InCure
Innate Immune Activation in Neurodegenerative Disease

Michael Heneka (Coordinator and P1), Róisín McManus (P1), Martin Korte (P2), Isabelle Le Ber & Morwena Latouche (P3), Rob Veerhuis (P4), Luigi Bubacco & Marina de Bernard (P5), Jesper Tegnér (P6)

The central nervous system (CNS) of mammals is an intricate and fragile structure, which can be easily modulated for information storage, however, it is also vulnerable to injury, invasive pathogens or neurodegenerative diseases (NDs). Microglia represent the innate immune system in the brain, perform many physiological functions necessary for the maintenance of tissue homeostasis, synapse remodelling and neurotrophic factor secretion. In NDs, and especially during chronic exposure to aberrant proteins or RNA, microglia maintain a persistent, sterile and pro-inflammatory immune response and neglect their physiological and beneficial functions. This chronic activation of the innate immune system in turn promotes the development and progression of NDs.

The aim of this project was to elucidate this activation by combining a systems biology approach with functional analysis in the three most common NDs (Alzheimer's disease, AD, Parkinson's disease, PD, frontotemporal dementia, FTD), for each of which an immune response was described as a central issue. Critically, we wanted to identify the shared and overlapping networks between these NDs, with a focus on the inflammasome, as we have previously demonstrated that the NLRP3 inflammasome is activated in patients with AD.
The InCure consortium has made significant progress, in particular with respect to the immune stimulation of microglia with Aβ in models of AD, with α-syn in models of PD and with TDP-43 in FTD. The results completely characterize NLRP3 inflammasome activation and function in microglia in each of these NDs, and highlight the negative impact of NLRP3 activation, where cells deficient in NLRP3 or treated with pharmacological inhibitors were protected from inflammatory mediators and had enhanced phagocytic function. Furthermore, we determined a cofactor, ASC-specks, which is necessary for the NLRP3 activation and AD progression. Additionally, we also identified that NLRP3 activation plays a key role in the pathogenesis of tauopathies that develop downstream after the Aβ-induced microglia activation. We found that the supernatant from cell culture-activated microglia can induce a severe neuronal phenotype that is dependent on the NLRP3 inflammasome. In addition, many of these *in vitro* results have been validated *in vivo* in animal models of disease. We also performed detailed analysis of these stimuli using human microglial cell cultures that further validated our results in mouse experiments.

We performed RNA sequencing and we identified several genes associated with the AD-associated microglia phenotype, that will be compared with the genes identified in the PD- and FTD-models (ongoing) and verification of these targets in murine and human tissue is also ongoing.

These results highlight the importance of modulating innate immune signalling in ND. Our *in vitro* and *in vivo* data clearly demonstrate a widespread protective effect of targeting the NLRP3 inflammasome in all NDs studied (i.e. AD, PD and FTD). These results are of utmost importance to patients with these diseases, and represent novel targets for treatment in these conditions. Importantly, our results were replicated by using pharmacological inhibition of the inflammasome *in vitro*, confirming the therapeutic potential of targeting this complex in these NDs.