Sorbonne Université/China Scholarship Council program 2021

Thesis proposal

Title of the research project: Rod-derived cone viability factor 2 for the treatment of inherited retinal blindness.

Joint supervision: Xiaoyuan Ren (detached from the Karolinska Institute)

Joint PhD (cotutelle): no

Thesis supervisor: Thierry Léveillard

Email address of the thesis supervisor: thierry.leveillard@inserm.fr

Institution: Institut de la Vision UMR-S 968

Doctoral school (N°+name): ED 158, “Cerveau, Cognition, Comportement”

Research laboratory:

Name of the laboratory director: José-Alain Sahel

Email address of the laboratory director: sahelja@upmc.edu

SORBONNE UNIVERSITÉ

Subject description (2 pages max):

1) Study context : With a 1 in 3,000-4,000 individuals, retinitis pigmentosa (RP) is the most prevalent form of inherited retinal degeneration in France, China and the rest of the world[1-3]. RP is clinically characterized by the loss of night vision resulting from a direct effect of the mutation that lead to death of rod photoreceptors, followed by a progressive loss of daylight vision resulting from the loss of cone function. Visual impairment is associated with lower employment rates, decreased productivity, decreased quality of life, anxiety, and depression[4]. RP is extremely genetically heterogeneous, what make corrective gene therapy extremely costly[5]. We have concentrated our effort on the prevention of loss of cone function though studies of the cellular interaction between rods and cones[6]. The nucleoredoxin like gene expresses two protein, the trophic factor rod-derived cone viability factor (RdCVF) that is secreted by rods and the thioredoxin protein RdCVFL expressed by rods and cones[7,8]. The administration of *NXNL1* gene products is a rational mutation independent therapy of RP[9,10]. We have also identified *NXNL2*, a paralogous gene that is also expressed in a rod-dependent manner in the retina[11]. The objective of the PhD thesis would be to explore the role of the RdCVF2 protein, encoded by the *NXNL2* gene, as compare to that of RdCVF.

2) Details of the proposal: The student will first study the visual phenotype of a mouse model of ablation of both *Nxnl1*[12] and *Nxnl2*[11] genes using ophthalmic facilities of the Institute. We expected that the two factors, RdCVF and RdCVF2 have distinct role for cones since BSG1, the RdCVF cell surface receptor is expressed in the inner segment of the cones while the RdCVF2 receptor that we have recently identified is expressed at the level of cone synapses. The results obtained will certainly motivate the comparison of the benefit of the combine administration of RdCVF and RdCVF2 using adeno-associated viral vectors in rodent models of RP with the help of a surgeon at the Institute. An autosomal recessive model, the *rd10* mouse and the autosomal dominant model, the P23H mouse in order to show that the expected benefit of the bi-therapy in mutation independent. Beside the translational program and dependent of the achievement, the PhD student will explore the mode of action of RdCVF2, downstream of its receptor, as we investigated the metabolic signaling of RdCVF[7], and following our current hypotheses.

3) References

1. Audo *et al.*, *Hum Mutat* **31**, E1406 (2010).http://www.ncbi.nlm.nih.gov/pubmed/20333770

2. Gao *et al.*, *Ophthalmology* **126**, 1549 (2019).http://www.ncbi.nlm.nih.gov/pubmed/31054281

3. Karali *et al.*, *Int J Mol Sci* **21**, (2019).http://www.ncbi.nlm.nih.gov/pubmed/31877679

4. Chaumet-Riffaud *et al.*, *Am J Ophthalmol* **177**, 169 (2017).http://www.ncbi.nlm.nih.gov/pubmed/28237413

5. Darrow, *Drug Discov Today* **24**, 949 (2019).http://www.ncbi.nlm.nih.gov/pubmed/30711576

6. Leveillard *et al.*, *Nat Genet* **36**, 755 (2004).http://www.ncbi.nlm.nih.gov/pubmed/15220920

7. Ait-Ali *et al.*, *Cell* **161**, 817 (2015).http://www.ncbi.nlm.nih.gov/pubmed/25957687

8. Mei *et al.*, *Antioxid Redox Signal* **24**, 909 (2016).http://www.ncbi.nlm.nih.gov/pubmed/27025156

9. Byrne *et al.*, *J Clin Invest* **125**, 105 (2015).http://www.ncbi.nlm.nih.gov/pubmed/25415434

10. Clerin *et al.*, *Int J Mol Sci* **21**, (2020).http://www.ncbi.nlm.nih.gov/pubmed/32120883

11. Jaillard *et al.*, *Hum Mol Genet* **21**, 2298 (2012).http://www.ncbi.nlm.nih.gov/pubmed/22343139

12. Cronin *et al.*, *Cell Death Differ* **17**, 1199 (2010).http://www.ncbi.nlm.nih.gov/pubmed/20139892

4) Profile of the Applicant (skills/diploma…):

The ideal candidate should have the following qualities

1. Meet the general criteria set out by the CSC (For more information, please visit: www.csc.edu.cn)
2. Good writing and communication skills in English, and have a valid English test certificate approved by CSC.

3. Hold or will obtain a master's degree in 2021 in medicine or medical science (biomedicine, molecular biology, biotechnology or equivalent)
4. Have lab experiences and knowledge in cell culture, molecular biology techniques, such as PCR, immunostaining, protein purification. Mouse handling experience is important.
5. Documented experience in writing and publishing scientific papers.

Contacts:

Thesis supervisor: Thierry Léveillard
Email address of the thesis supervisor: thierry.leveillard@inserm.fr