NEUROPHAGE

Phage-based targeted neural stimulation in neurodegenerative diseases

With more than 10 million people affected worldwide, Parkinson's Disease (PD) is one of the most common neurodegenerative diseases with major psychological, social, and economic impacts. PD is characterized by the progressive degeneration of the nigrostriatal dopaminergic pathway that physiologically facilitates the initiation of voluntary movements. This results in the imbalance of striatal outputs and impairment of the striatal D1-dopaminoceptive "direct pathway", leading to akinesia. The current pharmacological approaches control the symptoms in the early phase, but still suffer from long-term complications and drug-resistance issues. Among alternative methods, current implant technologies using microelectrodes for delivering stimuli (DBS) meet several problems that limit performance and safety of the implants, while optogenetics, a breakthrough in optical stimulation, requires gene therapy and implanted fiber optics.

We have recently shown that photovoltaic polymer nanoparticles (NPs) are able to efficiently stimulate denervated neurons on demand. As an alternative to invasive DBS or optogenetics, NEUROPHAGE aims at delivering these polymeric NPs using engineered brain-permeable M13 phages as nanocarriers for specific targeting and activation of D1-dopaminoceptive neurons in the striatum. To this aim, M13 phages will bear a docking system to recognize specific neuronal epitopes and an orthogonal cargo of polymeric NPs eliciting neuronal activation in response to near-infrared/ultrasound (NIR/US) stimulation. The NEUROPHAGE innovation, distinct from existing NP-based technologies, consists in using biological biocompatible and harmless vectors to bring active organic NPs in close proximity of selected target neurons.

This interdisciplinary project brings together expertise from seven research institutes across six European countries to tackle the development of such an innovative therapeutic strategy for PD and other neurodegenerative diseases. The Consortium includes the Center of Synaptic Neuroscience and Technology led by Fabio Benfenati at the clinical research hospital IRCCS Ospedale Policlinico San Martino in Genova, specialized in smart interfaces for neuronal activation, and two world-renown laboratories for research on basal ganglia physiopathology and therapy for Parkinson's disease, namely the INSERM Unit led by Jean-Antoine Girault in Paris and the Karolinska Institutet Unit led by Gilberto Fisone in Stockholm. The Consortium is enriched by the presence of excellent centers in the field of bionano interactions as the Center for BioNano Interactions (NUI-UCD) led by Kenneth A. Dawson, the Nanoscalic system group (HZDR) represented by Kristof Zarschler, the NanoBio Interface Lab of Matteo Calvaresi and the advanced preclinical imaging center (CAPI) directed by Ludek Šefc.

With the proven capability of the phage system to efficiently cross the blood brain barrier and the possibility to tune the NP properties to respond to NIR/US stimulation, our proposal holds a great promise for an effective, cell-specific, minimally invasive strategy to drive specific basal ganglia activation and rescue PD symptoms. This project will pave the way for a very flexible platform based on novel hybrid bio-nano interfaces applicable in vivo to rescue neural functions that are lost in neurodegenerative diseases.

Total Funding : 1.58 M€

Duration : 3 years

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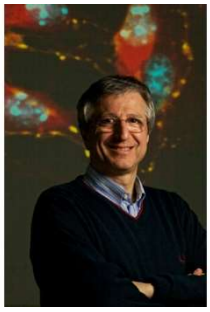

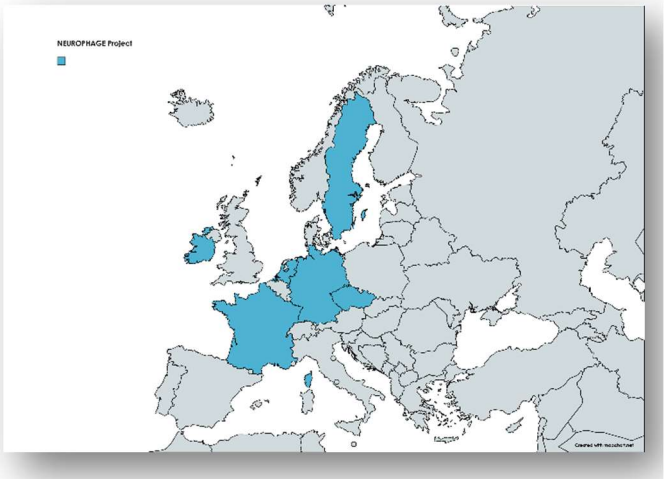

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