision, to one of a network of institutes across Africa. A combination of factors led to the realization of this next step. First, Neil Turok had been awarded a TED Prize in 2008. Prize winners are asked about their ambitious wish – what they would spend their prize money on. Turok's wish was that the next Einstein would come from Africa, and that this would be achieved through the harnessing of talent in Africa through a network of institutes, to becalled the Next Einstein Initiative. The second stimulus came from African countries themselves: individuals passionate about establishing such centres in their countries. A key early example was Senegal, through the efforts ofVincent Rivasseau, a French professor, lecturer at AIMS, and former AIMS SA Council member; and Mamadou Sanghare, a professor at Université Cheikh Anta Diop in Dakar. Senegal saw the light of day as the second institute, in 2011. This was followed by AIMS Ghana in 2012, AIMS Cameroon in 2013, Tanzania1 in 2014, and Rwanda, the newest member in 2016.

Thus, AIMS had evolved from a successful institute to a continental network, with a vision and mission of enabling Africa's talented students to flourish as independent thinkers, problem solvers and innovators capable of propelling Africa's future scientific, educational and economic self-sufficiency.

A similar funding model applied to all institutes, with commitments from governments of host countries being an essential component, together with funding from generous donor organizations and individuals.

In addition to the established Master's programme there are further postgraduate offerings. In 2017 a Master's programme in Mathematical Science for Climate Resilience was initiated, with support from the International Development Research Centre of Canada. The programme is designed to increase the contribution of African mathematical scientists to finding solutions to climate change-related challenges in Africa.

With the sponsorship of Facebook and Google and support from the global AI community, the Africa Masters of Machine Intelligence (AMMI) programme was launched in 2018. This programme provides young Africans with state-of-the art training in machine learning and its applications.

[1] AIMS Tanzania closed in 2019, leaving currently a network of five institutes.

4. Taking it to the next level

Over the years AIMS has expanded the scope of its activities, so as to contribute in addressing challenges and pursuing opportunities relevant to Africa over a broad front. This expansion in scope has led to the Network becoming a multi-faceted institution incorporating activities that lie at the intersections of science, research and innovation, and society. Descriptions of some of these initiatives follow.

Research

The link between postgraduate education and development with research is clear, and so the step towards establishing research as an area of activity at AIMS was a natural one. The AIMS Research Centre was established in 2008 at AIMS South Africa. The Centre hosts a number of research programmes which are pursued by a combination of resident researchers, visitors, postdoctoral fellows and research masters, and PhD students.

The focus at AIMS Research is on cutting-edge topics which relate to mathematical modelling in a multi-disciplinary context, particularly those that are most relevant to African development, and especially in fields where scientists in Africa have a competitive advantage and can engage in world leading research. Research focus areas include topics in pure mathematics, data science, climate science, agriculture and food systems, medicine and healthcare, and financial mathematics. Dynamic research centres now exist at all institutes in the Network.

Research activity in the Network was given a substantial boost through the establishment of a number of externally funded research chairs. The Alexander von Humboldt Foundation of Germany, with funding from the German Federal Ministry of Education and Research, initiated the German Research Chair Programme, which makes provision for altogether seven chairs, each institute having at least one such chair. In addition, the International Development Research Centre has funded a Canada Research Chair in climate change science, while the Carnegie Corporation of New York has provided support for a chair in data science.

AIMS, in collaboration with the Robert Bosch Foundation of Germany, created the ARETÉ Junior Chair Programme, which has allowed young researchers showing exceptional promise to build their research teams, develop their research profiles, and eventually be in a position to take up senior chairs and other similar positions as academic leaders.

Various initiatives have aimed to place researchers at the cutting edge of new technologies. Quantum Leap Africa (QLA) was created to catalyze top quality high-impact research in data science and smart systems engineering. This programme incorporates the AIMS Doctoral Training Programme in Data Science. A related initiative has been the African Data Science Intensive Programme, which draws on real-world problems to provide hands-on knowledge of the algorithms and techniques in data science and machine learning.

Continuing professional development of teachers

The AIMS Schools Enrichment Centre (AIMSSEC) was established at the same time as AIMS South Africa. AIMSSEC works with primary and secondary school teachers to increase their content knowledge and their pedagogical approaches and, in so doing, to raise the quality of teaching and learning mathematics. A three-month Mathematical Thinking Course has to date been completed by well over 2000 teachers.

Through a partnership with the Mastercard Foundation, AIMS runs a Teacher Training Programs (TTP) in Cameroon and Rwanda. AIMS TTP trains master trainers, who in turn train other secondary school mathematics teachers. The goal is to train over 10,000 teachers and in so doing to reach over a million secondary school students within five years in these two countries.

Through these innovative pedagogical approaches AIMS is playing a critical role in building a sustainable pipeline of home-grown talent in Africa.

Industry initiatives

The AIMS Industry Initiative builds and leverages industry partnerships to identify opportunities for AIMS students and alumni as well as industry partners. The interventions include short-term work placements, internships and employment.

AIMS, in partnership with the European School of Management and Technology (ESMT), Berlin, and with funding support from the German Federal Ministry for Economic Cooperation (BMZ) through the German Academic Exchange Service (DAAD), launched the AIMS ESMT Industry Immersion Program at AIMS South Africa in 2017. The program transfers competences from one of Europe's leading business schools to AIMS students and develops business links between African graduates and German businesses operating in Africa through internship and postgraduate employment.

A partnership with GlaxoSmithKline (GSK) through its Africa Non-Communicable Diseases Open Lab Programme has provided for year-long internships for AIMS graduates.

Public engagement

The AIMS House of Science Initiative aims to advance science communication and public engagement at AIMS, and in so doing to develop greater public understanding and appreciation of science, particularly in the context of societal development. Effort is directed towards promoting mathematics and science engagement, and working with AIMS students, researchers and alumni so that they are better able to undertake public engagement activities. The House of Science model took shape at AIMS South Africa and is being extended across the entire network of AIMS institutes.

Through such activities as well as special programmes such as Africa Science Week, Science and Cocktails, Pi Day or the International Day of Mathematics, AIMS is playing its part in demystifying mathematics and the sciences, and conveying something of the joy and excitement in working with mathematics, as well as of its pivotal place in addressing major challenges.

Next Einstein Forum

The Next Einstein Forum (NEF) is motivated by the belief that Africa's contributions to the global scientific community are critical for global progress. The NEF is a platform that connects science, society and policy in Africa and the rest of the world – with the goal to leverage science for human development globally.

The biennial NEF Global Gatherings are the Forum's most visible events. These position science at the centre of global development efforts by bringing together political and industry leaders, leaders from civil society, and global science leaders to engage in debate and to seek collaborative pathways to a brighter future for African science, and for Africa generally. The inaugural NEF Global Gathering was held in Senegal in 2016.

The NEF Community of Scientists includes the NEF Fellows, among Africa's best young scientists, while the Ambassadors, one from each African country, are the NEF's young science and technology champions.

5. Impact, and the future

How does one measure the impact of AIMS in this, the twentieth year of its existence? Well, we might start with some statistics. AIMS is proud to have produced over 2200 Masters graduates, 32% of whom are women. Alumni represent 43 countries, of a total of 54 countries in Africa. The alumni, some 70% of whom have remained in or returned to Africa, are serving as leaders in academia, industry and research. The journeys of

AIMS alumni, many of which are featured on the network's website, are profiles of inspiration and models for future generations of young Africans to follow.

AIMS researchers have been responsible for over 600 publications, and have advised more than 100 postdoctoral researchers. AIMS has been able to succeed through the support and involvement of more than 200 partners, over 500 academics who have served as lecturers, and more than 250 distinguished resident and visiting researchers.

All of these data present a picture of a highly successful academic institution whose impact on the African continent, when measured against that of universities and research institutions in Africa, is significant. But the impact of AIMS goes beyond these numbers, impressive as they are. Guided by its vision, values, and firm belief in the ability of African scientists to succeed when given the opportunities, AIMS has inspired young people to pursue their dreams to become mathematicians and scientists, and to do outstanding work on the continent.

The innovative nature of work at AIMS is best illustrated by the emphasis on having African scientists engage with areas and topics which are reshaping the world in which we live, a key example being the activities in data science. Such developments allow for African scientists to become real partners, rather than merely recipients, in the global scientific community, through collaborative efforts within Africa and between Africa and other parts of the world.

AIMS has taken its vision and mission to heart in reaching beyond the conventional boundaries of academia, and in so doing has contributed significantly to strengthening the backgrounds of teachers, bringing mathematics closer to broader society, and working with leaders in industry to the great benefit of alumni and institutions in the private and public sectors.

To coin a phrase, this is the end of the beginning. The challenge now is to work with academics, leaders in our universities, and governments, towards a truly pan-African presence and impact, with a trebling or more in the number of institutes from the current five pioneering members of the Next Einstein Initiative. It is hoped that the Network would serve as a model for similar such initiatives by other individuals and groups in Africa.

Acknowledgements

It is a great pleasure to acknowledge the commitment and contributions of teachers, researchers, university leaders and colleagues, partners, donors and alumni, whose efforts have made it possible for AIMS to be-

come the network of excellence that it is. I have been privileged to be part of the founding team of AIMS South Africa, to serve on its Council, and as a trustee of the AIMS South Africa Trust.

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Mathematics at Heart of Technological Breakthroughs

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https://youtu.be/YuBp6qOm3_Q

SESSION IV – CHEMISTRY / BIO-CHEMISTRY FOR HUMAN DEVELOPMENT, PEACE, AND PLANETARY HEALTH

Innovation by Evolution: Bringing New Chemistry to Life

Frances H. Arnold
California Institute of Technology. Nobel Laureate in Chemistry

I am a scientist/engineer who has spent her career observing and manipulating the evolution of proteins, breeding them in the laboratory to exhibit new traits. The scientist in me is delighted by what I learn and create using the most powerful design process, evolution. The engineer in me pushes me to implement that new insight into how biology innovates in order to solve problems for people. Thus I have worked on everything from converting biomass to jet fuel to replacing toxic insecticides with sex pheromones. I have explored and exploited the power of evolution with an eye to helping us live sustainably on this planet so that we can share it with people and with the other species on which we depend.

Nature is surely the best chemist of all time: her enzymes are responsible for all the marvelous and ingenious chemistry of the biological world. I want to make new versions, useful to us. I also want to explore the universe of chemistry that nature has never explored, at least as far as we know. Chemistry that humans need, and indeed in some cases invented. Chemistry that remains to be invented.

What an enzyme does is determined by its amino acid sequence, as encoded in DNA. The newest tools of molecular biology are remarkable. We can read DNA – an entire human genome can be sequenced for a few hundred dollars. We can write DNA – you can email your gene sequence to your favorite supplier, and you will get the actual DNA back in the mail. We can edit DNA: we can now go into a living cell and make changes to its DNA using tools like CRISPR-Cas. But what we struggle to do is *compose* it. To me, the code of life is like a Beethoven symphony, intricate and stunningly beautiful. Even composing the sequence of a new and useful enzyme is something humans have not yet learned how to do.

To sidestep our profound ignorance of how sequence encodes an enzyme function I turned to evolution, the simple process – indeed the algorithm – of mutation and natural selection that has given rise to the incredible diversity of the biological world, including the enzymes. This marvelous process, which works at all scales from molecules to ecosystems, has no counterpart in the world of human engineering.

Where could we go with evolution? There is a universe of possible proteins, the vast majority of which nature has never had a chance, or a reason, to explore. From the beginning of life to today, nature has made and tested only the tiniest fraction of the universe of possible proteins, and she has kept those relevant to the survival and fitness of the organism that makes it. But out in the universe of possibilities, there surely exist proteins whose functions can cure cancer, or solve the energy crisis. Perhaps even cure death and taxes… or at least taxes.

It may interest you to ponder the vastness of this protein space in order to appreciate the power of evolution. How does one discover a useful protein in the infinitude of possible proteins, a set larger by many orders of magnitude than all the particles in the universe? In his fascinating short story, the Library of Babel, Jorge Luis Borges described a collection of all possible books that can be assembled from an alphabet of letters. Most texts in Borges' library are gibberish, and his despairing librarians, for all their lifelong efforts, cannot locate a single meaningful sentence, much less a complete story.

Similarly, most protein sequences encode nothing we would recognize as meaningful. Unlike Borges' librarians, however, we are surrounded by proteins with meaningful stories. They can be scraped from the bottom of my shoe, captured from the air I breathe, or extracted from a database. These are the products of billions of years of work performed by mutation and natural selection. And evolution continues to create new ones. Thus, I decided to start my exploration by using this work of evolution, the existing functional proteins.

The challenge is to discover new sequences that deliver useful properties on a scale of weeks, rather than millennia. Many years ago now, I used the emerging tools of molecular biology to practice evolution in the test tube, exploring new enzymes by taking nature's simplest search strategy. By making random mutations at a low level and screening those mutated proteins for desired changes, we could nudge enzymes over just a few generations into new niches. Many people have now used that approach to make the enzymes in your laundry detergent, reagents for DNA sequences, enzymes that reduce pollution from livestock, and enzymes that are used to manufacture everything from paper to pharmaceuticals.

Even more exciting, however, is that we can use evolution not just to improve the chemistry nature has already discovered, but also to *innovate*. We can create enzymes for entirely new chemistry, not known in the biological world. Nature has done that countless times, after all, from the origin of life to today. So why not use evolution to explore possible futures of the chemistry of the biological world?

I will share one simple but fun example – enzymes that construct silicon-carbon bonds. Silicon is the second most abundant element on our planet, but as far as we know, the biological world assembles no Si-C bonds. Humans do it. We make billions of tons of products that contain these bonds – including probably 50 products in this room, in your earbuds, hair gels, caulks, sealants, paints. These materials are all made by chemistry invented by humans, using increasingly expensive platinum catalysts whose mining tremendously degrades the environment.

Starting with a chemical hypothesis, we tested simple proteins containing an iron atom in a heme, and discovered that a protein from a hot salty pool in Iceland could catalyze a simple carbene transfer reaction to make a new Si-C bond. Now this is not its natural function, but the protein, a cytochrome *c*, catalyzes the reaction when given the right reagents, which are not found in nature. In other words, the ability to do this chemistry is a 'promiscuous' activity of a protein that already exists. This chemical promiscuity is the fuel for evolution. We then evolved it in the laboratory so that the new enzymes does this chemistry more precisely and much more efficiently than any human-made catalyst.

I present this example because it illustrates beautifully how rapidly nature can innovate, using the diversity of functions and genetic materials that already exist in order to discover and evolve new functions. Novelty and adaptation to a changing world comes right out of what is already there!

This demonstration that biology can make such bonds surprised and delighted the world. It opened people's minds about what biology can do, and what it can learn to do. A sensational story from *Science* magazine with a headline mentioning silicon-based life helped send this news all around the world. We did not try to make silicon-based life in this work, but this question interests many and sparks wonder. We want to know whether life can be based on something other than what we already know. Our work merely showed that, given the right environment and starting materials, nature can quickly adapt to make entirely new bonds and materials.

I hope you will appreciate the wonder, and power, of evolution. Evolution has not stopped and will continue to innovate, and it will continue to create new chemistry. We can now explore possible futures of chemistry using nature's powerful design process, and starting from what has already been created.

I also want to share my vision of the future of chemistry, where we will be able to genetically encode new and important transformations and perform them in microbes, the chemical factories of the future. Why do this? I do it because nature's chemistry is clean and efficient, and because nature is a master of using renewable resources as a source of chemical feedstocks – think of sunlight and carbon dioxide. We need to do this for a sustainable future.

I took on a new job, almost two years ago now, as co-chair of President Biden's Council of Advisors on Science and Technology (PCAST). I got the call at a very dark time, December 2020, the deepest pit of the pandemic. Hospitals were overwhelmed, we had no vaccine and little in the way of reliable treatments. We had just finished four years with a President who dismissed science.

I took on this job, because I believe that our highest responsibility, in each generation, is to preserve our fragile planet; prepare for the future; and pass on a better world. I will share a few words I used when my appointment to PCAST was announced by the then President-elect, in January 2021.

Science-based decision-making has always been our most powerful tool for meeting that responsibility – perhaps never more so than today. In a moment of torrential divisions, science offers us a common shelter of facts and truth – within which we can begin to come together and, in time, begin to heal.

Science is not the cold solving of problems. It is a warm and beautiful exploration of the unknown – an expression of human curiosity that propels us forward, and allows us to fulfill our responsibilities.

The moment we fail to nurture it, we resign ourselves to living in the past and lose the chance to guide the future.

When we put science back to work for the benefit of all people – revitalizing our economy, fueling our climate response, broadening our perspective as we rebuild around greater equity and opportunity, we are making a society worth passing on to our children and our grandchildren.

Modeling the Human Brain in Development and Disease

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To say that the human cerebral cortex is the organ of civilization is to lay a very heavy burden on so small a mass of matter.
C. Judson Herrick (1926)

Abstract

Inspired by the iron-clad tenacity of past scientists we set out to understand the mechanisms of life's bricks, how they divide, which genes direct them, how they differentiate into specific lineages and how this intricate orchestration goes awry.

Much of the bridging between past and contemporary neuroscience lies in maintaining a close-knit relationship between the sciences that study the mind and reductionist science. It is through health that we conceptualize the fundamental properties of its nature but through disease that we appreciate them. Neurological disorders gather our attention as they challenge and alter communication and relationships by limiting and then extending them. To study phenotypes associated with human brain development, function, and disease, it is necessary to use experimental systems that are accessible, ethically justified, and can replicate human context.

Human pluripotent stem cell (hPSC)-derived brain organoids offer such a system, which faithfully reiterates features of early human neurodevelopment *in vitro*, including the generation, proliferation, and differentiation of neural progenitors into neurons and glial cells and the complex interactions among the diverse, emergent cell types of the developing brain in three-dimensions (3D). In recent years, numerous brain organoid protocols and related techniques have been developed to recapitulate aspects of embryonic and fetal brain development in a reproducible and predictable manner. Coupling our ground-breaking cerebral organoid technology with elegantly tailored cutting-edge genetic manipulations has enabled us to efficiently screen for disease-linked mutations serving as a boon when studying human neurobiology and neurodevelopmental disorders. Altogether, these different organoid approaches provide distinct bioassays to unravel novel, disease-associated phenotypes and mechanisms.

★★★

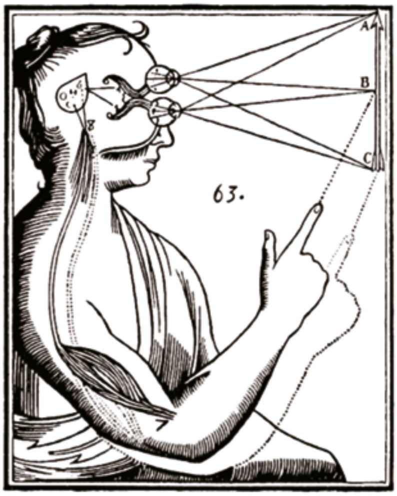
Understanding the brain is probably the greatest task of human biology for it encapsulates the purpose of humankind. The brain births ideas, feelings, cultures, motion, reflex, wisdom, and identity. It is an organ that has nothing short of divided and fused, perplexed and intrigued populations throughout history. The light shines on it; no dimming in sight, not even so much as a flicker as we gather ourselves sedulously attempting to satisfy our scorching thirst from ploughing away its many facets for the chance of grasping its veritable nature.

The Greek philosopher Aristotle believed that memory and consciousness were found in the heart, coining what we now refer to as emotional intelligence. The Egyptians, however, first described the basic anatomy of the brain and made the connection that it controls movement. The brain as an organ has interested populations and cultures amass, many reaching the same conclusions. Much of the early knowledge was based on observations by doctors who made poignant connections between human behavior, physiology and the brain.

A thousand years later the French philosopher Descartes distinguished the brain from the mind, thereby introducing the pertinent notion of dualism. This planted the seed that flowered into the scientific revolution where the brain earns the leading role sprouting different fields of neuroscience research. Like all sciences, neuroscience was approached from the macroscopic to the microscopic scale, offering plenty of fascinating discoveries and contributing to deep and often controversial discussions along the way.

Descarte's portrait by Frans Hals. Public domain.

The fascination over the complexity and importance of the human brain ensures quick progress in teasing out its many layers of anatomy and diverse functions. Strolling along the neuroscience history aisles one notices the quick succession of discoveries with Purkinje (Purkyně) describing the neuron, Broca identifying the region responsible for speech and Pavlov examining the physiology of involuntary reflexes earning him a Nobel Prize in Medicine. Soon after, electroencephalography (EEG) is developed to measure electrical activity in the brain and Sir Charles Sherrington wins the Nobel Prize for describing the existence of synapses and how reflexes occur as a result of nerves extending into muscles. A decade later Isidor Rabi wins the Nobel Prize for discovering nuclear magnetic resonance which made the development of magnetic resonance imaging (MRI) possible. Several researchers bring evidence that solidified Julius Bernstein's hypothesis that action potential is a product of ionic conductance. These technological breakthroughs permit Joseph Erlanger and Herbert Gasser to document the existence of different action potentials across different cells which ultimately leads to their Nobel Prize-winning discovery of the velocity of action potentials. Progress in physiological neuroscience is accompanied by the confirmation that acetylocholine is a neurotransmitter marking a landmark discovery for molecular neuroscience.



Descartes's illustration of mind-body dualism in "Treatise of Man".
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The variety of emerging fields quickly creates the need for more unified efforts in teasing out the complexity of our brain and it is now officially recognized as an independent discipline. The fast-paced progress in its diverse fields highlights the need for a deeper understanding of our nervous system by looking down to its founding units.

At this point a set of groundbreaking discoveries are made that influence and impact biology and medicine globally in an unprecedented way. Wilhelm His and Santiago Ramón y Cajal independently notice the presence of cells from which all types of neurons arise before migrating from the place of origin to increasingly more distant locations.[1,2] Ernest McCulloch and James Till identify the existence of cells in the adult bone marrow which can self-renew and are hematopoietic giving rise to all blood cell types, inaugurating the field of stem cell research.[3] As scientists curiously peak down the microscope into life's building blocks, cell biology and medicine have, unbeknown to them, been revolutionized. Martin Evans and Matthew Kaufman isolate and culture mouse embryonic stem cells opening up the possibility to study the function of specific genes during disease.[4] Soon after, James Thompson reports the derivation and culturing of human embryonic stem cells that retain their pluripotent state; their ability to give rise to different cell types.[5] Shinya Yamanaka astounds the scientific community by making a remarkable discovery that adult mouse fibroblasts can be reprogrammed into reacquiring a pluripotent state, much like that of mouse embryonic stem cells and calls them induced pluripotent cells (iPSCs).[6] Together with Takahashi they successfully derive iPSCs from human fibroblasts as well, alleviating the considerable and understandable ethical concerns of using human embryonic material for stem cell research.[7]

The hallmark properties of stem cells are the ability to self-renew by dividing indefinitely into daughter cells, while at the same time retaining the capacity to commit daughter cells to lineage-specific differentiation which is the more differentiated progeny that drives tissue specific development. Stem cells can be isolated from the blastocyst stage of the developing embryo, but they are also found to persist in niches of adult tissues, including the brain. Neural stem cells, like all stem cells, play important roles in tissues homeostasis, and in development. In adult organisms, they ensure continuous replacement of dying or damaged cells, while during development they generate most of the cell types in a developing organ. To fulfill this task, stem cells can maintain an undifferentiated state, but at the same time generate daughter cells that are lineage-restricted and ultimately undergo terminal differentiation. Understanding how the balance between self-renewal and differentiation is controlled within a stem cell lineage is important since defects in the control of this process can result in tissue degeneration or tumorigenesis. Neural stem cells are the focus of my lab's research, and our work has offered many insights into what is "there".

Building on the fundamental idea that biological mechanisms are conserved throughout evolution, biomedical research focuses on animal model organisms. Animal experimentation is widely used as a proxy for understanding human embryonic development and organ function.[8] A menagerie of animal species, both vertebrate and invertebrate, are employed in an attempt to answer more direct questions. Each model offers particular strengths (Fig 1).[9] Although some extrapolations lead to valid knowledge, other speculations do not translate quite as fluently. Human physiology is profoundly different from the mouse model system: it is perhaps unsurprising that there are huge differences in metabolism between

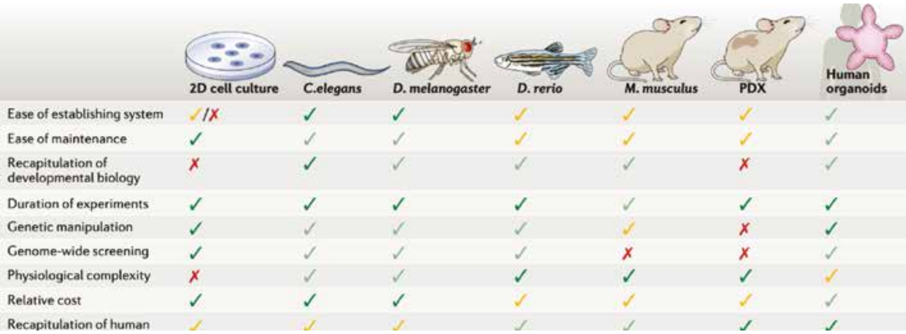

Figure 1. Comparison of organoids with other model systems. The most common model organisms that are used in biomedical research are Caenorhabditis elegans, Drosophila melanogaster, Danio rerio and Mus musculus, along with patient-derived xenografts (PDX). These models, as well as 2D cell cultures and human organoids, are assessed here for their relative benefits and limitations. Relative scores are represented as being the best (dark green tick), good (light green tick), partly suitable (yellow tick) and not suitable (red cross). Xenografts, tissues or organs transplanted between different species. (Figure from Kim, J et al. 2020).

humans and laboratory models, given that humans develop far slower than the other models[10] or the fact that continuous oscillations in the hippocampus, for the purpose of spatial navigation of rodents, are found not to be true in bats or monkeys. Even further, several biological phenomena that are specific to humans are not amenable to being reproduced in animal models. The human brain, for example, is far more complex than its mouse counterpart, owing partly to human-specific developmental events and mechanisms.11 Neurons in the human cortex, for example, arise from a cell type (outer radial glia) that is either not present – or is present only in minute numbers – in rodents.[11] Despite this and with, perhaps, a reluctant recognition that not all knowledge from the animal kingdom transcribes to the human, armies of scientists methodically reveal distinct aspects of brain development by using animal models.

Drosophila and Caenorabditis elegans models are instrumental in elucidating the principles of stem cell self-renewal and differentiation, uncovering molecular parallels for this process in different species. Understanding that one way to generate cellular diversity during development is to segregate cell-fate determinants predominantly into one daughter cell upon division, inspires us and others to ask how this process comes to be. Work mostly done in the fruitfly, *Drosophila*, suggests two different mechanisms by which this remarkable task can be achieved.[12] Already in interphase, cells which undergo such intrinsically asymmetric divisions use apical-basal or planar polarity of the surrounding tissue to set up an axis of polarity. As they enter mitosis, this axis is used to polarize the distribution of protein determinants and to orient the mitotic spindle so that these determinants are inherited by only one of the two daughter cells. Alternatively, they can orient their division plane so that only one of the two daughter cells maintains contact with the niche and stem cell identity (Fig. 2).[13] A stem cell, by orienting its mitotic spindle perpendicularly to the niche surface, ensures that only one daughter cell can maintain contact with the stem cell niche and retain the ability to self-renew. In contrast to intrinsically asymmetric cell divisions, which usually follow a predefined developmental program, niche-controlled stem cell divisions offer a high degree of flexibility. Occasionally, the stem cell can divide parallel to the niche, thereby generating two stem cells to increase stem cell number or to compensate for occasional stem cell loss. For this reason, niche mechanisms are more common in adult stem cells, whereas intrinsically asymmetric divisions predominate during development.

Clarifying the mechanism of asymmetric cell division in the Drosophila nervous system becomes the starting point of my contributions to stem cell biology. Building on what I learned during my post-doctoral work,[14,15] I team up with extraordinary and brave scientists in my lab to develop a conceptual framework for how the asymmetric cell division process occurs. We propose, test, and show that an axis of polarity is established during interphase guiding both the orientation of the mitotic spindle and the asymmetric localization of protein determinants during mitosis. Over several years, we identify a near-complete set of proteins involved in the various stages of the process and achieve a mechanistic understanding of asymmetric cell division. We find that it is the asymmetric localization of the so-called Par-proteins that establishes the polarity axis to guide asymmetric cell division. In mitosis, a polarized attachment site for microtubules established by the proteins Pins, Galphai and Mud orients the mitotic spindle while the kinase aPKC detaches protein determinants (Numb, Prospero and Brat) from one side and guides their accumulation at the opposite site[16–20] (Fig. 3. This mechanism enjoys wide acceptance in the field and becomes part of most developmental biology textbooks. Importantly it is conserved in mammalian stem cells highlighting the relevance of asymmetric cell division in stem cell biology especially considering the compelling connections to tumorigenesis that begin to emerge. Like, for example, the link we make between cellular metabolism

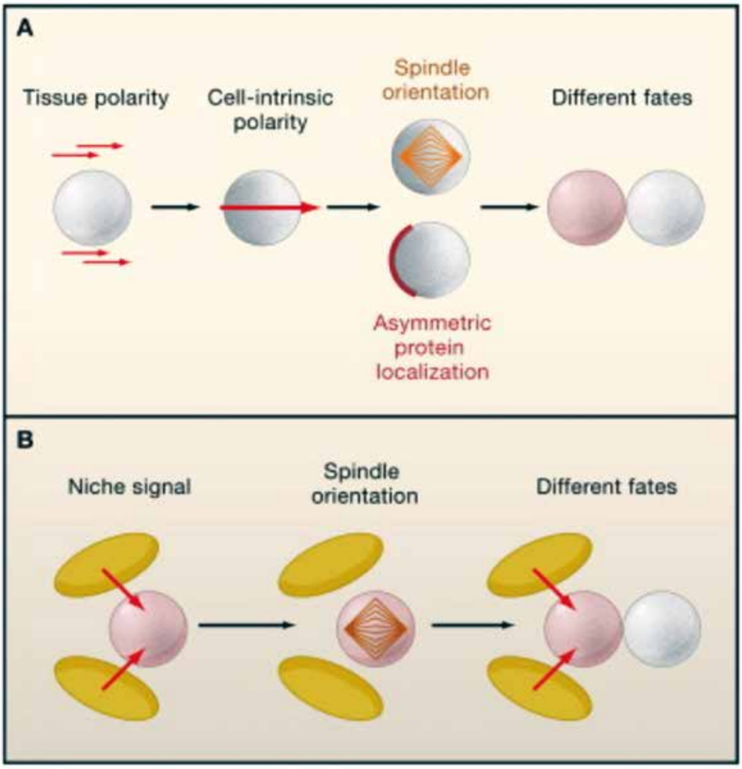

Figure 2. Extrinsic and intrinsic regulation of stem cell self-renewal by asymmetric cell division. (A) Stem cells can set up an axis of polarity during interphase and use it to localize cell fate determinants asymmetrically in mitosis. Orientation of the mitotic spindle along the same polarity axis ensures the asymmetric segregation of determinants into only one of the two daughters. (B) Stem cells may depend on a signal coming from the surrounding niche for self-renewal. By orienting their mitotic spindle perpendicularly to the niche surface, they ensure that only one of the two daughter cells continues to receive this signal and maintains the ability to self-renew. (Figure taken from Knoblich, JA 2008).

and immortalization of tumor-initiating cells by performing targeted metabolomics and *in vivo* genetic screening.[21]

Matching a gene to its function is necessary in detangling developmental processes but it is also a laborious process. Genetic screens become the go-to method for the elucidation of developmental pathways and work done in invertebrates is followed by an analysis of evolutionary conservation in mammalian model systems, often leading to clinical translation for humans. Pioneers, Christiane Nüsslein-Volhard and Eric Wieschaus

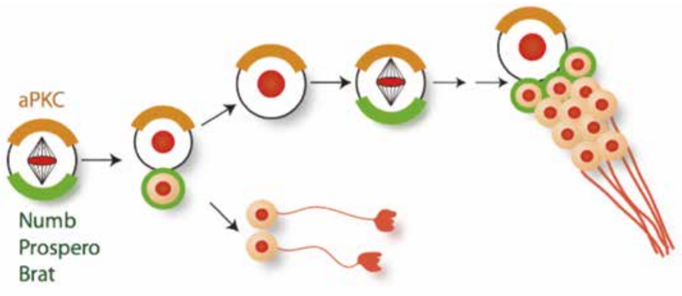

Figure 3. Axis of polarity establishment during asymmetric cell division. During interphase, Par proteins (like aPKC) localize asymmetrically creating a polarity axis which during mitosis will serve to guide asymmetric cell division. During mitosis, microtubules attach a polarized site to orient the mitotic spindle and aPKC locally phosphorylates cell fate protein determinants to guide them to the opposite site. Ultimately, the cell fate determinants Numb, Pros, and Brat segregate into the small daughter cell, the ganglion mother cell (GMC) that divides only once more to generate two differentiating neurons.

pave the way by screening through massive numbers of randomly induced mutant fly embryos for defects in developmental patterning and classify 15 genes as the key players during embryonic development in Drosophila.[22] In the wake of the discovery of stem cells and the establishment of the key tenets of stemness, another technology is appearing in an entirely unexpected way. As Andrew Fire and Craig Mello investigate gene expression regulation in C. elegans, they observe that double-stranded RNA blocks the expression of the respective gene and name this approach RNA interference (RNAi).[23] The ability to silence specific genes overcomes the main drawback of random mutagenesis approaches in that it is gene specific. RNAi allows large-scale genetic screens to reveal the functions of many genes through development. Consequently genome-wide RNAi studies are performed in mammalian stem cell cultures.[24,25]

Naturally, the wish to study stem cells *in situ* arises, where the interactions with the surrounding niche and the tissue-specific characteristics of individual lineages are maintained. In *Drosophila*, this becomes possible through the establishment of a transgenic RNAi library that can be expressed in a tissue-specific manner.[26] Together with my team we become the first to perform genetic screens in a tissue-specific manner within an entire organism. We focused on external sensory organs, where defects in asymmetric cell division or Notch signaling lead to visible phenotypes, like gain or loss of bristles. We use a library of 20,000 transgenic RNAi lines generated by Barry Dickson that result in informative loss-of-function phenotype data for 23% of all protein coding Drosophila genes, a data set that is still regularly queried by others in the field.[27]

Armed with all this knowledge, we now wonder how the finely tuned yet fragile homeostatic balance between stem cell self-renewal and differentiation is regulated. We perform genetic screens on neural stem cells using genome-wide transgenic RNAi and identify 620 genes that are potentially involved in controlling this balance in Drosophila neuroblasts (larval brain stem cells).[28,29] We quantify all phenotypes and derive measurements for proliferation, lineage, cell size, and cell shape. We identify a set of transcriptional regulators essential for self-renewal and integrate hierarchical clustering with interaction data to create functional networks to uncover the control of neuroblast self-renewal and differentiation. Our data reveal key roles for the chromatin remodeling Brm complex, the spliceosome, and the TRiC/CCT-complex showing that the alternatively spliced transcription factor Lola and the transcriptional elongation factors Ssrp and Barc control self-renewal in neuroblast lineages.[28,29] These efforts truly lay solid foundations for the mechanistic discoveries that ensued on stem cell immortalization and tumorigenesis.

Studies in Drosophila, undoubtedly enriched our scientific acumen of neural development but the gnawing need to intimately explore the least understood organ of our body, is ever-present. The complex architecture and function of the human brain enables us to perform higher cognitive functions. Abnormalities in the structure or function of the brain can lead to severe neurological and psychiatric disorders. It is becoming increasingly clear that many neurological and psychiatric disorders have their roots in neurodevelopment.[30,31] However, determining the neurodevelopmental cause and mechanisms of these brain disorders is challenging, due to the limited access to the human brain tissues. Given the large evolutionary distance between mouse and human, and the immense elaboration of the primate brain in size and complexity, there are many features unique to human brain development and diseases that are not seen in rodent systems.[32]

Standing on the shoulders of giants we can now see much farther than we ever thought possible and diving into the unknowns of the human brain seems to be more within our reach. But first a bridge must be built. A new model that does not rely on human primary material is needed. Madeline Lancaster in my laboratory, replaces mortar and pestle with pipette and culture dish and attempts to use human pluripotent stem cells to model key developmental events of the human brain *in vitro*. By combining classical cell culture approaches with recently developed methods enabling cells to grow three-dimensionally, we develop cerebral organoids, a tissue culture method that recapitulates human brain development.[33] The gap between animal models and human beings has been bridged.

Human brain organoids, otherwise known as cerebral organoids, are hPSC-derived self-organizing human pluripotent stem cell-derived three-dimensional culture systems that develop various discrete, although interdependent, brain regions. Cerebral organoids recapitulate the neurodevelopmental scheme to generate 3D tissue architectures that mimic various features of the developing fetal brain pertaining to cellular composition and tissue structure.[34] hPSCs cultured in appropriate media conditions form an embryoid body[35] or a spheroid[36] and undergo neural induction to adopt the neuroectodermal fate.[33,36,37] The neuroectodermal progenitors self-organize into multiple 3D structures featuring apical lumens called neural rosettes or neural buds reminiscent of the neural tube. After 1 month in culture, organoids exhibit neuronal differentiation (Tuj1, Fig. 4), leading to progressive expansion and thickening of cerebral tissues (Fig. 4).[38] By 2 months, different brain regions are visible, including forebrain and hippocampus (Fig. 5).[38]

The path to cerebral organoid generation is exciting but nothing short of challenging. Knowing we have made the first big leap into the systematic investigation of human brain development and disease we dedicate much time and effort to deepen our understanding and broaden our tool kit. We use brain organoids to examine the cell biological basis of a form of microcephaly, a disorder involving small brain size.[33,39,40] In fact, a variety of neurological disorders can be examined in cerebral organoids. We use RNA interference and patient-specific induced pluripotent stem cells to model microcephaly, a disorder that has been difficult to model in mice. We demonstrate premature neuronal differentiation in patient organoids, a defect that could help to explain the disease phenotype.

We then initiate the development of more organoid-based human disease models.41 We were able to reproduce the events leading to human brain cancer formation by electroporating mutagenic DNA constructs and introducing brain cancer specific mutations. Importantly, the new methodology some of the key events in human brain cancer, like the invasive nature of cancer cells, to be replicated *in vitro*.41 We demonstrated the usefulness of our cancer models for drug treatment by inhibiting tumor growth using EGFR inhibitors and predicting drug effects in a patient and tumor type specific manner. Cerebral organoids become very useful for

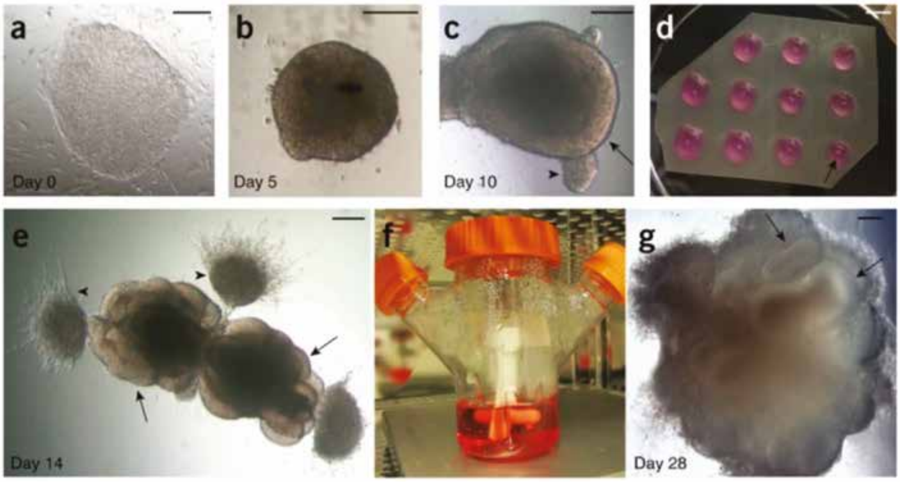

Figure 4. Progression of cerebral organoid development from human PSCs. (**a**) A colony of feeder-dependent human ESCs showing typical pluripotent morphology with clear boundaries and a uniform texture. (**b**) An EB at day 5 showing evidence of ectodermal differentiation, as indicated by the presence of brightened surface tissue, whereas the center is quite dark with dense non-ectodermal tissue. The EB also has a smooth surface, indicating healthy tissue. (**c**) An early organoid at day 10 showing smooth edges and bright optically translucent surface tissue consistent with neuroectoderm (arrow). This organoid also contains small buds of ectodermal tissue that is not organized radially (arrowhead). (**d**) Image of the neuroectodermal tissues embedded in Matrigel droplets on a sheet of dimpled Parafilm. The tissues are visible as small white specks within the droplet (arrow). (**e**) An organoid at day 14, after embedding in Matrigel, showing evidence of neuroepithelial bud outgrowth (arrows) that are optically clear and in several cases surround a visible lumen. Other outgrowths and migrating cells are also visible (arrowheads) that are not neuroepithelial. (**f**) The spinning bioreactor setup in the tissue culture incubator. Organoids are visible within the bioreactor as small white floating specks. (**g**) An organoid at day 28 of the protocol, revealing many large neural tissues (arrows) that have greatly expanded once embedded in the Matrigel. Scale bars, 200 µm (**a–c,e,g**) and 5 mm (**d**). (Figure from Lancaster et al, 2014).

elucidating and characterizing the teratogenic effects of the ZIKA virus and for predicting its mechanism of infection.42,43 In an attempt to extend those observations, we model the pathology of Herpes Simplex Virus in organoids. We succeed in recreating the pathology and could identify a potential therapeutic strategy for eliminating the virus from the fetal brain.44 We therefore convincingly show that three-dimensional organoids can recapitulate development and disease even in this most complex human tissue.

While we agree that organoids enable disease modeling in complex and structured human tissue, *in vitro*, like most 3D models, they lack sufficient

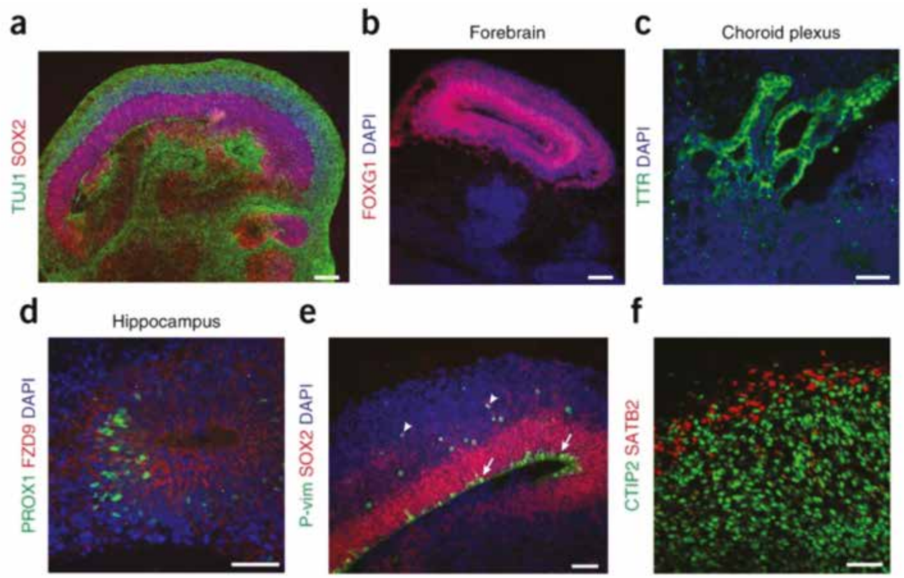

Figure 5. Staining for brain regions and neuronal cell identities. (**a**) Staining for neurons (TUJ1, green) and progenitors (SOX2, red) in a large continuous cortical tissue within an organoid. Note the organized apical progenitor zone surrounded by basally located neurons. (**b**) A forebrain region of an organoid staining positive for the marker FOXG1 (red). (**c**) Choroid plexus stains positive for the marker TTR (green), and it displays convoluted cuboidal epithelium. (**d**) Hippocampal regions stain positive for the markers PROX1 (green) and FZD9 (red), although the cells fail to spatially organize into recognizable dentate gyrus and CA regions. (**e**) Staining for mitotic radial glia (P-vimentin (P-vim), green) in a cortical region reveals inner radial glia undergoing mitosis at the apical membrane (arrows), whereas outer radial glia undergo mitosis outside the ventricular zone (arrowheads). All radial glia are marked by SOX2 (red). (**f**) Staining for cortical layer identities of advanced organoids (75 d). Later-born superficial-layer identity (SATB2, red) neurons populate more superficial regions of the organoid, whereas early-born deep-layer identity (CTIP2, green) neurons populate deeper regions of the organoid. DAPI in a–e labels nuclei (blue). Samples in a–e are 30–35 d after initiation of the protocol. Scale bars, 100 μm (a,b) and 50 μm (**c–f**). (Figure from Lancaster et al, 2014).

oxygen supply, leading to cellular stress. We hypothesize that drawbacks might prevent proper lineage commitment. We therefore set out to analyze brain organoid and fetal single cell RNA sequencing (scRNAseq) data using our own and other's datasets totaling over 190,000 cells. We describe a unique stress signature found in all organoid samples, but not in fetal samples. We demonstrate that cell stress is limited to a defined organoid cell population, and develop Gruffi, an algorithm that uses granular functional filtering to filter out stressed cells from any organoid scRNAseq dataset in an unbiased manner.[45] In this way, we offer a robust way to bioinformatically control for the adverse effects of cell stress thereby improving developmental trajectories and strengthening resemblance to fetal data.

In parallel we develop variable organoid protocols that permit us to study different parts of brain development. We push the boundaries by achieving the faithful reproduction of long-range neuron migration in the human brain by assembling dorsally and ventrally patterned organoids (Fig. 6). We recreated a polarity axis and demonstrate that this axis is maintained throughout the organoid culture, leading to correct interactions between the two brain parts. Like in the real human cortex, interneurons within these cultures correctly migrated from the ventral to the dorsal part allowing us to investigate their migration in real time and to test the effect of specific signaling pathways by using specific inhibitors.[46]

We and others share our appreciation for what seems to be a new technology with enormous potential. We now have a versatile tool that can be coupled to genetic screening permitting us distinct bioassays to unravel novel, disease-associated phenotypes and mechanisms. It comes as no surprise that we are enthusiastically combining decades of multi-disciplinary research outcomes and organoid technology to investigate what other model organisms helped frame the hypotheses on. In recent years, multiple breakthrough discoveries are made, and groundbreaking methodologies are developed. The most prominent of these is the development of the CRISPR-LICHT approach which is a method for genetic screening in 3D organoid systems that can now be applied to any set of human disease genes and any organoid system (Fig. 7).[47] The development of the CRISPR−Cas9 endonuclease technology has made diverse methods of genetic engineering readily available to all researchers.[48–51] Unlike the previous technologies, the Cas9 endonuclease is guided to the genomic sequence of interest as a means to generate a DSB by a guide RNA sequence (gRNA), making the system highly versatile and easy to apply.[52] We combined CRISPR/LICHT, CRISPR/Cas9 dropout screening with lineage barcoding to overcome the intrinsic variability of organoids (Fig. 7). This genetic loss-of-function screening within the modern era of organoid technology allows us to search through sets of genes that are suspected to be involved in a specific human brain disorder.47 We gather definite proof of gene-specific disease relevance while generating an organoid disease model that can be further exploited by the community to portray the disease mechanism or test therapeutic targets. The CRISPR-LICHT technology permits us to establish a mathematical model for organoid growth

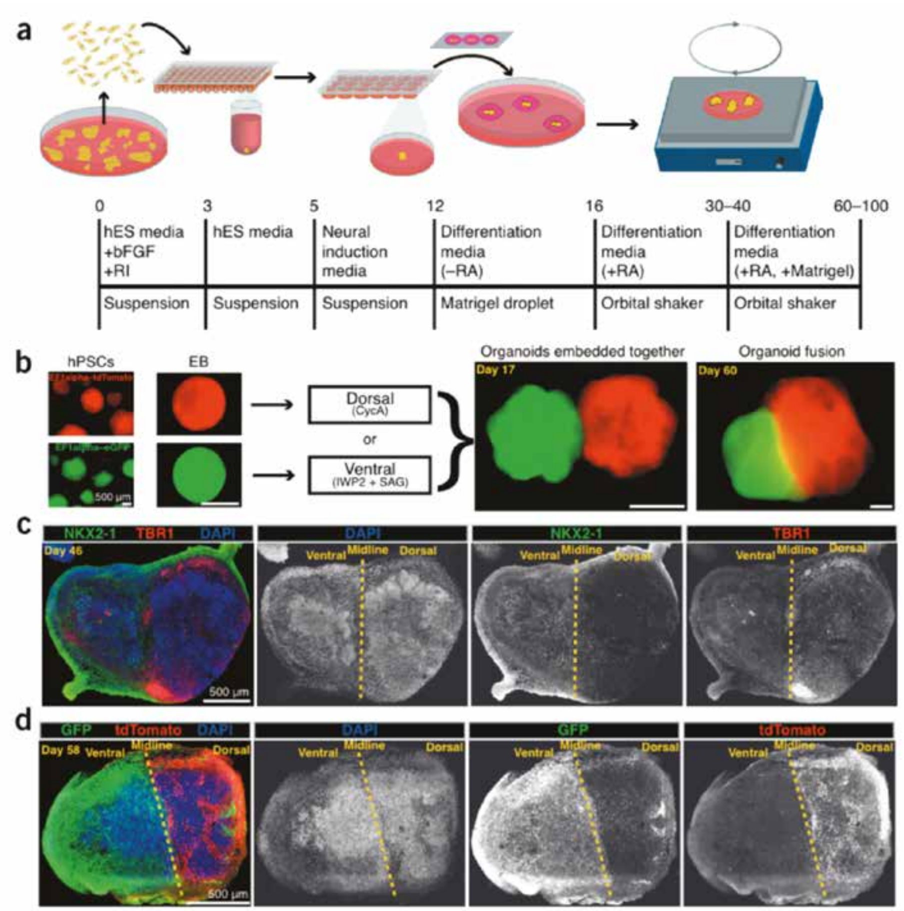

Figure 6. Fused cerebral organoids as a model for cell migration. (**a**) Schematic of the cerebral organoid fusion coculture method. (**b**) Representative widefield images at different stages of the organoid fusion procedure. Organoids are independently labeled with the indicated fluorescent reporters. (**c**) Tile-scan image of a of a ventral::dorsalCycA organoid fusion cryosection immunostained for a ventral (NKX2-1+) and a dorsal (TBR1+) marker. (**d**) Tile-scan image of a ventral/GFP+::dorsalCycA/tdTomato+ organoid fusion cryosection immunostained for GFP and tdTomato. (Figure from Bagley et al, 2017).

and to perform a statistical power analysis for the screen to define its scale and interpret its result. Using the methodology, we screened through 173 candidate microcephaly genes, identifying the unfolded protein response as a new process determining brain size in humans. Not only are we able to identify microcephaly genes with CRISPR-LICHT, but we also pinpoint

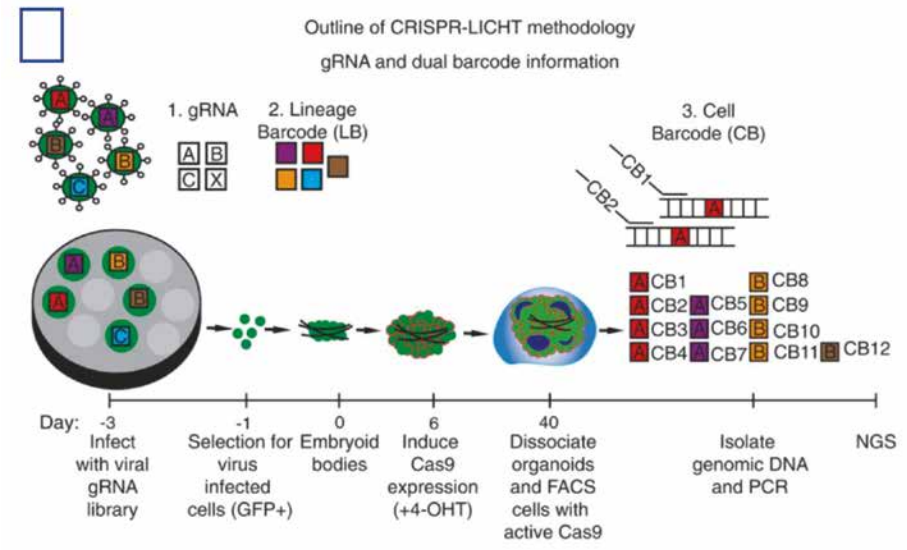

Figure 7. Screening in human cerebral organoids using CRISPR-LICHT identifies microcephaly-associated genes. Scheme describing the screening methodology. Stepwise introduction of gRNA and lineage barcode (LB) as well as cell barcode (CB) are indicated. FACS, fluorescence-activated cell sorting; NGS, next generation sequencing. (Figure from Esk et al, 2020).

a specific mechanism involved in controlling the size of the brain. The endoplasmic reticulum (ER) was identified as a main hub in controlling extracellular matrix protein secretion (Fig. 8). This mechanism affects the integrity of the tissue, and thus the brain size, and was identified as one cause of microcephaly.

The speed of discoveries is gathering momentum and we seem to be reaching one goal after the other with what appears to be effortless poise but which I can attest to being the merited success of many dedicated and charismatic scientists that lend their talent to stem cell research. It is true that the hypothesis-driven scientist fearlessly tests the *status quo* putting knowledge to practice and creating platforms for what will be the next ordinary or extraordinary step when claiming the unknown. As we approach the present times there is one more discovery we eagerly share. While using cerebral organoids to show that overproduction of mid-gestational human interneurons causes Tuberous Sclerosis Complex (TSC), a severe neuro-developmental disorder, we identify a previously uncharacterized population of caudal late interneuron progenitors, the CLIP-cells

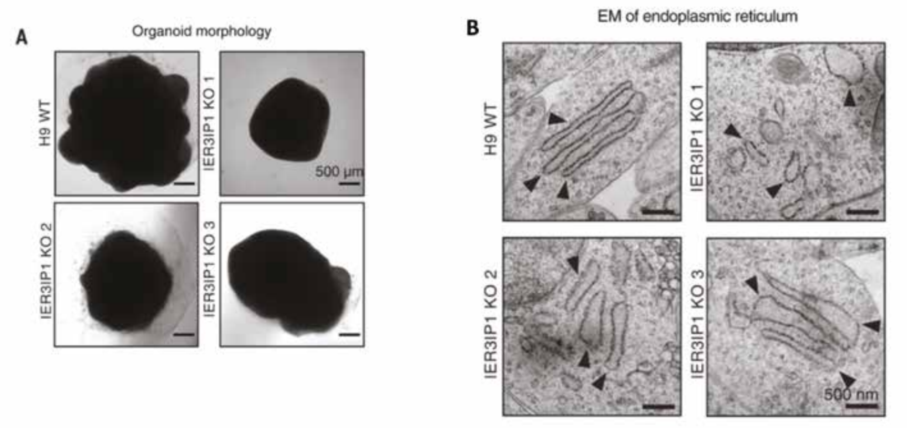

Figure 8. *IER3IP1* deletion results in a microcephalic phenotype and increased UPR and ER stress. (A) Bright-field images of WT and *IER3IP1* KO lines 1 to 3 at day 42. Scale bars, 500 µm. (B) EM images of ER structures in neural rosette areas of WT and *IER3IP1* KO organoids 1 to 3. Arrowheads indicate ER structures. (Figure adapted from Esk et al, 2020).

(Fig. 9).[53] We show that developmental processes specific to humans are responsible for malformations of cortical development (MCDs), which result in developmental delay and epilepsy in children. In TSC, CLIP cells over-proliferate, generating excessive interneurons, brain tumors, and cortical malformations (Fig. 10). Epidermal growth factor receptor inhibition reduces tumor burden, identifying potential treatment options for TSC and related disorders. The identification of CLIP cells reveals the extended interneuron generation in the human brain as a vulnerability for disease. In addition, this work demonstrates that analyzing MCDs can reveal fundamental insights into human-specific aspects of brain development. We predict that this work will have a long-lasting fundamental impact on the entire field of brain research and will sooner or later find its place in freshly updated textbooks on the disease.

Concluding remarks

The brain, like no other organ, births all thoughts and involuntary triggers. As a consequence it is a treasure chest storing cardinal information; hard to penetrate, retrieve and even understand. It is perhaps not random that many neuroscientists have originally studied philosophy while others moved from bench science to questioning the mind, its powers and limitations, its flexibility to expand and collapse on the path to enlightenment.

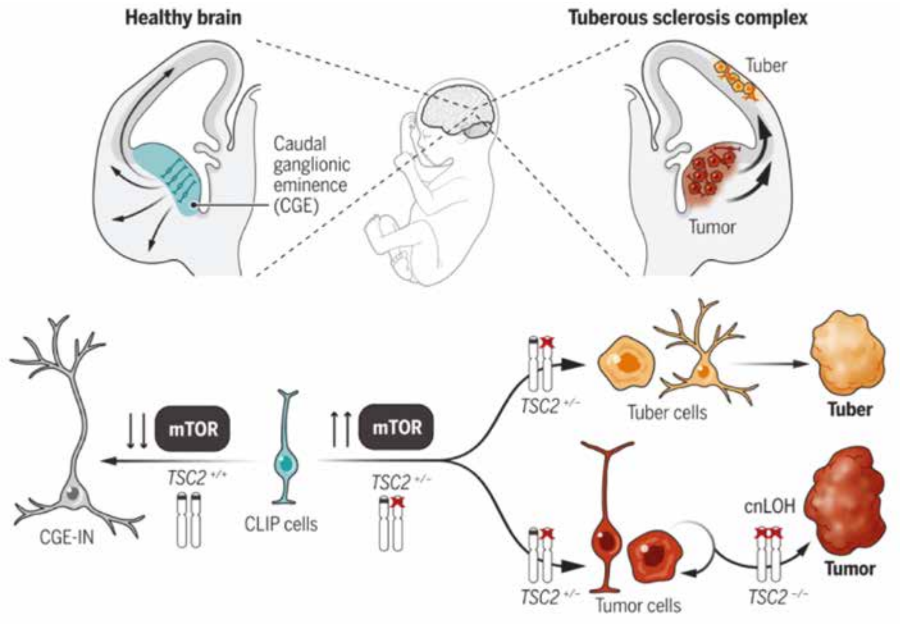

Figure 9. During mid-gestation, CLIP cells residing in the CGE generate interneurons that migrate into the cortex. (Top right) In TSC, CLIP cells generate brain tumors and cortical tubers. Heterozygous mutations in TSC2 result in excessive proliferation of CLIP cells, generating cell types of cortical tubers (orange) as well as brain tumors (red). During progression, the healthy allele is lost because of cnLOH, increasing tumor proliferation. (Image: Kellie Holoski/*Science*).

Such dynamic processes hosted within a tissue that is highly organized and almost fragile.

Human brain development is therefore, correctly described as a complex series of dynamic and adaptive processes that are genetically determined and environmentally influenced and which operate throughout development finally resulting in an organ that is responsible for the widest array of functions we know to exist. Attempting to decipher the genetic codes and molecular pathways that govern cellular function during brain development has been a long and arduous process. The discovery and characterization of stem cells revealed the tangles within the process while instrumentally influencing our understanding by offering the opportunity to make stem cell attributes our asset. Taking advantage of their self-organizing ability, we built a model that was the missing link between knowledge acquired from animal models and the mystery of the human brain.

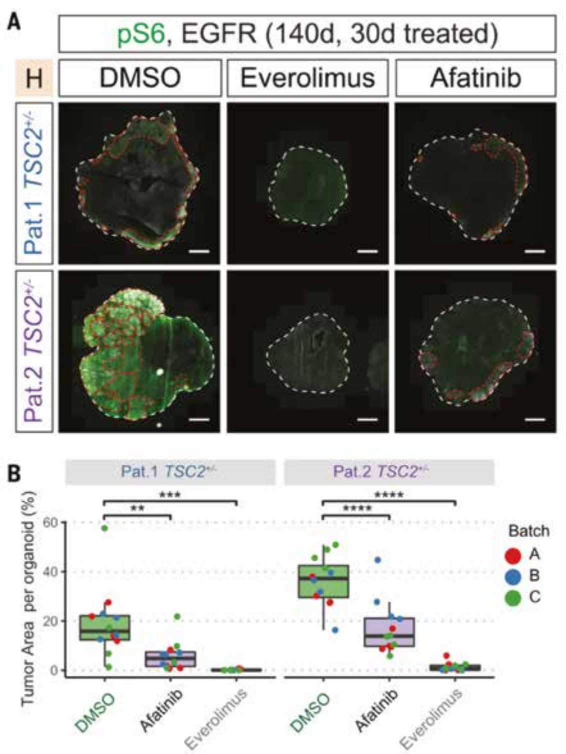

Figure 10. EGFR inhibition reduces tumor burden. (A) Immunostaining for pS6 and EGFR identified tumors (red lines) in the control group (DMSO) in both patients. Tumors were reduced through Afatinib and Everolimus treatment. (B) Quantification of tumor area per organoid. Tumors were identified as regions of overlapping pS6 and EGFR staining. Although tumors were detected in DMSO-control for both patients, Afatinib or Everolimus treatment both reduce tumor burden Scale bars, (A) 1 mm. (Figure from Eichmüller et al, 2022).

Born from the passion for evolving science to understand life, methodological developments have always been central to overcoming seemingly impossible obstacles turning improbable outcomes to acquired knowledge. Our lab has significantly contributed in shaping contemporary and future research on brain development in health and disease by careful, almost pedantic experimentalism, and with concentrated focus on multi-disciplinary, expansive and strategic research that pushes the boundaries daring to address the big open questions. At the heels of brain organoid technology, we intertwined quick and efficient gene editing to model diseases that were intractable in mice, including forms of microcephaly and brain cancer. The comparable complexity between human cerebral organoids and primary tissue promises to further our grasp of human-specific complex diseases such as autism and epilepsy but also as patient-specific *in vitro* cancer models, and for predictive drug testing. Single-cell technologies enhanced our ability to analyze molecular phenotypes at cellular resolution and detect emergent phenotypes that are difficult to tease out with traditional investigation methods.[54] Further adaptation of diverse single-cell -omics technologies to brain organoids expanded the set of discernable phenotypes, otherwise hidden, such as novel cell types and/or states that are altered during disease like in our microcephaly and tuberous sclerosis models. Without a doubt the field of brain organoid research is still young, but its applicability, diversity and potential encourage expedient progress. Given the rapid technical advances in the field, we believe that human organoid systems will provide unprecedented opportunities to improve human health.

To conclude, the brain is an organ that is more understood now than ever before but still to such a narrow degree. Despite the jaw dropping advancements across all scientific disciplines of neuroscience, we remain far away from fully understanding it although we appreciate the circuitous complexity of its nature. Attempting to predict what the path will look like in the future would only prove us wrong but what we know for certain is that, as described in this review, neuroscience research resembles a sequel that always has you wishing for more.

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Science During the Pandemic: A Journey From Basic Redox Biochemistry to Covid-19 National Public Health Advice

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Introduction

This manuscript describes a journey that connects basic biomedical research with science advise responsibilities in Uruguay in the context of the COVID-19 pandemic. This selected topic fits within the overall theme of the Pontifical Academy of Sciences Plenary Session 2022 on "Basic science for human development, peace, and planetary health" (8-9 Sept. 2022, Casina Pio IV, Vatican City) as it exemplifies how a solid background on basic and curiosity-driven research generates the potential for the fast provision and construction of scientific evidence-based solutions on emergent community or planetary problems.

Redox Metabolism in Humans: from Respiration and Bioenergetics to Redox Signaling and Oxidative Damage

Humans consume oxygen as an essential process for life. The lungs are the main organs that allow the transport of atmospheric oxygen in the gas phase to dissolved oxygen in the blood; once in the blood, oxygen is transported bound to hemoglobin in the red blood cells to the capillary of the different tissues where it is released and diffuses to the cells. Once inside cells, under normal conditions more than 99% of oxygen is consumed in the process of cellular respiration, where it is utilized on mitochondria (the key energy producing organelle) as the terminal acceptor of electrons arising from the oxidation of biomolecules such as carbohydrates, fatty acids and amino acids. The oxidation process permits to obtain energy for the cells and is coupled to the four-electron reduction of oxygen to water (*i.e.* at the terminal site of the mitochondrial electron transport chain) (Eq. 1).

$$O_2 + 4e^- + 4H^+ \rightarrow 2H_2O \qquad [1]$$

Still, biological redox[1] processes that use molecular oxygen also involve reduction by one- or two-electrons to yield "partially" reduced oxygen intermediates such as superoxide radical[2] (O2.-, Eq. 2) and hydrogen peroxide (H_2O2, Eq. 3).

$$O_2 + e^- \rightarrow O_2^{\cdot -} \quad [2]$$

$$O_2 + 2e^- + 2H^+ \rightarrow H_2O_2 \quad [3]$$

Both, $O2^{\cdot -}$ and H_2O_2 are reactive and short-lived intermediates (collectively grouped with other related biomolecules as "reactive oxygen species", ROS) [1] and can promote oxidative modifications in biomolecules including proteins, lipids and DNA. Depending on the steady-state levels of ROS, these species can play cell regulatory actions that promote adaptation and proliferation (*i.e.* cell signaling, low to moderate ROS levels) or promote cellular dysfunction and death (*i.e.* oxidative damage, high ROS levels). The latter condition also named as "oxidative stress" is associated to a variety of acute and chronic disease conditions and the process of aging, and was fully established as a concept in biomedicine in the mid 80s (reviewed in [2]).

Nitric Oxide and Superoxide Radical interactions: The Birth of the Biological Chemistry of Peroxynitrite

In the mid to late 80s, nitric oxide (NO) was discovered as a free radical that could play physiological functions. In fact, .NO initially characterized as a vasodilator, was later demonstrated to also exert actions as neurotransmitter and immunomodulator, among several other physiological functions (reviewed in (3)). The discoveries related to the ".NO pathway" in the regulation of vascular tone in humans led to the Nobel Prize in Physiology or Medicine in 1998. While the physiologists were at that time becoming increasingly interested in the "good" functions of .NO, a group of biochemists and biomedical scientists became interested in revealing some potentially "bad" or toxic effects of .NO when generated in excess and in conjunction with increased levels of ROS. In fact, increasing evidence

[1] The term "redox" is utilized to refer to complimentary chemical processes in which a molecule gains (reduction) and another loses (oxidation) electrons. Redox reactions in biochemical contexts involve electron transfer between molecules.

[2] A radical denotes a molecule that contains an unpaired electron in its outer molecular orbital.

was indicating that high levels of .NO could promote neurotoxicity and participate in processes such as mammalian cell death and pathogen killing (reviewed in [4]). Observing the "radical nature" of .NO and knowing that different radicals tend to react at extremely fast rates with each other, together with other emerging biological evidence, it was postulated that conditions that favor excess and concomitant formation of .NO and $O2^{\cdot -}$ in tissues promote the formation of peroxynitrite anion ($ONOO^-$), a strong oxidant and potentially cytotoxic intermediate [5–7].

$$^{\cdot}NO + O_2^{\cdot -} \rightarrow ONOO^- \qquad [4]$$

Early experiments found that peroxynitrite anion and its conjugated acid, peroxynitrous acid (ONOOH), could efficiently promote oxidations in biomolecules. These early discoveries expanded the view on how .NO and ROS could synergistically participate in oxidative and inflammatory

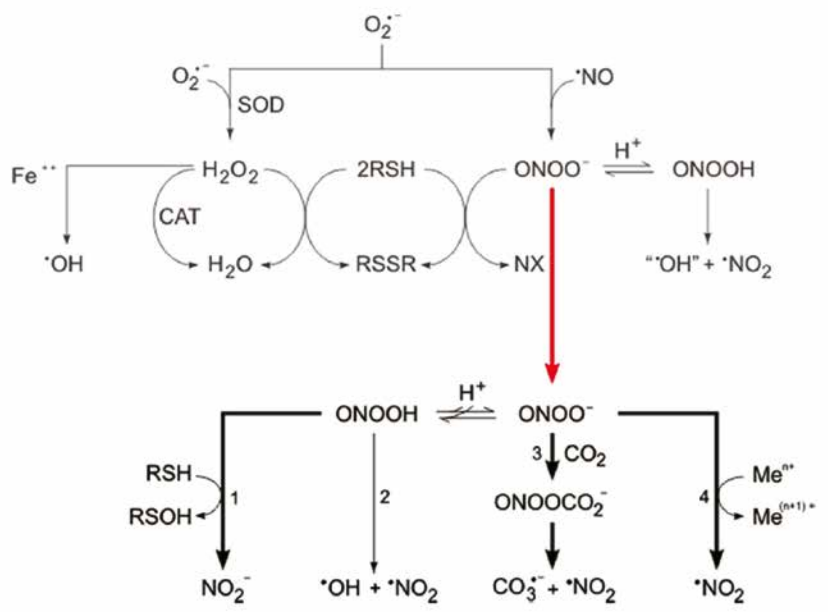

Figure 1. Scheme illustrating the biochemical mechanisms of peroxynitrite formation and subsequent oxidation reactions. The upper part of the scheme represents the diagram reported in the original paper in 1991 (6) and the lower part of the scheme represents an update (11). The red arrow connecting the upper and lower parts of the scheme indicates the evolution of the understanding of the biological chemistry of peroxynitrite over a 10-year period. Reproduced from Ref. (11).

pathophysiology [8]. This hypothesis was explored by a large number of groups worldwide and, at present, peroxynitrite is considered a pathogenic mediator in neurodegenerative processes, inflammatory processes and cardiovascular diseases, among several other conditions (reviewed in [9]). Thus, basic biochemical ideas on how peroxynitrite could be formed and participate in oxidative damage to biomolecules *in vivo* was progressively adopted as a new concept by the biomedical community and gradually translated to medicine. One of the early papers on the reaction of peroxynitrite with protein and non-protein thiols, contained what turned to be a valuable scheme to illustrate the general hypothesis [6]; after two decades, this work was recognized as a citation classic [10]. The original proposal and the updated view on the biological chemistry of peroxynitrite was presented in a more recent review (Fig. 1)[11].

From Redox Biology to COVID-19 Scientific Advice

The work on redox biochemistry and medicine through three decades of research [12] provided me with a unique opportunity to work in interdisciplinary projects, with joined contributions with chemists, physical-chemists, molecular and cell biologists, physiologists, pharmacologists and clinicians. But a major (and surprising) interdisciplinary challenge was presented to me on 2020. On March 13, 2020 the government of Uruguay declared a state of health emergency due to the diagnosis of the first cases of COVID-19 (Fig. 2)[13]. Soon after, on April 3, 2020, I was invited together with other scientists to a virtual meeting by a government of Uruguay top official and I was unexpectedly requested to create and lead a scientific advisory group to the Presidency to assist in the the management of the COVID-19 pandemic. The request was based on my background and track record on interdisciplinary research[3] and extensive knowledge of the local research community. Thus, after requesting some time to decide and eventually generate a general working plan, the Scientific Advisory Group (*i.e.* GACH[4]) was formally created in an *ad honorem* fashion on April 16, 2020 and announced by the President of the República Oriental del Uruguay, Dr. Luis Lacalle Pou, to the population on a national press conference. The creation of GACH was occurring in parallel to several other government measures and academic sector actions as shown in Fig. 2.

[3] I hold MD and PhD degrees from Universidad de la República, 1989 and 1991, respectively.

[4] GACH, Grupo Asesor Científico Honorario.

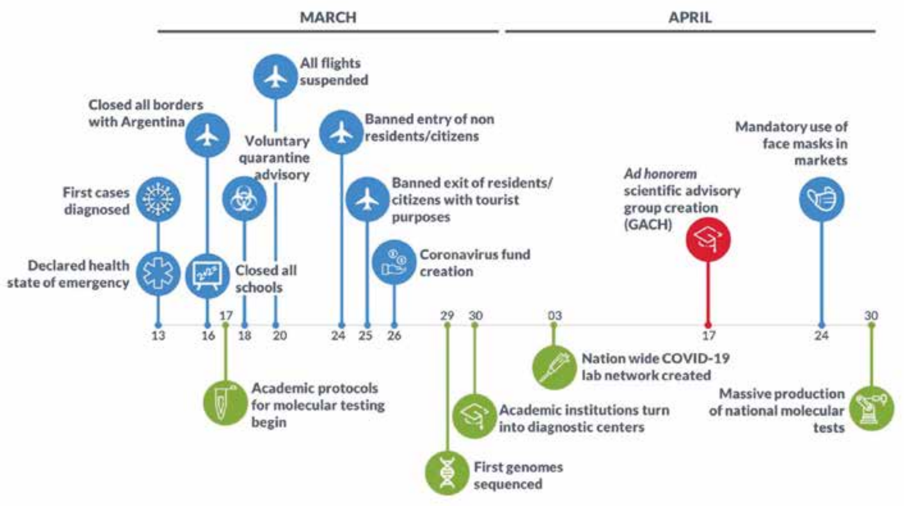

Figure 2. Timeline of key events during the first two months of the COVID-19 pandemic in Uruguay. Government decisions are shown in blue, Academic/Scientific contributions are shown in green and the creation of the *ad honorem* Scientific Advisory Group (GACH) is shown in red. The first reported cases and the declaration of the state of health emergency were in March 13, 2013. Reproduced from (13).

The Group was designed with two main areas, the *Health Area* lead by Prof. Henry Cohen (MD, clinician) and the *Data Science and Modelling Area* led by Prof. Fernando Paganini (PhD in mathematics and engineer); I served as the General Coordinator of the group. The three coordinators worked jointly to select an interdisciplinary group of 60 top national scientists and experts. The GACH was divided into subgroups depending on topics and expertise of the different participating scientists and regularly generated weekly reports to the government on COVID-19 issues; the GACH was also in permanent exchange with the rest of the scientific community and the Ministry of Health and other government agencies. The GACH members also provided interviews to the press and the coordinators participated in five national press conferences that delivered scientific evidence to the society on the biological, epidemiological and pathological dimensions of the problem and the key elements to be considered for disease mitigation. Some of the key reports are listed in Table 1. A major effort was made so that all GACH members maintained a cohesive and coherent vision of the problem, so plenty of analysis, discussions and exchanges of information and possible recommendations were internally processed before making public statements. All the reports were presented weekly to the President of the Republic and his direct team, and within 24-48 hrs were posted in the public domain (see Table 1); this methodology provided transparency and credibility to the advisory process. In late 2020 and early 2021, key expert advice was provided in relation to the fundamental issue of vaccine selection and design of the vaccination program in collaboration with the Ministry of Health. A complete report was presented to the Presidency on December 2020 and in a session of the Health Commission of the National Parliament on January 2021. The vaccination program started on March 1, 2021, and was delivered at a fast rate and counted with a large adherence of the population.

The eight fundamentals guiding the activities of the GACH towards the mitigation of the COVID-19 event were:

1. Four conceptual axis to reach a new normality: **progressiveness**, **regulation**, **monitoring** and **evidence**.
2. Diversity of disciplines in the Areas of Health and Data Science and Modelling.
3. Selection of excellent scientists, willing to work as a team and at a fast pace.
4. Generation of regular reports providing analysis and recommendations, taking into consideration and documenting all the national and international evidence.
5. Independent group, no political interference.
6. Weekly meetings with the government, and daily exchanges as needed, transferring the information generated by GACH.
7. Clear separation of roles: the GACH to provide scientific advice, the government to take the final decisions.
8. Transparent and frequent communication with society.

All the ca. 90 public reports generated by GACH at: https://www.presidencia.gub.uy/gach

Table 1. Key Public Reports by GACH

- Non-pharmacological intervention (NPI) strategies
- School re-opening
- Impact of COVID-19 in children
- Encouragement of the use of public spaces
- Impact of the health emergency on non-COVID health issues
- COVID-19 and nutrition
- COVID-19 and dental health practice
- Impact of COVID-19 on mental health
- COVID-19 and social behavioral changes
- Contingency plans for Intensive Care Medicine
- New treatments for COVID-19 patients
- Molecular tools for diagnosis
- Emphasis and reinforcement of the TETRIS strategy
- Data analysis, modeling and projections
- Epidemiological and integrated analysis: public health recommendations
- Mitigation strategies during the end of the year celebrations and summer tourism
- Vaccines and vaccination program (in collaboration with the Ministry of Health)

All reports are uploaded at https://www.presidencia.gub.uy/gach

The key role of scientific evidence-based decisions during the pandemic

In many periods of the evolution of the pandemic, especially in 2020, Uruguay had an exceedingly good control (commented in [14]), in spite of being geographically located in a region that did not have the pandemic under control. The analysis of the different phases of the pandemic in Uruguay and the evaluation of its overall management is under scrutiny now by a group of former members of GACH and will be object of a technical communication elsewhere in the future. Our preliminary analysis indicates that within the Latin American region, Uruguay was, on one hand, the country with the least impact on mortality and excess deaths (Fig. 3) (normalized by population) while, on the other hand, its "stringency index"[5] over time was for the most part in moderate values. Adherence of the population to non-pharmacological interventions during 2020 and to the vaccination program in 2021 was remarkable and there is a general national and international agreement that the participation of scientific

[5] https://ourworldindata.org/metrics-explained-covid19-stringency-index

Figure 3. Excess mortality of selected Latin American countries during the period March 2020-August 2022. Graphic generously provided by Prof. Fernando Paganini (coordinator of the Data Science and Modelling Area of GACH) with information from Our World in Data, https://ourworldindata.org/

advice by an independent group was very relevant on these individual and community behaviors [15].

The GACH experience was highlighted in the international medical literature as a valid approach in the COVID-19 event control, when comparing the responses to the pandemic of 28 countries [15]. In addition, the scientific system in Uruguay largely increased social and public visibility[6] and gained influence with the political sector that shows more willingness to request scientific advice for other public policy decisions and to discuss

[6] Significantly more press space (newspapers, radio, television) is dedicated to science topics, a much larger number of University students decided to begin scientific careers and the general public became aware of the existence of local science and scientists in Uruguay.

issues related to science budget.[7] Finally, the GACH did a great effort to minimize partisan divisions during the pandemic, as they constitute an additional risk factor within the pandemic [16, 17]; the GACH made it clear to both the political sector and society, each time it had the capacity to communicate this, especially during the most difficult times of the evolution of the COVID-19 event in Uruguay (February to May 2021).

The group resumed activities in July 2021, when the percentage of fully vaccinated population was over 50% and decoupling between mobility and infections (due to the accumulation of vaccine- and natural-mediated immunity) was confirmed [18]. The group received state honors from the President of the Republic in the main national auditorium broadcasted nationwide, and according to a national survey performed by an independent public opinion consultant group, 90% of the population was supportive of the scientific advisory work performed.[8]

Back to the basics: redox biochemistry to disrupt SARS-CoV-2 and new horizons in redox biology

During the work of GACH, our research group began studies on the structural biology of the SARS-CoV-2 spike glycoprotein, a key element on the virus surface needed to bind to the host cell and initiate the infection process. In particular, we explored how the spike glycoprotein structure could be disrupted by redox processes mediated by compounds that can "break" chemical bonds in the protein, *i.e. via* reduction of protein disulfides. The reduction process leads to instability in the spike receptor binding domain and resulted in decreased capacity to bind to the host-cell plasma membrane receptor (*i.e.* ACE-2) (Figure 4). The use of the reducing compounds, some of which are already in clinical trials for other lung disease conditions, and the subsequent conformational alteration in spike, decreased viral entry to mammalian host cells [19]. Nicely, this work reflected a new fertile international collaboration that started "at a distance" during the pandemic with USA-based groups; the contribution represents a *proof-of-concept* to open opportunities for future redox-based therapeutics to treat pulmonary lung infections, including those mediated by coronaviruses.

[7] In fact, as current President of the Academia Nacional de Ciencias del Uruguay, I participated in several meetings with the President, Ministers and Parliament members to discuss their commitment to increase the public budget for science in 2023 and the following years.

[8] https://www.cifra.com.uy/index.php/2021/07/08/evaluacion-del-grupo-asesor-cientifico-honorario/

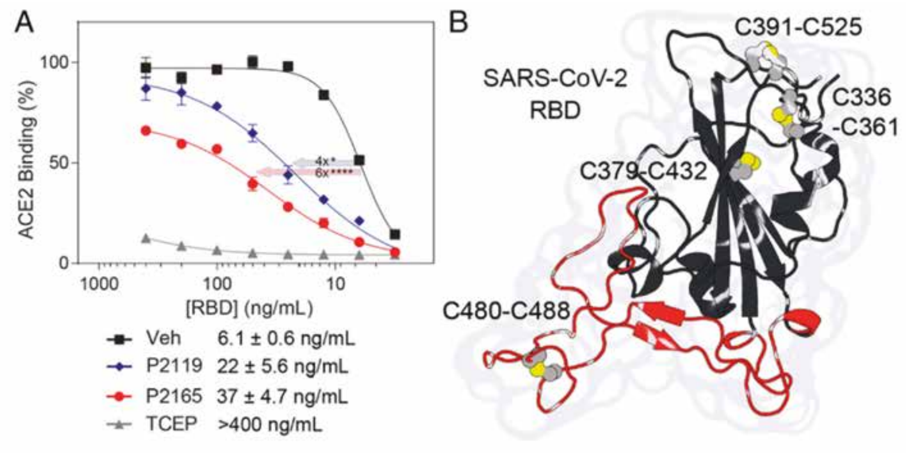

Figure 4. Reduction of spike glycoprotein disulfides and its influence in binding to the ACE-2 receptor. Panel A shows that reducing compounds (P2119, P2165, TCEP) decrease spike binding to immobilized ACE-2 receptor. Panel B shows the four disulfide bonds present at the receptor binding domain (RBD) of spike, some of which are amenable to reduction, which in turn, leads to increased structural instability. Reproduced from (19).

After finishing the highly demanding scientific advisory activity in the second semester of 2021, I have fully resumed research and academic activities. In this regard, in 2022 I communicated new ideas that may help to further develop the redox field in human health, disease and therapeutics [9, 20].

Final Comments

The journey described herein illustrates that the paths of basic sciences and their applications can be intertwined and serve major societal challenges. There is a need to foster the connections between *state-of-the-art* science and leading scientists with their engagement in pressing local, regional and planetary problems. This approach nurtures the *ethos of science* and helps the society and politicians to envision the potential and strength of a well-cultivated scientific system for the accomplishment of sustainable human development.

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Horizontal Gene Transfer in the Context of a Rich Biodiversity

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Nobel Laureate in Physiology or Medicine

Astrophysical research indicates that the Milky Way with our Solar System must have an age of about 4,000 million years. Life on our planet Earth must have started with primitive microorganisms about 3,500 million years ago, but it remains unknown how they originated. In the course of time stepwise evolution then gave rise to a multitude of different microorganisms and then also of various multicellular living organisms including plants and animals. This stepwise evolutionary progress resulted in today's high biodiversity on our planet Earth by a remarkable process of permanent creation. I will report here on results and implications that have recently become revealed by intensive research. Bacteria have served as excellent testing ground to uncover mechanisms of evolution because of their fast replication times, as I will now illustrate with some examples.

In general, biological activities are guided by genetic information carried in the genome. In E. coli bacteria the genome is generally a circular double-stranded DNA molecule. Its genetic information resides in the specific sequences of the 4 nucleotides adenine, thymine, guanine and cytosine. In comparison with our written language, the size of the bacterial genome corresponds to the size of a book. Some bacteria also carry so-called plasmids, small DNA molecules of the size of one page. This is, in general, also the size of bacterial viruses, which we call phages.

Single steps of microbial evolution require usually appropriate genetic variations in the genome. A number of specific mutational mechanisms can fulfil this request. So far, the studied mechanisms of genetic variation can be grouped into 3 strategies:

1. Point mutants with an alteration of one or a few adjacent nucleotides can result upon DNA replication at a site of a short-living tautomeric nucleotide. Tautomeric adenine pairs upon DNA replication with cytosine instead of thymine, and tautomeric guanine pairs with thymine instead of cytosine. A point mutation thereby results if this kind of replication error escapes a repair process shortly after its production.

2. Genomes are known to carry at various sites so-called mobile genetic elements. Occasionally such an element can excise from its location and then integrate at another site in the genome. This process is called transposition and it can sometimes produce a new functional fusion acting as genetic variant.
3. The third strategy to equip a bacterial cell with a novel genetic capacity is the horizontal (also called lateral) gene transfer. This process can involve conjugation, transduction or transformation. The thereby taken-up foreign DNA segments can be properly read by the recipient cell thanks to the universal genetic code.

Some intestinal bacteria carry a fertility plasmid F. Its function is to build a pair with another kind of bacterium in a mixed population and then transfer a segment of its donor DNA into its partner cell. Parts of this transferred DNA can then sometimes become integrated into the genome of the recipient cell. This process it called conjugation.

Upon transduction a bacterial virus such us phage P 1 having been replicated in a donor bacterium and carrying some genes of the donor bacterium can infect a recipient cell that may then integrate a segment of the donor DNA into its genome. If the phage renders the infected cell lysogenic the cell survives and the transduced genes from the donor cell can become expressed. The acquired DNA can sometimes represent a welcome new function for the recipient bacterium.

Some bacteria such as Streptococcus are able to take up DNA molecules liberated by other genetically related bacterial strains. This kind of horizontal gene transfer is called transformation.

Many bacterial strains are genetically equipped with a restriction/modification system. They can verify the origin of taken-up DNA molecules. Their own DNA is marked by methylation at each strain-specific sequence of a few nucleotides. This is done by the modification enzyme. The restriction enzyme can identify on the taken-up DNA the same nucleotide sequences that are not methylated. These non-methylated nucleotides then give rise to cut the taken-up DNA into fragments which are then acid solubilized by the cellular exonuclease, unless they have been protected from destruction by a fast integration into the genome of the recipient cell.

The intestinal E. coli bacteria serving for these experiments are propagated in the laboratory in appropriate growth medium at 37 degrees Celsius. Their generation time is then about 30 minutes. During their intensive growth they can occasionally produce a point mutant at any base-pair. Also, occasionally, one of the mobile genetic elements can transpose to another site in the genome. If the bacterial cells propagate in a mixture with other bacterial strains, as it is usually the case upon growth in a microbiome, it occasionally can happen that events of horizontal gene transfer occur by conjugation or by transduction. The 3 strategies of forming various genetic variants are relatively rare. Some of the produced mutants may enable their cells to also grow in an alternative growth medium in which the original bacteria are unable to propagate.

The processes of genetic adaptation described here occur in the involved bacteria by what we call self-organization. By self-organization we mean that the genome has the ability to reorganize by itself, but it does so at a rather low frequency in order to maintain most cells genetically stable, thereby not taking risks that would be too big for evolutionary progress. Another relevant conclusion is the fact that creation is a permanent process in view of the steady evolution of the living organisms in their also evolving living conditions. I am convinced that these conclusions are generally valid for living organisms.

Horizontal gene-transfer is not limited to micro-organisms. It can also occur by eukaryotic organisms as shown by systematic nucleotide sequence analysis.

Our human civilization still profits from the presence of a relatively rich biodiversity enabling occasional horizontal gene transfer to other kinds of organisms. But today's worldwide life-conditions implicate a steady loss of genetic information. A major reason for this bad situation resides in the increasing transformation of wildtype habitats on our planet by an intensive use of agriculture, human habitations and other purposes. We must be aware that our planet does not grow. Therefore, the human population should reach and then maintain a relatively stable size compatible with planetary limits. We have to be better aware that our human activities should take care of the remarkable richness of the planetary biodiversity. In view of the role played by a steadily occurring horizontal gene transfer in the biological evolution of any kind of living organisms, it is our duty to preserve the worldwide richness of all kinds of specific genes. We have to be aware that a longterm further evolution of life is likely to depend intensively on the available genetic capacities.

Advanced secure methods of genetic engineering can enable us to undertake horizontal gene transfer for relevant use. Examples are the production of Golden Rice and of bacteria able to produce spider silk.

In conclusion, the appreciated rich diversity of living organisms on our planet not only goes back to a common origin, but it can also profit from a common future by occasional horizontal gene transfer.

SESSION V – LIFE SCIENCES AND MEDICAL SCIENCE FOR HUMAN DEVELOPMENT, PEACE, AND PLANETARY HEALTH

Enlisting Stem Cells to Regenerate and Rejuvenate Skeletal Muscle by Inhibiting a Gerozyme

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Abstract

Stem cell therapies have the potential to revolutionize the treatment of human diseases by repairing or replacing damaged or aged organs and tissues. Stem cells, the crux of regenerative medicine, are transforming biomedical science. These cells hold tremendous promise for treating a range of diseases (Blau and Daley, 2019). Worldwide, there are many ongoing stem cell-based clinical trials. Stem cell therapies are being used to treat movement disorders like Parkinson's Disease or to restore sight to those with age-related macular degeneration or corneal abrasions. These examples underscore the remarkable progress that has been made in recent years using stem cell therapies to address some of the most devastating diseases.

Here we discuss a form of regenerative medicine that bypasses the need to isolate, cultivate, propagate, and transplant stem cells into the body. This approach entails stimulating the stem cells present in certain adult tissues and takes advantage of their inherent potential to repair tissue damage in situ. It overcomes complications of cell transplantation arising from immune rejection and is likely to be less costly and labor-intensive. The type of oral small molecule treatment we envision may be a viable strategy for the globalization of regenerative medicine to improve human welfare. In principle, such therapeutics could be developed at relatively low cost, easily disseminated, and readily administered. Clearly, this approach cannot address all of the needs of regenerative medicine; however, for a subset of disorders it poses an exciting alternative to stem cell transplantation. We present an example, our discovery of a gerozyme, a pivotal regulator of muscle aging, that can be inhibited using a small molecule in order to enhance the function of muscle stem cells and myofibers. This therapeutic strategy has the potential to overcome the loss of mobility and strength that plagues the lives of many individuals who suffer from muscle wasting.

Introduction

On the façade of the Casina Pio IV of the Vatican is a depiction of Aurora, the Goddess of dawn, and Tithonus, the prince of Troy (Figure 1). Aurora fell deeply in love with the mortal Tithonus and wanted to keep him as her lover forever. She pleaded with Jupiter to bestow immortality on Tithonus, and Jupiter granted her wish. However, Aurora had made a grave mistake; she failed to ask for eternal youth. Tithonus continued to age and was destined to live forever as a decrepit old man.

There has long been a quest for a treatment that increases our longevity. However, the quest for treatments that increase quality of life is equally important. Although we are living longer than previous generations, that increase in lifespan is not accompanied by an increase in healthspan. Instead, like Tithonus, for many people these extra years are plagued by age-related chronic illness (Bellantuono, 2018). Enhancing healthspan, or quality of life, is the focus of regenerative medicine. Clinical trials are underway in numerous countries. These studies primarily employ three major stem cell types: embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and adult stem cells (ASCs).

While ESCs have therapeutic potential, they are limited by their availability and by ethical concerns regarding their source (Lo and Parham,

Figure 1. The decrepit aged Tithonus, in his cradle, rocked by youthful Aurora. Photo of façade of Casina Pio IV in Vatican City by Lorenzo Rumori.

2009). iPSCs, discovered by Nobel Laureate and PAS member Shinya Yamanaka, are pluripotent like ESCs, and obviate destruction of an embryo required for ESC use (Takahashi and Yamanaka, 2006). iPSCs can be generated from any somatic cell. By transiently overexpressing four transcription factors, somatic cells are rendered pluripotent, able to propagate and increase in numbers almost indefinitely, and then differentiated into a range of specialized cell types such as cardiomyocytes and neurons. iPSCs enable in vitro modeling of heritable diseases using patient-derived cells (Yoshida and Yamanaka, 2017), as well as personalized drug screening (Sayed et al., 2016). IPSCs have been differentiated into dopaminergic neurons to correct the movement disorder associated with Parkinson's Disease following transplantation (Song et al., 2020). In addition, transplanted retinal pigment epithelial cells show promise for restoring sight to individuals with age-related macular degeneration (Mandai et al., 2017).

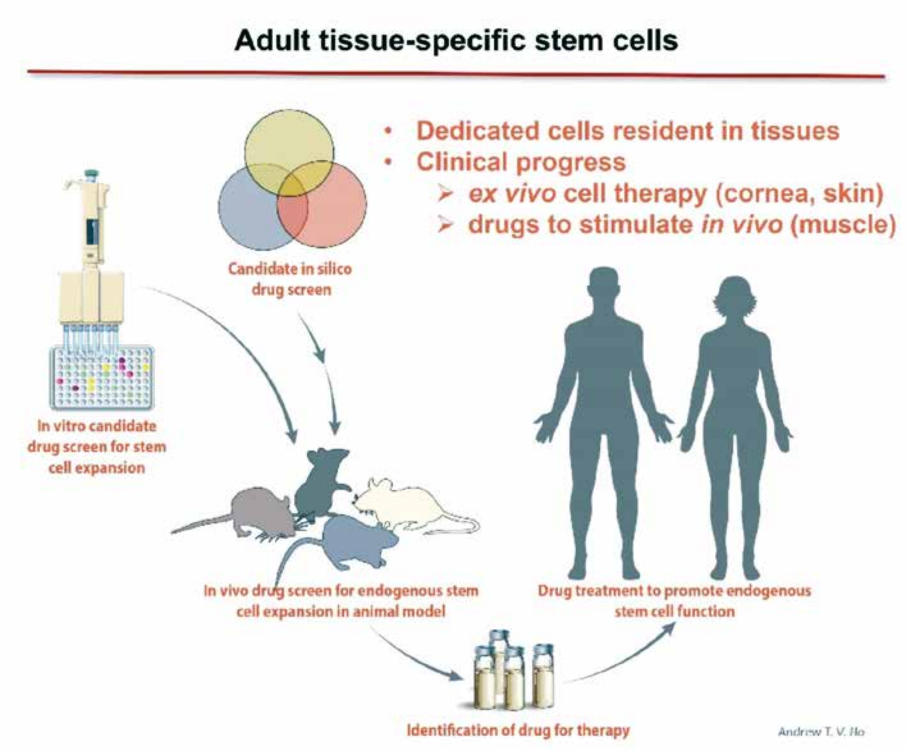

Figure 2. Adult Stem Cells (ASCs) hold great clinical promise. Upon injury, these tissue-specific stem cells, that are dedicated to repair the tissue in which they reside, can be stimulated to divide and regenerate the tissue.

An alternate source of stem cells are specialized cells, termed adult stem cells (ASCs), that reside in certain tissues of our body, dedicated to the repair of that tissue, and poised to spring into action upon injury (Figure 2). The first to be used clinically were the hematopoietic stem cells (HSCs) resident in the bone marrow, which rescued victims of radiation sickness after World War II and have been used extensively to treat malignant disease (Till and McCulloch, 2011). Notably, the ability to isolate and propagate the self-renewing HSC in vitro still remains an unmet challenge. Other tissue-specific stem cells have met this challenge, for instance skin stem cells, or holoclones, that were isolated from a boy with a congenital mutation that leads to the highly debilitating genetic blistering disease Junctional Epidermolysis Bullosa. The bedridden boy's stem cells were genetically engineered to express the missing protein and then transplanted to cover most of his body (Mavilio et al., 2006). Because they harbored the stem cell property of self-renewal, this treatment endured (Kueckelhaus et al., 2021), unlike the skin grafts used previously to treat burn victims (Gallico et al., 1984). Following treatment, the boy was able to attend school and even play soccer. Such advances highlight the exciting prospects for stem cell applications in regenerative medicine for improving quality of life.

Discovery of Muscle Stem Cells

In 1961, Mauro's striking electron microscopy images revealed satellite cells, mononucleated cells juxtaposed to multinucleated myofibers, which he postulated were self-renewing stem cells, present in the body for the purpose of growth and repair (Mauro, 1961). Satellite cells were eventually proven to be bona-fide muscle stem cells (Sacco et al., 2008), and soon after shown to be required for muscle growth and regeneration after injury (Lepper et al., 2011; McCarthy et al., 2011; Murphy et al., 2011; Sambasivan et al., 2011). Satellite cells, now commonly known as muscle stem cells (MuSCs), are a unique model for studying regeneration. MuSCs exist in a quiescent state in their niche until they are activated to self-renew or commit to differentiate, fuse, and develop into myofibers. Each of these steps can be tracked by the expression of a cascade of distinct transcription factors and exploited to study cell fate transitions in depth during development and how these cell fate transitions are recapitulated in regeneration (Porpiglia et al., 2017). MuSCs informed our understanding of stem cell dormancy, or quiescence (Brack and Rando, 2007). Myogenesis set the stage for our understanding of stem cell heterogeneity and the features and role of the stem cell niche in the active maintenance of the stem cell state.

Moreover, much has been learned about the molecules that mediate cell fusion essential to forming the multinucleate myofiber syncytium, the transcriptional and epigenetic activation of muscle-specific genes, metabolic reprogramming, and autophagy and mitophagy. These processes, that are essential to muscle growth, differentiation, and maturation, provide a blueprint for other adult stem cell types and how to gain mechanistic insights into their role in regenerating specific tissues (Fuchs and Blau, 2020).

Aging and Muscle Loss

Muscles contribute far more to our lives than strength. They are key to our sense of self and impact our ability to learn and remember, and to build and maintain relationships. Skeletal muscle is one of few organs that can be readily accessed and manipulated. Muscles can be exercised and trained, and that exercise and training directly correlates with increases in muscle size, endurance, and overall performance. Good musculature is also the basis of beauty and an indicator of health. The mind and body are inseparable, consequently few things are as devastating as a loss of mobility.

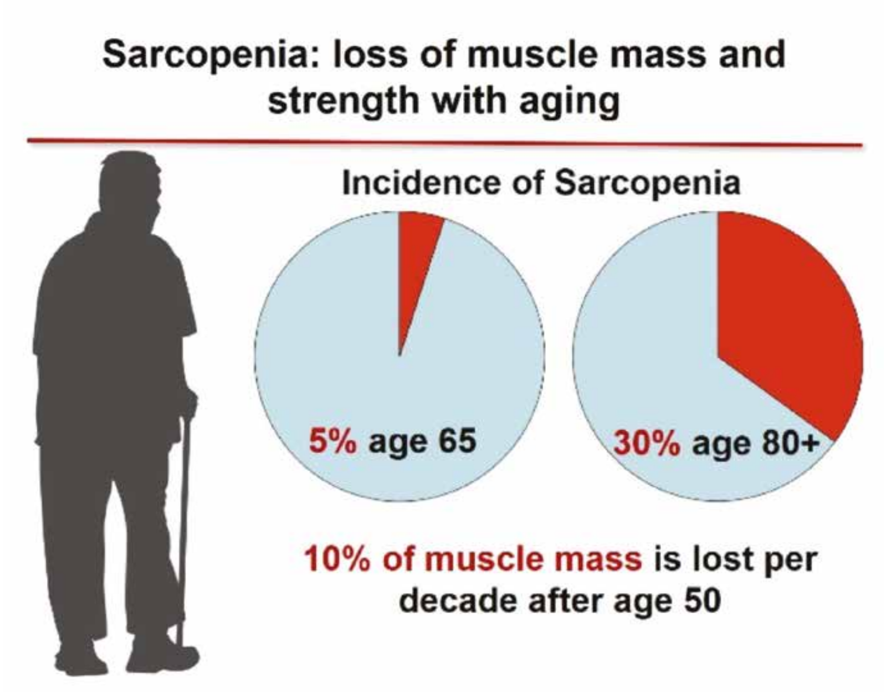

Figure 3. Incidence of sarcopenia increases with age.

Humans lose approximately 10% of their muscle mass every decade after age 50. The extreme form of this muscle loss, termed sarcopenia, impacts 5% of people aged 60-70, and 30% of people 80 years of age or older (Figure 3) (Fielding et al., 2011), and is a common complication of cancers (Colloca et al., 2019). This loss of muscle has profound consequences for longevity and quality of life. Sarcopenic adults are frail, unable to perform basic tasks such as rising from a chair, or walking. They are more likely to fall and become injured, leading to dependency and in many cases institutionalization, as well as increased risk of death (Tsekoura et al., 2017). Sarcopenia exerts a huge toll, not only on the patients themselves, but also on their families and communities. Despite its prevalence and impact, the management of sarcopenia is primarily focused on physical therapy for muscle strengthening and gait training. There are currently no pharmacologic agents available for the treatment of muscle atrophy due to disuse after a fall or disease, due to aging, or heritable muscle wasting as in Spinal Muscular Atrophy.

Gerozyme: A Pivotal Regulator of Muscle Wasting in Aging

The Blau laboratory recently formulated the hypothesis that there exists a class of enzymes whose action triggers a gene expression pathway common to a number of tissues in aging, which we termed "gerozymes" (Figure 4). The activity of a gerozyme increases progressively over the lifespan of an organism due to aberrant expression of "gerogenes" that promote aging, similar to the aberrant expression of oncogenes that promote cancer. The Blau group has recently identified the enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the prostaglandin degrading enzyme,

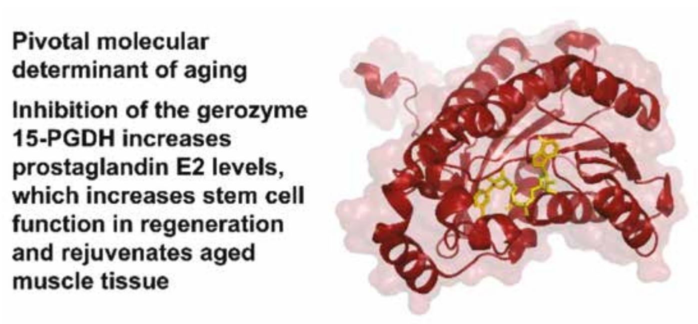

Figure 4. Discovery of muscle tissue Gerozyme 15-PGDH.

as a gerozyme in muscle. Below I describe how we identified 15-PGDH and describe how it triggers aging-associated changes in stem cell and tissue function. In addition, I describe a method to therapeutically target its activity using a small molecule inhibitor, which leads to increased Prostaglandin E2 (PGE2), which in turn induces muscle regeneration and rejuvenation(Ho et al., 2017; Palla et al., 2021). To our knowledge, 15-PGDH is the first gerozyme to be described.

Combatting Muscle Injury and Muscle Aging

We have discovered that inhibition of the gerozyme, 15-PGDH, remodels aged muscle morphology and augments strength by two complementary mechanisms (Figure 5). Inhibition of the 15-PGDH results in an increase in levels of PGE2, an inflammatory metabolite that we showed is part of the body's natural healing mechanism. The potency of this treatment derives from its dual function: PGE2 enhances aged muscle stem cell function in regeneration and acts directly on myofibers leading to their rejuvenated form and contractile function (Ho et al., 2017; Palla et al., 2021).

PGE2 signaling is essential for regeneration and strength recovery after injury

Exercise, a form of muscle injury, precipitates a skeletal muscle inflammatory response and activates local resident MuSCs. Diverse immune cell types infiltrate the injured tissue, and there is a sequential release of cytokines and growth factors. We postulated that an inflammatory mediator

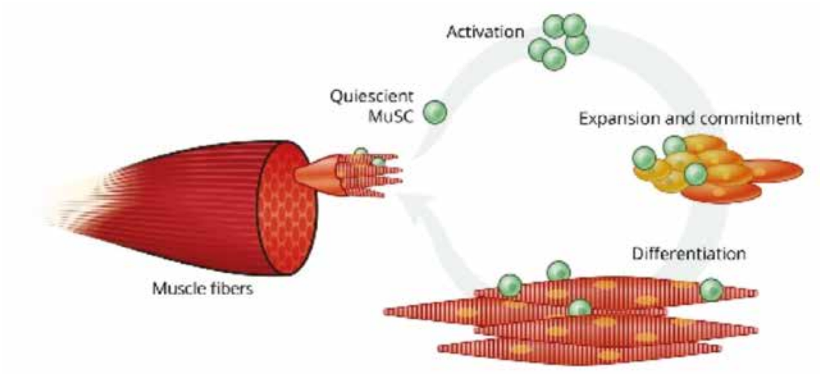

Figure 5. Inhibiting 15-PGDH activity regenerates muscle via two mechanisms. It increases PGE2 which (1) enhances aged muscle stem cell function in regeneration and (2) acts on and rejuvenates myofibers. Image by Andrew Ho.

could serve to activate MuSCs and promote their function in regeneration (Ho et al., 2017). We found that EP4, a G-coupled protein receptor for PGE2, is increased on MuSCs activated by injury and detected a surge in the levels of PGE2 in mouse muscle lysates temporally coincident with the surge in immune cell infiltration (Tidball, 2017). Treatment of MuSCs with PGE2 in culture increased their proliferative capacity and viability through cAMP-mediated activation of the transcription factor Nurr1.

To test whether PGE2 signaling is required for muscle regeneration and strength recovery, we generated a mouse model in which EP4 is specifically and conditionally ablated in MuSCs. Regeneration after muscle injury was impaired, and the young mice did not regain their strength. We analyzed the effects of treatment with a nonsteroidal anti-inflammatory drug (NSAID, like ibuprofen), which is known to block the production of prostaglandins by inhibiting COX-1 and COX-2 enzymes (Schoenfeld, 2012) and again observed a loss of regenerative capacity after muscle injury

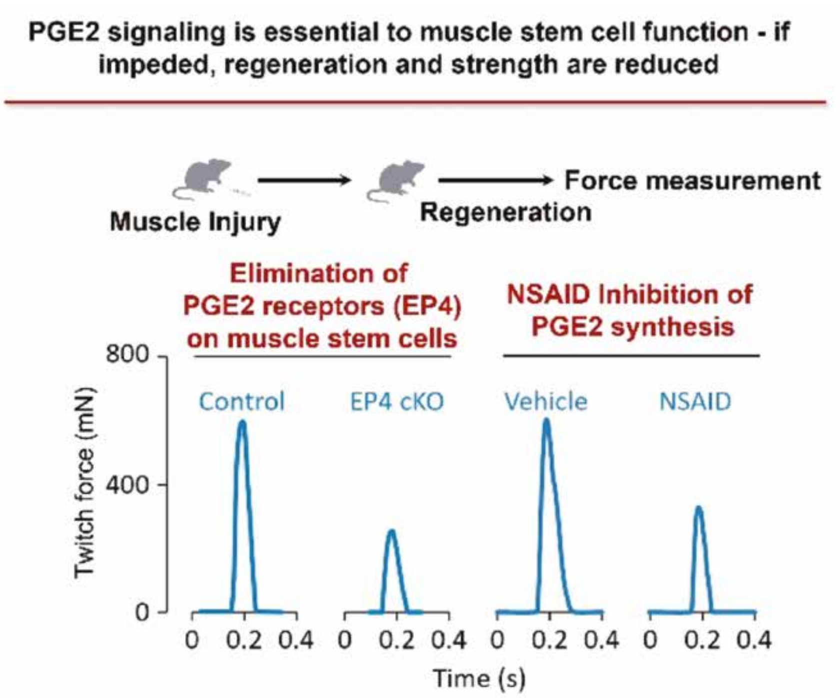

Figure 6. Elimination of PGE2 signaling, either by blocking the PGE2 receptor or by inhibiting its synthesis, decreases muscle stem cell function in regeneration and reduces strength after injury.

accompanied by a marked reduction in force (Figure 6). Together, these data show that PGE2 is essential to MuSC expansion and that PGE2 levels act as a rheostat that controls the efficacy of regeneration (Ho et al., 2017).

Aged MuSCs are less regenerative

Regenerative capacity declines with aging, although MuSC numbers remain relatively constant, indicating that a paucity of MuSCs is not the root cause of impaired regeneration (Brack and Rando, 2007). Instead, a subset of the aged MuSCs becomes dysfunctional, and is less able to proliferate and engraft (Cosgrove et al., 2014; Porpiglia et al., 2022). This impairment of regenerative function is further exacerbated by age-associated changes to the MuSC niche and systemic changes in the aging organism (Conboy et al., 2005; Gopinath et al., 2014). Data from my lab showed that the reduced function of aged MuSCs can be overcome in culture by the combined effects of a small molecule inhibitor of p38α/β MAPK and a hydrogel substrate with biophysical properties matching the soft elasticity of healthy young muscle tissue. These biochemical and biophysical cues synergize to stimulate the rapid expansion of functional aged stem cells to generate a MuSC population with rejuvenated function capable of restoring strength to injured aged muscles (Blau et al., 2015; Cosgrove et al., 2014; Gilbert et al., 2010).

15-PGDH is a Gerozyme: a pivotal molecular regulator of muscle aging and rejuvenation

During aging, skeletal muscles undergo detrimental structural and functional changes. The loss of function with aging arises from disrupted cell-cell interactions and aberrant cell signaling pathways, particularly those related to protein turnover, and mitochondrial function (Cohen et al., 2015; Frenk and Houseley, 2018; Lee et al., 2007; Lenk et al., 2010). We investigated the role of PGE2 in muscle atrophy and found by mass-spectroscopy that PGE2 declines and that the prostaglandin degrading enzyme, 15-PGDH, increases with aging and is the driver of that decline in aged muscles (Palla et al., 2021). We therefore postulated that 15-PGDH is a gerozyme, a pivotal molecular determinant of muscle aging. To fit the definition of a gerozyme, (i) inhibiting its activity should rejuvenate aged muscles and (ii) increasing its activity should cause young muscles to prematurely age.

We first tested this hypothesis by decreasing enzyme levels in aged mice via a localized intramuscular AAV9-sh15-PGDH gene therapy approach. We observed the expected significant reduction in 15-PGDH mRNA levels, protein levels, and specific activity coupled with an increase in PGE2 levels. We noted that depleting 15-PGDH led to a marked increase in cross-sectional myofiber area and a significant increase in both muscle mass and muscle force after only one month of treatment (Palla et al., 2021). Using a small molecule inhibitor of 15-PGDH (SW), we observed a similar 2-fold increase in PGE2 levels in aged mice, on par with PGE2 levels in young mice. Importantly, inhibition of 15-PGDH activity with SW promoted muscle hypertrophy and augmented both strength and endurance of aged mice. Thus, 15-PGDH met the first requirement of a gerozyme.

To address the second requirement of a gerozyme, we tested if ectopic expression of 15-PGDH suffices to cause aging of young muscle. We used an AAV9-mediated gene therapy approach to deliver 15-PGDH to the muscles of young adult mice. Mass spectroscopy revealed the expected marked decline in PGE2 and PGD2 levels in young muscles expressing 15-PGDH, similar to that observed in aged muscles. In addition, the average cross-sectional area of individual myofibers was diminished, muscle mass decreased, and force markedly declined in young adult mice. Importantly, aberrant expression of 15-PGDH in young muscle triggered changes in aging associated gene expression: increases in the expression of known markers of muscle atrophy, including atrogenes Trim63 (MuRF1) and Fbxo32 (Atrogin-1) (Milan et al., 2015; Sandri et al., 2004; Stitt et al., 2004) (Palla et al., 2021). Given the pleiotropic nature of aging, the dramatic induction of atrophy and muscle wasting caused by a relatively moderate increase in the activity of a single enzyme was both unexpected and striking. These experiments identify 15-PGDH as a gerozyme.

Identification of the cellular source of the gerozyme in aged mouse muscles

To understand how 15-PGDH exerts its deleterious effects we capitalized on an imaging technique known as (CODEX, CO-Detection by indEXing) to visualize simultaneously 40 cell-specific markers including 15-PGDH in young and aged muscle tissue sections. CODEX is a multiplexed tissue imaging technology that uses antibodies conjugated with unique DNA barcodes that are iteratively rendered visible by cycles of hybridization and chemical denaturation with fluorophore-conjugated complementary DNA probes(Black et al., 2021; Schürch et al., 2020). 15-PGDH was detected at significant levels in aged myofibers, as well as in interstitial cells, in particular CD11b+ and CD45+ macrophages, a finding confirmed by RNAseq. These results implicate both autocrine (via myofibers) and paracrine (via macrophages) PGE2 regulatory mechanisms that drive aging-associated changes in skeletal muscle function(Palla et al., 2021; Wang et al., 2022).

Rejuvenated muscle gene expression and morphology following gerozyme inhibition

A transcriptome analysis revealed a decline in deleterious signaling pathways linked to age-related muscle atrophy, particularly in protein degradation pathways and TGFβ signaling following one month of gerozyme inhibition. (Palla et al., 2021).

Strikingly, we observed a strong enrichment of mitochondrial pathways, including mitochondrial oxidative phosphorylation, ATP synthesis and other metabolic and energy generating functions in the aged muscle tissue transcriptome after SW treatment. SW increased the expression of components of all mitochondrial electron transport chain complexes. Additionally, mRNA levels of the master regulator for mitochondrial biogenesis peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Pgc1α) was restored to youthful levels. SW also increased overall mitochondrial content, and key measures of mitochondrial function such as citrate synthase and succinate dehydrogenase activity and increased mitochondrial membrane potential.

Most strikingly, transmission electron microscopic (TEM) images revealed that SW treatment led to a remarkable remodeling of the aged muscle tissue, restored aged mitochondria to a compact circular morphology

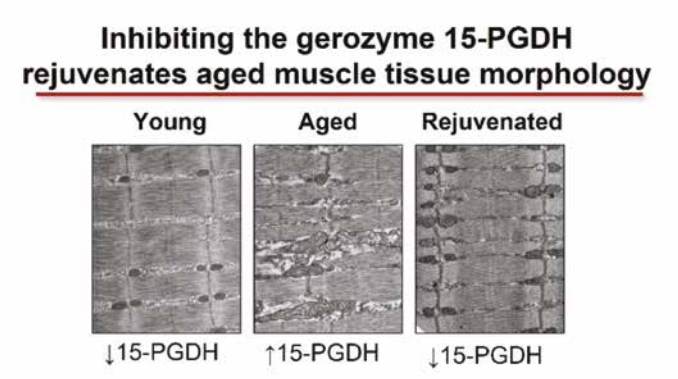

Figure 7. TEM images of young (left), aged (center) and SW-treated aged (right) mouse muscles. SW acts by inhibiting the activity of 15-PGDH, restoring PGE2 levels to those typically observed in young mice, leading to rejuvenated muscle tissue architecture.

resembling that seen in young, and increased overall mitochondrial abundance. In addition, myofibril widths increased, consistent with the increase in cross-sectional area and muscle mass (Figure 7). These images, of which thousands were quantified, provided evidence that a short-term drug treatment can lead to a remarkable tissue rejuvenation (Palla et al., 2021).

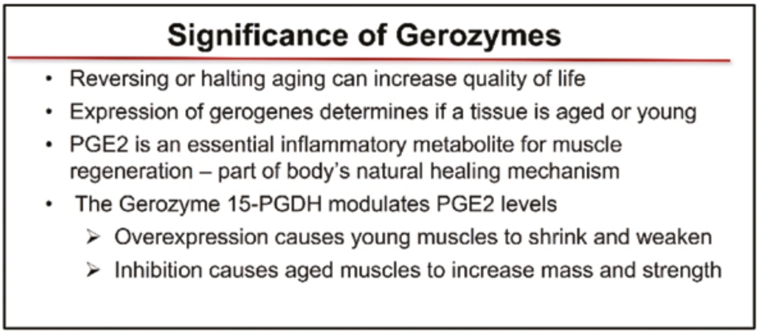

Figure 8. 15-PGDH is a gerozyme, an aging-associated enzyme.

Conclusion

We have established the prostaglandin degrading enzyme, 15-PGDH, as a skeletal muscle gerozyme - an enzyme that is a pivotal molecular regulator of muscle aging (Figure 8). Since 15-PGDH is also elevated in aged human muscles, we postulate that it plays a similar role in human muscle wasting. Because 15-PGDH is elevated in several tissues in aged individuals, it is possible that it has a broader role as a gerozyme in a range of tissues. Our research highlights the potency of the gerozyme, 15-PGDH, as a 'master regulator of muscle aging'. If expressed in young muscles, it causes premature muscle wasting similar to aging. Additionally, its deleterious effects in aged muscles can be surmounted leading to a rejuvenated tissue, with augmented function and the potential to increase quality of life.

Progress in regenerative medicine has been remarkable and the potential to treat some of the most intractable diseases is becoming a reality. Methods for stem cell production and delivery will become more streamlined and costs for stem cell therapies will certainly decrease making them more universally available. Here we present an alternative strategy. This approach capitalizes on activating adult stem cells, that are naturally present in many of our body's tissues, to regenerate function lost due to injury, heritable diseases, or aging. If the small molecule 15-PGDH inhibitor described here can be generated at low cost and in an oral formulation, it may be possible to disseminate it more broadly, setting the stage for other therapeutics to meet a need for more global therapeutics.

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Current State of Organ Transplantation

James Markmann
MD, PhD Chief of the Division of Transplant Surgery and Director of Clinical Operations at the Transplant Center at Massachusetts General Hospital,
and the Claude Welch Professor of Surgery at the Harvard Medical School, USA

https://youtu.be/TwTERMqOzJw

Discovering Prions and Developing Therapeutics for Prion Diseases

Stanley Prusiner
Director of the Institute for Neurodegenerative Diseases and Professor of Neurology and Biochemistry at the University of California San Francisco (UCSF), USA.
Nobel Laureate in Physiology or Medicine

https://youtu.be/LZSIW-eZasc

SESSION VI – ATMOSPHERIC SCIENCE, AND CLIMATE SCIENCE FOR HUMAN DEVELOPMENT, PEACE, AND PLANETARY HEALTH

Inexorable But Variable Climate Change: Signals and Noise

Susan Solomon
Lee and Geraldine Martin Professor of Environmental Studies, Department of Earth, Atmospheric and Planetary Sciences, MIT, USA

https://youtu.be/ymKJ44bkoCc

Saving the World by Construction

Hans J. Schellnhuber
Director Emeritus of the Potsdam Institute for Climate Impact Research (PIK), Germany

https://youtu.be/rbRZ3bfyI7o

SESSION VII – SCIENCE IN PHILOSOPHICAL AND RELIGIOUS PERSPECTIVES. SESSION IN HONOR OF H.E. MSGR. MARCELO SÁNCHEZ SORONDO, FORMER CHANCELLOR, THE PONTIFICAL ACADEMY OF SCIENCES

Science in Philosophical and Theological Perspectives. An Introduction

Jürgen Mittelstraß
PAS Academician, Director, Konstanzer Wissenschaftsforum,
University of Constance, Germany

When science looks at itself, it sees itself in its disciplinary structures, in its research strategies and in its methods. When philosophy looks at science, it takes an interest in theory structures, for example, in the structure of scientific laws and theory dynamics, that is, in the reconstruction of scientific developments. When theology (in its capacity as the academic, theoretical organ of religion) looks at science, it keeps an eye on the relation between faith and knowledge as well as on its part in the history of science. What these different perspectives – scientific, philosophical and theological – have in common is not only the awareness that they have been and still are linked with each other in many ways, but nowadays also the perception that science, with its knowledge, its projects and its institutions, is increasingly changing the world, intervening deeper and deeper in the life of people and society, solving problems and creating new problems as well.

One of the major problems created by science through its work derives from the fact that *orientational knowledge* is not keeping up with the *dispositional* (or *instrumental*) *knowledge* given by ever-growing scientific knowledge and skill. Dispositional knowledge is knowledge of causes, effects and means; orientational knowledge is knowledge of the right goals and ends. Dispositional knowledge is *positive* knowledge – the point is to build and enlarge scientific and technological knowledge. Orientational knowledge is *regulative* knowledge – the point is to orient our life in all its aspects, individual as well as collective.

Things do not look good for orientational knowledge today. Science has largely lost sight of this knowledge in its self-understanding and in its programmes; and, to a large extent, society has lost sight as well – and not only in political practice. The consequences are weakness of orientation, self-doubt and a tendency towards fundamentalism of various kinds. To put dispositional knowledge and orientational knowledge – the scientific and technological intellect – on the one hand, and ethical and political reason, on the other, in a reasonable relation to one another is therefore the essential task that modern societies face today. Or in other words: The *curious will*, which has found its theoretical expression in science, and the *good will*, which according to Kant is the ability to act according to principles of practical reason, must join forces again. There are good reasons enough. Take for example climate change, health, energy, and peace. Science, standing on its own, will not solve the problems referred to by these catchwords; and social practice, left on its own, will not solve them either. In the *technical cultures*, in which we live today, driven by the scientific and technological intellect, only a coalition of theoretical reason (science) and practical reason (ethics) will be able to solve our self-produced problems, problems produced by – or at least lying within the responsibility of – the successful scientific and technological intellect.

Philosophy, in the form of philosophy of science, focuses mainly on the epistemic nature of science and in practical (regulative) matters refers to general ethics; theology, on the other hand – in opposition to the idea of a limitless availability of things, the mastery of man over the world and himself – is above all concerned with pointing to a lasting *conditio humana,* according to which structures that are not at our disposition make up the centre of all epistemological and anthropological considerations. The concept of the *unavailable* stands for what *homo faber*, despite all the advances of modern science and technology, is incapable of achieving – and will never achieve as long as man remains true to himself as he has been so far. What exactly is meant by the unavailable is the fact that man will never be in a position to master all the conditions of his existence and his actions, that is to say, that these conditions are transformed into something available to himself.

And this includes the facticity that makes up his life, his world, his ideas, his hopes and his disappointments. The modern world, penetrated by science and technology, is the work of man and in fact determines individual as well as collective existence. But this does not mean that the unavailable melts into something available, something feasible and controllable. The general situation of man, the *conditio humana*, which is mirrored in the experiences of the finiteness of life – most stubborn and pitiless in the experience of approaching death – and of the contingencies and coincidences of life, has not changed. This, too, belongs to an orientational knowledge that cannot be replaced by dispositional knowledge and scientific certainties.

In other words, expressing this anthropological fact in an epistemological and ethical perspective: philosophy and theology remind science that it is not merely a *theoretical* (and *methodological*) subject, but also a *moral* subject. What is meant here is that science, on the one hand, stands for a particular *form of knowledge,* ruled by special criteria of rationality to which theories and methods are subjected. Examples are reproducibility (of scientific procedures and results) and intersubjectivity (the universality of its claims to validity and their fulfillment). On the other hand, science stands for a *social organisation*, that is a particular social form in which science is realized as a special kind of knowledge formation, and thus for an *institution*. This institution, in turn, is ruled by standards, not just epistemic but also moral standards like the standard or principle of *responsibility* – responsibility for the observance of its own (epistemic) standards, responsibility towards society (which is, after all, financing science) for its practice, responsibility for its impact on a world which is, in its modern forms, to a great extent the result of its (theoretical and practical) work. That again means, if this standard is observed: science, which takes on tasks of responsibility and the corresponding obligations, assumes a *moral form* and, thus, becomes a moral subject. This, in turn – aimed at science and all scientists and reminiscent of a Faustian dictum – can be formulated in the form of a *research imperative* or *research commandment*: *Let yourself be guided by the thirst for the new and the will to know what holds the world innermost together, but remember that it is no lesser goal to hold that world together with what you do in research and development.*

This research imperative (or research commandment) is an *epistemic* imperative, regarding principles of theory and method, as well as an *ethical* imperative, regarding principles of applicability and responsibility. In this respect, the research imperative includes a moral duty, without the observance of which the modern world would not maintain a human (and sustainable) course. This, once again, raises the question about the relation between science and orientation. As has been said: What is at stake is the relation between dispositional (or instrumental) knowledge, of which science is the eminent expression, and orientational knowledge, the necessary reinforcement of which is the task of all social institutions, including science as an institution. Performing this duty is, not least, the task of a philosophical and theological perspective on science.

Beyond Galileo: Facts, Values, and Historical Joints

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What greater honour could there be than to share some reflections at such an important forum to foster the encounter and integration of science and religion? Our former Chancellor Sánchez Sorondo's 80th birthday is a formal occasion, a particularly happy one because his career is synonymous with attention and dedication to philosophy. Philosophy is precisely the kind of knowledge that, better than any other, can outline questions and form categories that relate to science and religion. Chancellor Sánchez Sorondo was responsible for first defining the fundamental issues in this debate during his years at Pontifical Lateran University, where he was Professor of History of Philosophy from 1976 to 1998 and even Dean three times. Bishop Sánchez Sorondo has strenuously worked on healing fragmentations, seeking unity, and establishing the dialogue between philosophical disciplines and other forms of knowledge. More specifically, he has cultivated the relationship between philosophy and science, forging concepts and contexts useful for harmonizing seemingly different sensibilities.

Three questions are central to our plenary session:

1. What are new and emerging breakthroughs in sciences?
2. How have scientific breakthroughs come about?
3. How can they influence new, better, and more effective ways to reduce problems threatening people, peace, and the planet?

These are questions of considerable complexity because they open up profound epistemological issues. I have been asked to refer to one of the best-known Italians of all time, the great Galileo Galilei. I will humbly try to ensure that the figure of Galileo and his role in the development of philosophical and scientific thought can provide some insights to answer these questions.

1. The emerging new science at a historical turning-point

Modern science was born between the metaphor of the organism and the metaphor of the machine, inheriting the rich sensibility of the Renaissance: on the one hand, a passionate focus on naturalistic observation; on the other, a profound reworking of the mathematical tradition that reinforced astronomical knowledge. The spirit of renewal mingled with the use of established knowledge. The organization of new forms of *Scientia* was a slow and complex process that took root in the context of profound social changes. The universe's dimensions expanded thanks to new instruments, and nature revealed its most intimate structures. New cultural milieus arose, and philosophers and men of letters found in the academies new centers in which to engage in a mutual dialogue. This and much more took place while the Thirty Years' War was raging: new balances were established in Europe with the Peace of Westphalia (1648), while the New World continued to prompt further explorations and conquests across the ocean. The complexity and stratification of the cultural and social processes between the mid-fifteenth and the seventeenth century are reminiscent of what is happening today, noticeable differences notwithstanding. In many respects, we are living in a revolutionary era like Renaissance today. The urgencies related to the protection of the planet and energy management, migration, the swift circulation of information, and the new relationship between digital communication and politics are just some of the challenges that characterize our time, and which force us to realize that old interpretative categories are unable to explain the present. Valuing the potential of novelties rather above the difficulties posed by transformation is an attitude that can make our time an epochal moment of transition (bringing about an epochal change, and not a change of era, as Pope Francis says, *Evangelii gaudium* 52[1]), such as to leave a distinct and positive conceptual and material legacy.

Galileo lived in the context of a real change of epoch. In this context, he acted as the interpreter, promoter, and prophet of a more delimited and specific yet no less revolutionary change than the political changes taking place: the transformation of the old natural philosophy and the change associated with the new sciences. Many of Galileo's discoveries would deserve a Nobel Prize today: the use of the telescope to observe the heavens, the earthy nature of the Moon's surface, Jupiter's satellites, the observation of countless stars, Saturn's rings, sunspots, the law of the pendulum, the law of the falling bodies, and a partial understanding of the principle of relativi-

[1] "We are not living an epoch of change so much as an epochal change" (Pope Francis, *Address for the Meeting with the participants in the fifth Convention of the Italian Church*, November 10, 2015, available at the URL: https://www.vatican.va/content/francesco/en/speeches/2015/november/documents/papa-francesco_20151110_firenze-convegno-chiesa-italiana.html).

ty. One might discuss, for instance, what scientific prize Galileo's studies on the resistance of materials would merit today, or his intuition of the principle of inertia, even if this principle remained incomplete. It would also be necessary to invent a philosophical prize for the acute epistemological intuitions that stand out in *The Assayer*, a landmark work published exactly 400 years ago; a literary prize for the luminous prose in the Italian vernacular – of the sort that Italo Calvino[2] famously sought to award Galileo – would not be excessive. I leave it up to theologians to judge whether Galileo deserves a theological prize for his ability to identify methodological questions that even the Galileo Commission recognized when it reviewed certain aspects of the Galileo affair between 1981 and 1992.

The intuition of novelties is one thing, their systematic development quite another. Galileo could not fully organize all his knowledge, but he is not to be blamed for this. Even a genius needs a scientific community to help him codify and frame the content and consequences of each discovery: to do so, he would have had to wait for an established tradition of shared scientific research. Thus, we come to our first question: *What are these new breakthroughs in sciences?* Galileo brought many breakthroughs to science, including the just mentioned ones. We must acknowledge, however, that we need a definition of 'new'. If there is something 'new', there must also be something 'old'. In order to decide that a fact is new, we need to understand what an old fact is: a fact is old when it is known and explained by previous categories, perhaps still in use. Considering the most recent studies, we should make an initial distinction.[3] There are novelties obtained by looking for something that has been posited within a theory but has not yet been found, as recently it happened with Einstein's gravitational waves. In that case, we speak of prediction. Then there are some novelties which are neither sought nor supposed, unusual facts that are initially difficult to identify, as in the well-known case of Wilhelm Conrad

[2] I. Calvino replied to the writer Anna Maria Ortese by appealing to Galileo as "the greatest writer of Italian literature of any century" in a letter published in the Corriere della Sera on December 24, 1967.

[3] Only two references for a very complex debate: Zahar, E.G. (2001). The interdependence of the core, the heuristic and the novelty of facts in Lakatos's MSRP. *Theoria: An International Journal for Theory, History and Foundations of Science*, *16*(3(42)), 415–435; Worrall, J. [2010]: 'Error, Tests, and Theory Confirmation', in D.G. Mayo and A. Spanos (eds), *Error and Inference: Recent Exchanges on Experimental Reasoning, Reliability, and the Objectivity and Rationality of Science*, Cambridge: Cambridge University Press, pp. 125-54.

Röntgen: a specific form of serendipity which is not entirely coincidental, as it occurs within scientific studies and experiments.[4] This distinction impacts any generic definition of science, as in both cases, it is connected with scientific work practices and the nature of scientific knowledge.

2. Evolutive thinking

How did scientific breakthroughs come about? This is the second question we are investigating in our Plenary Session. How does science change, how does new knowledge emerge? What determines the turning points in science? Galileo's story is a notable one because politico-theological, scientific, and ontological problems are intertwined in his life and career.[5] One refers to the other, as typically in epochal changes. Conceptual boundaries can only exist when the questions and the logical and material tools to seek answers have become clear. Until this happens, there is a tension between the desire to understand and the realization that questions are reducible to doubts and uncertainties.

A range of issues marks Galileo's life, making it an emblematic case study of interrelationships between science, philosophy, and religion. Among the many politico-theological problems faced by Galileo, the most obvious one is the controversy with the Church: it must be recalled that Galileo abjured and remained a Catholic without abandoning his scientific convictions. He was aware that his writings were becoming popular in Northern Europe, and he was happy about this. About the scientific discoveries and problems addressed by Galileo, they were innumerable, and I have only listed some of them, although not exhaustively. Concerning those problems that we define as 'ontological' and relating to the nature of entities, we need only refer to the discussions and research on the nature of celestial bodies such as the Moon, already found in *Sidereus nuncius* (1610), the question of corpuscolarism, and the issue of the nature of light, which later in Galileo's career involved him in a dispute with the physician Fortunio Liceti (1640). Such 'ontological' problems are rooted in epistemological issues. I would like to return to *The Assayer*. This masterpiece is widely known as a treatise on the scientific method and as an exemplar of rhetoric and scientific communication. Indeed, the text is full

[4] W. Bynum, "Radioactivity", in *A Little History of Science*, Yale University Press, New Heaven-London, 2012, pp. 189-195.

[5] Allow to refer to the mine *Galileo Galilei, una storia da osservare*, Lateran University Press.

of passages that go in this direction. Galileo devised these argumentative stratagems for the real purpose of the work: weakening the arguments for geocentrism, including those by Tycho Brahe's epigones. The end justifies the means, and the means Galileo used were both experimental and conceptual. By relying only on the former, unfortunately, it was not easy to compete and win in the controversy because the Tycho-centrists also knew and used the same data and observations. It was therefore necessary for Galileo to refine his conceptual tools. Of course, this was a challenging task because changing concepts, categories, structures, and demonstrative techniques was, in some respects, more difficult than finding the stellar parallax with the inadequate instruments of the time. Galileo nevertheless attempted this strategy and set science on a path of innovation that made his revolution something more than a revolution in science: it made it an intellectual revolution.[6]

The philosophy of science developed over the last hundred years has sought to address the question of why science changes. Many answers have been devised, perhaps the best known being that by Thomas Kuhn, who identified both empirical and social reasons for scientific preservation or change.[7] The Kuhnian jargon, based on expressions such as paradigms, meaning variance, puzzle, normal science, and revolutionary science, is so well known that there is no need to discuss it here. Science as a collective enterprise had already been noted by Ludwig Fleck, who had spoken of 'thought collectives' (*Denkkollektiv*).[8] After Kuhn, Imre Lakatos sought new ways to integrate this historical approach with rationality criteria to explain the change in scientific theories.[9] More recently, this perspective has been updated by recognizing that science is the enterprise of a varied community, which also includes women (the great absentees in the history of science, and undoubtedly not due to any scientific demerits on their part), people of different social and geopolitical origins, and scholars with different cultural and personal backgrounds.

[6] W. Shea, *Galileo's Intellectual Revolution*, London: McMillan 1972.

[7] T. Kuhn, *The Structure of Scientific Revolution*, Chicago: University of Chicago Press (1st ed. 1962).

[8] L. Fleck, *Genesis and Development of a Scientific Fact*, Chicago: University of Chicago Press, 1979 (1st English translation).

[9] I. Lakatos, "Falsification and the Methodology of Scientific Research Programmes", in I. Lakatos, A. Musgrave, *Criticism and the Growth of Knowledge*, Cambridge: Cambridge University Press 1970, 91-196.

Data and observations are crucial factors in the crisis of a scientific theory when they bring out new facts. Nevertheless, a scientific crisis does not depend on facts alone. It depends on how the facts manifest themselves to the sophisticated experience of the scientist. Novelties are perceived as such because the old categories prove inadequate to understand them. It is therefore imperative to examine the logical, conceptual, and epistemological content inherent in a scientific theory if one wishes to understand it. We can generically conclude that between the input data and observations relating to a phenomenon and their conceptual explanation, there is a hypothetical outcome that is the compromise between what one already knows and what one expects to know. Each hypothesis is then further corroborated, refined, refuted. "One knows what one learns", said Aristotle (*An. Post.* I 1 71b5-7). So, we come to the third question.

3. With and beyond Galileo: curiosity-driven science

I have just quoted Aristotle. Bishop Marcelo Sánchez Sorondo is a philosopher who has long dealt with the classics of philosophy, primarily Aristotle. In 1993, he edited and presented a volume of contributions by professors from the lively philosophy faculty of the Pontifical Lateran University, where he was Dean.[10] Msgr. Sánchez Sorondo urged an engagement with the Stagirite's thought and with the Greek view of nature in general. Note the continuity with the concept of this lecture, which recalls Aristotle's words at the beginning of Book A of the *Metaphysics* (A.982 b 11-20):

> Now he who wonders and is perplexed feels that he is ignorant (...); therefore, if it was to escape ignorance that men studied philosophy, it is obvious that they pursued science for the sake of knowledge and not for any practical utility.

Wonder drives knowledge, an assumption already found in Plato. This view of human knowledge was later complemented by Thomas Aquinas, who recognized the mediated character of our knowledge: this mediation occurs through the human being standing in front of the object he has to study. "Unde hoc non est demonstratio sed suppositio quaedam" (Thomas Aquinas, *In I De coelo et mundo* I 1 num. 28): these are very relevant words when read from the perspective I am outlining. Scientific theories proceed via hypotheses and experiments, from one vital aspect to another, so knowledge is never definitive. What Aquinas could certainly not say when

[10] M. Sánchez Sorondo, *Physica, cosmologia, naturphilosophie. Nuovi approcci*, Roma: Herder-Università Lateranense, 1993.

referring to science is that scientific knowledge is always due to a community of cooperating scientists: even if some discoveries are attributed to individual scientists, the latter always implement what they inherit from past scientists and what is verified by scientists of the present and future.

Behind all great scientific discoveries lies this drive to know, fuelled by wonder and curiosity. The hypothetical dimension of scientific research moves us from enquiry to enquiry. A scientist's mind may rest after years of work, but a new generation of scientists will ask new questions. Galileo's curiosity was accompanied by the *libertas philosophandi*, which was instrumental in producing new ways of thinking. Only after their emergence can we speak of new systems of thought. But at that point, it is legitimate to ask what consequences they bring. When we speak of the consequences of science, the first defendant is technology. If we only think of Galileo, we realize that, on the one hand, he was busy studying kinematics, mechanics, astronomy, and material sciences. He advanced in his studies because he was not detached from the use of instruments: from the balance for statics problems to the telescope and the microscope – which he perfected – and the geometric-military compass. After him, the link between science and technology grew stronger and stronger, and it became increasingly evident that science and technology modify society. Thinkers like Hans Jonas reflected extensively on this topic, linking technical applications and the exercise of freedom.[11] This reveals the deeper link between curiosity and freedom, raising the question of whether freedom is an end in itself or whether it should always be directed towards some goal. The curiosity that drives scientists to learn about nature can help penetrate the mystery of human beings and creation, far from being a vicious movement of intelligence.

Here we come to the last question of the plenary session: *how can scientific breakthroughs influence new, better and more effective ways to reduce threats and problems for people, peace, and the planet?* Let's start from people. What is the link between scientific breakthroughs and respect for the human person? "Realities are greater than ideas" (Pope Francis, EG 231). Science is the speculative journey that teaches to ponder things, compare ideas with reality data, activate synergies and collaborations between scholars, question assumptions, expose errors, come to terms with uncertainty, evaluate methods and trust the resolutions they lead to. Here I would refer to the history of science in the 20th century, which saw the emergence of new

[11] Hans Jonas, *The Imperative of Responsibility. In Search of an Ethics for the Technological Age,* Chicago: University of Chicago Press, 1984.

theories and gave rise to those sciences we have seen discussed over the last few days. Science teaches humility, the most important of virtues for the growth of knowledge. However, it can only do so when it becomes aware of its history and epistemological foundations. Without this critical awareness, any scientist can become arrogant, if she forgets that scientific theories are the complex product of achievements and defeats, contradictions, win-wins, and paradoxes. The kind of humility that a self-aware science teaches is the ability of a discipline to question itself and remain open and adaptable, without falling into the abyss of absolutism and relativism. This scientific lesson should be taught to women and men of all ages.

As for peace, its relationship with science has been widely discussed, by influential scholars, especially on the historical level. In 1955, Albert Einstein and Bertrand Russell published the *Manifesto for Peace*, which inspired the Pugwash movement for disarmament and peace[12] at the end of last century. The importance of political engagement as a way to make both the scientific world and public opinion aware of new approaches to international security in the atomic age is evident. This is a sadly topical and urgent issue even now. From the post-World War II period to the present day, countless documents and political activities have directly involved scientists. “There is before us, if we choose, a continuous progress in happiness, knowledge and wisdom. Would we, instead, choose death, because we cannot forget our contentions?”, wrote Russell.[13] Rather than discussing physics for peace, mathematics for peace, economics for peace, and so on, we should talk about those women and men who practice science and find opportunities to reflect and promote peace. Their interaction and collaboration are the first sign of peace building.

Finally, we come to the planet, our *Common Home*. Science makes possible technologies and vice-versa. In the face of today’s environmental disasters, it is clear that this mutual dependence has not always been well-assessed. Indeed, we often speak of sustainable development, a concept distinct from sustainability. The latter refers to a balance between the environment, living species, and human actions, whereby the ecosystem is respected and does not suffer devastating shocks. On the other hand, sustainable development identifies that set of practices that can be pursued

[12] The text of the *Manifesto Russell-Einstein* is available at https://pugwash.org/1955/07/09/statement-manifesto/

[13] B. Russell, *Man’s Peril from the Hydrogen Bomb*, *The Listener*, no. 52, 30 December 1954, 135-6.

in the socio-political, economic, and scientific-technological spheres to achieve sustainability. For development to be sustainable, adequate cultural action is key, as a means to promote good practices but also as a correct way of understanding the continuity between human beings and the environment.

4. Conclusion: *Veritas* as *Gaudium*

Galileo's question is helpful to point out the need to discuss the integration of science and religion as pieces of knowledge. There is an urgent need to do more than just note the degree of personal integration between the two in a scientist's life. Even a dialogical approach or cross-fertilization to enrich discussion would not be sufficient. The purpose of this discussion is not only to engage in dialogue but to find methods and categories to develop a systematic and rigorous integration.

The PAS Plenary Sessions offer new narratives within which experts and practitioners can shape the collective vision of science in a way that respects the results of scientific research and the philosophical inquiry on science. Events such as this are most valuable when an anti-scientific spirit exists and is widespread and a clear signal is to be given: any cultural proposal must take science and all its results into close consideration. These narratives can become a common value, helping to understand science and its effects on political decisions and social customs, promoting its most edifying aspects.

Bernard de Fontenelle lamented the drudgery of the physical and mathematical sciences, but recalled that in Homer's time, it was a source of great wonder that a man could subject speech to a rhythm and measure. Fontenelle hoped that the scholars of his time would be remembered as the creators of great wonders.[14]

Thus, let me conclude by mentioning two key points that we must bear in mind for future generations' sake: the first is achieving a credible synthesis capable of harmonizing the contribution of science and its rigour with categories comprehensible to non-scientists and respectful of our *Common Home*.

The second key point is that there is more to knowledge than just effort and dedication: knowledge must lead to joy, and *scientia* does not

[14] B. de Fontenelle, *Poésies pastorales de Monsieur de Fontenelle. Avec un traité sur la nature de l'églogue, et une digression sur les anciens et les* modernes, Michel Guerout, Paris 1688.

rhyme with *tristitia*.[15] *Gaudium* is the measure of *veritas* itself. Awareness of the processuality and gradualness of the development of the scientific knowledge, the ability to share this knowledge with others, the possibility of making it an instrument for common growth, and the continual amazement at the fact that nature is given to human beings to be progressively understood via a collective effort that calls for humility and the sharing of satisfaction. All these aspects are embedded in a new style of reasoning that science is teaching today. So, science can indicate a style of knowledge, sharing, and learning that is very close to the recent criteria for the renewal of Church teachings. (*Veritatis Gaudium* 4). This style opens not only the mind but also the heart to joy since joy is what characterizes the Truth (*Veritatis Gaudium* 1). Furthermore, only that which gives joy can claim to be a timid reflection of a Truth that goes beyond us, to unite us.

[15] F. Marcacci, *Gaudium aude*! "*Fides et Ratio*" venti anni dopo come metodo per la ricerca nelle università, in *Lateranum* LXXXV/1, 2019, 171-187.

Three Philosophical Paths Beyond Scientism

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Introduction

What becomes obvious once one enters into the field of evangelism is that the supposed conflict between science and religion is a major reason why so many, especially the young, are disaffiliating from the traditional religions. Christian Smith, sociologist at the University of Notre Dame, has done particularly illuminating work in this regard. Time and again, the young "nones" that he surveys claim that science has either refuted religion or rendered it useless, an artifact from a past age.

Given its massive and evident success and given the extraordinarily useful technology that it has made possible, science looms in the minds of many in the West as the best, even unique, method for exploring the truth. By contrast, religion seems to be an arena of fantastic thinking, a pathetic intellectual space in which unsubstantiated and untestable claims are routinely made. The so-called "new atheists", who emerged in the years following the tragedy of September 11th, have hammered this point home. The great religious texts, they say, were written long before anyone had an adequate understanding of even basic scientific principles. This "bronze age" thinking, therefore, should be abandoned by any responsible person today. And when this scientific critique is coupled with a moral critique of the apparently violent and arbitrary God of the Old Testament, young people in great numbers feel the pull away from religion.

Addressing all of these issues is obviously beyond the scope of this short paper, but what I should like to do is to tackle the general problem of scientism, which is to say, the reduction of all knowledge to the scientific form of knowledge. Like its close cousin logical-positivism, scientism holds that authentic truth claims can be made only in regard to those matters treatable through the scientific method. Not only is this epistemic viewpoint hopelessly reductionistic, but it also shares with logical positivism the dubious distinction of being operationally self-contradictory. For the principle that the only legitimate form of knowing is the scientific form cannot itself be the result of a purely scientific examination. It is, in point of fact, a philosophical axiom. In the Derridean manner, I would like to tug on that loose string and see if we cannot unravel the weave of scientism. In accord with G.K. Chesterton's metaphor, I would like to crack open the skull of the devotee of scientism in order to let in more light.

The Radical Intelligibility of the World

In Plato's famous parable, the prisoner, chained in place within the cave and able to see only passing shadows on the wall, manages to escape and to access higher and higher levels of reality. The flickering images represent the world of our ordinary sense experience, the world legitimately explored by the physical sciences. But to see only that dimension is a pathetic epistemic impoverishment. The first step out of the cave is to appreciate the realm of mathematical objects, the pure abstractions of arithmetic and geometry. To grasp these *qua* abstractions is to move quite clearly out of the evanescent order of sensible reality. When one truly understands the quadratic formula or the simple equation 2 + 3=5, one has grasped a reality that does not come and go and that obtains in any possible world. Another way to express this is to say that the inquirer has moved from the visible to the invisible. I hesitate somewhat to use this language, for it gives the impression that there are two types of realities, some relatively solid and others relatively ghostly, that exist side by side. What I mean by the "invisible" is another dimension of reality, beyond the merely sensible, but that same time, deeply implicated in it.

David Tracy, emeritus professor at the University of Chicago, in a recently published essay entitled "The Ultimate Invisible", draws our attention precisely to this Platonic construal of the mathematical. "Aside from the religions", he writes, "the major form of invisibility in our time is that provided by mathematics and the mathematization of modern science nurtured in the early modern period by Galileo…". Tracy observes that the classical definition of the circle – a locus of coplanar points equidistant from its center – is easy enough to memorize but absolutely impossible to imagine or concretize in fact. A picture of a wheel might suggest to the beginner in geometry the notion of circularity, but it could never adequately represent it and hence could never suffice to answer the question "Why is the circle round?" In point of fact, we could never answer such a question by remaining in the field of the visible. "We *can* answer the question, but only by moving into a realm of intelligent supposing – a realm that can neither be seen nor imagined but can be supposed and understood". The inquiring mind *knows* these invisibilities by entering into intimate communion with them in their distinctive arena of existence.

Modern and now postmodern sciences are deeply indebted to mathematics, indeed, unthinkable apart from it. Tracy again: "Since Galileo, Descartes, Leibniz, and others, modern science has employed three essential elements: dispassionate empirical observations, mathematical conceptual formulations of its hypotheses and theories, and experimental testing of all its theories". If we focus on that second indispensable step in the scientific method, we see that the very disciplines that, in the minds of many today, most root us in the empirical order in point of fact lift us beyond it to the invisible order. Therefore, the search for intelligibility continues to lead us out of the cave and into more intense expressions of being. But the journey comes to a conclusion only when, to follow the Platonic master metaphor, we gaze up to the sun, the light that finally illumines anything that we perceive or know. Only when we "see" the one who gives intelligibility and hence who gives being, the one who, in Plato's language, lies therefore beyond the beings, do we come to rest.

But why should we suspect there is such a giver? David Tracy comments that the sciences come to the end of their capacity when they confront the puzzling limit question which they, on their own terms, couldn't possibly address, namely, why should the world be intelligible at all? Precisely because they rest, inevitably, on this very assumption, the sciences themselves could never answer this query. Albert Einstein himself grasped the nettle of this when he commented, "the most incomprehensible thing about the universe is that it is comprehensible". As Joseph Ratzinger argued in his indispensable *Introduction to Christianity*, the only finally credible answer is that there is a governing intelligence that has imbued the universe, in every detail, with intelligibility. In point of fact, this intuition, Ratzinger contends, is evident in our term "recognition" (re-cognition), a thinking again what has antecedently been thought. And once we grasp this notion, we come to the spiritual heart of Thomas Aquinas's epistemology. When the human knower finds *adequatio* with the form of the thing to be known, when he affects, in short, a real union with that intelligibility, he has attained, at the same time, an inchoate but deeply real oneness with the divine agent who has, through a series of secondary causes, imbued that object with form.

The Immateriality of the Mind

A second way of breaking the skull of the advocate of scientism and letting in some light is by examining the faculty of subjective consciousness that corresponds to the intelligibility of the world. Representing the classical and medieval consensus on the matter, Thomas Aquinas, with typical pith, said *intellectus in actu est intelligibile in actu* (the intelligibile in act is the intellect in act). Such a statement would be incoherent on an "observer-observed" model of epistemology, so typical of the modern sciences but it is luminously clear on an "objective participant" model that held sway in the pre-modern period. There is, in a word, a deep correspondence between the invisible intelligible patterns that the mind comes to know and the nature of the mind that knows them.

On a modern mechanistic or purely naturalistic reading, what we call mind or consciousness is, at most, an epiphenomenon of material forces in the brain following deterministic laws of cause and effect. To use very contemporary language, it is an emergent pattern of more elemental materials and energies. The seemingly intentional nature of consciousness becomes, on this reading, more or less an illusory product of efficient causes that produce it.

But this is repugnant to reason, however widespread the model is today. When the mind entertains and understands a pure intelligibility such as a mathematical relationship or a formal structure, it is not trading in material reality. It has conformed itself to the invisible and hence must itself belong, at least in its higher faculties, to that order of being. Similarly, to grasp, as any user of language must, the formal, syntactical structures of language is possible only if mind in some sense transcends mere imagination and perception. (This is, in fact, the burden of Thomas Aquinas's argument for the immateriality of the soul). Furthermore, the undeniable experience of teleology within one's consciousness, that one is acting for an end, cannot be reconciled with a purely physicalist account of mind, which is to say, one that assumes a deterministic physical substrate.

A classical argument for the immateriality of consciousness was made famous by C.S. Lewis in the twentieth century, but versions of it can be found throughout the tradition. The thrust of it is that an entirely naturalistic account of reality cannot explain the very ratiocinative process by which one would draw such a conclusion. Every act of deduction or formal reasoning involves the making of connections between premises and conclusion, connections that are causal indeed, but not in the materialist manner. David Bentley Hart took as indicative of the immateriality of the mind "the syntax and semantics of acts of reason, or of any mental acts whose internal connections appear to be conceptual or logical rather than merely physical". In Lewis's terms, if the mind is nothing but atoms bouncing off one another randomly or in accord with strict determinism, why would we ever be tempted to trust its deliverances as true, as adequate depictions of what is real? Once again, the very process of reasoning must represent a qualitatively different order of being than the realm of sheer mechanical causality.

With regard to the immateriality of the mind, a final consideration is in order. Any honest assessment of consciousness requires us to set aside merely passive or receptive accounts of mind. On the Humean or Lockean reading, intelligence is more or less an empty theatre in which the vague impressions of sense experience appear, but this is a grossly inadequate account. Instead, as Aquinas and Lonergan saw so clearly, the mind might originally be empty but empty like a stomach, not like a box, which is to say, ordered actively and energetically toward that which it seeks. The properly named *intellectus agens* restlessly and relentlessly asks of the data that it takes in the question *quid sit?* Under the influence of that inquiry, it abstracts an intelligible pattern from what was presented to the senses and preserved in memory. Yet, having made that abstraction, it continues to press, *quid sit?,* placing what it knows in every wider horizons of meaning, pushing finally toward the ultimate horizon of being itself, in Lonergan's language, the state of knowing "everything about everything". This teleological lure toward the fullness of being, in Christian terms, the beatific vision, is intrinsic to the mind itself and utterly transcendent to the order of finite, material being. It demonstrates, therefore, that a reduction of intellection to physical processes is absurd.

The Inescapability of Metaphysics

The deep ground for the scientism that plagues many young people today is in certain philosophical shifts that occurred in the late Middle Ages, most notably William of Occam's option for a univocal conception of being over an analogical conception. On the latter reading, on rich display in the metaphysics of Thomas Aquinas, the primary referent of the term "being" is God's manner of existence, and the proper use of that term to describe finite, creaturely realities is hence neither univocal nor equivocal but analogical. Accordingly, finite things are properly described as participating in the fullness of being which God alone possesses, or to state the same truth more technically, creaturely things are those that have received the *actus essendi* not unrestrictedly but rather according to a delimiting principle of essence. On this interpretation, furthermore, all creaturely beings, in the measure that they participate in God, are connected by the deepest bonds one to another. St. Francis's famous poem invoking "brother sun and sister moon" is perfectly in accord with this Thomist vision which sees all creatures as ontological siblings.

When this understanding was abandoned, the integrated vision fell apart. If, as Occam argued, the word "being" is used univocally of both God and creatures, then God becomes one being, however perfect and exalted, among many. Moreover, it is no longer appropriate to speak of creatures participating in the *esse* of God and hence it is mere fancy to speak of finite things as ontological siblings. Rather, as Occam himself put it, "outside of these absolute (unrelated) parts, there is no real thing". There is a very small step from Occam's shift to univocity to the rise of nominalism, for once the metaphysical bonds of beings to one another and to God are severed, it is easy enough to treat the universal dimensions of reality as mere abstractions or linguistic conventions.

Now the Occamist/nominalist God, one great being among many, was bequeathed, first to the Protestant reformers, most of whom studied in schools dominated by nominalism, and then to the founders of the modern sciences. Permit me to say just a word about the Protestant appropriation and then to say a bit more about the way the sciences took in this philosophy. Practically axiomatic to most of the Protestant founders is the view that God and humanity are essentially rivals, so that the more glory is given to us, the less glory is given to God, and vice versa. We can see this assumption behind both Luther's theory of justification by grace through faith alone and Calvin's insistence on a purely determinative divine sovereignty that essentially obliterates human freedom. Occamist nominalism had given rise to a competitive supreme being who existed over and against and in contrast to his creation. The analogical metaphysics of Aquinas, to the contrary, justified Irenaeus's famous adage *gloria Dei homo vivens,* for the sheer act of to-be itself is not in competition with those finite realities that participate in his manner of existence.

The same typically modern conception of the God-world relationship was taken as axiomatic by many of the founders of the physical sciences. Assuming that nature consists of discretely existing individual things, they bracketed the Aristotelian formal and final causality and embraced, almost exclusively, material and efficient causality. The vision that followed was mechanistic – things bouncing off of one another, one thing influencing and reacting to the motion of other things. And if God were brought into this picture, as he was, for instance, in Newton's conception of the universe, he was construed, in the nominalist manner, as one impressive mechanistic cause among many, the one who initiated the cosmic process or who intervened in it from time to time.

An exceptionally clear exemplification of this typically modern construal is the debate between William Paley and Charles Darwin. Paley, the Anglican apologist, famously compared the organisms of nature to a carefully constructed watch. It is inconceivable, Paley argued, that the delicate and complex organization of a watch came together by chance; by the same token, he insisted, the structures of physical organisms must have been assembled by an intelligent designer. Throughout *On the Origin of Species*, Darwin is in conversation with Paley, whom he obviously had read with great interest. His fundamental disagreement with the apologist is that the combination of random genetic mutation, time, and natural selection would adequately account for even the most complex arrangements within nature. No appeal to a watchmaker is necessary. What I find particularly interesting in this back and forth between Paley and Darwin is not so much their disagreement as their agreement, for both are operating out of a thoroughly mechanistic understanding of God. Though Paley affirms this God's existence and Darwin at least doubts it, they are on the same faulty nominalist ground, assuming that God is a being among many who may or may not play a role in assembling more elemental particles into complex wholes. Much of the conversation to the present day concerning God's relation to the world breaks along very similar lines, some lining up with Paley and many others with Darwin. But both miss the proper understanding of the God-world relationship, which is predicated upon the analogical conception of being.

A path forward is suggested by the peculiar fact that we refer to the totality of finite things as a "universe". The term itself indicates a "turning toward the one", *uni-versum*. Why would we not refer to the whole of nature simply as an aggregate of disconnected individual things and events, as the nominalist metaphysics would in fact suggest? What is the one to which this entire collectivity is turned? The classical answer is being. What all events and objects within the universe have in common is existence, the *actus essendi* that Aquinas describes. Even if we were to posit an infinity of different universes, they would still constitute a mega-universe, since all of them would have at least existence in common. By means of this intuition, we have moved, necessarily, beyond the merely mechanistic and materialistic and come into contact with a notion that is essentially unlimited. Next, by a simple logical move, which the classical tradition made effortlessly but which is lost on most moderns, we notice that the limited expressions of being that we find all around us – those things composed of essence and existence – must be derived from that reality in which essence and existence coincide. In a word, contingency must be reduced to non-contingency.

And this relationship is precisely what classical theism means by the term "creation". Read from one side, it is identical to God's own being; and read from the other, it is the radical dependence of created things upon the on-going influence of God's causality. Metaphysically far above any consideration of mechanistic causality or the ordered arrangements of parts is this fact of the world's relationship with the creator, which Herbert McCabe compared to the manner in which a song relates to a singer. This is why debates today between Darwinists and, say, the advocates of "intelligent design" miss the point entirely. The one who approaches the universe from the standpoint of its being can happily say, "a plague on both your houses".

Conclusion

I have indicated three paths for getting beyond the narrow scientism that dominates too many people today, and I have done so exclusively through philosophical argumentation. To a degree, I am following a prompt of Francis Cardinal George who once commented that before getting to the problem of religion and science, it would be best to address the problem of philosophy and science. For philosophy, though a non-scientific method, is an altogether rational method and hence might function as an attractive bridge to those impressed by the rationality of the sciences. The first path, regarding the intelligibility of the world, was given memorable expression by the pioneering physicist Eugene Wigner in his seminal 1960 article, "The Unreasonable Effectiveness of Mathematics in the Physical Sciences". Why should it be so that the patterns and relationships articulated by higher mathematics allow us to understand the physical universe so thoroughly? Why indeed, unless, as many scientists have suggested, the one responsible for nature is a mathematician.

And from this insight we move to the second path, that of the immateriality of the mind. Only an intelligence that transcends the evanescent world of matter and change could ever reason persuasively regarding that world and its intelligible patterns. From these two approaches we come to the third, namely, the inescapability of a metaphysical view of the finite universe. Beyond the intelligibilities inherent in the structure of created things, there is the elemental intelligibility of their very being, their *actus essendi*. And once this is grasped, we have moved necessarily beyond a merely mechanistic understanding of nature to a properly metaphysical, even mystical, perception of contingent being grounded in non-contingent being.

Science in Philosophical and Religious Perspectives

Archbishop Dr. Dr. h.c. mult. Antje Jackelén
The Lutheran Archbishop of Uppsala in Sweden and Primate, Church of Sweden

Thesis

If basic science is to be an effective force for human development, peace and planetary health, it needs the partnership of a credible hope. In fact, the success of basic science for people, peace and planet is dependent on a wisely grounded hope. Optimism is not enough; we need hope. And hope is a theological category. Given the current crises, vital relationships between science and theology are crucial to human development, peace and planetary health.

Text

Given a comprehensive summary of the planetary crises we are facing, we are at a moment of Kairos, where everything that is an expression of human dignity needs to cooperate – with science and religion having a special role in this cooperation, a given responsibility. We have multiple reasons to fear, to doubt, to resist and to fight as we strive for global sustainability and adaptability, because so many things can make us lose faith in the success of this endeavour, because so much human and non-human suffering is tormenting this planet. The least we can and must expect in this situation is that science and religion get their acts together and cooperate to the best of their abilities.

As we all know, the relationship between science and religion has changed over time – not only since Copernicus, Galilei, Darwin and Einstein. The myth that the relationship between the two is one of conflict has been debunked many times over. Today, we know that the history of science and theology is rather complicated with lots of influences in both directions. Tensions have eventually led to development, as for example concerning evolution. Harmony has sometimes been harmful, for example when race-biologists and theologians in the name of science became co-workers in the colonial oppression of the Sami, the indigenous people of Northern Europe, with consequences that up to this day cause shame, pain and conflicts.

The relationship between science and religion has shifted and developed also during the last forty years or so. To put it short and swift: In the eighties, science-and-religion dialogue was pretty much about physicists trying to bring theologians up to speed on quantum theory. Then, microbiologists entered the stage, saying: we don't really need this religious stuff. Genes, you know! They were followed by cognitive scientists who asked: Isn't religion sort of natural, after all? And we witnessed a renaissance of the *homo religiosus* hypothesis. And now climate scientists have knocked at the door, telling theologians and faith communities: we need you, or else... We need both the theory and the praxis of faith, or else we won't be able to flatten and reverse curves to save the planet for future generations of humans and a host of other species!

Mandated by the accelerating climate emergency, it seems that climate science is faced with a normative turn. The need to connect to politics on the one hand and to spirituality in faith and action on the other hand becomes ever more evident. The dynamics between beliefs, values and attitudes held, behaviours practised, and collective policies developed, can no longer be ignored.

By the way, it may be interesting to note that the term sustainability as we know it from the definition by the Brundtland commission was originally launched in a church context. In 1974, more than a decade prior to the Brundtland commission, a conference organized by the World Council of Churches on "Science and Technology for Human Development" took place in Bucharest. At that conference, the wording "sustainable and just society" was used. There are indications that the use of the term at the Bucharest conference directly influenced the Brundtland commission.

Be that as it may, the IPCC Sixth Assessment Report from 2022 states that religious beliefs impact experience of climate change (p. 1217). The report acknowledges that religious beliefs, values, and practices can be an asset in adaptation, but that they often also increase vulnerability due to discrimination and injustice, especially in minority situations.

Religious beliefs are relevant to awareness, coping and action. By providing a context of interpretation, they offer understanding and possibly even meaning to events that appear utterly harmful and meaningless. They can strengthen measures of mitigation and adaptation. However, they can also hamper and delay action, depending on doctrinal and communal understandings of, for example, punishment, trust, gender roles and eschatology. The so-called prosperity gospel and non-incarnational apocalyptic theologies that interpret the degradation of the environment as a messianic token can be extremely counter-productive.

Thus, mutual critical and self-critical engagement of science and religion is crucial when it comes to human development, peace and planetary health at this time of crises. Faith traditions need to understand the science in order to make their resources available for effective personal and collective response as well as to inform their preaching, teaching and liturgies. Climate science needs to understand the world of religion in order to get hold of what it takes to bring about the social dynamics demanded at this particular point in our planetary history.

When scientists seek knowledge about social tipping processes and look for small interventions that can have large effects in favour of sustainable development, religious beliefs, practices, and communities cannot be ignored. Most likely, social tipping points are connected to spirituality, because: if people are to make decisions that are costly to them (in terms of substantial change of lifestyle or sacrificing/abstaining from cherished things and practices), they will need a spiritual motivation and spiritually grounded coping mechanisms. These are superior to rational self-interest as sole motivator. And let us not forget that 85 per cent of the world's population are religiously affiliated.

Some relevant theological issues for the interaction between science and theology in regard to the climate crisis would be: informed morality; justice – including the strongest support to the least privileged; hearing both the cry of the earth and the cry of the poor, as Pope Francis put it in *Laudato si'* (§49); sense of wonder, love and beauty in relation to the planet (you protect what you love!); lament; personal and communal resilience; comfort; motivation to sacrifice for the common good; ability to handle sin, guilt, forgiveness, reconciliation and transformation/metanoia; development of a planetary diaconia.

The days should be gone when sermons blurred the difference between justification by grace through faith and the justification of a status-quo lifestyle that is detrimental to the planet and at odds with God's *oikonomia*. Instead, we need a spirituality of resilience, a spirituality of co-existence and a spirituality of hope. Let me explain briefly:

With a spirituality of resilience, we will be able to make sense of the fights of women and men for the future of their children, for people, peace and planet. We will continue to do research and write articles, teach and preach, give lectures and act in the public space – for the sake of healing, sustaining and adapting. With a spirituality of resilience, we will be able to confront the trends and powers that hamper our constructive engagement with the greatest challenges of our time. These powers are characterized by what I have called the five poisonous Ps, namely polarization, populism, protectionism, post-truth and patriarchy. With a spirituality of resilience, we will be able to confront polarization that tears apart what should belong together and work together. We will be able to resist populism that pits people and so-called elites – including scientific elites – against each other. We will be able to counteract protectionism that puts one's own country, one's own people and one's own interests first, at the expense of the common good for people and planet. We will be able to fight against post-truth, the contempt of truth that disfigures the vital triad of the true, the good and the beautiful, without which we cannot live. And we will be able to overcome patriarchy, which continues to deprive the world of the full flourishing of women and children, and in the end dehumanizes all humans, regardless of gender.

With a spirituality of co-existence, in both science and religion, 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 biodiversity; and we will be self-critical when it comes to our unavoidable anthropocentric lens. We will listen to creation's groaning and longing for the revealing of the children of God (Rom 8:19-23). With a spirituality 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 – and to react to these stories with empathy. We will be better at listening to the voices of indigenous peoples. They tell us, for example, that judgment day may mean that the animals will speak with clear voices, while we humans have to shut up. And we will understand with our minds and our hearts that divine justification and global, planetary justice belong together.

And yet, why is action on climate change so slow? Because we need more of a spirituality of hope. There is too little hope that liberates people to give up things for the greater good. Why is there so much fear of those who are strangers or just "other"? Because too many people lack hope that nurtures the courage to think and act outside the box. A deficit of hope combined with a surplus of fear is a serious condition. It can be fatal.

Credible hope, on the contrary, is liberating and empowering. It is hope that does not put bureaucratic processes or prestige first. It puts people first. It does not put human failure first; it puts human rights first. Also, it does not put one's own interests first. It puts the planet first.

Hope is a tough plant that can bear a whole lot and resist a whole lot. Nevertheless, hope is also vulnerable. Hope is both a gift that we receive and a muscle we need to train. We must cultivate our own hope, if we are to foster hope among people in situations of crisis and need, if we are to work for the well-being of our planet, if we are to care for God's creation.

Now, hope is a theological category. Hope is directly dependent on our willingness and capacity to bear uncertainty and relate not only to what is not yet known and hence subject to further research in known and yet-unknown disciplines, but also to what cannot be known despite all progress in science.

The relationship between reason and the unknowable was reflected prominently by the fifteenth-century philosopher and theologian Nicholas of Cusa. He is renowned for imaginative and provocative concepts such as "learned ignorance" (*docta ignorantia*) or "coincidence of opposites" (*coincidentia oppositorum*). He also speaks of the important distinction between *ratio* and *intellectus*. Both words mean reason or mind, but in different ways. *Ratio* is calculating, planning and controlling reason. After all, in Latin, ratio also means counting. We can get far with ratio. For complete understanding, however, we must also employ *intellectus*, insight. When our reason encounters the immeasurable and the unknowable, it employs *intellectus*, which knows that the unknowable is, precisely, unknowable. While *ratio* must surrender to the unknowable, *intellectus* can relate to it without reducing it to knowledge. Mastering this difference is what turns a knowledgeable person into a wise person.

In fact, a comprehensive understanding of the future requires both *ratio* and *intellectus*. We need to remember that *intellectus* is not the opposite of *ratio*. It does not entail irrationality. Rather, without *intellectus, ratio* is not fully reasonable. *Ratio* calculates, controls and monitors. The strength of *intellectus* is to look and listen, inwardly and outwardly, towards the horizon of the unknowable.

Our sense of control has been nurtured by the rationalist tendencies of modernity. With the help of technology, we have extended our human sphere of power and control. This development has led to the perception, partly illusionary but still very vivid, that we can plan, steer and control most events in our life. The Covid pandemic shattered this illusion abruptly and brutally. So do the consequences of climate change. *Ratio* is now being thrown into a sea of uncertainty. The abilities of our *intellectus* are in demand, more than before. We need prudent and wise ways to relate to the unknowable and the uncertain.

Ratio is a perfect instrument for making forecasts and extrapolating trends. This is what optimism and pessimism do: extrapolating and projecting based on past and current developments. Hope is more like *intel-*

lectus. It seems to me that optimism and hope are related to one another similar to how *ratio* and *intellectus* work together.

Hope enables us to see broader contexts and relates to the theological category of promise. Rather than just extrapolating, *intellectus* and hope also focus on how what is coming towards us from the future resonates with our highest values and our fundamental trust. Especially in times of crises, it is essential that both components of reason are actively employed. If not, we will have more or less pious expectations, but the real power of hope will illude us. Counting on the immeasurable and the unknowable is and remains the most sensible alternative, especially when living in a time of crisis. One might say that hope brings *ratio* and *intellectus* together in a way that renders an existential surplus.

Hope is a power with at least three different components. Hope does not flee from reality; therefore, hope must be able to harbour frustration, grief and anger at the forces that contradict the true, the good and the beautiful. Hope knows about our human imperfections, our vulnerability and our mortality as well as about our capacities and our responsibility as created co-creators and co-creatures. Hence, humility is another important component of hope. Hope is different from passively enduring the challenges of any given situation. Therefore, together with anger and humility, courage characterises hope. In most situations, we still have the possibility to choose a courageous path forward rather than the opposite.

Hope as anger, humility and courage is nourished by our personal and our collective experience, spanning the centuries of faith and prayer, which we can lean on and learn from. Hope suffers, feels and struggles in the crisis of the present. Hope prevails, because it can see life beyond destruction and suffering, beyond sorrow and pain.

Hope is relational. It consists of interconnections between anger, humility and courage. It faces the past, the present and the future. It nourishes and is nourished by all four basic relationships of human existence, that is, the relationship to God, to the whole of the creation, to all our fellow humans and to ourselves.

Hope empowers our desire for truth, love and justice. Anger, humility and courage provide it with energy. While hope is a gift, the active possession of this gift may imply struggle. On a personal level, we may become involved in the struggle between hope and despair. At the same time, the person who despairs is still within hope's reach, regardless of the extent to which doubt is pulling them in the opposite direction.

Hope must be understood from the perspective of love, as theologian Werner G. Jeanrond has pointed out. And love drives out fear. We are called upon to transform uneasiness and uncertainty into care and love as much as we can. Jeanrond regards love as the eschatological force par excellence. Hope is curious expectation regarding the outcome of God's project of love and our participation in it.

From this perspective we can be confident that God is involved in all true actions of hope. The cross of Christ stands at the centre of the universe, his outstretched arms embracing the whole of creation, not merely the Christian church. This way of thinking opens a truly hopeful perspective.

Statement of His Excellency Archbishop Paul Richard Gallagher

Archbishop Paul Richard Gallagher
Secretary for Relations with States and International Organizations of the Holy See

Your Eminence Cardinal Turkson,
Your Excellency Sánchez Sorondo,
Excellencies,
Distinguished Academicians,
Ladies and Gentlemen,

At the outset, I wish to thank Professor Joachim von Braun for the kind invitation to offer some concluding remarks at this Plenary Session.

I would also like to join all those who acknowledged His Excellency Bishop Marcelo Sánchez Sorondo for his precious service to the Holy Father as Chancellor of both the Pontifical Academies of Sciences and Social Sciences. Almost 24 years of tireless service! About a quarter of a century that has seen many and significant changes in the scientific field. Thank you, dear Bishop Marcelo and best wishes for your eightieth birthday, which took place yesterday.

We have come to the end of these two intense days in which the academicians and other scientists explored the driving forces and opportunities relating to basic science for human development, peace and planetary health. You did it from different points of view: astronomy, physics, mathematics, artificial intelligence, chemistry, life and atmospheric sciences, in order to find innovative ways to reduce the threats for people and our common home as well as to improve human welfare.

In front of your technical insights, I was asked to provide the perspective of the Holy See on the topic of this Plenary session – a perspective which can only start from an ethical point of view. Indeed, Aristotle stressed that ethics is the science of acting since it compares knowledge not to pure contemplation, but to praxis and action,1 and according to justice and conscious freedom, both of which are conditions specific to each person as a rational being. In fact, ethics must be understood as a discipline studying

[1] Cf. Aristotle, *The Nicomachean Ethics*.

the rules that guide and regulate human behavior, and therefore the criteria for action, while also taking into consideration both the motivations and the short and long-term consequences of decisions to be made.

From this perspective, I would briefly like to offer some reflections on the three issues addressed by this session: human development, peace and planetary health, with the hope of giving some inputs to contribute in the advancement of basic science in the awareness that science is not neutral. Engaging in science and conducting research involve choices that are anything but indifferent to the existence of the human being and the universe.

Let us start with the first topic at hand: human development. As you know, starting from Saint Paul VI's Encyclical Letter *Populorum progressio* of 1967, the Holy See adopted the concept of *integral human development*, which has been further explored in several documents of the papal magisterium, among which Benedict XVI's Encyclical letter *Caritas in veritate* on Integral Human Development in Charity and Truth from 2009. It is a development concept that brings together various dimensions, including the spiritual. As underlined in *Caritas in veritate*, "the correlation between its multiple elements requires a commitment to foster the interaction of the different levels of human knowledge [...T]he various disciplines have to work together through an orderly interdisciplinary exchange" (n. 30), marked by solidarity and inter-generational justice, while taking into account a variety of contexts: ecological, juridical, economic, political and cultural (n. 48). An orderly interdisciplinary exchange to be inspired by what we can call "caritas": "an extraordinary force which leads people to opt for courageous and generous engagement in the field of justice and peace" (n. 1). It should also be noted here that, "charity does not exclude knowledge, but rather requires, promotes, and animates it from within. Knowledge is never purely the work of the intellect. It can certainly be reduced to calculation and experiment, but if it aspires to be wisdom capable of directing the human person in the light of his first beginnings and his final ends, it must be 'seasoned' with the 'salt' of charity. Deeds without knowledge are blind, and knowledge without love is sterile [...] Human knowledge is insufficient and the conclusions of science cannot indicate by themselves the path towards integral human development. There is always a need to push further ahead: this is what is required by charity in truth. [...] Intelligence and love are not in separate compartments: love is rich in intelligence and intelligence is full of love" (n. 30). Indeed, this is my first point: promoting a true integral human development needs clear interdisciplinary collaboration, which should be inspired by a strong "knowledge and charity partnership for the common good". This is also the best way for the scientist to approach the mystery of life in wonder. This approach will help not only to unravel creation but also to continue the very work of creation with responsibility.

Oriented in this manner, integral human development, based on charity and knowledge, represents a fundamental pillar for promoting peace. Here, again, Saint Paul VI is quite clear, "Development is the new name for peace" (*Populorum Progessio*, n. 76). That is why the Holy See has continuously emphasized that a correct understanding of peace and security must consider elements not only of a political-military nature, but also of an ethical-moral, juridical and socio-economic nature as well. This is what we can rightly describe as *integral security*.2 Such "security" is not limited to a "defense through armaments", but must be "integral", that is, it must take into account all the different "facets" of security, including, for example, food security, environmental security, health security, economic security, social security. Integral security is anchored in the profound interdependence in which different actors in society coexist. To summarize, my second point is that integral human development, based on charity and knowledge, is a fundamental way of promoting peace and is strongly linked with the strengthening of integral security.

The third issue to address is planetary health. Here the papal magisterium can help us, once again. In 2015 Pope Francis published the Encyclical Letter *Laudato si'*, where he proposed the concept of *integral ecology*. This is a complex and multidimensional concept, which adopts a long-term perspective. Integral ecology cannot be reduced to the environmental dimension alone and requires an integral vision of life. This vision will not only allow us to better elaborate policies, indicators, research, investment processes and evaluation criteria, but also avoid misleading concepts of development and growth, as well as the risk of reductionism. Here we have arrived at my third point, which is that the true and interconnected realization of integral human development, integral security, and integral ecology represents a fundamental challenge to basic science by encouraging those in the field to answer to the threats facing the 21st century through trans-disciplinary dialogue.

[2] Cfr. the Contribution of the Holy See to the Tenth Session of the Review Conference of the Treaty on the Non-Proliferation of Nuclear Weapons, New York, 1-26 August 2022, *The Treaty on the Non-Proliferation of Nuclear Weapons: Ethical Dimensions and Security Challenges*.

It is not an easy task, since it requires a new vision of the world based on the ancient concept that *everything is interconnected* and, as a result, makes the response capacity of the various scientific fields more complex. This requires real scientific reform towards what many call the *pattern of sustainability*. This means decreasing what pollutes and destroys and increasing everything that safeguards and regenerates while, at the same time, learning from the precious treasure of nature.

It requires a paradigm shift *from the throwaway culture to the culture of care*.

Here, I would also like to expand the concept of sustainability to that of *integral sustainability*, based on the mandate of "cultivating and caring for" our common home (cf. Gn 2,15). These are two intimately interrelated actions concerning not only the natural environment, but also all those who live within it and share it with us, both now and in the future. We cannot care for our common home without cultivating it and vice versa. This implies relationships of mutual responsibility between human beings and nature (LS, 67). For too long this sense of "mutual responsibility" has been lacking in our societies and culture. Growing in awareness of this mutual responsibility between humanity and nature is the best way to respond to Pope Francis' hope that, "although the post-industrial period may well be remembered as one of the most irresponsible in history, nonetheless there is reason to hope that humanity at the dawn of the twenty-first century will be remembered for having generously shouldered its grave responsibilities" (LS, 165).

Let us, therefore, be cognizant of the fact that we have the ability and freedom to guide, develop and limit our power. This is a major challenge for the scientific community. However, it can be tackled through responsible commitment, based on charity and knowledge, to building the complex scientific paradigm in which integral human development, integral security, integral ecology and integral sustainability interact.

Thank you.

Words of Appreciation

H.Em. Cardinal Giovanni Battista Re

Dean of the College of Cardinals, Vatican City

https://www.youtube.com/watch?v=AfvCv9nZZpo

A 24-Year History of Service for the Pontifical Academy of Sciences

H.E. Msgr. Marcelo Sánchez Sorondo

Former PAS Chancellor, Vatican City

I would like to thank President Joachim von Braun for this special session of the Plenary devoted to a reflection on my 24 years of service as Chancellor. I would have liked to discuss in detail the important contributions the Academy has made over these years – as shown by the one hundred and twenty-five publications that are also on our website, as well as peer-reviewed publications. To these I should add the booklets that we prepare for each meeting, with enormous effort on behalf of the President, the Chancellor and the staff. Time is short and this is not the moment to do so. I will therefore limit myself to what I would call the major contributions.

First of all, I would like to answer a question I have always asked myself: why has the Pope had an Academy of natural and then social sciences since 1603, which he has maintained even in sometimes difficult circumstances? No other religion that I know of has an academy of science, and many

religious leaders have been interested in creating something similar. For the sake of brevity, I will answer in broad strokes. For the religion which we have the joy to profess: 'Christ is the Truth', as St John's Gospel says in many ways, giving a definitive answer to the question of truth. All other truth is a participation of that Truth by essence, which here we can only see by analogy, *Videmus nunc per speculum in aenigmate* (1 Cor 13:12). Therefore, the Church seeks and loves the Truth and all its participations. One of these participations is the epistemic project of the sciences. Truth is the goal of the whole universe, *finis totius Universi est veritas*, as one of the greatest thinkers, Thomas Aquinas, wrote (CG, I,1). So, the task of the sciences was and remains a patient yet passionate search for the truth about the universe, about nature and about the constitution of the human being, especially in relation to the human body and the human brain, which cannot be obtained in any other way. I like to call this form of truth, "epistemic project", according to contemporary philosophy, because in this search there have been many successes and some failures, triumphs and setbacks. However, even the interim results are a real contribution and a project for an ever-closer correspondence between the intellect and natural realities, on which later generations can build.

In addition, St John's Gospel itself indicates the fruits of this research and practice: 'The truth will set you free'. These words are perennially valid and illuminate with divine light the work of the scientists who refuse to subordinate their commitment and their research to anything but the truth and its power of liberation from all kinds of evils, such as ignorance, marginalisation, isolation, vice, hatred and violence. Truth is a good and does good. The truth of knowledge is liberating to the extent that it rises to the level of love and charity, especially towards the needy, the less fortunate and the marginalised.

The members of the Pontifical Academy of Sciences were deeply involved in this development, particularly with respect to epistemological and methodological questions as well as to interdisciplinary aspects which become ever more important in scientific research. The Academy deals with these questions and aspects not only in the context of its Plenary Sessions, for example on "Changing Concepts of Nature at the Turn of the Millennium" (R. Hide, J. Mittelstraß & W.J. Singer, 26-29 Oct. 1998), "Les enjeux de la connaissance scientifique pour l'homme d'aujourd'hui" (N. Cabibbo, P. Léna & M.S.S., 4 May 2000, in partnership with the French Academy), "Science and the Future of Mankind" (N. Cabibbo, W. Arber & M.S.S., 10-13 Nov. 2000), "The Challenges of Sciences" (N. Cabibbo & M. Sela, 23-24 Feb. 2001), "The Cultural Values of Science" (N. Cabibbo, W. Arber & M.S.S., 8-11 Nov. 2002), "Paths of Discovery" (W. Arber, J. Mittelstraß & M.S.S., 5-8 Nov. 2004), "Predictability in Science" (N. Cabibbo & W. Arber, 3-6 Nov. 2006), "The Evolution of the Universe and of Life" (N. Cabibbo & W. Arber, 31 Oct.-4 Nov. 2008), "Complexity and Analogy in Science: Theoretical, Methodological and Epistemological Aspects" (W. Arber, J. Mittelstraß & M.S.S., 5-7 Nov. 2012) or "Impacts of Scientific Knowledge and Technology on Human Society and its Environment" (W. Arber, J. Mittelstraß & M.S.S., 25-29 Nov. 2016), "Transformative Roles of Science in Society" (J. von Braun & M.S.S., 12-14 Nov. 2018), but also in conferences, workshops and study weeks, for example on, "Papal Addresses" (M.S.S., 2003), "The Educated Brain" (A. Battro, K.W. Fischer, P.J. Léna, 7-8 Nov. 2003), "Eschatology from a Cosmic Perspective" (G. Ellis & G. Coyne, 7-9 Nov. 2000), "Astrobiology" (Card. G. Lajolo & J.I. Lunine, 6-10 Nov. 2009) and "Contemplation on the Relations Between Science and Faith" (W. Arber, to Pope Benedict XVI & the members of the Bishops' Synod on 12 Oct. 2012).

So, as we have said, the first answer is that, for the Church, the epistemic project of science is a form of truth, as evidenced, inter alia, by Pope Francis' Encyclical *Laudato Si'* taking on board the conclusions reached by the Academy on global warming. This brings me to the first study week of my term as Chancellor, which was on "Geosphere-Biosphere-Climate Interactions" (L.O. Bengtsson, C.U. Hammer, 9-13 Nov. 1998). It testifies that the Academy is not only the mirror of science and the protagonist of research development, but also deals with issues related to the role of science for the common good of humanity and the planet. That study week was when Academician Paul Crutzen launched the idea of the considerable influence that human activity had on the conditions of the atmosphere, characterizing our era as the Anthropocene, i.e., an age in which human activity is the main factor of change in the biosphere. This was followed by important studies at PAS by M. Molina, V. Ramanathan and J. Schellnhuber, showing that human activity that uses fossil fuels and deforests the planet leads to global warming and health issues, as related, for example, in "Fate of Mountain Glaciers in the Anthropocene" (P.J. Crutzen, L. Bengtsson & V. Ramanathan, 2-4 Apr. 2011), "Sustainable Humanity Sustainable Nature: Our Responsibility" (P.S. Dasgupta & V. Ramanathan, 2-6 May 2014), "Biological Extinction. New Perspectives" (P. Dasgupta, P.H. Raven & A.L. McIvor, 27 Feb.-1 Mar. 2017), "Science and Actions for Species Protection. Noah's Arks for the 21st Century" (J. von Braun

& M.S.S. with partners from Natural History Museums, Zoological and Botanical Gardens, 13-14 May 2019) and in our first successful and widely disseminated e-book, *Health of People, Health of Planet and Our Responsibility. Climate Change, Air Pollution and Health* (J. von Braun, V. Ramanathan & W. Al-Delaimy, Springer Open 2020).

Other PAS meetings have also dealt with this interaction between scientific progress and social development, as well as the understanding of the epistemological structure involved and the ethical requirements, which has played an important role in the life and work of the Academy. The meetings on "Discussion on the Sustainable Development Goals" (M.S.S. & J. Sachs, 27 May 1999), "The Cultural Values of Science" (N. Cabibbo, W. Arber & M.S.S., 8-11 Nov. 2002), "The Signs of Death" (J.L. Bernat, C. Estol & M.S.S., 11-12 Sep. 2006) and on "Human right to Water" (Card. C. Hummes, L. Liberman & M.S.S., 23-24 Feb. 2017) testify to this persistent commitment. As proved by our meetings on "Bread and Brain, Education and Poverty" (A.M. Battro, I. Potrykus & M.S.S., 4-6 Nov. 2013) and "Big Data and Science" (W. Arber, T. Gojobori & R. Vicuña, 17-18 Nov. 2015), information technologies and the digital processing of information have transformed our way of life and our way of communicating in space and time over the last decades. Consequently, today we must consider connectivity as part of human dignity insofar as it responds to our relational being in search of truth, goodness and beauty, and therefore consider "Connectivity as a Human Right" (J. von Braun, R. Prodi & A. Battro, 10 Oct. 2017).

In this line of interaction, PAS has always had in mind the application of science to global food problems and, in particular, to solve the tragedy of hunger. The proceedings of the study week on "Reduction of Food Loss and Waste at the Beginning of the 21st Century" (J. von Braun, 11-12 Nov. 2019), and "Science for Survival and Social Development" (V.I. Keilis-Borok & M.S.S., 12-16 Mar. 1999), highlighted the special role of modern biotechnology in the improvement of plant characteristics.

In view of the distorted way in which these scientific results, and in particular those concerning genetically improved plant varieties, have been presented to the public, the Academy in the meeting "Transgenic Plants for Food Security in the Context of Development" (I. Potrykus, W. Arber & N. Cabibbo, 15-19 May 2009) identified and embraced beneficial new technologies for more precise and targeted improvements in agricultural plants, involving targeted alterations to the genome sequence or the transfer of specific genes from one organism to another. All food plants have been genetically modified in the past; such modification is therefore a very common process in both nature and in human activity. In short, as Emeritus President Werner Arber has repeatedly stated, especially at the Bishops' Synod on *The New Evangelization* at the invitation of Pope Benedict XVI ("Contemplation on the Relations Between Science and Faith", 12 Oct. 2012), "these genetic modifications are nothing more than a copy of the evolutionary processes in nature". So, genetically modified food plants, if they follow the dictates of science and ethics, can play an important role in improving agricultural products and human nutrition, as well as contributing to solve the problem of world hunger (St John Paul II, 2000). The clearest example is the so-called "golden rice" developed by our Academician I. Potrykus, a genetically modified rice variety that incorporates the genes needed to create a precursor of vitamin A, a deficiency which affects millions of people. This is just one of several plant modifications that have the potential to produce healthier food for everyone.

A synthetic approach to both the problem of climate change and the problem of food and hunger is pursued by President Joachim von Braun, using basic science as a platform for resilience to human and planetary challenges, especially hunger. This very topical approach started with the meeting on "Food safety and healthy diets" (12-13 Sep. 2018), continued with "Food loss and waste reduction" (Nov. 2019), and fully developed in "Resilience of people and ecosystems under climate stress" (V. Ramanathan, 13-14 July 2022) with the recognition of the multiple and interconnected current challenges, be it climate, biodiversity loss or inequality, in search of a science-based, holistic solution.

From the point of view of cosmology and anthropology, the results of the meetings on "Evolving Concepts of Nature" (2014) and "Sustainable Humanity, Sustainable Nature: Our Responsibility" (2014) show that cosmology between the end of the 20th century and the beginning of the 21st century is increasingly improving our understanding of the place of humans and their planet in the universe. The "wonder" (τὸ θαυμάζειν) that Plato and Aristotle put at the origin of thought is today witnessed in a particular way by astrophysical and physical sciences. Questions about the origin of the world are now being re-examined, thanks to the reflections of those who study the physical universe, its history and its laws. Encounters such as "Subnuclear Physics: Past, Present and Future" (W. Arber & A. Zichichi, 30 Oct.-2 Nov. 2011) have enabled us to understand the basic components of matter, and we are on our way to an increasingly coherent and unitary understanding of the whole structure of natural reality, which we have discovered is made up not only of matter and energy, but also of information and form. The latest developments in astrophysics are also particularly striking: they further confirm the great unity of the universe, which becomes clear at each new stage of our understanding of reality. Biology too, with the development of genetics, makes it possible to penetrate into the fundamental processes of life and to intervene in the gene pool of certain organisms by imitating some of these natural evolutionary processes, as demonstrated, for example, by the meetings on "New Developments in Stem Cell Research: induced Pluripotent Stem Cells and their Possible Applications in Medicine" (16-17 Apr. 2012), "Evolving Concepts of Nature" (24-28 Oct. 2014), "Cell Biology and Genetics" (23-24 Oct. 2017), to a large extent organised by W. Arber, N. Le Douarin and E.M. De Robertis, as also more recently by E. Fuchs and H.M. Blau on "Looking to the Future: Stem Cells, Organoids and Regenerative Medicine" (5-6 May 2022).

Beyond planetary and social emergencies, the Academy has organised numerous study weeks on human beings, their origins, their bodies, the masterpiece that is their brain, and their death. For example, the meeting on "Neurosciences and the Human Person" (8-10 Nov. 2012) organised by our Academicians A. Battro, S. Dehaene, and W. Singer, highlighted the areas in which the scientific approach is advancing and which are at the heart of what it means to be a human person. The rediscovery of the centrality of the human brain and its evolution relative to higher mammals, the processes of consciousness, the capacity for evaluation, decision-making and self-control, the formation of beliefs in a social group, the sense of self, the importance of education for the development of the human brain, as well as the philosophical explanation of the human soul as an incorruptible form from the activities of knowing and willing that give the body being and life, are amalgamated in a new synthesis that shows the status of the human being in times of the predominance of knowledge provided by the natural sciences. In addition, PAS has not neglected the major theme of the main stages of human morphological and cultural evolution with the workshops on "What Is Our Real Knowledge About the Human Being?" (N. Cabibbo & M.S.S., 4-6 May 2006), "Émergence de l'être humain" (Card. R. Etchegaray, H. de Lumley & M.S.S., Apr. 2013) and "Who was who and who did what, where and when?" (Y. Coppens, Apr. 2019). In this respect I also find very important the conclusion of the recent meeting on "Symbols, Myths and Religious Sense in Humans Since the First" (Y. Coppens & M.S.S., 27-28 Oct. 2021), organised by our Academician Y.

Coppens, who passed away very recently. Some of us would tend to trace the notion of "religious" sense back to 10 million years ago, to the age of the common ancestors of Chimpanzees and Humans; others would, on the contrary, wait for biological evidence (level of cerebral complexity) or archaeological evidence (manufactured objects, burials, rock art) before daring to attach "religious sense" to a Prehuman (Lucy, for example) or to a Human. But whether this sense is 10 million years old, 3 million years old or 500,000 years old, "one fine day" (which can be of a certain, progressive, duration), a "soul (ἡ ψυχὴ τὰ ὄντα πώς ἐστι πάντα)" (Aristotle, *De anima*, 431 b 20) does emerge from a long history of 14 billion years of Matter and 4 billion years of Life, giving unity to the Hominidae family whom, despite its hitherto unsuspected antiquity, we can thus call Human.

It is impossible to list here the many other discoveries and results that have expanded our knowledge and influenced our individual and social view of the human being and the world that the Academy has dealt with in this passage of the century: from advances in computational logic to the chemistry of materials, from "Education for the Twenty-First Century" (N. Cabibbo, P.J. Léna & M.S.S., Nov. 2001) and "The Educated Brain" (A.M. Battro, K.W. Fischer, & P.J. Léna, PAS & Cambridge Univ. Press, Nov. 2003) to "Children and Sustainable Development: A Challenge for Education" (P. Léna & A. Battro, 13-15 Nov. 2015) and "Narcotics: Problems and Solutions of This Global Issue" (Queen Silvia of Sweden & M.S.S., Nov. 2016), from "Emerging Basic Science Toward Solutions for People's Wellbeing" (J. von Braun & M.S.S., Nov. 2018), from "The Revolution of Personalized Medicine" (A. Ciechanover, 8-9 Apr. 2019) to "Science's Chances of addressing Covid for Survival" (J. von Braun, Oct. 2020), and "Impacts of Scientific Knowledge and Technology on Human Society and its Environment" (W. Arber, 25-29 Nov. 2016). Particularly topical in this regard is the meeting on "Robotics, AI and Humanity: Science, Ethics and Policy" (J. von Braun, M.S.S. & S. Zamagni, Springer Nature 2021) which continues the line of research undertaken with "Power and Limits of Artificial Intelligence" (W. Arber. A.M. Battro & S. Dehaene, Dec. 2016) on the idea that robots and AI are human-made instruments that can make the world a better place if they are united for the common good and the greater good of peace. Indeed, if technological progress increases inequalities, dependence, violence, arrogance and war, it is not true progress.

I do not want to conclude without noting another intense field of activity of the Academy, following an explicit request from Pope Francis.

Among the challenges facing the Church and the world today is the evil of human trafficking and modern slavery, the fight against which Pope Francis has led so courageously throughout his Pontificate, with the strong support of the Academy from the beginning of his mission. The trade in human beings is something that the Pope witnessed first-hand when he was Archbishop of Buenos Aires and which he then brought to our attention. Such indications from the Pope, coupled with the Academy's accumulated scientific experience, led to the development of many initiatives and meetings devoted to the fight against human trafficking and to the worldwide abolition of slavery. On 2 December 2014, at our headquarters in the Casina Pio IV, Catholic, Anglican, Muslim, Hindu, Buddhist, Jewish and Orthodox religious leaders signed a Joint Declaration of Religious Leaders Against Modern Slavery as a public statement of their commitment to work together in spiritual and practical action to eradicate this crime against humanity and restore dignity and freedom to its victims: "Modern slavery, in terms of human trafficking, forced labour and prostitution, organ trafficking, and any relationship that fails to respect the fundamental conviction that all people are equal and have the same freedom and dignity, is a crime against humanity". This decisive statement was prepared at the meeting on "Trafficking in Human Beings: Modern Slavery" (Card. R. Etchegaray & M.S.S., 2-3 Nov. 2013). Thanks to the Academy's intervention in a meeting at Casina Pio IV in 2015 with UN Secretary-General Ban Ki-moon, addressing trafficking is part of the UN Sustainable Development Goals. In fact, Target 8.7 of the Sustainable Development Goals (SDGs) states that countries will "Take immediate and effective measures to eradicate forced labour, and modern slavery and human trafficking, and ensure the prohibition and elimination of the worst forms of child labour, including the recruitment and use of child soldiers, and by 2025 end child labour in all its forms". In recognition of this, the Pontifical Academy of Sciences organised a meeting on "Modern Slavery and Climate Change: The Commitment of the Cities" (M.S.S., 21 July 2015) with the Mayors of many prominent cities of the world, and hosted the 2017, 2018 and 2019 Summits of "African Women Judges Trafficking in Persons and Organized Crime", to convene female judges, religious leaders, philanthropists, and academics to strategize about how to accelerate legal action to combat human trafficking across Africa. It is above all a question of recognising and being aware of the problem. Unfortunately, the new forms of slavery that go hand in hand with poverty, illiteracy, unemployment, isolation and inequality do not only affect migrant peoples, but also and above all take place in our countries, however developed they may be, in our states or provinces, in our cities, and tragically even in more families than one could imagine. What we also need to prevent modern slavery are more appropriate laws and the application of existing good laws. The human body, the image of God incarnate, cannot be bought or sold either in part or as a whole; it is only given freely for love. For example, the so-called Nordic model to combat prostitution is based on the principles that no human body should ever be for sale or purchase, and that demand is one of the main causes of prostitution. It criminalises the buyer, while the trafficked person is viewed sympathetically, as a victim. Prostitution has declined in countries where this model has been introduced, as trafficking activities bleed profits. Lastly, it is necessary to take care of the rehabilitation of the victims so that they can be reintroduced into society with jobs for the common good. An important lesson learned from the experience of the various good practices in this context is that a long-term strategy including rescue, reception, human and religious education, job or even vocational training, legal support and social integration is required to ensure the reintegration of victims into society. No less decisive have been the PAS meetings organised by our Academician Dr Francis Delmonico for the establishment of ethical standards in organ donation and transplantation, as well as for access to organs and tissues for all, in order to prevent the crime against humanity of organ trafficking and transplant tourism. At the "Summit on Organ Trafficking and Transplant Tourism" (F. Delmonico, Feb. 2017), the PAS joined WHO and the Transplantation Society in endorsing the Concept of National Self-Sufficiency which dictates that a nation should address its burden of end-stage organ disease with strong living and deceased donation programs, and combat as criminal the use of vulnerable people for organ trafficking.

Looking back on this Academic year, I note with admiration and appreciation the many important PAS declarations aimed at overcoming the various emergencies that afflict us, whether on "Science and innovations for a sustainable food system" (J. von Braun in collaboration with the UN Food Summit – 21-22 Apr. 2021); on the "Health of the Seas and Oceans" (J. von Braun & R. Danovaro, 8 June 2022); or to strengthen "Resilience of People and Ecosystems under Climate Stress" (J. von Braun & V. Ramanathan, 13-14 July 2022). Equally important are the meetings and declarations on "Reconstructing the Future for People and Planet" (H.J. Schellnhuber, 9-10 June 2022) in a sustainable way thanks to bioeconomy, and on "Covid-19: New Insights" (J. von Braun, 4-5 Nov. 2021), addressing the health problems caused by the pandemic with equity-oriented action. The second Summit on "The Role of Science in the Development of International Standards of Organ Donation and Transplantation" (F. Delmonico, 21-22 June 2021) was also decisive in the fight against human trafficking. The workshop on "Dreaming of a Better Restart" (J. von Braun, S. Zamagni & G. Beliz, 14 May 2021) in collaboration with our sister Academy, the PASS, was crucial to focalize attention on the socio-economic problems of the IMF debt of many countries.

In addition, our Statement on the need to engage science and politics to "Preventing Nuclear War and War Against Civilian Populations" (J. von Braun & M.S.S., 8 Apr. 2022) was particularly appreciated and timely. The existence of nuclear weapons poses serious security and safety threats to the countries possessing them and to the whole world. The Academy has always promoted "Science for peace" (N. Cabibbo & W. Arber, Jubilee Plenary Session, 10-13 Nov. 2020) and has spoken out fervently since the beginning of the nuclear age on the need to prevent the further use of nuclear weapons at all costs by proposing universal disarmament, as in the meeting "Less Nuclear Stocks and More Development" (Card. S. Tomasi & M.S.S., 10 Nov. 2014) with experts from the Holy See and the Russian Orthodox Church, as well as from other countries like U.S., Russia, Italy, Norway, etc. and institutions as the UN, Global Priorities, etc.

In brief, it is remarkable how the President and the Academicians who organised these meetings picked up on current challenges by identifying specific scientific opportunities to address each of these problems and to work with experienced people who know how to use science to solve them.

Last but not least, I would like to thank God "from whom every gift comes" for having given me the health, strength and grace to carry out this important service to the Church and to humanity for 24 years. I do not want to end without special thanks to St John Paul II, the Pope who appointed me, as well as to Benedict XVI and Francis, who confirmed me, for their solicitude towards me and the Academy. I would also like to thank Nicola Cabibbo (who died in August 2010, when he was still President of our Academy), President Emeritus for Life Werner Arber, and of course, Joachim, with whom I have developed close ties of friendship and to whom I owe support and trust, without which nothing could have been done.

I thank all those who, in one way or another, have proactively participated in PAS activities. In particular, I would like to express my thanks to the Cardinal of Honduras, Oscar Rodríguez Maradiaga, advisor to the Pope, for his admiration for the Academy and his willingness to collaborate and build a bridge with our beloved Pope Francis. Our shared wish is that he becomes a member of PAS. I would also like to thank dear Cardinal Turkson for accepting to be my successor as Chancellor, and I wish him every success in this decisive position for the good of the Church and humanity in these scientific times. I also thank Bishop Robert Barron for his participation and excellent lecture, as well as Archbishop Dr Dr hc mult Antje Jackelén for her participation and important theological concepts.

I would like to quote Pope Pius XI, who increased the Academy's prestige by making it the Pope's own "scientific senate" and who gave it its beautiful headquarters in the Casina Pio IV, when he said that "Amongst the many consolations with which divine Goodness has wished to make happy the years of our mission, I am happy to place that of our having being able to see not a few of those who dedicate themselves to the studies of the sciences mature their attitude and their intellectual approach towards religion. Science, when it is real cognition, is never in contrast with the truth of the Christian faith. Indeed, as is well known to those who study the history of science, it must be recognised on the one hand that the Roman Pontiffs and the Catholic Church have always fostered the research of the learned in the experimental field as well, and on the other hand that such research has opened up the way to the defence of the deposit of supernatural truths entrusted to the Church".

I would like to endorse the intentions and wishes expressed by fellow Academician Max Peruz in his letter to me shortly before his death: "Since 1961 I have attended and organised many study weeks and enjoyed that privilege very much, but the greatest privilege was to be a member of that unique body, a truly international Academy, covering all the natural sciences. I came across there many more people whom I would never otherwise have met, such as the Indian physicist Menon, and then there was the wonderful setting, that Renaissance court, overlooking the back of St Peter's like the view of the Matterhorn from Zermatt. I think the Pontifical Academy is a unique institution and I very much hope the Holy Father and his successors will continue to give it their support. I would be delighted if you were able to communicate any of this letter to the Holy Father and assure him again how much I appreciated my Membership" (*The Cultural Values of Science*, ed. cit., p. XXXII).

What is it that unites this quarter-century-long quest to all the research done by the Academy since its creation in 1603 if not the selfless love of truth? The testimony given by the Presidents of the most important Academies of the world on the occasion of the celebration of the "Four-Hundredth Anniversary of the Pontifical Academy of Sciences 1603-2003" (N. Cabibbo & M.S.S., 9 Nov. 2003) proves this point. May this Pontifical Academy be recognised and admired by future generations precisely for this epistemic project of truth that is science carried forward by the Academicians of the PAS with no other interest than truth and its fruits of liberation.

I want to end by saying that I feel like the "useless servant" of the Gospel of Luke, because all the good I have done derives from divine help and the collaboration of Academicians and staff, many of whom have become true friends. Errors and omissions are my own, for which I apologise. Thank you very much!

Commemorations of Deceased Academicians

Commemoration of Yves Coppens († 22 June 2022)

I was saddened to learn about the passing of French Paleoanthropologist Yves Coppens yesterday. He was among the leading paleontologists not only in France, but also globally.

His leadership in making discoveries in many parts of Africa, his efforts in mentoring, co-mentoring and supporting numerous students and young scholars, many of whom currently hold prominent positions and continue to train others, his contribution to raising and addressing broader issues in early hominin studies, his endeavor to popularize our field, which is often misunderstood in the public sphere and his commitment to educate those at the helm of power so the field of human evolution gets deserved attention and needed funding, are among his key contributions to paleoanthropology and science broadly.

Professor Coppens was also my PhD adviser and co-mentored my research at the University of Paris along with Dr. Denis Geraads of the CNRS. I am grateful to both and will take this sad occasion to express my gratitude to Prof. Coppens for his support. I saw Prof. Coppens last at a scientific gathering in 2019, and his passion and excitement about discoveries and his humorous, civilized and engaging attitude toward scientific discourse was intact. Out of that gathering came a book, which he co-edited at the age of 85! I look forward to gathering with those who knew him and his work to celebrate his life and pay tribute to his contributions.

Zeray Alemseged

Commemoration of Paul J. Crutzen († 28 January 2021)

Paul Crutzen died in January 2021 at the age of 87 years. He was Director of the Atmospheric Chemistry Department at the Max Planck Institute for Chemistry in Mainz, Germany, from 1980 to 2000.

Together with our Academician colleague Mario Molina and with F. Sherwood Rowland, he received the 1995 Nobel Prize for Chemistry for identifying how nitrogen oxides erode the earth's ozone layer, and for discovering the chemical processes that cause the ozone hole.

He became a Pontifical Academy of Sciences member in 1996.

He was the first to show how human activities damage the ozone layer. This knowledge about the causes of ozone depletion was the basis for the worldwide ban on ozone-depleting substances, a unique example of how basic science can directly lead to a global political decision serving people and planet.

Paul Crutzen's scientific work focused on the impact of humans on the atmosphere, climate and earth system. In addition to his research on atmospheric chemistry and the ozone hole, he also examined the potential consequences of a global nuclear war.

In the early 1980s, together with John Birks, he discovered that a darkening of the earth's atmosphere from the fires ignited by nuclear war would lead to a nuclear winter, resulting in a dramatic decline of the earth's habitability.

His findings were essential contributions to the global efforts and achieve achievements in nuclear disarmament. This was science for peace.

Paul Crutzen coined the term "Anthropocene", which he used to describe the current era in which human activity is shaping our planet through the profound influences in global atmospheric, biological and geological processes.

He commented on the scientific and social debates that followed his proposal on the concept of the Anthropocene. Together with his friend Professor Ramanathan, he warned early on the drastic measures that are needed at the international level to reduce the concentrations of greenhouse gases, in particular CO_2, through energy savings, renewable energy sources and sequestration of CO_2.

Paul Cruzten discussed the extent to which mankind exploits the natural resources of planet earth in numerous publications and public lectures. He typically ended presentations with a picture of himself and his grandson, calling on the audience to preserve the earth for future generations.

We pray for him and always remember our great colleague.

Joachim von Braun

Commemoration of Beatrice Mintz († 3 January 2022)

Beatrice Mintz was a pioneer. She earned her PhD from the University of Iowa in the 1940s. She then accepted a professorship at the University of Chicago before transitioning to the Fox Chase Cancer Research Center in 1960 so that she could exclusively focus on her research. She spent much time in the lab, building her own equipment and conducting most of her experiments personally. She was known for being efficient, organized, and self-sufficient, and for being a demanding but kind and supportive mentor. She delighted her coworkers with poetry featuring mice and by building mouse snowmen.

Mintz established herself as a thought leader in multiple fields, most notably developmental biology and cancer research. She would pose large questions and answer them. Much of her developmental biology work revolved around how complex tissues could arise from a single cell. Using chimeric mice she established the clonal origin of lineages for the pigment system, hematopoiesis, the somites, vertebrae, the skull, and muscles. She also was a pioneer in the development of mouse transgenic models, creating new mouse lines, initially by injection of DNA into blastocysts and later into the pronucleus. Her work was critical to our understanding of how relatively few embryonic stem cells generate the remarkable complexity of the fully developed animal.

Mintz's work on cancer was crucial to our understanding of how the cell's microenvironment contributes to the development of cancer. She placed tumorigenic teratoma cells into a normal mouse blastocyst and showed that the tumor cells became "normalized" by the embryonic environment and were able to generate tumor-free mice. This work clearly established that cancer is not only caused by genetic changes, but also by epigenetic alterations that can be reversed, a branch of cancer biology that is actively studied today. She also created a new model for melanoma research. Her transgenic mouse model showed that the melanoma tumor cells metastasized into skin and eye, and provide key insights into the complexities inherent to the development of melanoma.

Mintz won numerous awards during her career. She won a Fulbright Fellowship in 1951 to study at the Universities of Paris and Strasbourg. She was elected to the National Academies of Science in 1973, the President's Biomedical Research Panel in 1975, the American Association for the Advancement of Science in 1976, the American Academy of Arts and Sciences in 1982, and the American Association for Cancer Research in 2013. She was the first recipient of the Genetics Society of America Medal (1981), the Ernst Jung Gold Medal for Medicine (1990), and the March of Dimes Prize in Developmental Biology (1996). She was also awarded the New York Academy of Sciences Award in Biological and Medical Sciences (1979), Lewis S. Rosenstiel Award in Basic Medical Research Brandeis

University (1980), National Medal of Honor for Basic Research, American Cancer Society (1997), the Pearl Meister Greengard Prize, Rockefeller University (2008), the Szent-Györgyi Prize for Progress in Cancer Research, National Foundation for Cancer Research (2011), and the Lifetime Achievement Award, American Association for Cancer Research (2012).

Beatrice Mintz was a force of nature and a pioneering scientist at a time when few women were recognized. Her innovative research had a major impact on our understanding of development and cancer. She will be greatly missed.

Helen M. Blau

Commemoration of Enrico Berti († 5 January 2022)

Enrico Berti's training was essentially philosophical and for this reason, perhaps, he said that he "did not feel worthy to belong to this famous Academy, composed mainly of renowned scientists". He studied philosophy at the University of Padua, which was a famous center for the dissemination of Aristotelianism during the Renaissance, and has preserved some traces of this tradition to this day. He was professor of philosophy at the universities of Perugia, Geneva and Brussels, as well as professor of philosophy in Padua, where he directed a Centre for the history of the Aristotelian tradition. As a renowned philosopher he was elected member of the Accademia Nazionale dei Lincei (Rome), which participates with our Pontifical Academy of Sciences in the heritage of the ancient Accademia dei Lincei, the Academy of the Lynxes, the leader of which was Galileo Galilei. As a philosopher, Berti was elected member of the Institut International de Philosophie (Paris). As President of the International Programme Committee, he organised the 21st World Congress of Philosophy on behalf of the FISP (Fédération Internationale des Sociétés de Philosophie).

If someone generously proposed his name for this Academy, there must be a reason and I suppose it has to do with the main field of his vast philosophical interests, and that is the philosophy of Aristotle. He devoted many years of his life to this philosopher and to the history of his influence on European culture, with the result that he is known essentially as a scholar of Aristotle. The study of Aristotelian philosophy obviously gave him the basis to develop some important reflections in most fields of philosophical thought: logic, philosophy of language, philosophy of nature, metaphysics, ethics, politics, cosmology, etc. Moreover, as Aristotle was not only a great philosopher, but also a great scientist, especially in the fields of biology, psychology, anthropology and human sciences, the study of his works necessarily implied for Berti an interest in ancient and modern science as a whole. And since Aristotle's thought influenced the history of science throughout antiquity and the Middle Ages, not only in Christian countries but also in Muslim countries, the reconstruction of the Aristotelian tradition obliged him to study the sciences of late antiquity and the Middle Ages in their entirety.

In modern times, as is well known, Aristotle's thought was abandoned and rejected by the development of some sciences such as astronomy, mechanics and chemistry, and this rejection led to some extent to the birth of modern science. But Aristotle's teaching still has a fundamental role in the development of other sciences, such as biology, medicine and human sciences (psychology, linguistics, rhetoric). And even where Aristotle's influence was rejected and opposed, his logic and method remained a model for modern science.

In his studies on the presence of Aristotelian philosophy in the 19th, 20th and early 21st centuries, Berti showed that this influence was decisive not only on philosophers such as Hegel, Trendelenburg, Brentano, Moore, Heidegger, Gadamer, Austin, Ryle and others, but also on scientists such as Darwin, Jacob, Delbrück, Mayr, Prigogyne, Thom and others. The French mathematician Réné Thom, for example, experienced a real rediscovery of Aristotelian physics in his last years. For these reasons, Berti thought that it was impossible to adequately study Aristotle's philosophy and its connections with the contemporary philosophical debate without knowing the state of the discussion in the main fields of contemporary science. His important contributions to the PAS had compelled him to become involved in some of them, not as a philosopher of science, nor as a logician analysing the methods of science, but as a philosopher deeply interested in the contents of contemporary sciences in order to understand the universe, the planet and the condition of the human being in a cognitive world where science predominates. It can be said, therefore, that his work has contributed to some extent, quite decisively, to the new vision of the world that has shaped the Academy in this quarter of a century.

+ Marcelo Sánchez Sorondo

Commemoration of Michael Sela († 27 May 2022)

Michael was a giant in immunology, but not only. He was born in Poland in February of 1924 and immigrated in 1941 to what was then British Palestine, which in 1947 became the Independent State of Israel. He started to study Life Sciences in the Hebrew University of Jerusalem. In 1946 he received his Master's Degree. He then stopped his scientific career and moved to Italy to help bring Jewish Holocaust refugees from Europe to Israel. He then continued to work in the Israeli Embassy in Prague, Czechoslovakia and helped procure weapons for the newly-born Israeli Army that helped it enormously to win the War of Independence. In 1950 he joined the Weitzman Institute of Science, of which he later became the President, and established there a brilliant career working mostly on synthetic antigens.

This work led him to identify an antigen involved in the pathogenesis of multiple sclerosis against which he and his colleagues, Dvora Teitelbaum and Ruth Arnon, developed a very successful drug, Copaxone.

Michael received numerous prizes for his work, including the Israel Prize, the most prestigious Israeli accolade, the Wolf Prize and the Otto Warburg Medal. He was a member of numerous learned bodies, including the Israeli National Academy of Sciences and Humanities, the U.S. National Academy of Sciences and, of course, the Pontifical Academy of Sciences.

His life covered much more than science. He was a lover of culture, in particular of classical music and the Opera, and donated generally, as a philanthropist, along with his wife Sarah, to the Israeli Philharmonic Orchestra and the Israeli Opera. Many of his trainees are scattered all over the world in academia and industry. Some made breakthrough achievements of their own, like Zelig Eshhar, who developed the CAR T treatment. What a luminous career! May his memory be blessed.

AARON CIECHANOVER

Self-Presentations of New Academicians

Zeresenay Alemseged

https://youtu.be/20Fl-p9o5tk

Chien-Jen Chen

https://youtu.be/3XJHj-JUYPs

Jennifer Doudna

https://youtu.be/KEgFujWGICo

Edith Heard

https://youtu.be/OS6xuNqSNmE

Stanley Prusiner

https://youtu.be/LZSIW-eZasc

Susan Solomon

https://youtu.be/xaSQslMBJCo

Ewine F. van Dishoeck

It is a true honor to be elected as an Academician to this fantastic Academy. I was born and raised in Leiden, The Netherlands, a small well-known university town and it is also where I spent most of my professional career. My parents had given me at birth a saying that proved to be very characteristic of the rest of my career, *vires acquirit eundo*, from Virgil's *Aenead*. Loosely translated it means, "she gathers her strengths *en route*": basically, as you go along, step by step, you gather your knowledge and your strength.

For high school I attended a grammar school with lots of Latin and Greek and I did not get my first days of science until, as a teenager, we spent six months in San Diego where I was enrolled at a public high school. Thanks to a wonderful African American teacher, I was introduced to science. Because I also had a good chemistry high school teacher in The Netherlands, I went to study chemistry at the University, but I discovered there that I liked physics just as much and so I became a quantum chemist, as we call it. I was determined to continue my career in that area, were it not for the fact that the professor had passed away and there was not going to be a successor for a long time.

These are the unusual things that happen in a person's life. It was my then boyfriend and now husband, Tim de Zeeuw, who actually just had a lecture on molecules in space – they were being discovered then – and he said, "Isn't that something for you?" One thing led to another and I was introduced to the world's expert at Harvard, Professor Alexander Dalgarno, and that is how my launch into becoming an astrochemist was initiated. The interstellar medium is really a wonderful chemical laboratory in order to study basic molecular processes; my own focus has been on how molecules fall apart by UV radiation.

After my PhD I went to Harvard as a junior fellow, then to Princeton, both the Institute and the University, and then I was attracted as a faculty member to the California Institute of Technology, the Planetary Sciences Division, where I spent two fruitful and formative years.

After six years in the U.S. we went back to The Netherlands and there, over the last 30 years – and blessed by a fantastic group of PhD students and postdocs – we have been working towards the scientific goal of elucidating the origins of stars and planets, how are they formed, and especially following the trail of molecules from clouds to disks and more recently from disks to planets. My research has a special focus on water but we also study other small and more complex molecules, both in the gas and ice. Our astrochemical work in Leiden, with my colleagues, combines the "golden triangle" of observations, laboratory experiments and models.

Astronomy is driven by large facilities and I have been fortunate that, during my career, some of the major parts of the electromagnetic spectrum have been opened up, both from the ground and by space missions; and exactly those parts of the spectrum that we need for studying molecules, namely the infrared and the millimeter parts where they have their vibrational and rotational transitions. But all of these big telescopes have very long lead times, 20 to 30 years, and so therefore I have also spent significant time and effort to make them happen, together with many of my colleagues across the world. The Herschel Space Observatory, the Atacama Large Millimeter Array and, most recently, the James Webb Space Telescope with which I became involved in the late 1990s.

In addition, I firmly believe that it is the responsibility of all scientists to contribute to science and society in a broader fashion and so, in addition to serving and working on the many big telescopes, I also put in significant efforts to bring people together both in terms of different disciplines and in making them work together. I have been the Director of The Netherlands Research School for Astronomy, NOVA, for the past fourteen years, i.e., and the alliance of all Dutch universities with an astronomy department which together carry out a joint research and instrumentation program. I have also been President of the International Astronomical Union for the last three years, working there with 12000+ members from >100 countries not just on science and organization of conferences, but especially in using astronomy as a tool for education at school level, for public engagement and for capacity building in the developing countries, using as our motto that "*we are all world citizens under the same beautiful sky*".

I have a personal passion for outreach to the general public and a special interest in art and astronomy. In 2019, I co-curated an exhibition on *Cosmos: Art & Knowledge* in the Leiden Boerhaave science museum, and in 2022 *Toward the beginning: science and art with the James Webb Space Telescope*, in the Gallery of the Leiden University Hospital.

I look forward to using these experiences that have spanned across the world to work with all of you here at the Academy. Thank you very much.

Elaine Fuchs

I was appointed in 2018, but I was unable to attend my induction ceremony. Then the pandemic hit in 2020, moving the meeting to a virtual format and postponing my induction again. Now, through virtual meetings, a 2022 workshop which I co-organized for the Vatican and finally this in-person September meeting, I've had the opportunity to witness how valuable and important this Academy is for the world of science, for bridging different disciplines and sharing different perspectives for positive outcome. I am so fortunate to be a part of this wonderful Academy and its mission.

In my own scientific career, I was initially trained as a physical chemist. As a graduate student at Princeton University, I then began working in carbohydrate chemistry. As I neared completion of my PhD studies, I heard a seminar by then the late Howard Green, who was able to take a piece of human skin and isolate from it cells that he could passage endlessly without their losing the ability to make skin. I soon joined his lab at MIT, where I began a career at the biomedical interface, bringing molecular biology to the fascinating problem of how cells within our body are able to make and repair tissues.

The cells that we were culturing from skin were the first tissue stem cells that were ever cultured in a lab. Howard Green went on to use that technology for the treatment of burn patients. It is still in place today. I was interested in how these adult stem cells worked, what gave them these properties to divide endlessly to be able to make tissue and repair tissue.

It turns out that every tissue of our body has reservoirs of tissue stem cells that are dedicated to be able to replace dying cells and repair damaged tissue. We're losing 80 billion cells a day from our body, and the stem cells of our body repair and replace them.

As a young Professor, I elucidated the genetic basis of a group of different blistering skin disorders. Knowing the genetic bases for inherited childhood skin disorders has served as the platform for gene editing and gene replacement to correct defects in the skin of affected children, work that has been done by a colleague of mine, Michele de Luca. The pioneering technology of Green has also been used to culture corneal epithelial cells and restore corneal blindness. In the current decade, the field now has the ability to culture and study the properties of a many different tissue stem cells. Cell and organoid culture has revolutionized the field of stem cell biology as we know it today and the use of stem cells in a regenerative setting.

So, over my independent career beginning at the University of Chicago with the experience that I've described to you, but then also continuing at Rockefeller University for the last twenty years, I continue to work on how stem cells divide, how they make tissue, how they repair wounds. As we understand more and more about the process, it has allowed me to focus on how stem cells in tissues cope with the stresses of our environment. Our skin is exposed to not only wounds, but also mechanical stress, ultraviolet radiation, noxious agents, pathogens, infections and allergens. By understanding how the stem cells in the tissue respond, we can begin to understand how the stem cells go awry in disorders such as chronic inflammatory disorders and cancer. For instance, in the treatment of cancers, what often makes people sick is that the therapeutics harm our normal tissues as well as our cancer tissue. It's our premise that if we can understand enough about the differences between normal stem cells and cancer stem cells we should be able to design therapeutics that will kill the cancer cells without harming the normal stem cells. So those are the kinds of experiments that my students and postdocs are doing now in the laboratory. With regards to inflammatory disorders, we discovered that stored within the DNA of its nucleus, a skin stem cell retains memories of its past experiences. 'Epigenetic memory' enables the cell to repair wounds faster the next time skin encounters an injury. It enables tissues to respond to pathogens it has never encountered before. But it also has downsides – heightened reactions to inflammation and possibly even increased susceptibility to cancer. We're working on how we can erase the bad memories that stem cells have that contribute to chronic inflammatory disorders and still keep the good memories that stem cells have in terms of being able to repair wounds. These kinds of avenues continue to inspire me after four decades of research in tissue stem cell biology.

Jane Lubchenco

Thank you, Mr President. It is a great honor to introduce myself to this esteemed group. Instead of summarizing my C.V., I plan to share a little about how I see my work and what it is telling us. (A short bio appears at the end.)

I'm an ecologist and environmental scientist. My research focuses on interactions among species in an ecosystem and between the environment and human well-being. I focus on connections. I see the world and its components as complex adaptive systems. Especially at a time of global challenges such as climate change, loss of biodiversity and inequity, scientific insights about human-environment interactions and findings about which features of complex adaptive systems lead to resilience are urgently needed and immediately relevant.

My research on climate change, biodiversity, and ocean ecosystems has been both 'basic' and 'use-inspired' (as defined by Donald Stokes in his *Pasteur's Quadrant* to mean producing fundamental advances in knowledge that are immediately relevant to societal challenges). In addition to producing and leading scientific advances, I focus on engaging with society, sharing scientific knowledge widely, making it accessible, and training and empowering scientists to be effective communicators and co-produce solutions. Scientific knowledge is more relevant than ever and urgently needed, but to be useful, it has to be accessible, credible, salient, understandable, and useable. In short, I work actively to fulfill scientists' collective social contract: include a focus on wicked problems and their solutions; commit to sharing knowledge and engaging widely; and act with humility, transparency and honesty.

For most of my career, I have been an academic – initially at Harvard and now at Oregon State University, but I have also spent considerable time bringing science to and engaging with the public, journalists, the private sector, a wide range of civil society and philanthropic organizations, and governments – through my own work and by creating opportunities for others.

Recently, I have served in a variety of positions in the U.S. government, alternating government service with academic activities. In 2008, President Obama invited me to be an inaugural member of his 'Science Team' and to serve as the Under Secretary of Commerce for Oceans and Atmosphere and to lead the federal agency that produces and uses scientific information to deliver climate, weather, and ocean services and stewardship – the National Oceanic and Atmospheric Administration (NOAA). After 4 productive years leading NOAA, I returned to academia, first as the Distinguished Visitor in Public Service at Stanford University and then as University Distinguished Professor and Valley Chair in Marine Biology at Oregon State University. In 2014, I was named the State Department's inaugural U.S. Science Envoy for the Ocean, a position for which I travelled internationally over two years as a science diplomat to focus on ocean issues in China, Indonesia, South Africa, Mauritius and the Seychelles. In 2021, I returned once again from academia to government service to work under President Biden as the Deputy Director for Climate and Environment in the White House Office of Science and Technology Policy – a position I hold today. Although my position is in the White House, I appear here today at the Pontifical Academy of Sciences in my personal capacity, not speaking for or representing the Biden Administration.

Looking across these diverse experiences and knowledge acquired, and channelling our earlier discussions about the importance of science communication, I'd like to tell you a story.

This is a story about the ocean and scientific knowledge. It touches on the relationships between people and the ocean and what scientific knowledge is telling us about problems and solutions. As you may know, the ocean represents about two-thirds of the surface area of the planet and an astonishing 98% of the living space of Earth. The ocean sustains and feeds us; it connects us. As our life-support system, it has made life on Earth possible. And it harbors untold secrets. We have only begun to uncover the treasure trove of knowledge hidden beneath the waves.

You will note that I use the word 'ocean' in the singular. Yes, there are many ocean basins – the Atlantic, the Pacific, the Indian, etc. – but they are all connected. In truth, there is only one ocean.

For most of human history, people thought the ocean was so immense, so bountiful, so resilient, that it was impossible to deplete or disrupt it. We thought we could take as much as we wanted and dump as much as we pleased – with no real consequences. Fisheries seemed endlessly bountiful, with ever-new target species discovered as peopled fished farther and farther from shore and deeper and deeper. The 1960's slogan "dilution is the solution to pollution" encapsulated our thinking about dumping wastes in the ocean: its size made it the perfect place to dilute or hide whatever we didn't want. We assumed that the ocean was infinitely bountiful and resilient. In short, the main narrative about the ocean was that "It was too big to fail".

The last few decades have shown many of us the folly of that thinking. You've seen images of depleted fisheries, disgusting plastic pollution, larger and more persistent red tides, bleached coral reefs, dead zones – one problem after another, with very real consequences for people as well as life in the ocean. These problems are so overwhelming and diverse that many people have thrown up their hands saying, "It's hopeless!" They feel that the problems are too complex; the vested interests are too powerful; and the solutions are not obvious or feasible. And so, in just a few decades, the dominant narrative about the ocean has shifted from 'The ocean is too big to fail' to now 'The ocean is too big to fix".

I note that in some places, both narratives exist today. Some people still look at the ocean and see an endless opportunity without responsibility – more minerals, more oil and gas, more fisheries.

Fortunately, science is pointing the way to a third, more hopeful narrative. Scientists are telling us that in fact, the ocean is central to solving many of our global problems – from climate change and food security to equity and economic development. Around the world, there are small-scale examples of these solutions, but they are not at the scale or pace that we need. For example, a scientific analysis concluded that we could get as much as 20% of the carbon emission reductions we need to reach the 1.5-degree Paris Agreement target from the ocean – by tapping ocean renewable energy; protecting and restoring blue carbon ecosystems like mangrove forests, saltmarshes and seagrass beds; decarbonizing shipping and more. Science is flipping the script on the ocean – the ocean is no longer the victim, but a powerful source of solutions. So, in short, what we are seeing through new scientific findings, discoveries, engagement and demonstration is that, in fact, the ocean is not too big to fail, nor is it too big to fix, but it is, in fact, so central to our future it's too big to ignore.[1]

Yes, there is urgency. Yes, the challenges loom large. But this new narrative for the ocean provides a path forward because it exemplifies social and natural sciences coming together to provide both knowledge and hope through engagement with society.

Thank you.

Short bio – The Honorable Jane Lubchenco, Ph.D.

Jane Lubchenco is Deputy Director for Climate and Environment at the White House Office of Science and Technology Policy. She is on loan from Oregon State University where she serves as University Distinguished Professor and Valley Professor of Marine Biology. She is a marine ecologist with expertise in the ocean, climate change, and interactions between the environment and human well-being. She served as the U.S. Under Secretary of Commerce for Oceans and Atmosphere and Administrator of the National Oceanic and Atmospheric Administration (NOAA) and inaugural member of President Barack Obama's Science Team from 2009-2013. From 2014-2016, she was the first U.S. State Department Science Envoy for the Ocean, serving as a science diplomat to China, Indonesia, South Africa, Mauritius and the Seychelles. In 2021, she was tapped to bring environmental and climate science to the Biden Administration in the White House Office of Science and Technology Policy.

Dr. Lubchenco is one of the "most highly cited" ecologists in the world with eight publications as "Science Citation Classics". She is an elected member of the National Academy of Sciences, the American Philosophical Society, The Royal Society, The World Academy of Sciences, and the Pontifical Academy of Sciences, among others. She has received numerous awards recognizing her leadership, service, and contributions to science and society. These awards include 24 honorary doctorates (most recently from Oxford University), a MacArthur ('genius') Fellowship, and the highest honors given by the National Academy of Sciences (the Public Welfare Medal), the National Science Foundation (the Vannevar Bush Award), and the Department of Commerce (Gold Medal Award), and the

[1] Lubchenco, J. and S.D. Gaines. 2019. A New Narrative for the Ocean. Invited editorial. *Science* 364 (6444) p. 911 DOI: 10.1126/science.aay2241 https://science.sciencemag.org/content/364/6444/911

highest honor given to a civilian by the U.S. Coast Guard (Distinguished Public Service Award).

Dr. Lubchenco has served as the President of numerous professional scientific societies including the Ecological Society of America, the American Association for the Advancement of Science (AAAS) and the International Council for Science (ICSU). She has served on multiple national commissions including the Pew Oceans Commission, the Joint Ocean Commission Initiative, and the Aspen Institute Arctic Commission. She has led or contributed to multiple regional, national, and international scientific assessments on climate change, biodiversity, Marine Protected Areas, the ocean, and the intersection of science and society. Recently, she co-chaired the Expert Group for the High Level Panel for a Sustainable Ocean Economy, a pioneering partnership across 17 serving heads of state or government to harness science and action to protect the ocean effectively, produce from it sustainably, and prosper equitably.

She co-founded three organizations that train scientists to be better communicators and engage more effectively with the public, policy makers, media and industry: the Leopold Leadership Program (later the Earth Leadership Program), COMPASS, and Climate Central. She founded and led the MPA-Project, a global partnership to provide science-based understanding of Marine Protected Areas to achieve multiple environmental and social outcomes. When not serving in a government position, she actively connects science to the public and policy makers through a range of philanthropic, civil society, governmental and intergovernmental organizations and activities.

Dr. Lubchenco received a B.A. in biology from Colorado College, a M.S. in zoology from the University of Washington, and a Ph.D. in ecology from Harvard University. She has held faculty appointments at Harvard University, Stanford University, and Oregon State University.

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