TRIAGE

TRanslating Individual Alzheimer GEnetic risk into disease phenotypes

Socio-economic needs for advances in the treatment of Alzheimer's Disease (AD) are more pressing than ever. Lessons learned from clinical trial failures have led to important conceptual advances. The field notably shifted away from a purely neurocentric view, largely since Genome-Wide Association Studies identified several risk genes that are primarily expressed in microglia and not in neurons. The challenge is now to leverage this massive amount of genetic data to decipher disease mechanisms and design effective therapeutic interventions for AD. The fact that personalised genetic profiles (polygenic risk scores) can be generated opens unique possibilities for stratification of patients and personal medicine.

We here propose to develop a method to link the individual genetic risk of developing AD to functional information about the underlying disease process and manifestations with focus on the microglia. We will genotype 200 participants from a memory-clinic based cohort of individuals with biomarker-proven AD at different clinical stages (prodromal, early, mid and late dementia stage). We will also include 180 participants from a longitudinal observation cohort of older adults at high genetic risk of developing AD. We will calculate Polygenic Risk Scores and profile the immune system of all individuals, and integrate those data with clinical data to obtain a complete map linking genetic profiles and disease manifestations across the entire spectrum of AD.

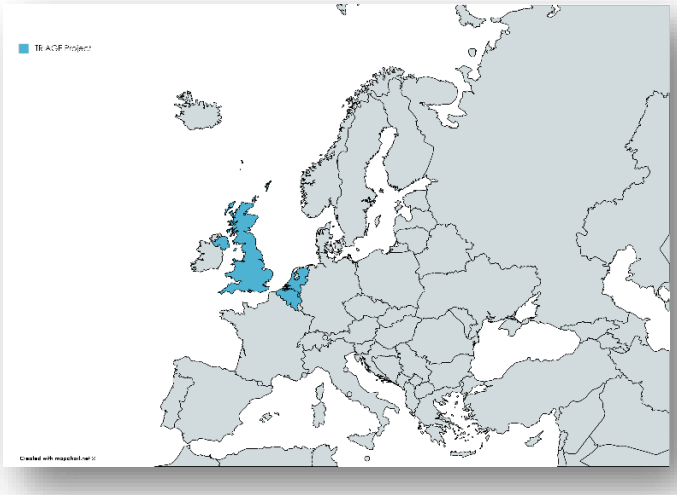
From a selected subset of individuals across this map, we will generate induced pluripotent stem cells and differentiate them into microglia. We will then investigate microglia responses unbiasedly by single-cell RNA sequencing and functionally on synapse, amyloid and Tau effects, both in vivo in the context of a mature brain, after transplantation into mouse models for Aβ and/or Tau pathology, and in vitro in brain organoids. Both datasets will be benchmarked against ex-vivo human brain tissue. We will investigate how different PRS affect the response of microglia to amyloid plaques, neuronal tangles and their interaction with synapses. This work will establish how AD genetic risk translates into microglia behavior, and point to molecular and cellular pathways contributing to pathogenesis.

By maximally exploiting clinical and research data and linking them to an individual risk score, this project will establish a roadmap towards precision medicine for AD. Our results will reveal novel therapeutic targets in AD and lay the foundations of a pre-clinical drug testing platform for AD. They will also help refine inclusion criteria for future clinical trials and ultimately translate into guidance for personalised healthcare decisions.

Total Funding : (TBC)

Duration : (TBC)

Coordinator : Bart De Strooper
✉ :
Bart.DeStrooper@kuleuven.vib.be



Consortium Members

Prof. Dr. Bart De Strooper, MD, PhD	Professor at Department for Neurosciences, KU Leuven, Professor at Institute of Neurology, UCL (London); Head VIB Laboratory for the Research of Neurodegenerative Diseases, Belgium
Valentina Escott-Price	Cardiff University (Dementia Research institute) , UK

	Jeroen Pasterkamp	UMC (University Medical Center, Utrecht), The Netherlands
	Rik Vandenberghe	UZ Leuven (University Hospital Leuven), Belgium