Topic 3- Inflammation and Alzheimer's disease (AD): modulating microglia function – focussing on TREM2 and CD33

Inflammation is considered as a pathological hallmark of AD.

However the exact state of functional activation of microglia and astrocytes in AD and the causative link between inflammation/microglia activity and AD is still an under-explored area of research.

Multiple Genome-wide Association Studies' (GWAS) studies and integrated systems biology approaches have identified and linked genes involved in modulating and executing microglia mediated inflammation to AD.

Amongst those TREM2 (which variant R47H is the second strongest genetic risk factor for late onset AD (LOAD) after ApoE4) and CD33 have been recently confirmed as linked to LOAD

All information indicative

Inflammation and Alzheimer's disease

Key Objectives (1)

Explore whether a decrease or increase of brain microglia phagocytic activity and/or cytokine release is causative for or protective to neurodegenerative/ageing phenotypes

- If so, at what stage in the progression of AD-related phenotypes
- Is modulation of microglia is able to delay progression of AD-phenotypes
- What are the effects of activated microglial cells on T cells and B cells
- Can receptor-mediated microglial phagocytosis be dissociated from a more generic inflammatory response in the brain and could this dissociation be exploited therapeutically?

All information indicative

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Key Objectives (2)

- Explore the roles of CD33 and TREM2 in microglia activity to identify druggable points of interactions/pathways modulating the receptors and microglial function/brain inflammation to:
  - determine what differentiates a tissue protective or even restorative microglial cell from a tissue destructive one and how this phenotype can be influenced
  - determine the relative roles of microglial-bound TREM2 and CD33 receptors versus their shed counterparts and in which cell populations the receptors are expressed
  - Explore how/if shedding of TREM2 (that is both constitutive and induced by inflammation) can be influenced to modulate the relative amounts of cell-bound and shed TREM2 receptors.

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Key Objectives (3)

- Develop and identify needed tools not readily available, like e.g. improved antibodies directed against TREM2
- Conduct limited drug screening to provide tool compounds to contribute to the above objectives
- Explore if there are important differences between mice and human immune system, and particularly between mice microglia and their human counterparts. Human systems should be integrated to maximise the relevance of the studies.
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Key deliverables (Knowledge)

- Confirmation if an early (related to AD-phenotypes in vivo , e.g. plaque load or tau pathology) increased or decreased activation of microglia impacts on neuronal function
- Analysis if a late (related to AD-phenotypes in vivo , e.g. plaque load or tau pathology) increased or decreased activation of microglia worsens AD-related phenotypes
- Identification of CD33 and TREM2 pathways offering druggable intervention to modulate microglia phagocytic/motility function

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Key deliverables (Tools)

- Validated tools to knock-down and over-express targeted genes and suitable reagents to quantify knock down or overexpression, to confirm findings by gene knock-down or over-expression studies in disease relevant preclinical models
- The identification of small or large direct molecule modulators of CD33 or TREM2 or pathways regulating both genes microglial function by provision of:
- robust assays for constitutive and inflammatory shedding of TREM2;
- standard cell lines (preferably human) expressing TREM2 +/- CD33 +/- DAP12;
- robust TREM2 -and CD33-dependent phagocytosis assay in cell culture;
- robust TREM2- and CD33-signalling reporter line in cell culture.
- Identification and characterisation of endogenous ligands of CD33 and TREM2.

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Industry consortium contributions

Industry will be contributing to all Work Packages, but in particular will bring in expertise in later-stage activities like small molecule identification and qualification.

Contributions will be on:
joint scientific leadership, coordination and project management, sound track record and experience in AD preclinical and clinical research assay development, *in vivo* pharmacology, drug screening, glycochemistry, medicinal chemistry, *in vitro* pharmacology, ADME-T / PK, imaging, IT (deep sequencing, systems biology/bioinformatics)

Tools, samples and animal models will be also made available (see topic text for full list)

initiative

All information indicative

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Applicant consortium

- *Expertise:* AD and in neuro-inflammation linked to AD, small animal imaging, in vivo and ex vivo pharmacology, translational medicine to bridge findings and results of neuro-inflammatory processes/pathways from preclinical species to humans, ITand project management.

- *Resources:* access to relevant preclinical models (e.g. transgenic AD, TREM2, CD33 models, TREM2 and CD33 cellular models), translational tools, access to state of the art in vivo facility and small animal imaging, biomarkers, bioinformatics tools, biobanks and bio-samples (e.g. AD brain tissue, samples for GWAS TREM2/CD33), engagement of SMEs able to contribute relevant technologies