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Human Mini-brains as a New Platform to Identify and Validate Pharmaceutical Compounds for the Treatment of CJD

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NOTE: PRESENTATION NOT PROVIDED BY PRESENTER.
FOR HIGHLIGHTS, SEE BELOW.

Project Objectives:

In this project we propose to develop a novel in vitro model of Creutzfeldt-Jakob disease based on induced pluripotent stem cells (IPSC). Towards this goal we have adopted the recently described "mini-brain" technology which has been shown to recapitulate many characteristics of neurological diseases. By overexpressing different forms of PRNP upon IPSC differentiation, we will induce and accelerate PrP aggregation.

The human mini-brains will be infected with different prion strains and we will follow the development of PrP aggregates and amyloid plaques by immunohistochemistry. Our aim is to provide a platform to assess the efficiency of pharmaceutical compounds. Most notably, IPS cell lines obtained from families with PRNP mutations such as GSS can be included in this assay, offering a new, more relevant avenue for disease modeling and the development of novel treatments.

Project Overview:

The critical need for new experimental models for therapeutic research into prions is underlined by the huge discrepancy observed between promising data observed with molecules selected to treat prion-related disorders in current *in vitro* models and disappointing results in human with CJD treatment trials. *In vitro* models, generally developed on non human cell lines, do not reflect the physiopathology of prion diseases while *in vivo* rodent models are long, heavy and far from the human situation even with transgenic mice expressing human PrP. Given the dramatic differences between mice and humans, methods that recapitulate paradigms of human brain development in vitro have enormous potential.

Groundbreaking work recently demonstrated that adult human somatic cells (from skin or blood) could be reprogrammed to induced pluripotent stem cells (iPS cells) (Takahashi et al., Cell 2007; Yu et al., Science 2007). Since iPS cells can be derived directly from adult tissues, they not only bypass the need for embryos, but can be made in a patient-matched manner, which means that each individual could have his own pluripotent stem cell line which can propagate indefinitely and give rise to every other cell type in the body, notably neurons. iPS cells not only have a great potential for regenerative medicine, but can already be used in personalized drug

discovery efforts and understanding the patient-specific basis of disease.

Recently, a major leap was achieved by developing a method to grow miniature human brain-like structures (cerebral organoids) from iPS cells *in vitro* (Lancaster et al, Nature 2013). These cerebral "organoids" also called "minibrains" recapitulate a surprising number of features of human embryonic brain development, heralding a new phase of modeling human disease. In the laboratory we have adapted this new approach to provide a platform for studying the pathogenesis of proteinopathies such as CJD.

We have recently developed a novel technique to increase the sensitivity of the detection of abnormal PrP, which will provide a key element in the characterization of the pathology in vitro. In the particular case of prion pathologies, it is essential to develop models which can be followed in the long term following infection. In order to accelerate disease progression, we have developed a vector allowing the overexpression of different forms of PrP. If PrP aggregates are generated as expected, therapeutic molecules will be evaluated.