Job Title	Marie-Curie post-doc fellowship application Topic: αSyn aggregation, UPR and Parkinson's disease
Main Research Field	Life Sciences (LIF)
Sub Research Field	Medical Science Biology
Key words	Protein-misfolding disorders, Parkinson's disease, UPR, drug candidate
Job Description	**Targeting the unfolded protein response (UPR) to reduce α-Synuclein aggregation toxicity in the context of Parkinson's disease** **State of the art -** Parkinson's disease (PD) is the most common neurodegenerative condition after Alzheimer's affecting around 1 in 500 people, which corresponds to an estimated 6.2 million people worldwide and 1.2 million people in Europe alone. Parkinson's disease typically occurs in people over the age of 60. Prevalence increases rapidly over the age of 60 years. Incidence of Parkinson's is forecast to double by 2050 primarily as a result of the ageing population; thus, the high financial burden PD places on society will increase. Parkinson's disease etiology is still unknown and no cure is available yet; **understanding the molecular mechanisms underlying this pathology is thus of major importance.** Parkinson disease is part of a group of diseases classified as protein-misfolding disorders (PMDs) which also includes Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis. PMDs share common pathological features characterized by the accumulation of abnormal protein inclusions and oligomers of an underlying protein. The pathological hallmarks of PD are triggered by the loss of dopaminergic neurons in the *substantia nigra pars compacta* and the presence of intracellular inclusions known as Lewy bodies. The latter are formed by fibrillary and ubiquitinated aggregates of α-Synuclein (αSyn). Although the molecular mechanisms underlying PMDs remain largely obscure, it appears that the disturbance of several aspects of the proteostasis network contributes to the progression of these neurodegenerative diseases. **The impact of ER (endoplasmic reticulum) stress on the progression of neurodegenerative diseases is particularly scrutinized.** Indeed, studies addressing the impact of ER stress on PD have consistently indicated that chronic ER stress is a pathological event that contributes to the degeneration of dopaminergic neurons of the *substantia nigra*. ER stress is thus a salient feature of PD. ER stress engages an adaptive signaling cascade known as the Unfolded Protein Response (UPR). Signs of ER stress are observed in human postmortem tissue derived from PD patients and are

	temporally and spatially associated with abnormal protein aggregation and the occurrence of neuropathological features. ER stress is also observed in animal and yeast models overexpressing αSyn. UPR failure thus contributes to PD conditions that might be corrected by adequate boost of this adaptive response. **Objectives -** We have recently identified an original compound named #1063 which promotes the survival of cells exposed to PD-inducing neurotoxins. Our preliminary data suggest #1063 may act *via* an UPR/ISR pathway (unpublished data). The Marie-Curie fellowship aims at **deciphering the therapeutic potential of #1063 in PD models in which αSyn aggregates.** Relevant approaches including the use of a yeast-based model, of an *in vitro* cell-based model as well as an organotypic brain slice culture model could be used. **<u>References</u>** - C. Hetz, The unfolded protein response: controlling cell fate decisions under ER stress and beyond. *Nat Rev Mol Cell Biol* **13**, 89 (2012). - I. Tabas, D. Ron, Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. *Nat Cell Biol* **13**, 184 (2011). - E. Colla *et al.*, Endoplasmic reticulum stress is important for the manifestations of alpha-synucleinopathy in vivo. *J Neurosci* **32**, 3306 (2012).
Supervisor	Cécile Voisset is a researcher at INSERM (French National Institute for Rechearch in Health) at Inserm UMR 1078 (Genetics, Functional Genomics and Biotechnology). U1078 hosts world class specialist in genetic and functional approaches. With expertise and a significant publication record in human pathogens, she is author of 46 peer-reviewed papers among which J Virol, Nat Com, Sci Rep and PNAS, and 3 patents. An up-to-date CV and bibliometrics are available online. C. Voisset is leading her own group at Brest, France, and has already supervised 12 Master students, 5 phDs and 1 postdoc. She is implicated in several research projects dealing with different protein misfolding disorders. C. Voisset spend 10 years as postdoctoral fellow in 3 laboratories where she has worked on Retroviruses, Hepatitis C, EBV and Prions. After several years in the prions field, she became a permanent researcher at Inserm where she now focuses on the characterization of new therapeutic pathways to curb the spread of the pathological conformation of proteins associated with proteinopathies. **<u>3 publications on the proteinopathies field</u>:** -Nguyen PH, Hammoud H, Halliez S, Pang Y, Evrard J, Schmitt M, Oumata N, Bourguignon JJ, Sanyal S, Beringue V, Blondel M, Bihel F, Voisset C. SAR Study around Guanabenz Identifies Two Derivatives Retaining Antiprion Activity but

	Having Lost α2-Adrenergic Receptor Agonistic Activity. **ACS Chemical Neuroscience**, 2014, 5(10):1075-82. -Billant O, Léon A, Le Guellec S, Friocourt G, Blondel M., Voisset C. The dominant-negative interplay between p53, p63 and p73: A family affair. **Oncotarget**, 2016, 7:69549. -Blondel M, Soubigou F, Evrard J, Nguyen PH, Hasin N, Chédin S, Gillet R, Contesse MA, Friocourt G, Stahl G, Jones GW, Voisset C. Protein Folding Activity of the Ribosome is involved in Yeast Prion Propagation. **Scientific Reports**, 2016, 6, 32117. cecile.voisset@univ-brest.fr *https://www.researchgate.net/profile/Cecile_Voisset*
Department/Research:	Inserm, the main French life science research institute, is a label of excellence. Inserm labelled labs are at the forefront of innovation. Inserm UMR1078 labs are located in the School of Medicine of Brest University (UBO), on the main Hospital campus, in Brest town center. This research unit gathers Inserm's researchers, clinicians and lecturers specialized in the study of various human diseases or cancers. Our good knowledge of the yeast model as a tool for pharmacological and genetic screening, as well as cellular, *ex vivo* and animal models for various pathologies allow us to exploit the knowledge acquired to isolate and develop new active compounds and lead original translational approaches allowing to correct the molecular defects at the origin of pathologies. The group within which the fellow will develop his project aims at characterizing new therapeutic approaches to curb the spread of the pathological conformation of proteins associated with proteinopathies. Other models of proteinopathies and specific techniques are available within the collaborative international network set up and led by C. Voisset. We have all the necessary facilities (L2 cell culture lab, animal care, and imaging platform) to develop the proposed project.
Suggestion for interdisciplinary / intersectoral secondments	The proposed project is based on a collaborative consortium led by C. Voisset and F. Bihel (medicinal chemist, Strasbourg, France), and involves C. Hetz (Buck Institute for Research on Aging, USA & Santiago de Chili). This collaborative network has to be reinforced by the applicant.
Skills Requirements	We are looking for a highly-motivated, open-minded experienced scientist (2-3 years after PhD) willing to diversify their individual competences in terms of skills acquisition through advanced training and international mobility. The fellow will be eager to acquire and transfer new knowledge in the context of an original and innovative scientific project in a French laboratory at the forefront of human health research.

	The Marie-Curie fellow will have to propose a project around αSyn aggregation, UPR and Parkinson's disease. The candidate will have the chance to apply for long-term opportunities. Technical skill and expertise requirements: -Protein misfolding neurodegenerative diseases -Protein aggregation, amyloids -Cell culture, Molecular Biology, Fluorescence Microscopy, Biochemistry Scientific skills requirements: -application to grants and/or awards -participation to national and international conferences -communication and training skills Required Languages: English (minimum B2 level). Publication rate required: at least 2 papers during the PhD, 1 per year since the PhD as 1st author, among which at least 2 papers in significant journals. The candidate will have published in each of the laboratories frequented.