

Catalyst Fund @ Campus Biotech 2018 Laureates Press Kit



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Press Release - April 11th, 2018

Five proposals win initial “catalyst” funding

Researchers from Campus Biotech were invited to develop joint projects with partner research institutes and bid for funding from the Bertarelli Foundation. The laureates have been announced, April 11th see full program on pp.18-19), during the 2018 Bertarelli Symposium held at Harvard Medical School.

Less than a year ago, Martin Vetterli and Ernesto Bertarelli announced the launch of the Catalyst Fund @ Campus Biotech. The aim of this five-million-Swiss Franc fund is to promote and accelerate translational research projects on the nervous system in which one or more teams from Campus Biotech (in Geneva) join forces with partner research institutes.

The first call for proposals is now complete, and five projects have been selected for funding. “The proposals were of a remarkably high calibre,” says Patrick Aebischer, who chaired the selection committee. Ernesto Bertarelli adds: “We are delighted to provide funding for these projects. They each represent the vision of innovation and collaboration which led us to create Campus Biotech and make it the home of such partnerships between scientists and institutes in the region. Our congratulations to the recipients of this first round of grants and their shared aim of achieving transformative results for patients. We look forward to following the progress of their research.”

Each of the five projects will receive 300,000 francs, which will be used to kick start their research and which will aim to ensure that the results can be turned into clinical applications.

Optogenetic therapy to restore eyesight

The project proposed by Bernard Schneider (EPFL's Brain Mind Institute) and Sonja Kleinlogel (University of Bern) aims to bring a method of vision restoration to the stage of clinical trials. One in 300 people is visually impaired owing to a loss of light-sensitive retinal photoreceptors, manifesting in pathologies such as age-related macular degeneration or retini-

tis pigmentosa. Sonja Kleinlogel's novel optogenetic gene therapy works by introducing and stimulating a synthetic protein into remaining retinal interneurons, turning these cells into “replacement photoreceptors” and ultimately restoring the patient's natural vision. This therapy has already been tested in the lab but still lacks a viral vector adapted for humans that will guide the novel light-sensing protein efficiently to the right retinal cells.

Treating vision problems after a stroke

Motor and language impairment are common deficits after stroke, yet 30% of victims suffer from vision problems such as loss of parts of the visual field (hemianopia). The project headed by Friedhelm Hummel and involving four colleagues from EPFL, HUG, Hôpital du Valais and the Clinique Romande de Réadaptation (Sion) will use a multimodal approach by functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) simultaneously to map out activity in the visual system following a stroke to better understand the mechanisms of recovery. This will form the basis for rehabilitation strategies involving non-invasive brain stimulation and visual training. The third phase of the project is dedicated to determine potential biological markers allowing to predict individual treatment effects. This will pave the way for patient-tailored targeted therapies towards personalized medicine.

Treating hallucinations in Parkinson's patients

More than half of people suffering from Parkinson's disease experience hallucinations – a feeling of presence is one of the most common forms. The neurological processes at play have been studied in Olaf Blanke and Dimitri Van De Ville's labs at EPFL and can now be triggered using robotic tools. By teaming up with Paul Krack (Geneva University Hospital), the researchers will be able to go further in exploring these processes in patients suffering from Parkinson's. Their first objective will be to detect the biomarkers associated with these hallucinatory states and then develop non-pharmacological and non-invasive therapeutic approaches based on neurofeedback to counteract them. Their results may one day be applied to hallucinations linked to schizophrenia and other neurodegenerative diseases.

Restoring fine motor skills

A cervical spinal cord injury can lead to partial or total paralysis of the legs, arms and hands. Electrical stimulation applied to nerve fibers below the lesion has already proven effective at restoring leg movement and function. But this method will need to be significantly refined before it can enable patients to recover sufficient motor skills in their hands to carry out day-to-day tasks. Tomislav Milekovic (University of Geneva) and Marco Capogrosso (University of Fribourg) plan to carefully map out both healthy and damaged neural networks in an effort to identify the sections involved in controlling the hands. These signals could subsequently control the electrical stimulation delivered by an implant placed on the spinal cord below the injury.

Controlling the paths of pain

Nearly 20% of the population suffer from chronic pain. Yet such pain is still poorly understood and in many cases cannot be treated with drugs over the long term owing to side effects. Stéphanie Lacour (EPFL) and Isabelle Décosterd (Lausanne University Hospital – CHUV and FBM-University of Lausanne) focus on the hyperexcitability of pain nociceptive neurons and the ion channels that activate them. They are developing the tools needed to create a mechanistic model that could lead to innovative therapies – involving gene therapies, optogenetics and neurotechnologies. One of their goals is to develop an optoelectronic implant that can be applied to the sciatic nerve of mice, along with a platform for optical control and signal detection.

See the following pages for a complete description of the projects

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The winning projects in details (1/5)

Implementing and upscaling an optogenetic gene therapy for the restoration of vision

Sonja Kleinlogel
Principal investigator
University of Bern

Schneider, Bernard
Co-Investigator, Bertarelli platform
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Abstract of the proposal

Background: One in three hundred people worldwide suffer from complete or partial blindness as a result of photoreceptor degeneration. This includes patients with hereditary diseases such as retinitis pigmentosa (RP) and age related conditions such as dry age-related macular degeneration (AMD). Since 2013, retinal electronic chips can be implanted that restore rudimentary vision over a small area of the visual field. And recently, cell-based optogenetic therapies with the potential to restore retina-wide high-acuity contrast vision have been developed. Optogenetic therapies render blind retinas light-sensitive through exogenous expression of opsin proteins in the surviving inner retinal neurons. Typically, the optogenetic therapies target either the retinal ganglion cells (RGCs; the retinal output neurons) or the retinal ON-bipolar cells (OBCs; interneurons that relay the photoreceptor signal to the RGCs). Unlike RGC-targeted therapies, the highly sophisticated inner retinal processing mediated by the amacrine cell circuitry remains intact when targeting the OBCs and consequently, OBC-targeted therapies possess an unparalleled potential to restore natural vision. The Kleinlogel group developed the currently most favored optogenetic designer tool for OBC-targeted vision restoration, Opto-mGluR6 (patent WO2012174674 A1), a chimeric protein comprising the light-sensing domains of the photopigment melanopsin and the signaling domains of the native receptor of OBCs, mGluR6. A gene therapy with an adeno-associated virus (AAV), injected into

the vitreous humor of the eye (the “jelly” within the eyecup) shall deliver Opto-mGluR6 to the OBCs of future patients. However, specific targeting of OBCs in human (ex vivo) retinas and non-human primates (in vivo) is presently not possible due to the lack of suitable promoters and AAVs. To overcome this issue the Kleinlogel group has recently designed an AAV library that was converged, by in vivo directed evolution in the mouse eye, to AAV capsid variants capable of transducing OBCs. In addition, the lab has designed synthetic, potentially OBC-specific promoters. These gene therapeutic tools need to be evaluated in combination with Opto-mGluR6 in relevant translational models.

Goal: Our clear goal is clinical entry of an Opto-mGluR6 gene therapy, potentially putting Switzerland at the forefront of emerging optogenetic gene therapies. Scaling up GLP-like production of a therapeutic AAV variant carrying Opto-mGluR6 under an in-house OBC-specific promoter will enable dosage and toxicity testing in a large animal model and give us “freedom to act” for clinical admission.

Methods: In a first step, we will evaluate the transduction patterns of selected AAV library capsid variants and synthetic OBC-specific (PR_{OBC}) promoters. In a second step, we will combine selected capsid variants with a specific PR_{OBC} to drive Opto-mGluR6 expression for functional evaluation in translationally relevant models, such as the degenerated mouse retina, ex vivo human retinal explants or enucleated human eyes. These experiments will reveal Op-

to-mGluR6 expression patterns for each capsid/promoter pair, the best method of injection into a human eye and the capability of functional vision restoration. Finally, the therapeutic vector is scaled up in production with a GLP-like packaging protocol for large animal testing.

Significance: Enabling an OBC-targeted gene therapy will overcome the last remaining hurdle towards an Opto-mGluR6-based therapy with the potential to restore near natural vision in blind patients. The proposed study is key to convince authorities and investors of the validity of our Opto-mGluR6 approach and to participate in a clinical trial.

Significance

Our long-term goal is to launch a clinical trial for an Opto-mGluR6 based gene therapy, ideally within Switzerland. Presently there is no cure for patients with advanced stages of photoreceptor degeneration. Retinal electronic implants can restore some crude vision; however, the success varies tremendously from patient to patient, with some regaining some ability to read and others being left suffering from side-effects, such as the perception of irritating random light flashes (phosphenes) without any visual improvement. Also, retinal implants only restore vision in a very small field of view below the implant. This does not hinder the retina to degenerate further, finally resulting in a tissue unavailable to electrical activation. And finally, the procedure of implanting is invasive and bears the risk of permanent retinal

injury, in particular since a degenerated retina is destabilized.

Gene replacement therapy was in recent years successfully used to correct for degeneration-causing mutations in the photoreceptors and the supporting retinal pigment epithelium and over 200 patients have already been injected into the eye with AAVs. AAV gene therapy is a one-time, ambulant procedure and has been shown to be well tolerated in the eye. However, gene correction therapies for the restoration of vision are only useful very early in the disease process, if not before disease onset, which leaves the challenge of diagnosing and treating patients timely. Optogenetic gene therapy combines the advantages of both above-mentioned therapies by providing a non-invasive and pan-retinal treatment for late stages of photoreceptor degenerations. Light sensitivity in a blind retina is restored by expressing an optogenetic protein in the remaining inner retinal neurons, thereby creating “replacement photoreceptors”. The Kleinlogel Lab has developed the currently most sophisticated optogene for vision restoration, Opto-mGluR6, which has the potential to restore high-quality vision, including face recognition and reading capabilities, in a patient.

The winning projects in details (2/5)

Re-Orchestration of interregional oscillatory activity in the visual system to promote visual recovery after stroke (Re-Orchestrate-4-Vision)

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Abstract of the proposal

Stroke is the world's third leading cause of death and the leading cause of severe, long-term adult disability. Stroke is often catastrophic and affects all aspects of an individuals' life. Apart from significant direct costs for hospital- and home-based rehabilitation and care, there are also indirect, societal costs, such as loss of productivity. Aging of the population and the respective increase of stroke (1.5-2 fold until 2050) may further increase the stroke-related demands to health-care systems and the society in the future.

Lesions within the primary visual cortex or its immediate afferents are likely to result in deficits (blind spots) in the visual field, termed hemianopia/quadranoopia. Actually, approximatively 30% of stroke victims suffer from visual disturbances, half of whom suffer from partial or total visual hemi-field loss. As a result, day-to-day activities, such as reading, driving, and navigating, are significantly impaired, devastating independence, professional integration and quality of life. Compared to the motor or language area, there are currently no widely accepted and clinically proven therapies available for visual field recovery. Hence, there is a great need of developing novel, innovative treatment strategies to enhance the functional recovery from these deficits.

The present proposal uses unique technical approaches (e.g., simultaneous TMS-fMRI) to better understand the pathophysiology of hemianopia and to provide the basis to develop an innovative interventional strategy based on non-invasive brain stimulation (NIBS) combined with a novel visual training paradigm.

By using a multimodal, systems neuroscientific approach, we aim to characterize the underlying mechanisms of hemianopia and based on this, to develop personalized (re)-training paradigms enhanced by tailored brain stimulation strategies. By this, we will be able to determine factors, which allow to predict the course of recovery and to define personalized treatment parameters for the individual patient, with the overarching goal to improve significantly residual visual function and enhance functional recovery. This will set the basis for innovative precision medicine approaches with patient-tailored treatment strategies to push the effect of interventional treatment to the individual maximum for patients suffering from visual field impairment.

To achieve these goals, the proposal consists of three main work-packages (WP). The first WP will be dedicated to the testing a model of a transient lesion in the visual system. It will especially enable us to disentangle the respective roles of the retino-geniculate and retino-colliculo circuitries whereby 'unaware' visual signals influence behavior in an experimental model of blindsight, which constitute a hallmark of hemianopia (WP1). The second WP will be targeted to determine neurophysiological biomarkers able to predict recovery, treatment responses and personalized treatment approaches (WP2). The third WP will use the knowledge acquired from WP1 and WP2 and the respective biomarkers to apply innovative individually adjusted, physiologically motivated NIBS to enhance impaired visual functions in chronic and subacute stroke patients. We will adopt a stepwise

approach: NIBS will be first combined with a highly controlled visual training task and as a long-term goal, we will benefit from the resources available at Biotech Campus and combine NIBS with an enriched and personalized virtual reality environment close to real life scenarios.

These proof-of-principle studies will encourage the development of a home-based adaptive device, which will allow continuous and intensive rehabilitative treatment with novel, personalized neuro-technologies in a cost-effective way. The long-term goal is to translate this concept into innovative semi-invasive or invasive stimulation systems combined with VR applications to account for the fact that neurorehabilitation is a long-term, maybe even lifelong, task aiming at continuously improving recovery from devastating visual field defects.

Significance

Impaired vision exerts dramatic effects on daily life functions and quality of life with the respective consequences for the patients, their relatives, health care systems/providers and socio-economics. Therefore, there is a fundamental mandate to determine a more sophisticated picture and understanding of processes of visual (re-)organization, (re-) learning and recovery after a visual system damage. This enhanced understanding will pave the way for translational steps of neuro-technology-based treatment strategies from the experimental bench to the bedside of clinical daily life, to significantly improve treatment,

outcome and long-term quality of life of patients and their peer-environment. The significance of the proposed project in more specific can be summarized in five main points.

- **Novel, cutting-edge approach of studying the effects of a lesion of the visual system on orchestrated visual network activity: a simultaneous TMS-fMRI virtual lesion approach.** The combination of transcranial magnetic stimulation (TMS) and simultaneous fMRI offers a unique way to causally examine the interaction between different network components of visual processing and the effect of a (transient) lesion to this network, providing a systems neuroscience model for a stroke lesion (WP1). The technical set-up of performing TMS online during fMRI acquisition is a challenging approach, which can only be performed in a few laboratories in the world, such as at Campus Biotech. The stimulator within this project is of the novel generation with extensive stimulation parameters allowing high-frequency stimulation with enough power essential for such a project and is currently to our knowledge the only one in the scientific world within the simultaneous TMS-fMRI set-up at Campus Biotech.
- **Development of a non-invasive biomarker for determining visual processing integrity.** We will test and validate a novel plasticity inducing protocol targeting specific visual pathways (WP2) that will probably develop towards a biomarker for visual processing integrity and treatment stratification.

The winning projects in details (2/5)

Re-Orchestration of interregional oscillatory activity in the visual system to promote visual recovery after stroke

(Re-Orchestrate-4-Vision)

- **Physiologically motivated, personalized interventional strategies to improve visual functions.** Based on the knowledge acquired in WP1 and WP2, we will exploit the concept that neural oscillations are a core mechanism supporting visual information computation in the brain. Neuronal oscillations are orchestrated by synchronized activity on a frequency level. For instance, during visual processing, local fast oscillatory computation at higher frequencies is embedded in oscillations at lower frequencies representing rather long-range interactions (cross-frequency interactions). Here, we plan to modulate this complex orchestration of interregional cross-frequency interactions by altering experimentally interregional cortical oscillations using **transcranial alternating current stimulation (tACS)** (WP3). This personalized and physiologically adjusted intervention will be tuned to achieve maximal individual interventional effects. The proposed project will open new avenues for interventional tools, towards personalized translational precision medicine approaches in patients suffering from a stroke in the visual system with consecutive hemi-field deficits.
- Finally, these **proof-of-principles studies** will encourage the **early stage of technological development towards a home-based setup**, which later on, could imply the use of **semi-invasive** or **invasive** stimulation devices for a **closed-loop ambulatory solution to provide long-term assistance to this frequent and devastating disorders.**

In summary, the expected results will be of relevant interest **of a large neuroscientific community and clinical neuroscientist, of health care providers** and have the potential to be an interesting **target** for **R&D** approaches. Besides this, the current project is fully aligned to the concept of the **'health valley'** at the Arc Lemanic, leveraging the tight collaboration between academic institutions (**EPFL**), university hospitals (**HUG**) and non university hospitals (**Hôpital du Valais, Sion** and the Clinique Romande de Réadaptation) for bringing together excellent clinical and scientific expertise to be able to perform translational clinical neuroscience with a relevant number of patients.

The winning projects in details (3/5)

Novel biomarkers and therapeutics for hallucinations in Parkinson's disease using robotically-driven neurofeedback

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Abstract of the proposal

This project aims at developing new biomarkers of hallucinatory states, as well as non-pharmacological and non-invasive methods to treat them in Parkinson's disease. For this purpose, we will combine two recent technological-scientific breakthroughs by the Blanke and Van De Ville labs at Campus Biotech, allowing us to respectively control hallucinatory states with novel robotic systems, and to extract and regulate activity in target brain regions and networks. These two cutting-edge methods will be implemented in three incremental studies to regulate the brain activity responsible for hallucinations in healthy volunteers and patients with Parkinson's disease, in hope of decreasing their occurrence. The clinical evaluation of hallucinatory states will be performed in collaboration with the Krack lab at the University Hospital of Geneva, known internationally for its work on the behavioral and neural underpinnings of Parkinson's disease. If successful, our method may lead to better diagnosis and treatments for hallucinations in Parkinson's disease, as well as other conditions such as schizophrenia or neurodegenerative diseases for which efficient treatments are still missing.

Significance

Parkinson's disease (PD) is the second-most common neurodegenerative disorder, affecting 1% of the population over 65 years of age. Although PD is defined primarily as a movement disorder with the classical symptoms of resting tremor, rigidity, and bradykinesia, it also manifests in a wide variety of non-motor symptoms including hallucinations and psychosis (Postuma & Berg, 2016). The relevance of hallucinations in PD is illustrated by a very early onset during the disease, even before initiation of antiparkinsonian treatments (Pagonabarraga et al., 2016). Hallucinations are experienced by more than half of patients (Fenelon, Soulas, de Langavant, Trinkler, & Bachoud-Levi, 2011; Fenelon, 2000). Hallucinations affect an estimated 3 million patients with Parkinson's disease and 30 million patients with schizophrenia worldwide causing major health costs (e.g., respectively \$23 billion and \$120 billion per year in Europe and US). Among the different hallucinations reported by patients with PD, the most prevalent are presence hallucinations (PH), defined as the sensation that somebody is nearby when no one is actually present. Although PH have been linked to cortical dysfunction (Arzy, Seeck, Ortigue, Spinelli, & Blanke, 2006), their detailed mechanisms as well as their link to the subcortical-cortical pathophysiology of PD is unknown. Hallucinations and especially PH are not only frequent in PD, but also clinically relevant as they are associated with negative clinical outcome

such as psychosis, depression, early home placement, higher mortality, and dementia (Fenelon et al., 2011; Fenelon, 2000; Kataoka & Ueno, 2015). Novel treatments for hallucinations in PD (and beyond) are needed. Although many treatment options exist for the motor symptoms of PD, the management of PD patients with hallucinations is challenging because anti-parkinsonian treatments such as dopaminergic treatments may induce or augment hallucinations (Fenelon et al., 2011; Kataoka & Ueno, 2015). The reduction of dopaminergic treatments does not abolish hallucinations in many cases. The addition of anti-psychotic treatments to treat hallucinations exacerbates motor deficits, does not abolish hallucinations, and is associated with severe side effects including higher mortality risk (Weintraub et al., 2016). Moreover, the efficacy of neurosurgical and behavioral hallucination treatments is limited and in the former case associated with side effects. As hallucinations in PD are under-investigated and as detailed laboratory-based induction methods are lacking, their underlying brain mechanisms are completely unknown. As a result, the development of novel pharmacological, neurotechnological, or behavioural therapies that target hallucination control is very slow (Diederich, Fénelon, Stebbins, & Goetz, 2009).

Of key importance are two recent technological-scientific breakthroughs by the Van De Ville and Blanke labs, which we plan in the present project to further improve, combine, and adapt for the first time to PD patients in order to design a new medical procedure

that diagnoses and treats hallucinations. Importantly, the new procedure will be developed in close collaboration with the Krack lab at HUG, by whom the participating PD patients will be recruited and investigated. Specifically, we plan to further develop and integrate the robotic devices of the Blanke lab (able to control PH and related hallucinations in the MR scanner) with the realtime functional MRI brain imaging expertise (rt-fMRI) of the Van De Ville lab (able to extract and regulate activity in target brain regions and networks) and the clinical expertise of the Krack lab to develop the first neurotechnological treatment for hallucinations in PD, worldwide. Our patented robotic devices, combined with latest rt-fMRI analysis may allow us in the next phase to develop a clinical trial involving new patents, with impact for patients with PD, but also in other clinical conditions with hallucinations such as schizophrenia and other psychiatric or neurodegenerative diseases.

The winning projects in details (4/5)

Brain-controlled neuromodulation of the cervical spinal cord for the restoration of arm and hand movement in tetraplegia

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Abstract of the proposal

The problem: Every year, as many as 500,000 people around the world lose the ability to move due to spinal cord injury (SCI). More than half of those cases affect functional use of hands and arms. For these people, restoring the ability to reach and grasp is the highest priority. However, even the most promising techniques to restore hand and arm function have so far recovered only crude movements.

Goal of the project: We propose to leverage our previous work on the use of brain-controlled neuromodulation to recover locomotion in nonhuman primates, to design and implement a novel neuroprosthetic system for the recovery of hand and arm function after cervical spinal cord injury.

Background: SCI disrupts the bi-directional communication between the supraspinal brain and brainstem centers generating movement commands, and the spinal circuits below the lesion that generate and coordinate limb movements. Epidural electrical stimulation (EES) can improve voluntary control of the lower limbs in rodents and humans with motor complete paralysis. We have recently shown that brain-controlled neuromodulation of the spinal cord enabled nonhuman primates to regain control of a paralyzed leg to walk bipedally as early as 6 days after thoracic SCI. There, intra-cortically recorded activity of a motor cortical neuronal ensemble controlled bursts of EES at specific locations on the lumbar spinal cord at the appropriate phases of gait.

Knowledge gap: The strategy of using brain-controlled neuromodulation may be applied to the cervical spinal cord after high cervical spinal cord injury to restore lost hand and arm functions. However, contrary to the stereotyped and patterned leg walking movements, recovery of dexterous hand and arm movements will require a technique that can obtain more accurate and comprehensive control signals robust to the effects of SCI. This technique may be developed by studying interactions between areas of the sensorimotor cortical network before and after SCI. While thoroughly studied and known to be profoundly involved in generating and controlling movement, the interactions between these areas on the level of neuronal ensembles, and the effect of SCI on those interactions, is still largely unknown.

Our proposed solution: Here we propose to study the neuronal network interaction of spinal and cortical sensorimotor areas before and after cervical SCI. To this end, we will apply state-of-the-art computational tools on activity of neuronal ensembles from several areas of this network. We will record the activity using multiple microelectrode arrays in nonhuman primates during reaching and grasping. We will exploit these tools to develop a computational technique that can decouple cortical signals related to pure hand and arm movement intentions invariant to the somatosensory feedback. We will then leverage gained knowledge to engineer a brain-controlled neuromodulation technology that directly links these pure movement intention signals to EES bursts applied at the cervical spinal cord below the injury. Finally, we will validate the efficacy of this novel neuroprosthesis to restore dexter-

ous reaching and grasping movements in nonhuman primates after unilateral cervical SCI.

Path towards our goal: This project will deliver the proof of concept for brain-controlled neuromodulation of the cervical spinal cord in a relevant animal model. If successful, we will leverage our findings to seek approval for clinical trials testing the safety and efficacy of this therapy. All the devices used in our project are currently tested in clinical trials or have been designed with the intention of seeking approval for medical use. This opens a practical pathway for rapid translation of our neuroprosthesis into clinical therapy that has the potential to help people with hand and arm paralysis.

Impact: The joint efforts of our groups will result in the development of a novel therapy for the treatment of people with hand and arm paralysis. At the same time, the project will provide valuable data and increase the understanding of neural control of hand and arm movements in a clinically relevant primate model, both before and after SCI. Our technique for extraction of pure movement intention signals can generalize to other neuroprosthetic applications. Our project will strengthen collaborations in the growing network of young investigators across the Western Switzerland, catalyzing the birth of a Swiss excellence hub for innovative translational neurotechnologies.

Our vision: Our long-term goal is to develop and com-

mercialize an effective, practical and clinically-relevant hand and arm neuroprosthesis to restore movements lost to spinal cord injury. We are not seeking for successful experiments, but for the definition of a clear path towards clinical translation.

The winning projects in details (5/5)

Optogenetic modulation of peripheral nociceptive neurons and neuropathic pain

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CHUV

Abstract of the proposal

Context. Chronic pain represents a critical global health concern with moderate to severe chronic pain affecting almost 20% of the general population. Currently available options for the treatment and management of chronic pain are limited due to the complexity of pain mechanisms and conditions but also the severe side effects of pharmacological treatments.

Our ideas. A key issue is hyperexcitability and identification of receptors and channels involved in pain transmission and modulation, and doing so in realistic experimental setting i.e. in vivo in awake, freely behaving conditions. Prof. Lacour's team is developing novel neurotechnology tools that enable realistic in vitro interrogation of peripheral nerves and long-term in vivo interfaces. Prof. Décosterd's lab has developed a transgenic mouse line expressing the excitatory channelrhodopsin (ChR2) in Nav1.8 nociceptive neurons and is exploiting it to decipher activity-dependant central sensitization. Joining our groups, we propose an interdisciplinary approach combining optogenetics, gene therapy, neurotechnology and animal neuropathic pain models to advance our mechanistic understanding of neuropathic pain and test a potential therapeutic approach to alleviate pain symptoms.

Experimental plan. We will exploit our recent developments in microfabricated electrode interfaces for

pain modulation in mouse models.

Two neural interfaces will be produced: (1) a wireless optoelectronic cuff implant optimised to deliver blue and/or yellow light stimuli to the mouse sciatic nerve, and (2) a nerve-on-chip platform allowing for electrical and optical stimulation and high signal-to-noise ratio extracellular recordings from explanted nerve rootlets. The later will allow for a realistic ex vivo characterization of neuronal silencing and efficient screening of viral-vectors gene delivery. Our goal is to efficiently express the inhibitory Archaeorhodopsin proton pump (Arch-3) in peripheral sensory neurons. We will evaluate two viral-mediated gene delivery vectors (recombinant adeno-associated virus vectors rAAV2/6 and the newly designed rAAV2-retro, produced at the Gene Therapy platform under the guidance of Dr. Bernard Schneider, that will be injected in the sciatic nerve of mice. Four weeks later, we will explant the nerves and conduct optically driven extracellular electrophysiology in a dedicated nerve-on-chip platform to quantify transduction efficacy.

In vivo, spatial and temporal delivery of light stimuli will be delivered through a soft, miniaturised optoelectronic nerve interface and controlled wirelessly through dedicated ultra-lightweight electronic hardware. The implant will be prepared using thin film materials and designed to produce minimal foreign body reaction over time. We will then compare silencing of nociceptive neurons through light activation of the inhibitory opsin Arch3 in transgenic and non transgenic mice. The last part of the project will be dedicated to the exploration of clinically relevant approaches by combining gene delivery and optoelectronic implant

light application. Our aim is to discover if silencing peripheral sensory neurons can reduce subsequent activity-dependant central (spinal) changes and alleviate nerve-injury related pain hypersensitivity.

Our team will leverage access to Campus Biotech state-of-the-art and shared facilities including the Neural Microsystems and Preclinical Research Platforms and the Bertarelli platform for Gene Therapy to gain more insight into the mechanisms and possible treatment options of neuropathic pain.

Future therapeutic developments. Our project will address an important unmet technological need to implement gene therapy and associated implantable optoelectronic interfaces in the context of neuropathic pain management.

Significance

Persistent pain is a leading cause of disabilities worldwide. Current treatments are mostly ineffective and often bear serious side effects. We propose the convergence of new neurotechnologies based on gene therapy and electroceuticals to create a path towards pain therapeutics.

Acute, physiological pain is an essential defence mechanism that warns against damage to the body, whereas chronic pain serves no known helpful function. **Neuropathic pain** occurs as a consequence of lesion or dysfunction of the somatosensory system and represents the most difficult type of pathological pain to alleviate. The prevalence of neuropathic

pain syndromes is evaluated at 6.9% of the population where the two most frequent origins are represented by limb pain in the context of disc hernia (the hernia compresses and alters spinal nerves) and chronic postsurgical pain when peripheral nerves are severed. Neuropathic pain manifests as spontaneous pain, and the sensitivity to external stimuli is generally augmented in the territory of the non-injured nerves (extraterritorial pain), with typical presence of allodynia (i.e. intense pain induced by an innocuous stimulus such as light contact with clothes) and hyperalgesia (exaggerated pain after noxious stimulus). Current treatment is mostly unsuccessful in > 50% of patients, and the persistence of pain is the drive for an emotional state of suffering, mood disorders and alteration of cognitive functions altogether leading to large socio-economical consequences.

In the present project we are mainly interested in **reducing the abnormal activity** generated in the peripheral nerve, in injured and adjacent non-injured primary sensory neurons. This barrage of inputs from the periphery results in activity-dependent central sensitization, making the spinal cord more responsive to subsequent sensory input. Irreversible activity-dependant neurodegenerative processes such as cell death of central inhibitory interneurons occurs leading to disinhibition after nerve injury. In addition, modification in the reactive glia has been discovered and largely contributes via neuroinflammation to the state of central sensitization.

In the past, using peripheral nerve blockade, we investigated the role of ectopic activity from peripheral nerve to the development and maintenance of neuro-

The winning projects in details (5/5)

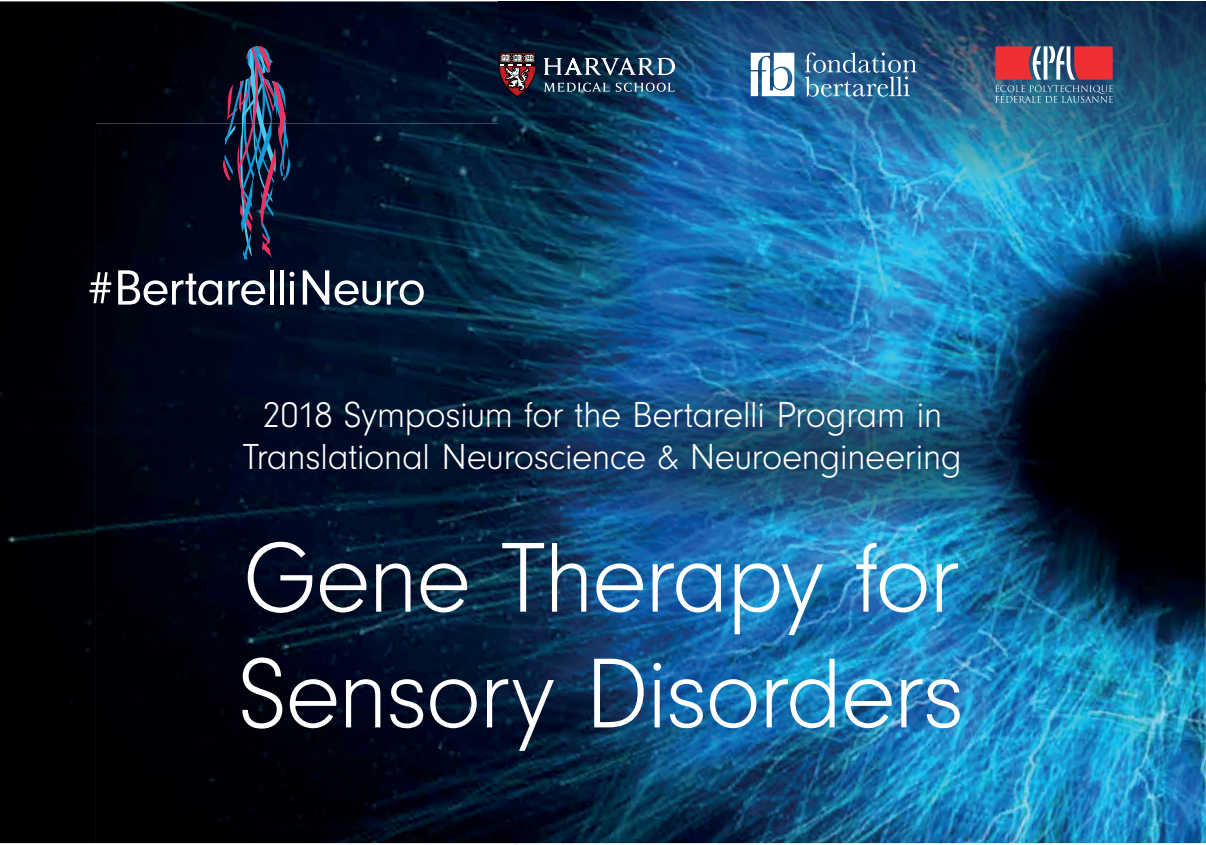
Optogenetic modulation of peripheral nociceptive neurons and neuropathic pain

pathic pain in experimental model of nerve injury. One week long nerve blockade with local anaesthetic entrapped in biodegradable microspheres was used by our group to demonstrate that during the period of the block, (i) microglial activation in the dorsal horn of the spinal cord is substantially reduced, (ii) proliferation of microglia is almost abolished, and (iii) cell death of spinal inhibitory neurons is prevented. Nevertheless, the barrage of peripheral activity re-emerges once the block wears off and is sufficient to re-initiate the above-mentioned central modifications. In spite of these evidences, mainly for technical reasons, little is known on a long term silencing of peripheral inputs, and central activity dependant changes.

The combination of long-term optoelectronic nerve implants and expression in the peripheral nerve of inhibitory opsin would circumvent the difficulty in experimental models of a long-term blockade of nociceptive neurons. By switching on and off light stimulation in living animal models, we would therefore be able to determine if, after a certain period of time, abolition of peripheral input can prevent the development of central changes and prevent the development of pain hypersensitivity after nerve injury. Furthermore, peripheral nerves are relatively easily accessible when considering a therapeutic approach combining peripheral nerve stimulation and viral-vector driven gene therapy. This is the global context and the long-term goal of the present project.

At the end of this two-year project, we will have demonstrated in mouse models **the feasibility of silencing peripheral nociceptive neurons activity** via

inhibitory viral-vector opsin delivery in the peripheral nerve and optical stimulation through a soft optoelectronic implant system. We will have manufactured the miniaturised peripheral nerve interface, defined the best viral-vector for inhibitory opsin delivery, and brought a proof of concept that inhibiting abnormal peripheral activity can impair the development of chronic peripheral neuropathic pain.



Wednesday, April 11, 2018
8.30am – 6.30pm

Keynote Speakers

David R. Liu, PhD

Professor of Chemistry and Chemical Biology, Harvard University and Vice-Chair of the Faculty, Broad Institute

Botond Roska, MD, PhD

Co-Director, Institute of Molecular and Clinical Ophthalmology Basel

Katherine High, MD

President and Chief Scientific Officer, Spark Therapeutics

Harvard Medical School
Martin Conference Center
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Boston, MA

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Gene Therapy for Sensory Disorders

Annual Symposium of the Bertarelli Program in
Translational Neuroscience and Neuroengineering

Harvard Medical School, Martin Conference Center, 77 Avenue Louis Pasteur, Boston, MA
Wednesday April 11, 2018

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, 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, 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. Manocha, 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, Jules-Gonin Eye Hospital Stem Cell and Gene Therapy for Retinal Degeneration
4:45 - 5:45pm	Keynote Lecture – Katherine A. High, President and Chief Scientific Officer, Spark Therapeutics, Philadelphia PA Overview of the Development Program for Voretigene Neparvovec: Challenges and Solutions
5:45 - 6:15pm	Closing Remarks
6:15 - 7:45pm	Reception



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