THERAPEUTIC ANTIBODIES DIRECTED AGAINST APP-C99 REDUCE AΒ PRODUCTION

J. Houacine¹, T. Bolmont¹, L. Aeschbach¹, M. Oulad-Abdelghani², P. Fraering¹

¹Swiss Federal Institute of Technology, Lausanne, Switzerland, ²IGBMC, Strasbourg, France

Introduction: No treatment is currently available to prevent or reverse Alzheimer's disease (AD), the most common form of senile dementia. The amyloid-β (Aβ) senile plaques, one of the principal histopathological hallmarks of AD, are mainly constituted of the highly hydrophobic Aβ peptides prone to aggregation and fibrillarization. Aβ peptides are produced after processing, by γ-secretase, of the 99 amino-acid-long amyloid precursor protein C-terminal fragment (APP-C99). Apart from being a precursor of Aβ production, the role of APP-C99 in the pathogenesis of AD remains poorly understood.

Aims: To lower Aβ production and senile plaque formation, we developed an innovative therapeutic approach that consists of targeting APP-C99 with specific monoclonal antibodies to prevent its processing by γ-secretase.

Methods: We generated monoclonal antibodies targeting APP-C99, after mice immunization with recombinant human APP-C99 adopting an active conformation, as witnessed by its processing by purified γ-secretase.

Results/conclusion: Taken together, our findings indicate that antibodies targeting APP-C99 can lower Aβ production by impairing APP-C99 processing. Whether it can delay amyloid plaque deposition by lowering Aβ production in vivo is presently under investigation. Monoclonal antibodies directed against APP-C99 impaired its processing and decreased Aβ production in cell-based assays.