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|  | We are looking for a candidate to apply to a **PhD fellowship**, in the framework of a highly competitive joint doctoral program between Institut Pasteur and Sorbonne Université. |  |
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| **CRIPSR gene editing to correct audition and vision sensory deficits** |
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| Because of their high prevalence, untreated decline of hearing and vision sensory deficits has a vast economic & societal impact, impeding communication, later leading to social isolation, depression, reduced physical and cognitive functions. Over the last years, comparative studies of the hearing and visual sensory systems enabled us to shed light on their key normal functioning & enabled an integrated view of the disease mechanisms behind hearing and vision loss in Usher syndrome, the major cause of deaf-blindness in humans (Geleoc & El-Amraoui 2020). Applicability and validation of efficient gene therapies to stop or correct Usher senses are urgently needed. The recent and constant improving gene editing tools (e.g., novel Cas9 variants, base editors and prime editors) provide novel opportunities for the treatment of rare diseases (Delmaghani & El-Amraoui 2020). Capitalizing on pre-established molecular, structural and functional clinical endpoints for Usher syndrome, the goal of this project is to develop and validate specific delivery to non-dividing target cells in the sensory organs, and analyze in vivo the efficacy and safety of gene editing targeted therapy.The present project is designed to take advantage of the data from patient induced pluripotent stem cell (iPSC)lines (mechanistic disease signature, validated sgRNAs, and Cas9 gene editing tools) to validate their efficacy in an in vivo context. Planned objectives include:1. Monitor where, when and how inner ear and retinal abnormalities manifest in already available defective mice to establish relevant Usher clinical trial endpoint metrics to weigh therapeutic efficacy.
2. Evaluate and validate in vivo the delivery and efficacy of gene editing via CRISPR/Cas9, aiming to restore normal sensory modalities in available defective mice.

The project is interdisciplinary, with cutting-edge techniques in cell biology, imaging, physiology (some benefiting from external collaborations), and CRISPR/Cas9 gene editing tools designed to enable a thorough and accurate phenotyping and treatment of available Usher models (Dulon et al. 2018). 3D organoids from USH1 patient and control IPSC will provide key insights into the early stages of USH1 phenotype in a human cellular context, while our animal models offer key readouts to monitor USH1 mutations’ impact in an in vivo context. Delmaghani S\* and **El-Amraoui, A**\* **(2020)** The inner ear gene therapies take off: current promises and future challenges. ***J. Clin. Medicine*,** 9, 2309; doi:10.3390/jcm9072309. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7408650/>Geleoc G**\***. **El-Amraoui A\***. **(2020)** Disease mechanisms and gene therapy for Usher syndrome. ***Hear. Res.*** 4:107932**. (**https://www.sciencedirect.com/science/article/pii/S0378595519304733**)** DulonD\*, et al > **El-AmraouiA\***. **(2018)** Clarin-1 defect results in a rescuable auditory hair cell synaptopathy. ***J. Clin. Invest.*** 128(8):3382-3401. doi:10.1172/JCI94351. <https://www.jci.org/articles/view/94351> |
|  | Applications are open for **students holding a Master degree** (five years of academic education), **or equivalent from a university within or outside France, by the start of the PhD in October 2021**Applicants should send a detailed CV and a motivated interest to aziz.el-amraoui@pasteur.fr as early as possible (**Deadline is May 15**, 2021) in order to allow sufficient time to prepare the final proposal for the selection/interviews committee. Prior skills on animal handling and phenotyping or gene editing is a plus, but not required. |  |