The Pontifical Academy of Sciences

Workshop on

Stem Cells and Their Promise for Regenerative Medicine

Casina Pio IV, Vatican City, 5-6 May 2022

The reflections of your Plenary Session on the sciences and the survival of humanity also raise the issue of similar scenarios that could originate in the most advanced laboratories of the physical and biological sciences. May we remain quiet in the face of such prospects? As great as the responsibility of politicians may be, it does not exempt scientists from acknowledging their own ethical responsibilities in the effort to halt not only the manufacture, possession and use of nuclear weapons, but also the development of biological weapons, with their potential to devastate innocent civilians and indeed, entire peoples.

Dear friends, once again, I thank you for your research and your efforts to confront these grave issues in a spirit of cooperation and shared responsibility for the future of our societies. In these months, the entire world has depended on you and your colleagues to provide information, to instil hope and, in the case of countless medical professionals, to care for the sick and the suffering, often at the risk of their own lives.

Message of His Holiness Pope Francis on the occasion of the Plenary Session of the Pontifical Academy of Sciences

Rome, from Saint John Lateran, 7 October 2020

The Pontifical Academy of Sciences workshop on

Stem Cells and Their Promise for Regenerative Medicine

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The discovery of stem cells was a remarkable breakthrough in biological research. Two major types of stem cells exist during the lifecycle of multicellular organisms: *embryonic stem cells*, resulting from the early divisions of the egg, characterized by their "pluripotency", i.e. the capacity, that they share with the egg cell itself, to produce all the cell types found in the adult organism, and the *tissue-specific stem cells* present in the tissues and organs of the adult. The latter play an important role in renewing the cells of the various organs during the entire life. They are particularly active in tissues and organs in which the lifespan of the differentiated cells is short, like blood, skin and the inner cell layer covering the intestinal cavity, as well as skeletal muscle. These adult stem cells are highly specialized and can only produce the tissue in which they reside. They are "unipotent" or "multipotent". These adult stem cells will be the subject of this workshop. Scientists have learned to grow them in a dish into mini-versions of the mouse and human organs from which they derive. This so-called "organoid technology" opens new avenues for the study of development, physiology and disease and for personalized medicine. In the future, cultured mini-organs may replace organ transplants from donors and open the way to regenerative medicine.

PAS Academicians: Nicole Le Douarin, Elaine Fuchs, Helen Blau

The conference will take place in the Casina Pio IV in the Vatican City, and on Zoom. Formal proceedings will kick off at 9:00 a.m. (Rome time) on both days.

Speakers will have 25 minutes: 10/15 minutes for their speech, and 10 minutes for a brief Q&A. At the end of all talks in a Session, the chair will moderate a solutions-oriented General Discussion (30 minutes).

We kindly ask you to send us copy of your presentation no later than Friday, April 25, at the following email address: pas@pas.va
If you have slides or other visuals to accompany your presentation, please share those with us as well. While participants should feel free to project slides from their own computer, we'd like to compile the full set in case of any technical difficulties.

Thursday 5 May 2022

09.00 - 09.15 Welcome, *Joachim von Braun, PAS President*

09.15 - 9.30 Introduction, *Marcelo Sánchez Sorondo, PAS Chancellor*

Advances in iPSC Technology

09.30 - 9.55 Recent Progress in iPS Cell Research and Application
Shinya Yamanaka, Kyoto University, PAS Academician

09.55 - 10.20 Retinal Degeneration
Masayo Takahashi, Kobe City Eye Hospital, Japan

10.20 - 10.45 Parkinson's disease
Lorenz Studer, Memorial Sloan Kettering Cancer Institute, NYC

10.45 - 11.15 General Discussion

11.15 - 11.45 Coffee Break

Embryonic development

11.45 - 12.10 Studying mammalian embryonic development in culture
Janet Rossant, University of Toronto

12.10 - 12.35 iPSC-derived Blood Lineages for Clinical Translation
George Daley, Harvard Medical School

12.35 - 13.00 General Discussion

13.00 Lunch

How Studying Stem Cells in Model Systems can advance regenerative medicine

14.45 - 15.10 The planarium and pluripotent neoblasts
Alejandro Sánchez Alvarado, Stowers Institute for Medical Research

15.10 - 15.35 Limb Regeneration and its Implications for Regenerative Medicine
Elly Tanaka, IMP, Research Institute of Molecular Pathology, Vienna

15.35 - 16.05 General Discussion

How Stem Cells Cope With Changing Tissue Environments and Assaults

16.05 - 16.30 Skin stem cells
Elaine Fuchs, Rockefeller University, NYC, PAS Academician

16.30 - 16.55 Hematopoietic stem cells
Sean Morrison, University of Texas Southwestern Medical School, Dallas

16.55 - 17.20 Innate Immunity and Intestinal Cell Fate
Richard Locksley, University of California San Francisco

17.20 - 17.50 General Discussion

17.50 - 18.20 Coffee Break

Organoids

18.20 - 18.45 Organoids of simple epithelial tissues and their promise for medicine
Hans Clevers, Hubrecht Institute, Netherlands

18.45 - 19.10 Lung organoids: windows to mechanism and therapy of lung disease and cancer
Carla Kim, Harvard Medical School

19.10 - 19.35 Brain organoids and modeling disease
Juergen Knoblich, IMBA Vienna, PAS Academician

19.35 - 20.00 General Discussion

20.00 Dinner

Friday 6 May 2022

Stem Cells and Disease States

09.00 - 09.25 Therapeutic approaches to muscle wasting in aging and disease
Helen Blau, Stanford

09.25 - 09.50 Cellular Reprogramming Approaches for Cardiovascular Disease
Deepak Srivastava, Gladstone Institutes

09.50 - 10.15 Combined cell and gene therapy for Epidermolysis Bullosa
Michele De Luca, University of Modena and Reggio Emilia, Modena, Italy

10.15 - 10.40 Treatments for leukemias through understanding hematopoietic stem cells
Catriona Jamieson, University of California San Diego

10.40 - 11.10 General Discussion

11.10 - 11.40 Coffee Break

Looking to the Future

11.40 - 12.05 Informational Molecules and Delivery Systems for Regenerative Medicine
Robert Langer, Massachusetts Institute of Technology

12.05 - 12.35 Final Discussion

12.35 - 14.35 Lunch

15.00 Visit to the Vatican Museums

Speakers

Casina Pio IV, The Vatican, 5-6 May 2022

Helen M. Blau, Ph.D. is the Donald E. and Delia B. Baxter Foundation Professor and Director of the Baxter Laboratory for Stem Cell Biology at Stanford University. Blau is world-renowned for her work on nuclear reprogramming and demonstration of the plasticity of cell fate using cell fusion. Her laboratory recently identified a novel hallmark of aging, the Prostaglandin E2 degrading enzyme, 15-PGDH, and showed that its inhibition augments aged muscle stem cell and myofiber function, increasing muscle mass and strength. She is a member of American Academy of Arts and Sciences, National Academy of Medicine, and National Academy of Sciences. PAS Academician.

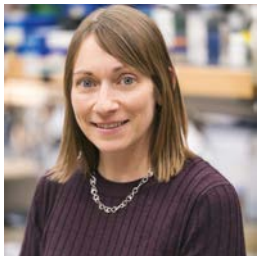
Hans Clevers obtained his MD degree in 1984 and his PhD degree in 1985 from the University Utrecht, the Netherlands. His postdoctoral work (1986-1989) was done with Cox Terhorst at the Dana-Farber Cancer Institute of the Harvard University, Boston, USA. From 1991-2002 Hans Clevers was Professor in Immunology at the University Utrecht and, since 2002, Professor in Molecular Genetics. From 2002-2012 he was director of the Hubrecht Institute in Utrecht. From 2012-2015 he was President of the Royal Netherlands Academy of Arts and Sciences (KNAW). From June 2015-2019 he was director Research of the Princess Máxima Center for pediatric oncology. As of March 18th, 2022 Hans Clevers is the Head of Pharma Research and Early Development and a Member of the Enlarged Corporate Executive Committee of F.Hoffmann-La Roche Ltd, in Basel Switzerland.

George Q. Daley, MD, PhD is Dean, Caroline Shields Walker Professor of Medicine, and Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. His research has focused on stem cell and cancer biology, with an emphasis on hematopoietic development and diseases of the bone marrow, blood and immune system. Daley earned his AB and MD degrees from Harvard and a PhD in biology from MIT. He has been a trainee, fellow and staff physician at the Massachusetts General Hospital, Brigham and Women's Hospital, Dana Farber Cancer Institute and Boston Children's Hospital. Prior to becoming Dean at HMS, he was an investigator of the Howard Hughes Medical Institute and Director of the Pediatric Stem Cell Transplantation Program of the Dana Farber Cancer Institute and Boston Children's Hospital. He is an elected member of the National Academy of Medicine and the American Association of Arts and Sciences.

Michele De Luca is Full Professor of Biochemistry, Director of the Centre for Regenerative Medicine "Stefano Ferrari" at the University of Modena and Reggio Emilia and Scientific Director and founder of the university spin-off Holostem, the first biotech entirely devoted to development of ATMPs for cell and gene therapy based on epithelial stem cells. He received his MD at the University of Catania and his specialization in Endocrinology at the University of Rome. De Luca is author of over 130 peer reviewed international publications, has been invited speaker in over 350 international meetings and seminars and has received numerous international awards, including The New York Academy of Science & Takeda Pharmaceuticals Innovator in Science Award, Eurordis Black Pearl Award, ISSCR Innovation Award, ISSCR Public Service Award and Louis-Jeantet Prize. He is a leading scientist in the field of epithelial stem cell biology aimed at clinical application in Regenerative Medicine and played a pivotal role in epithelial stem cell-mediated cell and gene therapy.

Elaine Fuchs is renowned for her research in skin biology, its stem cells and associated disorders, including cancers and inflammation, publishing >360 manuscripts. She received her Ph.D. from Princeton, postdoctorate at MIT, and has been faculty at University of Chicago and now Rockefeller University, where she is an Investigator of the Howard Hughes Medical Institute. Her awards include the National Medal of Science, L'Oreal-UNESCO Award, International Society for Stem Cell Research Innovation Award and the Gairdner International Award. Fuchs holds membership in the National Academy of Sciences, National Academy of Medicine, American Philosophical Society, Pontifical Academy of Sciences and the Royal Society.

Catriona Jamieson, MD, PhD is a leading physician-scientist who discovered missplicing, RNA hyper-editing, and splice isoform switching as mechanisms governing human cancer stem cell maintenance in selective niches. This pioneering cancer stem cell research has transformed therapies, including JAK2 and sonic hedgehog-inhibitor trials for myeloproliferative neoplasms and leukemia stem cell targeting. Her research and efforts lead to the 2019 FDA approval of fedratinib for the treatment of adult patients with intermediate-2 or high-risk primary or secondary Myelofibrosis. She also sent the first bioreactors with cancer organoids that detect activation of cancer stem cell properties in real-time into space on April 8, 2022, as part of the Integrated Space Stem Cell Orbital Research (ISSCOR) Program. The purpose is to identify biomarkers for early detection, and interventional leads and lay the groundwork for future cancer stem cell research in space. She is a Professor of Medicine, Chief of the Division of Regenerative Medicine, the Koman Family Presidential Endowed Chair in Cancer Research, Deputy Director of the Moores Cancer Center, and the Director of the Sanford Stem Cell Clinical Center at the University of California San Diego. Dr. Jaimeson received the 2017 MPN Hero's Award, the Moores Cancer Center Rell Sunn Award in 2020 (past awardees include Roger Tsien, Kary Mullis, Tony Hunter, Brian Druker, Carl June, J. Craig Venter), and the Top Doctor for the 10th consecutive year by Castle Connolly in 2021.



Dr. Carla Kim is a Professor of Genetics at Boston Children's Hospital and Harvard Medical School. The broad interest of her lab is to use stem cell biology to better understand how mechanisms governing normal lung biology are impacted in disease and cancer. They created 3D co-culture organoid systems that allow them to visualize the formation of airway- and alveolar-like structures from lung epithelial progenitor cells. Using this platform, they are defining how progenitor cells are regulated by cell-cell communication between epithelial cells and mesenchymal cells. The tools they have developed also make it possible to understand the cell autonomous and paracrine mechanisms of lung progenitor cell biology that are altered in pulmonary diseases and in lung cancer. Their work is being applied to lung diseases ranging from premature infant lung disease to cystic fibrosis to diseases of aging. Their expertise in epigenetic regulation of lung cells has revealed new therapeutic approaches for particular subsets of lung cancer patients that are now being pursued in clinical studies. Dr. Kim received her Ph.D. in Genetics from the University of Wisconsin—Madison in 2002 and performed postdoctoral research at the MIT Center for Cancer Research. She joined the Stem Cell Program at Children's Hospital Boston and established her laboratory in September 2006.

Juergen Knoblich is Scientific Director of the Institute of Molecular Biotechnology in Vienna. He is a developmental neuroscientist studying human brain development and psychiatric disorders. His group has developed a method for growing human brain tissue in the lab. They can recapitulate human embryonic brain development during the first trimester and analyze the developmental defects leading to neurological disorders. PAS Academician.

Robert Langer is one of 12 Institute Professors at MIT – the highest honor that can be awarded to a faculty member. He has written over 1,500 articles, which have been cited over 363,000 times; his h-index of 299 is the highest of any engineer in history and the 3rd highest of any individual in the world. He cofounded 40 companies including Moderna. His over 220 awards include the United States National Medal of Science and the United States National Medal of Technology and Innovation (he is one of 3 living individuals to have received both honors), the Charles Stark Draper Prize (called the Engineering Nobel Prize), Queen Elizabeth Prize for Engineering, Albany Medical Center Prize, Breakthrough Prize in Life Sciences, Kyoto Prize, Wolf Prize for Chemistry, Millennium Technology Prize, Priestley Medal (highest award of the American Chemical Society), Gairdner Prize, Dreyfus Prize in Chemical Sciences, and the BBVA Frontiers of Knowledge Award in Biomedicine. He holds 36 honorary doctorates.

Nicole Marthe C. Le Douarin My work deals with the development of the nervous and the hemopoietic and angiogenic systems in the vertebrate embryo. I devised a cell marking technique which enables the migration and fate of cells to be followed within the embryo during the entire developmental period. With my colleagues, we have particularly studied the fate of the neural crest, an embryonic structure composed of pluripotent stem cells. Neural crest cells undergo extensive migrations within the embryo and differentiate into a large variety of cell types. The neural crest plays a crucial role in the construction of the vertebrate head and of the peripheral nervous system. It also yields pigment and endocrine cells. We established the embryonic origin of the hemopoietic stem cells and how the development of the immune system proceeds in the embryo and early post-natal life. We demonstrated that immune tolerance to self involves, in addition to the elimination of self reactive T cells in the thymus, an active mechanism which consists in the production in the thymic environment of regulatory cells that suppress the activity of the effector T cells that have escaped thymic elimination.

Richard Locksley is the Sandler Distinguished Professor of Medicine and Investigator in the Howard Hughes Medical Institute at the University of California, San Francisco, USA, where he served for many years as Head of the Division of Infectious Diseases before his current role as Director of the Sandler Asthma Basic Research Center. His laboratory addresses the foundations of allergic immunity with an emphasis on innate lymphoid cells and their intersections with stem cell microenvironments in promoting tissue resilience to environmental perturbations. He is a member of the American Academy of Arts and Sciences and the National Academy of Sciences.

Sean Morrison completed a BSc in biology and chemistry at Dalhousie University (1991), a PhD in Immunology at Stanford University (1996), and a postdoctoral fellowship in neurobiology at Caltech (1999). He is currently an Investigator of the Howard Hughes Medical Institute (since 2000) and Director of Children's Research Institute at the University of Texas Southwestern Medical Center (since 2011). The Morrison laboratory studies the intrinsic and extrinsic mechanisms that regulate stem cell self-renewal (particularly in the hematopoietic system) and the role these mechanisms play in cancer (particularly leukemia and melanoma). Dr. Morrison is a former President of the International Society for Stem Cell Research and has been elected to the US National Academy of Medicine (2018) and the National Academy of Sciences (2020).

Janet Rossant, CC, PhD, FRS, FRSC is Senior Scientist and Chief of Research Emeritus at the Hospital for Sick Children in Toronto and President of the Gairdner Foundation. She is an internationally recognized developmental and stem cell biologist, exploring the biology of the early embryo and its stem cells and their applications to understanding and treating human disease. She has also been actively involved in ethics and public policy discussions around stem cell research and genetic modifications. She is a member of Royal Societies of London and Canada and the US National Academy of Sciences. In 2021 she received the ISSCR Achievement Award.

Alejandro Sánchez Alvarado, PhD, received a BS in molecular biology and chemistry from Vanderbilt University in Nashville, TN, and a PhD in pharmacology and cell biophysics from the University of Cincinnati College of Medicine in Cincinnati, OH. He performed postdoctoral and independent research at the Carnegie Institution of Washington, Department of Embryology in Baltimore, MD. In 2002, he joined the faculty of the University of Utah School of Medicine in Salt Lake City where he held the H.A. & Edna Benning Presidential Endowed Chair. In 2005, he was named a Howard Hughes Medical Institute Investigator. He joined the Stowers Institute for Medical Research in Kansas City in 2011 and became Executive Director and Chief Scientific Officer of the Stowers Institute in 2020. Sánchez Alvarado is a member of the National Academy of Science, the American Academy of Arts and Sciences, and the Latin American Academy of Sciences, a Kavli Fellow of the National Academy of Sciences USA, a Fellow of the Marine Biological Laboratory in Woods Hole, MA, a Fellow of the American Association for the Advancement of Science, a recipient of a National Institutes of Health MERIT award and the EE Just Medal for Scientific Achievement and as of 2021, the Priscilla Wood Neaves Endowed Chair in the Biomedical Sciences at

the Stowers Institute for Medical Research. He has served on numerous scientific advisory committees and boards including the National Advisory Council of the National Institute of General Medical Sciences, National Institutes of Health, and presently serves on the Board of Directors of American Century Investments.

Deepak Srivastava is President of Gladstone Institutes, Director of the Roddenberry Stem Cell Center, and Professor at the University of California, San Francisco. Srivastava received his B.S. from Rice University, M.D. from University of Texas, trained in pediatrics at UCSF, and in pediatric cardiology at Harvard. Srivastava's laboratory discovered genetic bases for cardiac defects and revealed complex gene networks that regulate progenitor cells to adopt a cardiac cell fate and subsequently fashion a functioning heart. He has leveraged this knowledge to reprogram fibroblasts into cardiomyocyte-like cells for regenerative purposes. Srivastava served as president of the International Society for Stem Cell Research and is a member of the National Academy of Medicine.

Lorenz P. Studer, MD, is the Director of the Center for Stem Cell Biology at the Memorial Sloan Kettering Cancer Center. His lab has established many of the techniques for turning human pluripotent stem cells into diverse cell types of the nervous system. He has used patient-specific stem cells for modeling various human disorders and identified strategies to measure and manipulate cellular age. Finally, he has led efforts to develop novel cell-based therapies for Parkinson's disease. Recent awards related to his studies include a MacArthur Fellowship, the Ogawa-Yamanaka Prize, and the Jacob Heskel Gabbay award in Biotechnology and Medicine.

Masayo Takahashi received her M.D. in 1986, and her Ph.D. in 1992, from Kyoto University. After an assistant professorship in the Department of Ophthalmology, Kyoto University Hospital, she moved to the Salk Institute in 1996, where she discovered the potential of stem cells as a tool for retinal therapy. She returned to Kyoto University Hospital in 1998, and was appointed Associate Professor at the Translational Research Center in 2001. She joined the CDB as a Team Leader of the Lab for Retinal Regeneration in 2006. In 2013, her team launched a pilot clinical study of autologous iPS cell-derived RPE cell sheets for exudative aged-related macular degeneration (AMD), and performed the first RPE cell sheet graft transplantation in September 2014. In August 2019, she started a new career as president of the start up company Vision Care Inc. Her aim is to understand these diseases at a fundamental level and develop retinal therapies.

Elly Tanaka received her AB at Harvard, her PhD at UCSF and post-doctoral work at University College London. She became groupleader at the Max Planck Institute of Molecular Cell Biology and Genetics Dresden then Professor at the TU Dresden and since 2016 Senior scientist at the Institute for Molecular Pathology, Vienna. She is interested in how to reconstitute and regenerate complex tissues. She uses natural models of regeneration such as the axolotl, as well as patterning processes in embryonic stem cell derived organoids.

Shinya Yamanaka, MD, PhD is the Director Emeritus and Professor of the Center for iPS Cell Research and Application (CiRA) at Kyoto University and a professor of anatomy at UC San Francisco. He is also a senior investigator and the L.K. Whittier Foundation Investigator in Stem Cell Biology at Gladstone Institutes, as well as a Representative Director of Public Interest Incorporated Foundation, CiRA Foundation. He is most recognized for his original research on induced pluripotent stem (iPS) cells. Since his breakthrough finding, he has been the recipient of many prestigious awards, including the Nobel Prize in Physiology or Medicine (2012). PAS Academician.

For the biographies of PAS President and Chancellor, please see www.pas.va.

Logistics

IN-PERSON ATTENDANCE
Dress Code is formal business attire.
Food: We will provide coffee breaks, lunch and dinner on May 5, and a coffee break and lunch on May 6. If you have any food allergies or dietary requirements, please let us know in advance.
Covid restrictions: In-person participants will be required to follow all testing and travel protocols. Travel insurance that covers any extra accommodation expenses in the event of a mandatory quarantine is mandatory.
Please continue to refer to government pages and https://tinyurl.com/2p98p266 to understand evolving travel requirements.
The Vatican requires proof of full vaccination/Covid passport for entry. For those staying at the Domus Sanctae Marthae, the Domus requires proof of full vaccination plus a Covid test, which can be the same one the guests have used to board the plane.
During the workshop, participants are kindly requested to keep their FFP2/KN95 masks on indoors, except when giving their speech and during coffee breaks and meals.
Should you require tests for your return journey, there are a number of pharmacies just outside the Vatican walls where both PCR and rapid tests can be done without an appointment.
Security: invites are strictly personal. Please remember to bring a valid ID.

VIRTUAL ATTENDANCE: A zoom link will be sent to virtual participants before the event, with the request not share it with external parties.

FOR MORE INFORMATION
Please refer to www.pas.va and www.pass.va for further information on the Academies, the Academicians, and current and past events.
You can also view previous PAS workshops on the Casina Pio IV YouTube channel:
www.youtube.com/c/CasinaPioIV

Memorandum

5 May 2022
A bus will leave the Domus and Hotel Il Cantico at 8.45 a.m. to accompany participants to the Casina Pio IV, where the meeting will start at 9.00 a.m.
After dinner, at 9.00 p.m. the same bus will take you back to your hotel.

6 May 2022
A bus will leave the Domus and Hotel Il Cantico at 8.45 a.m. to accompany participants to the Casina Pio IV, where the meeting will start at 9.00 a.m.
At 3 p.m. please gather at the Casina Pio IV main entrance. An English-speaking guide will take you to the Vatican Museums.
At 5.30 p.m. the bus will take you back to your hotel.

Front cover “Icon of the Holy Trinity”, Andrei Rublev, c. 1410
Pope Francis and back cover image by Gabriella Clare Marino/PAS

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For further information please visit: www.pas.va and www.endslavery.va
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Wi-Fi Network: Academy-guest | Password: G@rdens1936

v.27, April 13, 2022