Identification of personalised inflammatory profiles of ageing and senescence modulating the predementia speed of symptomatic progression which are modified by risk factors for dementia (PREADAPT)

University of Cologne (Germany), Fundació ACE (Spain), University of Bonn (Germany), University College London (UK), Institute Pasteur de Lille (France), Rigshospitalet (Denmark), University of Luxembourg (Luxembourg).

Different genetic and environmental factors modulate the protein levels of the senescence-associated secretory phenotype (SASP) during ageing, leading to chronic systemic inflammation and neuroinflammation, and affecting basal brain senescence. Thus, a combination of individual genetics, comorbidities, and proteomics may provide personalised information on the risk for progression to dementia of the Alzheimer's type. Consequently, we decided to 1) define a SASP profile in CSF and plasma, 2) explore the added value of SASP profiles for the personalized prediction of cognitive decline, 3) assess the causality between SASP profiles and progression to dementia of the Alzheimer's type, and 4) explore the effect that specific therapeutic interventions have on SASP profiles.

CSF and plasma levels of SASP proteins will be measured in independent cohorts by targeted multiplex proteomics and regularisation will be used to generate a weighted combination of the SASP proteins that most accurately predict the patients' chronological age. We will then analyse the association between this predicted age (biological age) and harmonized neuropsychological measurements as a readout for cognitive decline. All results will be integrated in a meta-analysis. Then, mediation analyses will be used to quantify the proportion of the effect of each dementia-associated risk factor that is conveyed by SASP. Next, the causality between SASP profiles and progression to dementia of the Alzheimer's type will be assessed with mendelian randomization to overcome reverse causation problems. Furthermore, the association between genetic markers and SASP profiles will be evaluated using GWAS data available for each cohort, which will then allow to explore the role of SASP in larger Alzheimer's disease genetic consortia without proteomics data. Finally, SASP profiles will be evaluated in interventional studies for patients at risk of dementia of the Alzheimer's type to investigate the relationship between responsiveness to intervention and degree of SASP change.

So far, the levels of ~3000 proteins were measured in CSF and plasma samples from different cohorts and the patients' biological age was calculated using a set of 38 SASP-related proteins. The biological age displayed a mean absolute error of 4.0 in the training dataset (DELCODE cohort) and 4.9 in the test dataset (ACE cohort) with a Pearson correlation coefficient of 0.6 in both datasets. Interestingly, MMP-10, one of these SASP-related proteins, was found to be associated with increased risk of progressing to dementia of the Alzheimer's type and to display an incremental predictive value. Furthermore, the neuropsychological outcome measures for the validation of SASP profiles across cohorts have been defined and harmonised. Preliminary versions of the global cognitive factors have been created and the

analyses to assess their model fits both cross-sectionally and longitudinally have been already conducted.

This unique setting will enable PREADAPT to identify, at pre-dementia stages, age-related profiles informing on the personalised future risk for cognitive decline and progression to dementia. From a translational perspective, PREADAPT will also provide the first evidence showing that a SASP personalised risk profile may respond to specific interventions. Furthermore, PREADAPT will generate several tools to access, mine and disseminate all data generated to researchers outside PREADAPT. In the next months, the association between biological age and cognitive decline, and the causality between biological age and progression to dementia of the Alzheimer's type will be evaluated. Finally, the effect of genetics or the intervention of modifiable risk factors for Alzheimer's disease on the biological age will be assessed.