SORBONNE UNIVERSITÉ

PROGRAMME INSTITUTS ET INITIATIVES

Appel à projet – campagne 2021

Proposition de projet de recherche doctoral (PRD)

Choisissez l'institut ou l'initiative :

Institut Universitaire d'Ingénierie en Santé- IUIS

Intitulé du projet de recherche doctoral (PRD): Sonogenetic therapy for visual restoration

Directrice ou directeur de thèse porteuse ou porteur du projet (titulaire d'une HDR) :

NOM : **Picaud** Prénom : **Serge**
Titre : Directeur de Recherche ou
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Unité de Recherche :
Intitulé : Institut de la vision
Code *(ex. UMR xxxx)* : UM80

École Doctorale de rattachement de l'équipe (future école doctorale de la doctorante ou du doctorant) : **ED158-Cerveau, cognition, comportement**

Doctorantes et doctorants actuellement encadrés par la directrice ou le directeur de thèse (préciser le nombre de doctorantes ou doctorants, leur année de 1e inscription et la quotité d'encadrement) :

Mathieu Provansal 100%

Co-encadrante ou co-encadrant :

NOM : **Sahel** Prénom : **José-Alain**
Titre : Professeur des Universités ou HDR ☐
e-mail : j.sahel@gmail.com

Unité de Recherche :
Intitulé :
Code *(ex. UMR xxxx)* :

École Doctorale de rattachement : **ED158-Cerveau, cognition, comportement**
Ou si ED non Alliance SU :

Doctorantes et doctorants actuellement encadrés par la directrice ou le directeur de thèse (préciser le nombre de doctorantes ou doctorants, leur année de 1e inscription et la quotité d'encadrement) : 0

Co-encadrante ou co-encadrant :

NOM : Prénom :
Titre : Choisissez un élément : ou HDR ☐
e-mail :

Unité de Recherche :
Intitulé :
Code *(ex. UMR xxxx)* :

École Doctorale de rattachement : **Choisissez un élément :**
Ou si ED non Alliance SU :

Doctorantes et doctorants actuellement encadrés par la directrice ou le directeur de thèse (préciser le nombre de doctorantes ou doctorants, leur année de 1e inscription et la quotité d'encadrement) :

Cotutelle internationale : ☐ Non ☐ Oui, précisez Pays et Université :

Selon vous, ce projet est-il susceptible d'intéresser une autre Initiative ou un autre Institut ?
☐ Non ☐ Oui, précisez Choisissez l'institut ou l'initiative :

SORBONNE UNIVERSITÉ

Description du projet de recherche doctoral *(en français ou en anglais) :*

Problematic and state of the art

Sight loss was recently rated as the worst possible health outcome, across ethnic groups (Scott, Bressler et al. 2016). Vision loss principally raises concerns about a decrease in quality of life and a loss of independence (Scott, Bressler et al. 2016). There are still an estimated 285 million visually impaired individuals and 39 million blind people worldwide. Due to population growth and ageing, the number of blind or visually impaired individuals could triple by 2050 (Scott, Bressler et al. 2016). Some types of blindness are curable (cataracts, uncorrected refractive errors), but others are stille leading to blindness consecutive to the degeneration of photoreceptors, as in age-related macular degeneration (AMD), or to the loss of retinal ganglion cells communicating visual information to the brain, as in glaucoma, diabetic retinopathy and optic neuropathies. In high-income countries, the most common causes of blindness are AMD (16-19%), glaucoma and diabetic retinopathy (14-16%) (Bourne, Stevens et al. 2013). We recently developed visual restoration at the retinal level through both retinal prosthesis (Palanker, Le Mer et al. 2020, Prevot, Gehere et al. 2020) and optogenetic therapy (Chaffiol&, Caplette& et al. 2017, Gauvain, Akolkar et al. 2021) but these do not apply for patients having lost retinal ganglion cells who require visual restoration at the cortical level.

In the 1960s, Brindley and Lewin developed the first cortical prosthesis and showed that patients could perceive phosphenes upon electrical stimulation of the visual cortex with 39/80 electrodes (Brindley and Lewin 1968). Unfortunately, patients progressively lose this artificial vision. A more recent study confirmed the potential for restoring some visual sensation but with a kinetics too slow for vision (Beauchamp, Oswalt et al. 2020). Penetrating electrodes have been shown to elicit visual perception in patients at much lower currents than can be achieved with surface electrodes (Bak, Girvin et al. 1990). A recent study demonstrated visual recognition of letters with such penetrating electrodes in the visual cortex of primates (Chen, Wang et al. 2020). These studies demonstrated the need for cortical stimulation in the cortical depth to recover vision. However, penetrating electrodes are known to induce a chronic inflammatory reaction around the electrodes, resulting in the long-term loss of electrical contact (Fernandez, Greger et al. 2014).

Optogenetics has recently provided an alternative by rendering neurons photosensitive to light through the expression of a microbial opsin to activate or inhibit neurons This approach has revolutionised neuronal circuit analysis, especially in rodents, due to the ease of gene manipulation (Kim, Adhikari et al. 2017). However, applications to large animals; such as non-human primates remain limited (El-Shamayleh and Horwitz 2019). For visual restoration, rendering neurons photosensitive in the visual pathway can enable clinicians to reintroduce visual information dowstream to the degenerated neurons. This optogenetic therapy is already in clinical trial at the retinal level for diseases with a loss of photoreceptors. Our primate study led to such a clinical trial targeting retinal ganglion cells (Gauvain, Akolkar et al. 2021). However, for restoring vision at the cortical level, one obvious difficulty hampering these developments is the application of light into primate brain structures. The manufacture of optrodes and optic guide arrays can overcome such problems, but at the expense of rendering the technology invasive (McAlinden, Cheng et al. 2019). Ultrasound waves overcome these issues of light propagation, as they propagate readily through the brain tissue, the dura mater and, to some extent, through the skull. Ultrasound waves have been used to modulate neuronal activities (Tufail, Yoshihiro et al. 2011) but the natural sensitivity of neurons to ultrasound is dependent on high levels of acoustic energy. Unfortunately, high ultrasound energy entails for a risk of heating- and ultrasound-mediated tissue damage (Kim, Chiu et al. 2014, Lee, Lee et al. 2016).

Sonogenetic therapy has been proposed as a means of increasing the sensitivity of neurons to ultrasound through the expression of ultrasound-sensitive proteins in vivo. Various proteins have been proposed for such sonogenetic strategies (Ibsen, Tong et al. 2015, Huang, Fan et al. 2020, Yang, Pham Pacia et al. 2020). However, this objective remains a very challenging subject.

Objective

Our aim is to develop sonogenetic therapy to restore vision at the cortical level in blind patients having lost the eye to brain connection. Preliminary studies have already provided a proof of concept. The objective of the PhD thesis will be to demonstrate that this strategy can provide perception of movement and objects through behavior in a large animal model following the characterization of its neuronal activation at the single cell level and at the mesoscopic level.

Justification et adéquation de l'approche pour l'appel d'offres.

Sonogenetic therapy appears as an appropriate strategy because it should enable clinicians to stimulate neurons at distance through the dura even in the cortical depth. The technology requires two components: one AAV vector to drive expression of the ultrasound sensitive protein and one ultrasound stimulator. Therefore, this therapeutic strategy relates to the Institut universitaire d'ingénierie en santé as it will require bioengineered AAV vectors as well as a medical device to translate visual images into ultrasound patterns. For such development, we have already developed a wide expertise in AAV production at the Vision Institute, as already illustrated in the project on optogenetic therapy. For the development of the ultrasound stimulator, we have established a strong partnership with Dr Mickael Tanter, a specialist in ultrasound technology.

Pr José-Alain Sahel is an internationally recognized ophthalmologist, who has contributed to the field of visual restoration through clinical trials. His department was the first to implant the American Argus II showing the potential for reading in blind patients (da Cruz, Coley et al. 2013). More recently, his department tested for the first time in the world the PRIMA implant, which provide the best visual acuity for a retinal prosthesis (Palanker, Le Mer et al. 2020). The clinical trial for optogenetic therapy was initiated in his department. In the PhD project, Pr Sahel will define the medical needs, control the device adequacy to the clinical application, plan the surgeries for the medical device.

Dr Serge Picaud is a physiologist who devoted most of its last 10 years to visual restoration. His team worked on different topics from the electrode material (diamond, graphene), the chip design, the visual stimulator. Recently, the team has validated the PRIMA retinal implants (Prevot, Gehere et al. 2020) and demonstrated efficacy of optogenetic therapy on large animals (Chaffiol&, Caplette& et al. 2017, Gauvain, Akolkar et al. 2021). The team has also developed ultrasound imaging for the visual cortex (Blaize, Arcizet et al. 2020).

Serge Picaud and José Sahel have received the Charpak-Dubousset award in 2019 from the French academy of medicine for their work on visual restoration. Their contribution to the field resulted in the creation of the start-ups Pixium vision for retinal prostheses (PRIMA) and Gensight Biologics for optogenetic therapy.

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