VCP Interacting Drugs as a novel strategy for the treatment of Alzheimer’s disease

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France

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VCP Interacting Drugs as a novel strategy for the treatment of Alzheimer's disease

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Alzheimer’s disease (AD) is the most prevalent cause of dementia in elderly aged of 65 and over. Yet, there are no curative drugs and current treatments remain symptomatic. AD is a multifactorial slow and progressive dementing disease that combines two pathophysiological mechanisms: the amyloid pathology and the Tau pathology. The first one results from extraneuronal aggregation of amyloid-beta (Aß) peptides that derive from cleavages of a large

transmembrane precursor named amyloid protein precursor (APP). The second one corresponds to intraneuronal accumulation and aggregation of abnormally modified microtubule-associated tau proteins, to form the so-called neurofibrillary tangles. So far, most efforts have been focused on either part of the pathology, especially the amyloid pathology. However, current clinical trials against amyloid pathology failed to show an improvement of the cognitive status of patients in clinical phase III.
Protein mis-folding, protein aggregation and prion-like diffusion of protein pathogens are mechanisms common to several neurodegenerative diseases including AD. Protein homeostasis and degradation systems such as the proteasome, autophagy, endosome/lysosome and endoplasmic reticulum associated degradation (ERAD) are central cellular mechanisms for the clearance of misfolded proteinaceous aggregates. At the intersection of autophagy, ubiquitin-proteasome system and ERAD, is VCP (Valosin Containing Protein), also referred to as p97, TER94 or CDC48. VCP belongs to the family AAA-ATPase (ATPase with multiple cellular activities) which is essential for several cellular processes including the removal of misfolded proteins. Therefore, VCP constitutes a potential therapeutic target for the treatment of neurodegenerative diseases.
In our collaborative project targeting AD pathophysiology between chemists and neurobiologists of Inserm UMR-S1172 (formerly, UMR 837 and EA4481 GRIOTT) and AlzProtect company, several compounds named MSBD (Melnyk et al. WO 2006 051489) have been developed and one compound (compound 29 in Melnyk et al. 2015) is currently in clinical phase I. To our knowledge, these compounds are the first to act on both APP metabolism (increase in APP-CTFs and sAPPa, decrease in Aß) and the Tau pathology by improving the cognitive deficits in transgenic mouse models of both amyloid and Tau pathologies. The investigation of the MSBD molecular target led to the identification of VCP.
Our preliminary data suggest that MSBD repress the production of Aß and promote Tau proteolysis, both in vitro and in vivo, through a VCP-dependent mechanism. However, the precise mechanism remains to be unraveled. Therefore, one of the main questions we have to address is how MSBD modify the activity of this AAA-ATPase and consequently modulate both the amyloid and tau pathology. The present research proposal aims at addressing this question and further validate VCP as a therapeutic target for the treatment of neurodegenerative diseases and develop more potent families of VCP modulators as potential drugs against AD.

Lay Summary
Further information available at:

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