CHF5074, in clinical development for the treatment and prevention of Alzheimer's disease, acts as a microglial modulator switching microglia from M1 to M2 activation state

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Neuroinflammation is considered to play a prominent and early role in Alzheimer's disease. Recently, CHF5074 has been showed to reduce TNFα and CD40L levels in cerebrospinal fluid of healthy subjects. In this study, we analysed the time-dependent changes in the expression profile of pro-inflammatory and anti-inflammatory microglia in co-cultures exposed to beta-amyloid 1-42 (Aβ) and CHF5074.

Astrocyte-microglia co-cultures were prepared from new born mice and exposed to a single dose of 10 μM soluble Aβ at 14° DIV. Co-cultures were treated with 3 μM CHF5074 and the RNA was isolated 2 days and 8 days later.

In co-cultures exposed to Aβ, we detected an early M1 pro-inflammatory expression of TNFα, IL-1β and iNOS mRNAs. These effects picked at two days and fell to basal level at 8 days. Co-exposure to CHF5074 totally suppressed the expression of pro-inflammatory genes at two days.

In order to evaluate the protective microglial activation (M2) we considered mRNA levels of MRC1 (mannose receptor type C-1), TREM2 (triggering receptor expressed on myeloid cells-2) and ARG1 (arginase-1). In co-cultures exposed to Aβ, we detected a reduction of MRC1 and no changes of TREM2 or ARG1 mRNAs. Co-exposure to CHF5074, but not to ibuprofen or R-flurbiprofen, significantly increased mRNA levels of both MRC1 and TREM2.

Our results obtained in a cell-based model of Aβ-induced neuroinflammation strongly suggest that CHF5074 can directly modulate inflammatory response by switching microglia M1 into a M2 activation mode, independently from interaction with circulating cells and apart from modulation of Aβ generation.