Validation of MT5-MMP as a new therapeutic target in Alzheimer’s disease and mechanisms of action

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Validation of MT5-MMP as a new therapeutic target in Alzheimer’s disease and mechanisms of action

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Research Abstract
Our global objective is to better understand some of the proteolytic pathways operating in amyloidogenesis and neuroinflammation, which are key processes in neurodegeneration and cognitive decline in Alzheimer’s disease (AD). AD is the most devastating neurodegenerative disorder with a major socio-economic burden that is accentuated by the absence of effective treatments curing or slowing down the progression of the disease. Despite a variety of therapies

currently under investigation, the discovery of a cure does not seem to be within reach at this point. Therefore, there is urge in identifying new targets in the triggering/progression of the disease and understanding the underlying molecular mechanisms preceding irreversible cognitive deficits. It is in this context that the MAD5 project seeks to bridge some of the molecular mechanisms underlying amyloidogenesis and neuroinflammation across different stages of AD. To this end, two leading CNRS laboratories from Marseille and Sophia-Antipolis with complementary skills have joined forces to develop the MAD5 project in the context of an ongoing collaboration. Together, they have generated over the last three years consistent preliminary data now submitted for publication 1. Using in cellulo and in vivo models of AD, in particular transgenic mice (Tg) that develop the main symptoms of AD, we demonstrated for the first time that a member of the matrix metalloproteinase (MMP) family of proteinases contributes to the amyloidogenic processing of amyloid precursor protein (APP), as well as the concomitant inflammatory response. This prompts us to hypothesize that this MMP is a new important factor that could contribute to Alzheimer's pathogenesis and hence a novel potential therapeutic target. In order to further validate these hypotheses and gain insight into the underlying mechanisms of action, our specific aims are to:
1. Assess the impact of the modulation of this MMP on the pathological process and the cognitive decline in transgenic mice that develop some of the symptoms observed in AD patients.
2. Assess the impact of the MMP modulation on neuroinflammation and the asssociated mechanisms of action.
3 Assess the functional interactions of this MMP with APP and other key elements of the amyloidogenic pathway.

The main originality of MAD5 is that it unveils a new important element of the proteolytic puzzle that opens new research avenues to study the mechanisms of AD pathogenesis. These new areas of research should be complementary and/or alternative to those classically studied under the exclusive scope of well-known ß- and ?-secretases.

The impact of MAD5 is expected at different levels: 1) To identify new molecular pathways that contribute to AD pathogenesis, and lead eventually to innovative therapeutic strategies without the side effects observed when inhibiting ß- and/or ?-secretases. 2) To identify APP processing proteinases that should contribute to better understand the amyloidogenic role of APP. 3) To improve our knowledge of the functional interplay between neuroinflammation and amyloidogenesis, which is still a major unsolved question in AD. 4) To identify a new neuroinflammatory signalling pathway that could be crucial for the comprehension of neuroinflammation in AD and other neurodegenerative diseases. 5) To implement and validate molecular tools that could be used as templates for drugs that could modify MMP activity/interactions.
In all respects, and to the best of our knowledge, the MAD5 project has little competition worldwide at this point, and our consortium is ideally placed to lead present and future researches on the validation of a new promising target in AD.

Further information available at:

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