BERTARELLI-FUNDED RESEARCH PROJECTS, 2012-2017

Project Title: **Biomolecular therapeutic delivery into the inner ear for hair cell regeneration and re-innervation** (funded 2012-2014)

PIs: **Zheng-Yi Chen**, Harvard Medical School and Massachusetts Eye and Ear
Jeffrey A. Hubbell, École Polytechnique Fédérale de Lausanne

Project Summary
The main objective of our project is to use a bioengineering approach to develop new methods that can be used to activate inner ear growth factor signaling for hair cell regeneration and neuron protection. In addition we will also explore the use of nanoparticles for targeted delivery to the inner ear subtypes.

Project Title: **Establishing a two-step protocol for hair cell and auditory neuron regeneration** (funded 2012-2014)

PIs: **Lisa Goodrich**, Harvard Medical School
Matthias Lutolf, École Polytechnique Fédérale de Lausanne

Project Summary
The hope for treating many types of age-related hearing loss--which affects more than 10% of adults in developed countries--is to regenerate hair cells of the inner ear. These hair cells are present at birth, but no more are ever generated in the life of a person and their degeneration causes hearing loss. Stem cell therapies are daunting because delivery and integration of stem cells into the cochlea is difficult. However, we can use stem cells to identify chemical factors that would promote the conversion of other, endogenous cochlear cells into hair cells.

Project Title: **Functional neural repair of sensory and motor systems using complementary training, pharmacological, genetic and neurostimulation strategies** (funded 2012-2014)

PIs: **Zhigang He and Clifford Woolf**, Harvard Medical School and Boston Children's Hospital
Stéphanie P. Lacour and Grégoire Courtine, École Polytechnique Fédérale de Lausanne

Project Summary
The estimated yearly incidence of spinal cord injury (SCI) is approximately 40 and 15 cases per million inhabitants in the USA and across Western Europe, respectively. More than half of these patients suffer from complete SCI, for which no clinical treatment is available. The ultimate goal of this collaborative project is to develop a combinatorial bioengineering strategy capable of promoting both sensory and motor functional recovery after spinal cord injury.

Project Title: **Gene therapy to treat deafness** (funded 2012-2017)

PIs: **Jeffrey R. Holt**, Harvard Medical School and Boston Children's Hospital
Patrick Aebischer, École Polytechnique Fédérale de Lausanne

Project Summary
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 will explore 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.

Project Title: **New generation of auditory brainstem implants** (funded 2012-2017)

PIs: **Daniel J. Lee and M. Christian Brown**, Harvard Medical School and Massachusetts Eye and Ear
Stéphanie P. Lacour and Nicolas P. Grandjean, École Polytechnique Fédérale de Lausanne

Project Summary
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.

Project Title: **Brain networks in children with autism** (funded 2015-2017)

PIs: **Dara Manoach and Andre van der Kouwe**, Harvard Medical School and Massachusetts General Hospital
Dimitri Van De Ville, École Polytechnique Fédérale de Lausanne

Project Summary
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.

Project Title: **Developing new methods for diagnostics of hearing loss** (funded 2012-2017)

PIs: **Konstantina Stankovic**, Harvard Medical School and Massachusetts Eye and Ear
Demetri Psaltis, École Polytechnique Fédérale de Lausanne

Project Summary
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.

Project Title: **Tissue engineering the macula** (funded 2015-2017)

PIs: **Michael J. Young**, Harvard Medical School and Schepens Eye Research Institute
Matthias P. Lutolf and Yvan Arsenijevic, École Polytechnique Fédérale de Lausanne

Project Summary
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 color 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.
