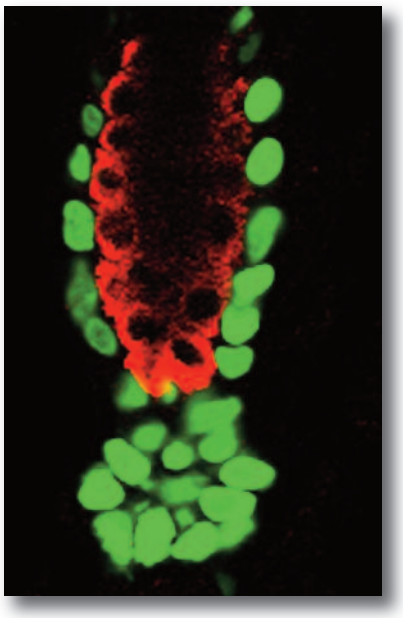
THE PONTIFICAL ACADEMY OF SCIENCES

Working Group on

New Developments in Stem Cell Research: induced Pluripotent Stem Cells and their Possible Applications in Medicine

16-17 April 2012 • Casina Pio IV



VATICAN CITY 2012

Man, the agent of scientific research, will sometimes, in his biological nature, form the object of that research. Nevertheless, his transcendent dignity entitles him always to remain the ultimate beneficiary of scientific research and never to be reduced to its instrument. In this sense, the potential benefits of adult stem cell research are very considerable, since it opens up possibilities for healing chronic degenerative illnesses by repairing damaged tissue and restoring its capacity for regeneration. The improvement that such therapies promise would constitute a significant step forward in medical science, bringing fresh hope to sufferers and their families alike. For this reason, the Church naturally offers her encouragement to those who are engaged in conducting and supporting research of this kind, always with the proviso that it be carried out with due regard for the integral good of the human person and the common good of society.

(His Holiness Benedict XVI, Address to Participants in the International Conference Promoted by the Pontifical Council for Culture, Clementine Hall, Saturday, 12 November 2011)

New Developments in Stem Cell Research: induced Pluripotent Stem Cells and their Possible Applications in Medicine

PROLOGUE

The concept of *stem cell* goes back to the discovery, in the early 1960s, of the mechanisms through which blood cells, whose life span is short, are constantly renewed. It was shown that this is achieved by a small number of undifferentiated pluripotent progenitor cells, present in the bone marrow, that are endowed with the capacity to self renew. Cells with such characteristics were subsequently found in practically all tissues of the adult body that are permanently rejuvenated in the majority of multicellular organisms.

In some primitive species, such as the flatworm *Planaria*, stem cells present in the adult make the animal able to multiply asexually. A major breakthrough in this field was the demonstration that the cells of the early mammalian embryo are endowed with stem cell properties that can be captured and maintained indefinitely in culture. It appeared that the embryonic stem cells that were obtained by this technique, named *ES* (*Embryonic Stem*) *cells*, constituted an inexhaustible source of pluripotent cells.

The double capacity of stem cells to self renew in an undifferentiated state while being able to yield a large diversity of cell types in their progeny, was recently shown to be under the control of defined genes. This has recently led to a second breakthrough: the possibility 'to turn the old into the young', that is, to convert differentiated cells of an adult into cells that have most of the characteristics of the pluripotent cells of an embryo. The so-called iPS cells (*induced Pluripotent Stem cells*), have, since 2006, opened new avenues of research in Cell and Developmental Biology and also new hopes in regenerative medicine.

Basic and applied research on the different types of stem cells is of major interest for several reasons. First they will contribute to enlighten some of the most critical biological problems such as the mechanisms underlying cell differentiation, the maintenance of the differentiated state, the intimate relationships between cell differentiation and proliferation, as well as the deregulation of these processes in cancer.

One can also expect that the capacity to re-programme already differentiated cells via the *iPS* cell technology will make it possible to use – for therapy – the cells of the patient. This will have the advantage of avoiding the use of the 'controversial' ES cells derived from human embryos and the immune rejection of the transplant.

Thanks to these new discoveries, novel opportunities will very likely be available to improve the life of human beings. This is why the Council of the Academy decided that the most recent scientific developments in this exciting field of research should be expounded to the Academy by PAS Academicians together with the most prominent international specialists and subjected to in depth discussion. In fact, I think it is important that society leaders be aware of the extraordinary progress that has been accomplished during the last year with a better understanding of the identity of iPS cells and the new possibilities offered by the reprogrammation of adult, differentiated cells.

Nicole M. Le Douarin

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PROGRAMME

Monday, 16 April 2012

	Morning Session
9:00	*Welcome* **W. Arber**, President of the Pontifical Academy of Sciences
9:05	*Introduction* **Nicole M. Le Douarin**
9:30	*Stem Cells and the Perpetuation of Life* **Alejandro Sánchez Alvarado**
10:10	Discussion
10:30	Coffee Break
11:00	*Normal and Neoplastic Stem Cells* **Irving Weissman**
11:40	Discussion
12:00	*Stem Cells, Reprogramming, Therapy: Promise, Problems, Reality* **Rudolf Jaenisch**
12:40	Discussion
13:00	Lunch at the Casina Pio IV
	Afternoon Session
15:00	*The Nature and Potential of Embryonic Stem Cells* **Austin Smith**
15:40	Discussion
16:00	*Mechanisms of Cellular Reprogramming* **Konrad Hochedlinger**
16:40	Discussion
17:00	Coffee Break
17:30	*Wnt signaling, Lgr5 stem cells and cancer* **Johannes C. Clevers**
18:10	Discussion
18:30	*Innate vs. Induced Pluripotency: Stem Cells in Biomedical Research* **Oliver Brüstle**
19:10	Discussion
19:30	Departure from the Casina Pio IV by bus to attend the concert at Villa Aurora (Palazzo Boncompagni Ludovisi)
20:00	Concert followed by dinner
22:00	Bus leaves Villa Aurora to take participants back to the Domus Sanctae Marthae

Tuesday, 17 April 2012

	Morning Session
9:00	*Regulating Regeneration: Stem Cells, Newts, and Niches* **Helen M. Blau**
9:40	Discussion
10:00	*Skin Stem Cells: Their Biology and Promise for Regenerative Medicine* **Elaine Fuchs**
10:40	Discussion
11:00	Coffee Break
11:30	*Opportunities and Limitations for Neuronal Replacement in the Adult Brain* **Arturo Alvarez-Buylla**
12:10	Discussion
12:30	Lunch at the Casina Pio IV
	Afternoon Session
14:30	*A Phase I/II Cell Therapy Trial for Duchenne Muscular Dystrophy* **Giulio Cossu**
15:10	Discussion
15:30	*Regenerative Medicine and Ocular Surface: Toward the Light* **Graziella Pellegrini**
16:10	Discussion
16:30	Coffee Break
17:00	*Phase I Trials for ALS and Malignant Brain Tumors: A "Translation" of Neural Stem Cell Biology* **Angelo Vescovi**
17:40	Discussion
18:00	*Generating Functional Dopaminergic Neurons from Human Fibroblasts in a Direct Approach* **Vania Broccoli**
18:40	Discussion
19:00	*From Cellular Therapies to Tissue Reprogramming and Regenerative Strategies in the Treatment of Diabetes* **Camillo Ricordi**
19:40	Discussion
20:00	General Discussion and Final Statement by Nicole Le Douarin
20:45	Dinner at the Casina Pio IV

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LIST OF PARTICIPANTS

Prof. Arturo Alvarez-Buylla PhD
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Prof. Werner Arber
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Dr. Vania Broccoli, PhD
Stem cells and Neurogenesis Unit
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San Raffaele Scientific Institute
Milan (Italy)

Prof. Oliver Brüstle
Director, Institute of Reconstructive
Neurobiology, University of Bonn;
Scientific Director LIFE & BRAIN GmbH
Bonn (Germany)

Prof. Johannes C. Clevers
Hubrecht Institute
Utrecht (The Netherlands)

Prof. Giulio Cossu
Professor of Stem Cell Biology
University College
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Prof. Elaine Fuchs
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Prof. Rudolf Jaenisch
Professor of Biology
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Prof. Nicole M. Le Douarin
Collège de France, C.N.R.S.
Institut d'Embriologie Cellulaire et Moléculaire
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H.E. Msgr. Vincenzo Paglia
Vescovo di Terni, Narni e Amelia
Curia diocesana di Terni
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Prof. Graziella Pellegrini
Cell Biology
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Prof. Camillo Ricordi
Scientific Director and Chief Academic Officer
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Prof. Alejandro Sánchez Alvarado
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Howard Hughes Medical Institute &
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H.E. Msgr. Marcelo Sánchez Sorondo
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Prof. Angelo Vescovi
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BIOGRAPHIES OF PARTICIPANTS

Arturo Alvarez-Buylla is Professor of Neurological Surgery, Heather and Melanie Muss Endowed Chair and Principal Investigator, Brain Tumor Research Center, at the University of California at San Francisco. He has an international reputation for his work in developmental neuroscience and stem-cell neurobiology research. His principal research interests are in neurogenesis of the adult mammalian brain, the assembly of the brain, brain tumors and repair, and the ontogeny and phylogeny of behavior. His expertise encompasses the fields of developmental biology, developmental neuroscience, neurobiology, molecular and cellular neurobiology, and learning and plasticity. An innovator and inventor as well as a scientist, Dr. Alvarez-Buylla has designed a device for mounting tissue sections on histological slides, a digital stereotaxic apparatus for mice and song birds, a computer-based mapping system for tissue sections, and a fluorescent staining technique. He belongs to the Society for Neuroscience, International Brain Research Organization, Society for Biochemistry, Academia de Ciencias de America Latina, Real Academia de Ciencias Exactas, Físicas y Naturales (Spain) and International Society for Stem Cell Research. Selected Honors and Awards include Undergraduate International Fellowship – Universidad Nacional Autonoma de Mexico; Gavino Barreda Medal; Robert L. Sinsheimer Award in Molecular Biology; Jacob Javits Award; Neuronal Plasticity Prize (France); Catedra Miguel Aleman (Mexico); The Givaudan-Roure 2004 Lecture and Award; Catedra Santiago Grisolía (Spain); Catedra Ramón y Cajal, Sociedad Española de Neurología (Spain); Prince of Asturias Award for Technical and Scientific Research (Spain). His recent publications include: Ihrie RA, Shah JK, Harwell CC, Levine JH, Guinto CD, Lezameta M, Kriegstein AR, and Alvarez-Buylla A. Persistent sonic hedgehog signaling in adult brain determines neural stem cell positional identity. *Neuron* 2011; 71(2):250-62; Ihrie RA and Alvarez-Buylla A. Lake-front property: a unique germinal niche by the lateral ventricles of the adult brain. *Neuron* 2011; 70(4):674-86; Martínez-Cerdeño V, Noctor SC, Espinosa A, Ariza J, Parker P, Orasji S, Daadi MM, Bankiewicz K, Alvarez-Buylla A, Kriegstein AR. Embryonic MGE precursor cells grafted into adult rat striatum integrate and ameliorate motor symptoms in 6-OHDA-lesioned rats. *Cell Stem Cell* 2010; 6(3):238-50.

Helen Blau received her B.A. from University of York in England and her M.A. and Ph.D. from Harvard University. She is currently the Donald E. and Delia B. Baxter Professor and Director of the Baxter Laboratory for Stem Cell Biology in the Microbiology and Immunology Department and the Stanford Institute for Stem Cell biology and Regenerative Medicine in the Stanford University School of Medicine, Stanford, California. Dr. Blau currently serves on the Ellison Medical Foundation Scientific Advisory Board and the Helmsley Trust and is an elected member of the American Academy of Arts and Sciences, the Institute of Medicine of the National Academy of Sciences and a fellow of the American Association for the Advancement of Science. Awards include the Senior Career Recognition Award of WICB of the American Society of Cell Biology; the FASEB Excellence in Science Award; an Honorary Doctorate from the University of Nijmegen, Holland; a Nobel Forum Lecture at the Karolinska Institute in Stockholm, a Rolf-Sammet-Fonds Visiting Professorship at the University of Frankfurt, and a Fulbright Senior Specialist award to study and teach at the Institut Pasteur in Paris and is the 2011 AACR-Irving Weinstein Distinguished Lecturer. Professor Blau's research area is regenerative medicine with a focus on stem cells. She is world renowned for her research on nuclear reprogramming and demonstrating the plasticity of cell fate using cell fusion. Her laboratory has also pioneered the design of biomaterials to mimic the in vivo microenvironment and direct stem cell fate. Her muscle heterokaryon experiments proved that silent muscle genes can be activated in diverse adult cells and that the differentiated state of a cell requires continuous regulation and is dictated by the balance of regulators present at any given time. Most recently, her lab used this cell fusion approach to define a novel role for the enzyme AID in mammalian DNA demethylation and reprogramming cells toward pluripotency. The Blau laboratory also engineers artificial *in vitro* platforms that recapitulate key features of *in vivo* stem cell microenvironments, or niches. These studies address a major limitation, as most tissue-specific stem cells cannot currently be cultured without loss of stemness. Her findings are leading to more efficient iPS generation, cell based therapies and the discovery of novel molecules and therapies that will impact muscle wasting diseases and hematopoietic malignancies. Her laboratory uses a multi-disciplinary approach to overcome major clinical hurdles by elucidating the molecular nature of cell intrinsic regulators and extrinsic niche components that induce adult stem cell self-renewal, pluripotency, and function in mammalian regeneration. Dr. Blau took part in a similar workshop at the PAS in 2003.

Vania Broccoli leads the "Stem Cell and Neurogenesis" Unit at the San Raffaele Scientific Institute in Milan (www.sanraffaele.org/stem_cells_neurogenesis.html). He is a neurobiologist interested in unraveling the molecular mechanisms that control key processes of brain development such as neural stem cell identity maintenance, neural commitment and migration, neural network establishment and function. Lately, his group has applied new technologies of direct cell reprogramming to convert mouse and human skin fibroblasts into functional dopaminergic neurons. He now aims at further developing these approaches to establish safe and efficient systems for producing functional human neurons suitable for cell replacement therapies in infantile neurological and neurogenerative disorders. Vania Broccoli established his laboratory in 2003 at the San Raffaele Scientific Institute and focused on revealing the molecular mechanisms controlling neuronal differentiation and cerebral cortex development. From 1999 to 2002 he worked at the Telethon Institute of Molecular Medicine

(TIGEM) as associate scientist. As post-doctoral fellow, from 1996 to 1998, he worked in Prof. W. Wurst's laboratory in Munich, unraveling the role played by the transcription factor Otx2 in shaping midbrain-hindbrain junction and controlling dopaminergic neuronal ontogenesis. From 1993-1996, as PhD student in Prof. E. Boncinelli's laboratory, he studied the mechanisms of brain regionalization and differentiation, in particular, focusing on the Emx and Otx transcription factors during cerebral cortex development. He is contract Professor at the Medical School of the Vita-Salute San Raffaele University.

Oliver Brüstle is Professor of Reconstructive Neurobiology at the University of Bonn. He is also Co-Founder and Scientific Director of LIFE & BRAIN GmbH, a biomedical enterprise serving as translational hub of the University of Bonn Medical Center. Trained as an M.D., he conducted research and clinical work in neuropathology and neurosurgery at the universities of Zurich and Erlangen, respectively. In 1993 he joined the laboratory of Ron McKay at the National Institutes of Neurological Disorders and Stroke in Bethesda, MD, USA to study neural stem cells. Upon his return to Germany in 1997, he started is own lab and, in 2002, became director of the newly founded Institute of Reconstructive Neurobiology. His field of interest is stem cell research with a particular focus stem cell-based disease modeling and nervous system repair. *Selected Publications*: Koch, P., Breuer, P., Peitz, M., Jungverdorben, J., Kesavan, J., Poppe, D., Doerr, J., Ladewig, J., Mertens, J., Tüting, T., Hoffmann, P., Klockgether, T., Evert, B.O., Wüllner, U., Brüstle, O. (2011) Excitation-induced ataxin-3 aggregation in neurons from patients with Machado-Joseph disease. *Nature* 480:543-6; Koch P, Opitz T, Steinbeck J, Ladewig J, Brüstle O (2009) A rosette-type, self-renewing human ES cell-derived neural stem cell with potential for in vitro instruction and synaptic integration. *Proc Natl Acad Sci USA* 106:3225-3230; Opitz T, Scheffler B, Steinfarz B, Schmandt T, Brüstle O (2007) Electrophysiological evaluation of engrafted stem cell-derived neurons. *Nature Protoc* 2:1603-1613; Nolden L, Edenhofer F, Haupt S, Wunderlich TF, Siemen H, Brüstle O. (2006) Genetic engineering of human embryonic stem cells by cell-permeable Cre recombinase. *Nature Methods* 3:461-467; Zhang SC, Wernig M, Duncan ID, Brüstle O, and Thomson JA (2001) In vitro differentiation of transplantable neural precursors from human embryonic stem cells. *Nature Biotech* 19:1129-1133. Author Brüstle O, Jones KN, Learish RD, Karram K, Choudhary K, Wiestler OD, Duncan ID, and McKay RDG (1999) Embryonic stem cell-derived glial precursors: a source of myelinating transplants. *Science* 285: 754-756.

Hans Clevers obtained his MD degree in 1984 and his PhD degree in 1985 from the University of 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 of Utrecht and, since 2002, Professor in Molecular Genetics. Since 2002, he is Director of the Hubrecht Institute in Utrecht. Hans Clevers has been a member of the Royal Netherlands Academy of Arts and Sciences since 2000 and is the recipient of several awards, including the Dutch Spinoza Award in 2001, the Swiss Louis Jeantet Prize in 2004, the Memorial Sloan-Kettering Katharine Berkan Judd Award in 2005, the Israeli Rabbi Shai Shacknai Memorial Prize in 2006, the Dutch Josephine Nefkens Prize for Cancer Research, the German Meyenburg Cancer Research Award in 2008, the Dutch Cancer Society Award in 2009, the United European Gastroenterology Federation (UEGF) Research Prize in 2010 and the Ernst Jung Medical Award 2011. He obtained an ERC Advanced Investigator grant in 2008. He is Chevalier de la Légion d'honneur since 2005.

Giulio Cossu is Professor of Stem Cell Biology at University College London. He was previously Director of the Division of Regenerative Medicine at the San Raffaele Institute and Professor of Histology in Milan. He received his MD degree from the University of Rome in 1997 and worked as Fogarty fellow at the University of Pennsylvania, as Professor at the University of Rome and as Visiting Professor at the Institut Pasteur. He is EMBO Member and Senior Editor of EMBO Molecular Medicine. Giulio Cossu is recognized for his pioneering work on skeletal myogenesis and for developing the first cell therapy protocol with stem cells for muscular dystrophy. He discovered vessel-associated progenitor cells, mesoangioblasts that were used for the first successful cell therapy protocols of muscular dystrophy in dystrophic mice and dogs. These data set the basis for a "first in man" phase I/II clinical trial based upon allotransplantation of donor mesoangioblasts from an HLA-identical donor in patients affected by Duchenne muscular dystrophy that started in March 2011 and is currently in progress. He is author of more than 170 publications in peer-reviewed journals and is currently coordinator of a large EC network focused on stem cell based-therapies (Optistem).

Elaine Fuchs is the Rebecca Lancefield Professor in Mammalian Cell Biology and Development at The Rockefeller University, New York, and an Investigator of the Howard Hughes Medical Institute. Fuchs has published >260 scientific papers and is internationally known for her research in the biology of skin stem cells and their role in normal tissue development and cancer. Fuchs is a member of the National Academy of Sciences USA and a foreign associate of EMBO. Her honors include the US National Medal of Science, L'Oreal-UNESCO Award and Albany Prize in Medicine (shared with Drs Shinya Yamanaka and James Thompson). She is immediate past President of the International Society for Stem Cell Research.

Konrad Hochedlinger is an Associate Professor at the Department of Stem Cell and Regenerative Medicine of Harvard University, a Principal Faculty at the Harvard Stem Cell Institute and an Investigator at the Massachusetts General Hospital Cancer Center and Center for Regenerative Medicine. He received his B.Sc. in biology and his Ph.D. in genetics from the University of Vienna. From 1998-1999, he worked with Erwin Wagner at the Research Institute of Molecular Pathology in Vienna and from 2000-2006 as a Visiting Graduate Student and then Postdoc with Rudolf Jaenisch at the Whitehead Institute/MIT. During his stay at the Whitehead Institute, he worked on nuclear transfer in mice to show that terminally differentiated lymphocytes and malignant melanoma cells remain amenable to reprogramming into a pluripotent state. In his own lab, Dr. Hochedlinger continued work on nuclear reprogramming by focusing on a novel method that had been previously developed by Dr. Yamanaka and involves introducing defined transcription factors into somatic cells, generating induced pluripoent stem (iPS) cells. Dr. Hochedlinger's lab reproduced and improved this technology and contributed to an understanding of its mechanism. For example, his team showed that iPS cells can be generated without the use of integrating viruses, thus eliminating a major

roadblock for their potential use in therapy. He is currently using the mouse and human system to further elucidate the mechanisms of *in vitro* reprogramming. Dr. Hochedlinger is a Kimmel and V Scholar and has been awarded the NIH Director's Innovator Award in 2007, the International Society of Stem Cell Research Young Investigator Award and the Howard Hughes Medical Institute Early Career Award in 2009.

Rudolf Jaenisch received his doctorate in medicine from the University of Munich in 1967. He was head of the Department of Tumor Virology at the Heinrich Pette Institute at the University of Hamburg before becoming a Founding Member of the Whitehead Institute for Biomedical Research and a Professor of Biology at MIT in 1984. He has coauthored more than 390 research papers and has received numerous prizes and recognitions, including membership in the National Academy of Sciences and a United States National Medal of Science award in 2011. The Jaenisch laboratory focuses on understanding epigenetic regulation of gene expression (the biological mechanisms that affect how genetic information is converted into cell structures but that don't alter the genes in the process). Most recently, this work has led to major advances in our understanding of embryonic stem cells and "induced pluripotent stem" (IPS) cells, which appear identical to embryonic stem cells but can be created from adult cells without using an egg. In 2007, the Jaenisch lab was one of three labs worldwide that reported successfully taking cells from mouse tails and reprogramming them into IPS cells, by over-expressing four master gene regulators. Later that year, the lab followed up by further manipulating IPS cells to treat sickle-cell anemia in mice, the first proof in principle of therapeutic use of such cells. In 2008, the lab reported that neurons derived from IPS cells successfully integrated into fetal mouse brains and reduced symptoms in a Parkinson's disease rat model. In another experiment, researchers demonstrated that fully mature, differentiated mouse B cells can be reprogrammed to IPS cells. Researchers are now studying ways to optimize the creation of IPS cells, including finding alternatives to the potentially cancer-causing retroviruses used to transform the adult cells into IPS cells. In the long run, IPS cells offer major promise for use in regenerative medicine, potentially supporting the growth of healthy cells and tissues derived from a patient's own cells. Closer in time, the cells will allow scientists to transfer complex human diseases into Petri dishes for study, taking a first step toward analyzing the conditions and developing a therapies. In addition to its stem cell work, Jaenisch's lab is investigating epigenetic mechanisms for certain types of cancer and for brain development, studying how conditions such as Parkinson's Disease, Adrenoleukodystrophy and Rett Syndrome occur.

Vincenzo Paglia (born 21 April 1945) is the bishop of the diocese of Terni-Narni-Amelia in Italy. He is one of the founders of the Community of Sant'Egidio. He has been responsible for inter-religious dialogue and has opposed a cooling of relations with Jewish leaders. He was educated at the Pontifical Roman Minor and Major Seminary. He obtained a Licenciate in Philosophy as well as a Licenciate in Theology, both from the Pontifical Lateran University, Rome. He also obtained a Master's degree in Pedagogy from the University of Urbino, Italy. Since the early 1970s he has been involved with the Community of Sant'Egidio, being one of its co-founders. In 1973 he was appointed Rector of the church of Sant'Egidio which had become the centre of the Sant'Egidio Community. In 1981 he was parish priest at Santa Maria in Trastevere and prefect of the Third Prefecture in Rome. Among his international commitments his work for Albania deserves special mention. He was the first priest to enter the country after the free elections in March 1991. He obtained the re-opening of the Seminary, the restitution of the Cathedral, and paved the way for the relations between Albania and the Holy See. In 1999 he negotiated with Rugova and Milosevic during the war in Kosovo and has acted as 'special ambassador' several times. He supports the Fondazione Cellule Staminali and the Neurothon onlus association which have their main headquarters in his diocese of Terni-Narni-Amalia.

Graziella Pellegrini (born in Genoa, Italy, 12 July 1962) is Associated Professor of Cell Biology, University of Modena and Reggio Emilia, Director of the Cell Therapy Program and Qualified Person in the Centre for Regenerative Medicine "Stefano Ferrari" of the same University. She is R&D Director of Holostem Terapie Avanzate S.r.l. Prof. Pellegrini was Chief of Laboratory of the Epithelial Stem Cell Regional Research Center of the Veneto Eye Bank Foundation (2002-2007), Deputy Head of Laboratory of Tissue Engineering at the Istituto Dermopatico dell'Immacolata, Rome (1996-2002), Senior Investigator in the Department of Cellular and Molecular Biology at Advanced Biotechnology Center, Genova (1993-1995), Head of Laboratory in Cellife Biotechnology, Milan (1991-1993) and Investigator in Laboratory of Cell Differentiation, Istituto Nazionale per la Ricerca sul Cancro, Genova (1988-1991). She graduated in Chemistry and Pharmacy. She is founding member of International Ocular Surface Society, member of 9 scientific societies and member of national and international commitees. She is the author of around 50 scientific publications in major international peer reviewed journals and author of 2 international patents. She has been an invited speaker in more than 80 international meetings and symposia.

Camillo Ricordi, M.D. is the Stacy Joy Goodman Professor of Surgery, Distinguished Professor of Medicine, Professor of Biomedical Engineering, and Microbiology and Immunology, and serves as Scientific Director and Chief Academic Officer of the University of Miami Diabetes Research Institute. At the University of Miami Leonard M. Miller School of Medicine, Dr. Ricordi also serves as Chief of the Division of Cellular Transplantation, Department of Surgery, Director of the Diabetes Research Institute Cell Transplant Center and Responsible Head of the cGMP Human Cell Processing Facility. Dr. Ricordi has also served as Co-Director of the Executive Office of Research Leadership (2001-03) and as Senior Associate Dean for Research (2003-06) at the UM Miller School of Medicine. A native of New York, Dr. Ricordi completed graduate and post-graduate studies in Milan, Italy. He then moved to Washington University in St. Louis, Missouri, where he received an NIH Research Trainee Award (1986-88). Dr. Ricordi subsequently spent four years (1989-93) as Director of Cellular Transplantation at the University of Pittsburgh Transplantation Institute. Since 1993, he has been at the University of Miami, Leonard M. Miller School of Medicine. Acknowledged by his peers as one of the world's leading scientists in cell transplantation, Dr. Ricordi is well-known for inventing the machine that made it possible to isolate large numbers of islet cells (insulin-producing cells) from the human pancreas and for performing the first series of clinical islet transplants that reversed diabetes after implantation of donor purified islets into the liver of recipients with diabetes. The procedure is now used

by laboratories performing clinical islet transplants worldwide. Dr. Ricordi has also developed highly innovative strategies in an attempt to transplant cells and organs without the continuous requirement for anti-rejection drugs. Dr. Ricordi was president of the Cell Transplant Society (1992-94), co-founder and chairman of the National Diabetes Research Coalition (Chairman 1997), co-founder and president (1999-2001) of the International Association for Pancreas and Islet Transplantation (IPITA), and a member of the council of The Transplantation Society (2002-08). He also served on the council of the American Society of Transplant Surgeons (2000-02), on the National Institutes of Health (NIH-NIAID) Expert Panel on clinical approaches for tolerance induction, on the FDA Biologic Response Modifiers Advisory Committee, on the NIH/NCRR Islet Cell Resources (ICRs) Executive Committee, on the NIH-NIDDK Strategic Planning Committee and on the NIH-NIAID Expert Panel on Transplantation Research. He is currently serving as Chairperson of the Clinical Islet Transplant Consortium (NIDDK-NIAID). Dr. Ricordi has received numerous honors and awards, including the 2001 Nessim Habif World Prize in Surgery (University of Geneva), the 2002 Outstanding Scientific Achievement Award and the Lilly Lecture at the 2002 Congress of the American Diabetes Association. In 2009 Dr. Ricordi was Knighted by the President of the Republic of Italy and in 2010 he was one of the few surgeons ever inducted into the Association of American Physicians (AAP). Dr. Ricordi is currently serving on the editorial boards of *Cell Transplantation* (Editor-in-Chief), *American Journal of Transplantation* (Associate Editor), and *Transplantation*. He also served on the boards of *Transplantation Proceedings*, *Tissue Engineering*, and *Graft* (Editor-in-Chief, 1998-2002). An Adjunct Professor at the Wake Forest Institute for Regenerative Medicine, Wake Forest University, and at the Karolinska Institutet in Stockholm, he also serves as President of ISMETT (Mediterranean Institute of Transplantation and Advanced Therapies) in Palermo, Sicily and on the board of the DRI at H. San Raffaele Institute in Milan, Italy. Dr. Ricordi has authored over 600 scientific publications, and as an inventor, he has been awarded 11 patents.

Alejandro Sánchez Alvarado is an Investigator of the Stowers Institute for Medical Research and the Howard Hughes Medical Institute. He received his Bachelor's Degree in Molecular Biology and Chemistry from Vanderbilt University in 1986, and his Ph.D. in 1992 in Pharmacology and Cell Biophysics at the University of Cincinnati School of Medicine, where he studied mouse embryonic stem cells and their in vitro differentiation under the tutelage of Dr. Jeffrey Robbins and Dr. Thomas Doetschman. In 1994 he joined the laboratory of Dr. Donald D. Brown at the Carnegie Institution of Washington, Department of Embryology as a postdoctoral fellow, and in 1995 was appointed Staff Associate. It was during this period that Dr. Sánchez Alvarado began to explore systems in which to molecularly dissect the problem of regeneration. In 2002 he became an Associate Professor and was promoted to full Professor in 2004 in the Department of Neurobiology and Anatomy at the University of Utah School of Medicine, where he was later appointed H.A. & Edna Benning Presidential Professor (2010). Dr. Sánchez Alvarado has served in the National Advisory Council, National Institutes of General Medical Sciences, NIH (2008-2012), and is currently on the scientific advisory boards of the Mount Desert Island Biological Laboratory, Bar Harbor, MA; The Eugene Bell Center for Regenerative Biology and Tissue Engineering, Woods Hole, MA; the UCL Centre for Stem Cells and Regenerative Medicine, London, UK; the Institute for Stem Cell Biology and Regenerative Medicine, Bangalore, India; and the Latin American Society for Developmental Biology. He is also a Kavli Fellow of the National Academy of Sciences USA, and the recipient of a MERIT award from the National Institutes of Health and the E.E. Just Medal for Scientific Achievement, from the American Society for Cell Biology. He is also co-director of the Embryology course at the Marine Biological Laboratory in Woods Hole, MA. Dr. Sánchez Alvarado's current research efforts are aimed at elucidating the molecular and cellular basis of animal regeneration using the free-living flatworm *Schmidtea mediterranea*.

Austin Smith, Wellcome Trust Centre for Stem Cell Research, University of Cambridge, obtained his Ph.D. from the University of Edinburgh in 1986. Following postdoctoral research at the University of Oxford, he joined the Institute for Stem Cell Research at the University of Edinburgh (formerly Centre for Genome Research) in 1990 as a group leader. In 1996, he was appointed Director of the Centre. He was appointed MRC Research Professor in 2003. He took up the post of Director of the Wellcome Trust Centre for Stem Cell Research at the University of Cambridge in the autumn of 2006. Professor Smith's expertise is in the field of stem cell biology and he has pioneered key advances in the field of Embryonic Stem (ES) Cell research. His research focuses on the molecular and cellular controls of embryonic and somatic stem cells, and on interconversion between pluripotent and tissue-restricted states.

Angelo Luigi Vescovi (born in Bergamo, Italy, 1962), received his Ph.D. in Biological sciences in 1987 and worked as a post-doctoral fellow at the University of Calgary (1991-94). During that period, he worked with Prof. Samuel Weiss, participating in the initial isolation of neural stem cells from the adult mammalian brain. He has spent the last two decades has head of a group that investigates on the most basic aspects of neural stem cell biology, including regulation of cell fate, proliferation, differentiation and plasticity. In 1999 Vescovi's group reported on the initial isolation, expansion and transplantation of stem cells from the human brain and introduced the concept of a transgermal differentiation potential being a prerogative of brain stem cells (*Science*, 1999). Since then, Prof. Vescovi has been actively working to develop clinical applications for human neural stem cells in neurological disorders. He collaborated in providing evidence in support of the concept of delivering neural stem cells through systemic injection, to reach multiple lesion sites and dampen inflammatory damage in multiple sclerosis (*Nature*, 2003) and is now working at extending the use of this approach to non-inflammatory CNS disorders. Lately, Vescovi's group has shown the existence of cancer stem cells in malignant human gliomas and proposed a novel, potential therapeutic approach for human glioblastomas, based on enforcing the differentiation of cancer stem cells (*Nature*, 2006). He is currently the principal investigator for the first European phase I clinical trial for amyotrophic lateral sclerosis with human neural stem cells. Among other similar duties, professor Vescovi has acted as scientific consultant for the Select Committee on Stem Cells of the House of Lords (England) and for the European Commission. In the year 2000, he was an emeritus speaker at the Word Economic Forum in Davos. Amongst other awards, in 2001 the Royal House of Savoia knighted him, for scientific achievements, under the auspices of the Order of Saint Maurice and Lazzarus. In 2001 he received the Award of the Italian Association for Cancer Research (AIRC), in 2002 the Award of the Italian Life Science Association for Scientific Accomplishments and in 2011 the Hotchkiss Best Fellow Award by the University of Calgary.

Irving L. Weissman received his B.S. from Montana State University and an M.D. from Stanford University. During medical school he did research on thymus cell migration with Jim Gowans in 1964 at Oxford University, England. He was a postdoctoral research associate in Dr. H.S. Kaplan's department at Stanford University, and was appointed a faculty position in the Department of Pathology, Stanford School of Medicine in 1969. He has been an Investigator of the Howard Hughes Medical Institute, the Karel Beekhuis Professor of Cancer Biology and Chair of the Immunology Program. In 2002 he became Director of the Stanford Cancer/Stem Cell Institute, which was split into the Stanford Institute of Stem Cell Biology and Regenerative Medicine, and the Stanford Cancer Center in 2003; Weissman was Director of both. He remains director of the Stem Cell Institute, which will house the first PhD program devoted to stem cell biology in the nation. His most recent non-university service include being on the NIAID Blue Ribbon Panel for the NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats, (2004 – present); as an Appointee of the Senate Rules Committee, California Legislature (2003 – present); and on the Board of Scientific Counseling, Memorial Sloan Kettering Cancer Center; serving as Chairman, Section 43 (Immunology), National Academy of Sciences (2001 – present); serving as a member of the Board of Trustees of McLaughlin Research Institute (1992 – present); serving as Chairman and member of the Scientific Advisory Board, McLaughlin Research Institute (1992 – present); and serving as External Director to both the Montana Land Reliance and the Montana Trout Unlimited, (1992 – present). Among his awards and honors are the Simon M. Shubitz Award for Excellence in the Field of Cancer Research, from the University of Chicago (2010); winning the Passano Award from the Passano Foundation (2009); being named a Fellow in the American Association for the Advancement of Science, Chicago, Illinois in 2008; an Honoree of the Arthritis Foundation of Northern California Chapter's 2007 Tribute Dinner; winning the Jessie Stevenson Kovalenko Medal, National Academy of Sciences Council (2004); winning the J. Allyn Taylor International Prize in Medicine (2003); being elected to the Institute of Medicine of the National Academy of Sciences (2002); receiving the Van Bekkum Stem Cell Award (2002); being named California Scientist of the Year (2002); being named the Irvington Institute Immunologist of the Year (2001); winning the E. Donnall Thomas Prize to recognize pioneering research achievements in hematology, American Society of Hematology (1999); winning the Leukemia Society of America de Villier's International Achievement Award (1999); serving as President of the American Association of Immunologists (1994); being elected a Fellow of the American Association for the Advancement of Science (1990); being elected to the National Academy of Sciences (1989); and winning the Pasarow Award for Outstanding Contribution to Cancer Biology (1989). Dr. Weissman's main research interests are 1) hematopoietic stem and progenitor cells, 2) central nervous system stem and progenitor cells, 3) lymphocyte differentiation, 4) homing receptors, 5) normal and neoplastic hematolymphoid development, and 6) the phylogeny of stem cells and alloreactivity in protochordates. Author of over 700 publications, he also holds 31 patents. Dr. Weissman took part in a similar workshop at the PAS in 2003.

For the biographies of the other Academicians of the PAS, cf. Pontificia Academia Scientiarvm, *Yearbook* (Vatican City 2008), p. 15 ff. and www.pas.va/content/accademia/en/academicians.html

MEMORANDUM

1) On 16 and 17 April 2012 a bus will leave the Domus Sanctae Marthae for the Academy, 15 minutes before the beginning of the morning session (8.45 am). On 16 April, at the end of the afternoon session, a bus will take the participants from the Casina Pio IV to Villa Aurora (see programme) and then back to the Domus Sanctae Marthae after dinner. On 17 April a bus will leave the Academy after dinner to take participants back to the Domus Sanctae Martha.

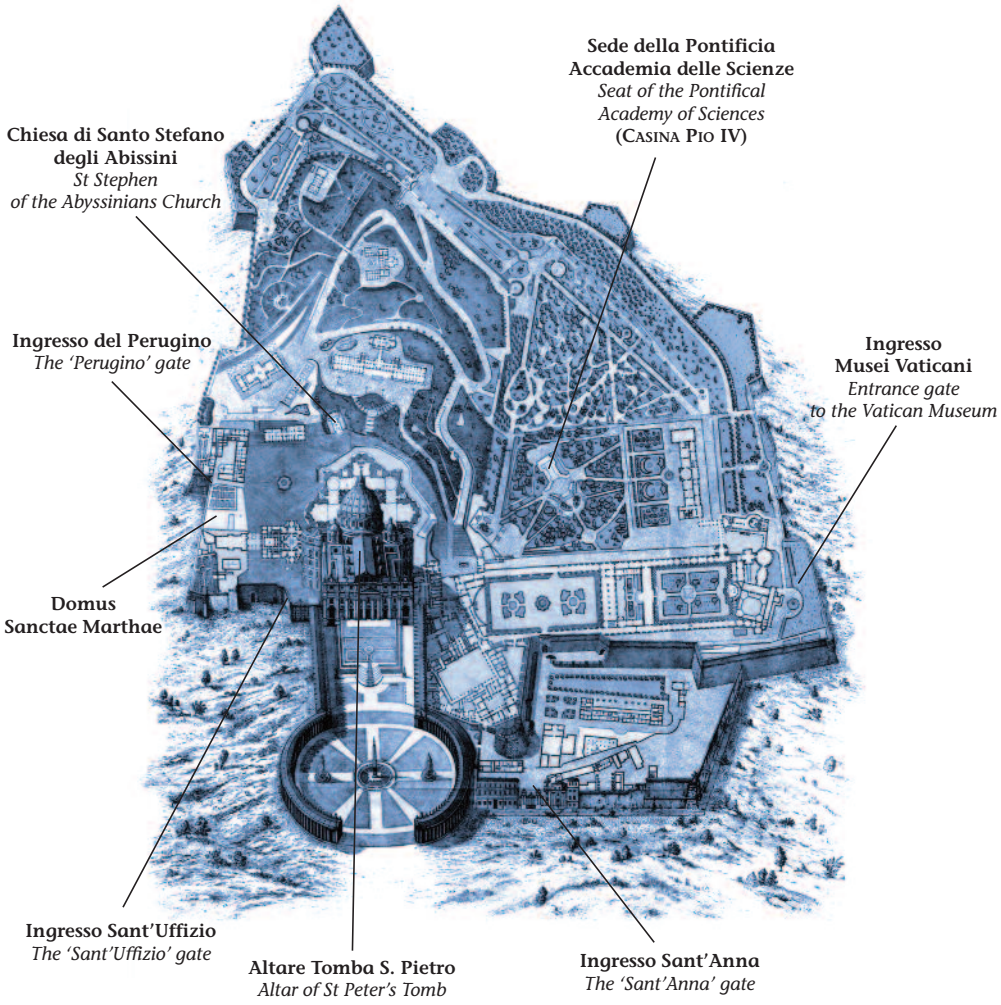
2) Lunch and dinner for the participants will be served at the Academy except dinner on 16 April, which will be served at Villa Aurora. If you are a vegetarian, please let us know as soon as possible.

3) Wifi is available in the Casina Pio IV's Conference hall. Please log in to the network called WLAN_PADS using "guest" as the username and "password" as the password.

4) Cable internet access is available at the Domus Sanctae Marthae at 7.50€ per day.

5) A visit to the Vatican Museums can be arranged for accompanying persons. Please leave your name with the secretariat in order to form a group.

Note
Please give your form for the refunding of expenses to the secretariat as soon as possible so that you can be refunded immediately.



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Front cover: Homeostasis and repair of the adult tissues depend upon tissue-specific stem cells. They usually reside in a special niche and cycle infrequently. This figure shows hair follicle stem cells (green) and one of their important niche components (red), which signal to the stem cells to keep them quiescent.
Courtesy of Prof. E. Fuchs ©2011.