#BertarelliNeuro

Gene Therapy for Sensory Disorders

2018 Bertarelli Neuroscience Symposium

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2018 Symposium of the Bertarelli Program in Translational Neuroscience and Neuroengineering

Harvard Medical School
Martin Conference Center, Boston MA

Wednesday April 11, 2018

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ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Welcome to the Martin Conference Center for the 2018 Symposium of the Bertarelli Program in Translational Neuroscience and Neuroengineering, a joint venture of Harvard Medical School (HMS), the École polytechnique fédérale de Lausanne (EPFL) and the Bertarelli Foundation.

The theme of this year's Symposium is Gene Therapy for Sensory Disorders.

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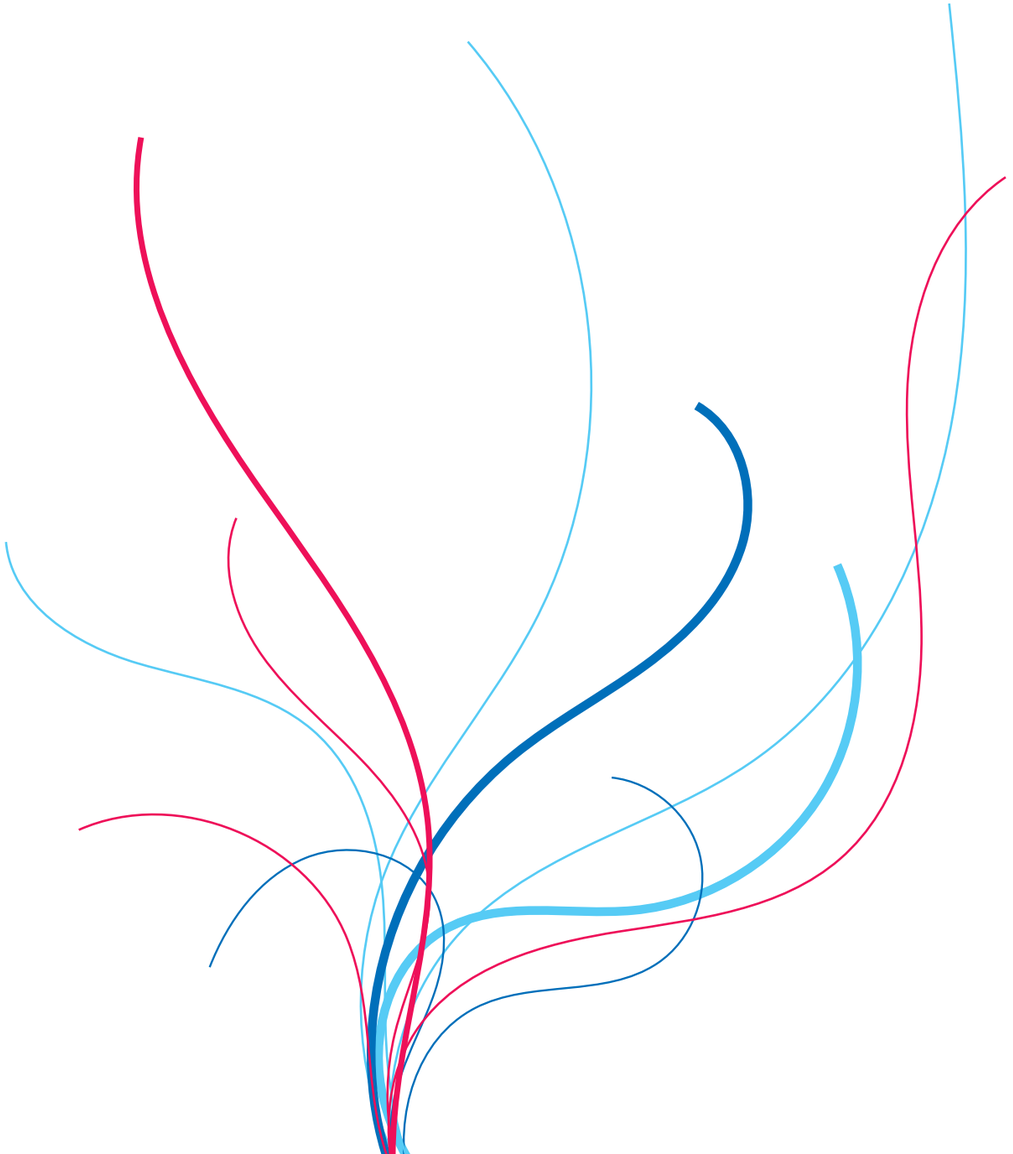
Time	Event
8:30 - 9:00am	Coffee and Pastries
9:00 - 9:15am	**George Q. Daley,** Dean, Harvard Medical School **David P. Corey,** Bertarelli Professor of Translational Medical Science, Harvard Medical School Opening Remarks
9:15 - 9:45am	**Omar Akil,** University of California San Francisco Restoration of Hearing in the Otoferlin KO Mouse Using Dual AAV Vectors
9:45 - 10:45am	**Keynote Lecture – David R. Liu, PhD,** Professor of Chemistry and Chemical Biology, Harvard University and Vice-Chair of the Faculty, Broad Institute Treatment of Autosomal Dominant Hearing Loss by In Vivo Delivery of Genome Editing Agents
10:45 - 11:15am	Break
11:15 - 11:45am	**David P. Corey,** Bertarelli Professor of Translational Medical Science, Harvard Medical School New AAV Vectors for Gene Addition Therapy
11:45 - 12:15pm	**Jeffrey R. Holt,** Boston Children's Hospital and Harvard Medical School Novel Gene Therapy Approaches for Hereditary Hearing Loss
12:15 - 1:15pm	Lunch
1:15 - 2:15pm	**Keynote Lecture – Botond Roska, MD, PhD,** Co-Director, Institute of Molecular and Clinical Ophthalmology Basel Restoring Vision
2:15 - 3:15pm	**Konstantina M. Stankovic,** Massachusetts Eye and Ear and Harvard Medical School Optical Imaging of the Inner Ear for Diagnosis and Therapy of Hearing Loss
	Daniel J. Lee, Massachusetts Eye and Ear and Harvard Medical School **Stéphanie P. Lacour,** École polytechnique fédérale de Lausanne Next Generation Auditory Brainstem Implants (ABIs): Translation to Clinical Implementation
	Dara S. Manoach, Massachusetts General Hospital and Harvard Medical School **Dimitri Van de Ville,** École polytechnique fédérale de Lausanne Imaging Brain Networks in Children with Autism
3:15 - 3:45pm	Break
3:45 - 4:15pm	**David A. Williams,** Boston Children's Hospital and Harvard Medical School Using Gene Modified Hematopoietic Stem Cells to Treat Cerebral Adrenoleukodystrophy
4:15 - 4:45pm	**Yvan Arsenijevic,** École polytechnique fédérale de Lausanne Stem Cell and Gene Therapy for Retinal Degeneration
4:45 - 5:45pm	**Keynote Lecture – Katherine High, MD,** President and Chief Scientific Officer, Spark Therapeutics, Philadelphia PA Overview of the Development Program for Voretigene Neparvovec: Challenges and Solutions
5:45 - 6:15pm	**Ernesto Bertarelli,** Bertarelli Foundation Closing Remarks
6:15 - 7:45pm	Reception

Speaker biographies

In presentation order



George Q. Daley
Dean, Harvard Medical School

George Q. Daley, MD, PhD, is the dean of Harvard Medical School and the Caroline Shields Walker Professor of Medicine at HMS. He is an internationally recognised leader in stem cell science and cancer biology and a longtime member of the HMS faculty whose work spans the fields of basic science and clinical medicine. He has been professor of biological chemistry and molecular pharmacology at HMS since 2010 and an investigator of the Howard Hughes Medical Institute since 2008. In July 2016, he became the Robert A. Stranahan Professor of Pediatrics and Professor of Biological Chemistry and Molecular Pharmacology at HMS. He previously held, as its inaugural incumbent, the Samuel E. Lux, IV Chair in Hematology/Oncology at Boston Children's Hospital.

Daley's research focuses on the use of mouse and human disease models to identify mechanisms that underlie blood disorders and cancer. His lab aims to define fundamental principles of how stem cells contribute to tissue regeneration and repair and improve drug and transplantation therapies for patients with malignant and genetic bone marrow disease. He was an inaugural winner of the National Institutes of Health Director's Pioneer Award for highly innovative research (2004).

Omar Akil
University of California San Francisco

Omar Akil, PhD, is an assistant professor in the Saul and Ida Epstein Laboratory in the Department of Otolaryngology – Head and Neck Surgery at the University of California, San Francisco. He received his doctoral degree in biochemistry and enzymology from the University of Casablanca Morocco. He moved to Johns Hopkins where he started his research training, working on the mammalian cochlea and exploring the basis of efferent neuronal transmission and outer hair cell function in the inner ear. In 2004, he moved to the University of California San Francisco, where he began investigating hearing loss in mouse models of human genetic and acquired forms of deafness. His recent work has focused specifically on the restoration of hearing in mouse models of human genetic hearing loss using virally mediated gene therapy.

David R. Liu
Harvard University and the Broad Institute

David R. Liu, PhD, is the Richard Merkin Professor and director of the Merkin Institute of Transformative Technologies in Healthcare at the Broad Institute of MIT and Harvard, and vice chair of the faculty at the Broad Institute. He is also professor of Chemistry and Chemical Biology at Harvard University and a Howard Hughes Medical Institute investigator. Liu's major research interests include the evolution and intracellular delivery of proteins with therapeutic potential and the development and application of genome editing agents. Liu graduated first in his class at Harvard in 1994; in 2015 he was named one of the top twenty translational researchers in the world in 2015 by Nature Biotechnology, and one of the ten most influential scientists of 2017 by Nature.

David P. Corey
HMS

David P. Corey, PhD, is the Bertarelli Professor of Translational Medicine in the Department of Neurobiology at HMS. His laboratory works both on elucidating the molecular composition of the mechanotransduction complex in auditory receptor cells, and on developing new viral vectors for gene therapy for the inner ear. He has served on the advisory council of the National Institute on Deafness and Other Communication Disorders, has chaired the Organizing Committee for the Molecular Biology of Hearing and Deafness meeting, and has co-organized the Mechanics of Hearing meeting. He has received the Award of Merit from the Association for Research in Otolaryngology. At Harvard Medical School, he currently directs the Bertarelli Program in Translational Neuroscience and Neuroengineering, and co-directs the Harvard Medical School Center for Hereditary Deafness.

Jeffrey R. Holt
Boston Children's Hospital and HMS

Jeffrey R. Holt, PhD, is professor of otolaryngology and neurology at Harvard Medical School and the F.M. Kirby Neurobiology Center at Boston Children's Hospital, where he is also the director of research in otolaryngology. He is well-known as an expert in hair cell physiology, and for identifying TMC1 and TMC2 as components of the hair-cell transduction channel. Holt and colleagues have also developed techniques to study human stem-cell derived hair cells. He and his colleague Gwenaëlle Géléoc are pioneers in inner ear gene therapy.

Botond Roska
Institute of Molecular and Clinical Ophthalmology, Basel

Botond Roska, MD, PhD, received an MD in Budapest, Hungary, and a PhD at the University of California, Berkeley. He was a junior fellow in the Department of Genetics at Harvard Medical School before starting his own research group at the Friedrich Miescher Institute for Biomedical Research in Basel, Switzerland. He has recently been named co-director of the new Institute of Molecular and Clinical Ophthalmology in Basel. Dr. Roska investigates neuronal circuits in the retina, thalamus, and visual cortex; he is interested in using the knowledge gained to understand the circuit basis of neurological diseases and to design new therapies.

Konstantina M. Stankovic
Massachusetts Eye and Ear and HMS

Konstantina M. Stankovic, MD, PhD, is associate professor of otolaryngology at Harvard Medical School and Sheldon and Dorothea Buckler Chair in Otolaryngology at Massachusetts Eye and Ear. She has received the Young Investigator Award from the Association for Research in Otolaryngology and the Benjamins Prize for research from the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum. She has served as president of the American Auditory Society. Stankovic's research is focused on improving diagnosis and therapy of sensorineural hearing loss by combining biotechnology with molecular biology. It has provided novel insights into the molecular basis of neurofibromatosis type 2 and vestibular schwannoma-induced hearing loss.

Daniel J. Lee
Massachusetts Eye and Ear and HMS

Daniel J. Lee, MD, FACS, is associate professor of otolaryngology at Harvard Medical School and director of the Pediatric Ear, Hearing and Balance Center at Massachusetts Eye and Ear. His clinical interests include cochlear implant surgery for single sided deafness, auditory brainstem implant surgery for children and adults who are not candidates for the cochlear implant, and surgery for superior canal dehiscence. Lee's laboratory focuses on improving the current auditory brainstem implant using novel conformable arrays and the development of new generation cochlear implants and auditory brainstem implants based on optogenetics.

Stéphanie P. Lacour
EPFL

Stéphanie P. Lacour, PhD, holds the Bertarelli Foundation Chair in Neuroprosthetic Technology and is professor in microengineering and bioengineering at the School of Engineering at the Ecole polytechnique fédérale de Lausanne. She received her PhD. in electrical engineering from INSA de Lyon, France, and completed postdoctoral research at Princeton University (USA) and the University of Cambridge (UK). She is a co-founding member of the EPFL Center for Neuroprosthetics. Her lab seeks to advance fundamental concepts in man-made electronic systems applied to biology, integrating principles of electrical engineering with biology, medicine and ultimately health. Specifically, the focus is on designing and manufacturing electronic devices with mechanical properties close to those of the host biological tissue so that long-term reliability and minimal perturbation are induced in vivo and truly wearable systems become possible.

Dara S. Manoach
Massachusetts General Hospital and HMS

Dara S. Manoach, PhD, is a professor of psychology in the Department of Psychiatry at Massachusetts General Hospital and Harvard Medical School. She is a neuropsychologist who uses multimodal neuroimaging techniques to illuminate the neural and genetic bases of cognitive deficits in neuropsychiatric and neurodevelopmental disorders, particularly schizophrenia and autism. The ultimate goal of this work is to identify mechanisms of cognitive impairment that can guide the development of targeted treatments. Manoach received her PhD from Harvard University in experimental psychology, completed a clinical psychology internship at McLean Hospital and a postdoctoral fellowship in clinical neuropsychology at Beth Israel Deaconess Medical Center, an affiliate of Harvard Medical School. At MGH she directs the Cognition and Psychopathology Laboratory at the Athinoula A. Martinos Center for Biomedical Imaging.

Dimitri Van De Ville
EPFL

Dimitri Van De Ville, PhD, is associate professor at the Ecole polytechnique fédérale de Lausanne and is also affiliated with the University of Geneva. His laboratory is located at the Campus Biotech in Geneva. He received his PhD at Ghent University, Belgium, before moving to EPFL. His laboratory focuses on extracting brain states from fMRI measurements using advanced modelling approaches based on network science and dynamical systems. Recent work also includes neurofeedback using real-time fMRI. Van De Ville was awarded the Pfizer Research Award in 2012, the NeuroImage Editors' Award in 2013, the NARSAD Independent Investigator Award in 2014, and the Leenaards Award in 2016. He was the Chair of the IEEE Biomedical Imaging & Signal Processing TC and is now the founding chair of the new EURASIP Biomedical Image & Signal Analytics SAT.

David A. Williams
Boston Children's Hospital and HMS

David A. Williams, MD, is chief scientific officer and senior vice-president at Boston Children's Hospital and President of the Dana-Farber/Boston Children's Cancer and Blood Disorders Center. He also serves as the director, Division of Hematology/Oncology, Boston Children's Hospital. He is the Leland Fikes Chair of Pediatrics at Harvard Medical School. He is actively involved in gene therapy trials for blood, immunodeficiency and neurological genetic diseases and has been the investigator, co-investigator or sponsor (IND holder) of four previous and four current gene therapy trials. He recently served as president of the American Society of Hematology. He is co-founder of the Transatlantic Gene Therapy Consortium and the North American Pediatric Aplastic Anemia Consortium. His basic research has focused on hematopoietic stem cell biology, including genetic diseases of the blood and specifically molecular and biochemical analysis of the interaction between hematopoietic stem cells and the bone marrow supporting environment. He was elected to the National Academy of Medicine in 2003 and is a fellow of the American Association for the Advancement of Science. He is co-founder of Orchard Therapeutics and Alerion Biosciences.

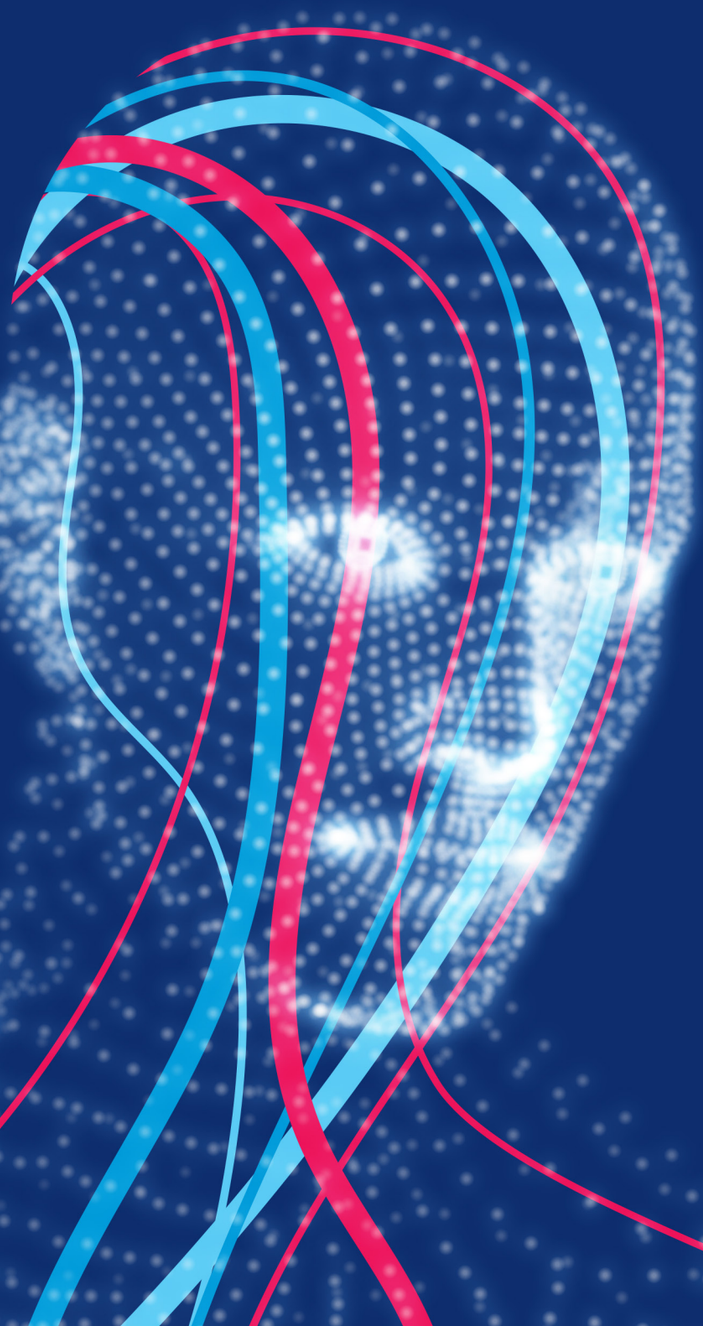
Yvan Arsenijevic
Jules-Gonin Eye Hospital

Yvan Arsenijevic, PhD, is associate professor at the University of Lausanne at the Jules-Gonin Eye Hospital. He graduated from the University of Geneva, Switzerland, in 1990, and pursued further training there in neurosciences. With Sam Weiss at the University of Calgary, he isolated and identified neural stem cells during development and in the adult brain. Arsenijevic returned to the University of Lausanne, where (with Patrick Aebischer) he demonstrated that the adult human brain contains multipotent progenitors in different brain areas. His laboratory in the Department of Ophthalmology is currently focused on retinal degeneration mechanisms and regenerative medicine using gene therapy strategies and pluripotent cells to validate therapeutic approaches. He received the 2013 Alfred Vogt Award, a Bayer Global Ophthalmology Award, and the 2017 Alfred Vogt Prize.

Katherine High
Spark Therapeutics

Katherine A. High, MD, received her AB from Harvard University and an MD from the University of North Carolina School of Medicine. Her research began with gene therapy for hemophilia and evolved to encompass potential gene therapies for multiple inherited disorders. She has been director of the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia and president of the American Society of Gene & Cell Therapy, and she served on the FDA Advisory Committee on Cell, Tissue and Gene Therapies. She was a member of the faculty at the University of Pennsylvania and of the medical staff at CHOP, and was an Investigator of the Howard Hughes Medical Institute. She now is president and chief scientific officer at Spark Therapeutics, which developed Luxturna for treating blindness. In December 2017, this became the first FDA-approved gene therapy using viral vectors.

About the program



The Bertarelli Program in Translational Neuroscience and Neuroengineering is a joint research and education program between Harvard Medical School and the École polytechnique fédérale de Lausanne [EPFL]. Launched in 2010, its team of scientists are addressing some of the most important issues in medical neuroscience, issues that, once solved, will have life-changing outcomes for patients. Its focus is not just on initiating research, but also on establishing cross-border and cross-institution working communities, within which knowledge can better be shared.

The aim of this collaborative project is to begin to bridge the existing gap between basic and translational neuroscience. In working to achieve its mission, the program has brought together the complementary specialities of two world-class universities: One, EPFL, with a unique strength in engineering and technology; the other, Harvard Medical School, whose mission is to alleviate human suffering caused by disease.

With the first round of sponsored projects having been concluded, in 2014 Ernesto Bertarelli, on behalf of the Bertarelli Foundation, signed an agreement with Harvard Medical School and EPFL to extend and develop the program, funding five new research projects.

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The Five Bertarelli Research Projects

Developing new methods for diagnostics of hearing loss: Konstatina M. Stankovic (MEE and HMS) and Demetri Psaltis (EPFL)

Summary: Developing new imaging methods for the inner ear, leading to a new way for diagnostics for hearing loss.

One of the great challenges in diagnosing hearing problems is that the physician cannot see the tissues and cells of the inner ear. In contrast, simple optical methods allow inspection of the retina of the eye. In this continuation proposal the researchers will collaborate to develop new imaging methods for the human inner ear. While they have previously showed that they can image the inner ear with minimal invasion, they will now extend advanced endoscopic two-photon technology to allow subcellular imaging, they will use the fluorescence of two natural metabolic products to assess the health of the inner ear, and they will extend initial results to enable imaging of the whole hearing organ. These experiments draw on the highly complementary skills of the two investigators to develop new methods for diagnostics for hearing loss.

New generation of auditory brainstem implants: Daniel J. Lee, M. Christian Brown (MEE and HMS) and Stéphanie P. Lacour, Nicolas Grandjean (EPFL)

Summary: Auditory brainstem implants, using high-density, flexible electrodes to help patients who cannot receive an implant due to a damaged inner ear of auditory nerve.

The cochlear implant, a device that bypasses the deaf inner ear to convey electrical signals directly to the auditory nerve, has been the most successful neural prosthesis over the past few decades, with over 200,000 in use worldwide. However, some patients cannot receive an implant due to a damaged inner ear or auditory nerve. In their 2011 Bertarelli project, the researchers optimized design and fabrication of experimental auditory brainstem implants, using high-density, flexible electrodes. Experiments were short-term, and only in mice. In this project, they will extend the research to long-term experiments in mice to test the safety, durability, and effectiveness of the devices. They will also extend the flexible electrodes to human tissue, to optimize the geometry and stimulation parameters that will allow eventual use in human patients.

Gene therapy to treat deafness: Jeffrey R. Holt (BCH and HMS) and Patrick Aebischer (EPFL)

Summary: Continuation of a successful project from 2011, is exploring new viral vectors to carry genes into the mechanosensary cells of the inner ear.

For more than a decade hopes have been pinned on gene therapy to correct inherited disorders in humans. There are, for example, over 300 distinct inherited forms of deafness, which cause congenital deafness in about 1 in 1000 newborns, and these might be treated by gene therapy to replace defective genes. A longstanding problem for gene therapy for hearing loss, however, is that very few viral vectors will enter the mechanosensory cells of the inner ear.

This continuation of a successful project from 2011 is exploring new vectors to carry genes into these sensory cells and will broaden the range of treatable genetic deafness. The researchers will also use modern genome editing technologies to repair specific mutations that cannot be corrected by simple gene replacement.

Brain networks in children with autism: Dara S. Manoach (MGH and HMS) and Dimitri Van De Ville (EPFL)

Summary: Improving how autistic children can be scanned by Functionial magnetic resonance imaging (fMRI); using those scans to test abnormal connectivity between brain regions (hypothesised as a cause of autism); identifying those aspects of brain connectivity that correlate with specific types of autism.

Functional magnetic resonance imaging (fMRI) has successfully allowed us to watch brain activity in humans during experimental tasks, revealing which brain regions are specialized for which computational functions. fMRI has also begun to be used to understand disorders of brain connectivity—the information flow between these regions. But movement of the head during imaging can distort the image, and children with autism tend to move more than others, impeding diagnosis.

These researchers will first develop methods to detect and correct for head motion in children and other difficult patients. They will then use fMRI scans of autistic children to test abnormal connectivity between brain regions, which is hypothesized as a cause of autism. Finally they will identify aspects of brain connectivity that correlate with specific types of autism, and ask whether connectivity can be improved with current autism treatments. These experiments will address general problems of fMRI in moving patients, with specific studies of autistic patients and the role of connectivity in this disorder.

Tissue engineering the macula: Michael J. Young (HMS and SERI) and Matthias P. Lütolf, Yvan Arsenijevic (EPFL and Jules-Gonin Eye Hospital)

Summary: The overall goal of this project is to develop cell lines that could be transplanted into the retina to reverse certain forms of blindness, and to discover drugs that could prevent or reverse retinal degeneration.

Retinal degenerative diseases are leading causes of incurable blindness and are often characterized by loss of the light-sensing photoreceptor cells. Because the regenerative capacity of the retina is extremely limited, cell transplantation strategies hold promise to restore lost function. Researchers have had some success in isolating the progenitor cells that can turn into photoreceptors, yet knowledge of the optimal stage of differentiation for transplantation is lacking.

The overall goal of this project is to develop cell lines that could be transplanted into the retina to reverse certain forms of blindness, and to discover drugs that could prevent or reverse retinal degeneration. This will be done in three stages: First, researchers will coax progenitor cells to become cone photoreceptors, the type of photoreceptor responsible for colour vision and high-acuity vision. Second, researchers will engineer scaffolds that can support the growth and differentiation of these photoreceptors. The third stage is to use such scaffolds as a platform to test potential compounds that can reverse retinal degenerative disorders.

The Bertarelli Education Program

Central to the Bertarelli Program is its education initiative, designed to complement and extend the impact of the research underway between both institutions and to provide opportunities for students to pursue their research with some of the most distinguished scientists in their fields through exchange programs.

As well as enabling Harvard medical and graduate students to experience summer fellowships at the EPFL, the Education Program grants provide the means for EPFL students to spend a year in Boston conducting their Master's research with an HMS-affiliated laboratory.

About the Bertarelli Foundation

The Bertarelli Foundation was founded in 1998 by Maria Iris, Dona and Ernesto Bertarelli in memory of Fabio Bertarelli, who in the 1970s brought Serono, his family's business, to Switzerland and helped lead the development of the life science sector in the Lake Geneva region. For the first ten years the Foundation worked primarily to establish and develop healthcare projects which built upon the legacy of the Serono Foundation. It focused particularly on the promotion of knowledge-sharing amongst clinicians and ethicists on issues concerning reproductive health and the treatment of infertility, which reflected the advances made in this field by Serono.

A decade later, the Bertarelli Foundation further developed its outlook to focus on two key areas of interest to its trustees: Marine conservation and science; and neuroscience research.

Today the Foundation tackles some the biggest issues in these fields by developing partnerships with scientists, NGOs and governments around the world. As a result, it is helping to provide real solutions to critical problems, ranging from creating Marine Protected Areas and combating illegal fishing, to overcoming congenital deafness and other sensory ailments.

The Bertarelli Foundation also supports important projects in local communities in parts of the world where the trustees have lived or worked – particularly in Switzerland, the United States of America, the region of Tuscany in Italy and the north-west of England.

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