**F1-02-03** MICROGLIA HETEROGENEITY IN THE HUMAN ALZHEIMER’S BRAIN

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**Background:** Microglia are the resident immune cells of the central nervous system (CNS), related to the monocyte/macrophage lineage. In response to disease processes, microglia can acquire a wide range of morphological appearances hinting that they can perform different functions. Evidence from experimental models has helped to define specific functional phenotypes but it has become recognised that the response is complex and likely to be multidimensional. Genetic variation in innate immunity genes influences risk of Alzheimer’s disease implicating microglia. We have explored in detail the role of microglia in human brain ageing and dementia using the MRC Cognitive Function and Ageing Study (CFAS). **Methods:** Inflammation was investigated in 298 cases using immunohistochemistry against microglial ionised calcium-binding adaptor molecule 1 (Iba-1), lysosome marker CD68, macrophage scavenger receptor A (MSR-A), Fcγ receptor 1 (CD64) and the antigen presenting function HLA-DR. The data were analysed with regard to cognition, AD pathology (β and Tau) and APOE polymorphism. **Results:** Overall, MMSE was associated negatively with CD68 and HLA-DR and positively with CD64 and Iba1. Among the cases without dementia, associations were observed for: diffuse plaques with all markers except MSR-A. HLA-DR and Iba1 were negatively associated with tangles. In the cases with dementia and AD pathology, the strongest associations were observed between CD64 and diffuse plaques, CD68 and neurotic plaques and tangles, and MSR-A with neuritic plaques and tangles. With regard to the APOE polymorphism, ε2 was associated with expression of Iba1 and MSR-A and ε4 with CD68, CD64 and HLA-DR. **Conclusions:** Our findings indicate that different microglial populations coexist in the AD brain, with microglia responding differently to Aβ and tau in subjects with and without dementia. Thus it is likely that microglial response influences the development of dementia. Interestingly, the findings suggest that APOE polymorphism is associated with the microglial profile.

**F1-02-04** IMAGING NEUROINFLAMMATION IN NEURODEGENERATIVE DISEASES (INMIND): CONCEPTS AND FUTURE DIRECTIONS

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**Background:** Positron Emission Tomography (PET) is one of the key molecular imaging technologies which allows the location and quantification of the expression of molecular target structures in vivo by employing specific radiopharmaceuticals. PET allows the translational and reverse-translational assessment of disease-specific molecular alterations over time, during the disease course and under therapeutic intervention. The aim of the lecture is to demonstrate (i) the current state-of-the-art of tracer technology for assessing microglial activation and (ii) implementation of old and new microglial imaging strategies in various disease models and human application. **Methods:** For 30 years, imaging the activation of microglia cells in vivo by PET is accomplished by employing the mitochondrial translocator protein 18kDa (TSPO) as molecular target. TSPO is over-expressed by activated microglial cells, and in some conditions also by astrocytes. Over the last decade, about 50 radiopharmaceuticals targeting TSPO have been developed and investigated, only some of them have reached clinical application so far. As the biology of TSPO in relation to microglial function is not fully understood yet, interpretation of TSPO-based imaging results is sometimes difficult. Therefore, new microglial target structures such as cannabinoid type 2, P2X7, and COX2 receptors, respectively, are all being explored for imaging. **Results:** All research data presented originate from joint efforts within the INMIND consortium. **Conclusions:** The ultimate goal is to differentiate various microglial phenotypes (such as M1 and M2) during the disease course for the overall aim to establish imaging-guided therapeutic modification of microglia function to enhance their neuroprotective and repress their neurodestructive function.

**SUNDAY, JULY 19, 2015**

**FEATURED RESEARCH SESSIONS**

**F1-03** LONGITUDINAL STUDY OF PRE-SYMPTOMATIC ALZHEIMER’S DISEASE BIOMARKERS: A FOUNDATION FOR RESEARCH ON PREVENTION

**F1-03-01** POTENTIAL OF AD BIOMARKERS TO REVEAL THE PRESYMPTOMATIC DISEASE PROCESS AND THE EFFECTS OF TREATMENTS THAT MAY RETARD IT

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**Background:** The evolution of AD spans some 30 years, over much of which time symptoms are absent. This lack of available symptomatic endpoints is a fundamental problem for prevention research. Disease progression may be revealed, however, by various biomarkers that change over time. Preventive interventions can retard or halt this progression of pre-symptomatic disease (and its markers) thereby deferring the later onset of symptoms. In theory, therefore, pre-symptomatic biomarker trajectories can be used to select individuals for prevention trials and to identify preventive treatments with preliminary evidence in favor of their probable efficacy. **Methods:** Several issues confront longitudinal biomarker studies as indicators of pre-symptomatic disease progression: 1) we need validation of biomarker trajectories as true indicators of pathogenesis, i.e., of subsequent symptom onset; 2) we must identify which individual biomarkers are best suited to this purpose at various stages of disease development; and 3) we need analytic methods that can encompass the multiple metrics employed to reflect the disease progress while avoiding difficulties with multiple comparisons. Successful example applications of this approach will help demonstrate its value. **Results:** We present data from the BIOCARD and Canadian PREVENT-AD studies, two programs that are currently characterizing the progression of biomarkers in persons at high risk of AD dementia. BIOCARD enrolled 349 cognitively normal persons at baseline and has obtained serial cerebrospinal fluid (CSF), neuroimaging and cognitive measures markers for up to 18 years. The study is examining (validating) these markers, either alone or combination, as predictors of subsequent symptom onset. PREVENT-AD has up to two years of biomarker data from 241 individuals with a parental history of AD. It assesses sensorineural abilities (olfaction, central auditory processing) as well as CSF and advanced neuroimaging markers as indicators of pre-symptomatic AD progression. It also includes a nested randomized, placebo-controlled biomarker-endpoint trial