ImmunoTools *special* Award 2014

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Developing an early reliable blood-based biomarker of cognitive deterioration

Alzheimer's disease (AD) is the most common neurodegenerative disease worldwide, occurring in older adults typically aged over 65 and resulting in the progressive loss of memory and cognitive function. Currently there are approximately 24 million people worldwide suffering from dementia, 70% of which can be attributed to AD and this is expected to quadruple by the year 2050. The economic burden of these conditions is huge and it is putting enormous pressure on governments and health-care systems and in the US costs incurred reach $172 billion annually.

A major challenge is to identify a biomarker that is indicative of the earliest changes in cognitive function and which would therefore enable earlier and hopefully more effective treatment intervention. Potential biomarkers developed so far are expensive and/or invasive such as markers developed through magnetic resonance imaging (MRI) or by analysis of cerebrospinal fluid (CSF) via lumbar puncture procedures. A blood-based biomarker is the ideal since it would be relatively inexpensive, widely-available and less invasive.

Our previous data have shown that a cohort of normal older adults can be subdivided into those whose episodic memory is consistent with their estimated IQ (cognitively intact), or those whose episodic memory is discrepant with their estimated IQ (cognitively compromised). Blood samples analysed from these cognitively compromised individuals revealed an increased pro-inflammatory profile compared with their cognitively intact group (*Downer et al 2013*). With age, neuroinflammatory changes generally occur in the brain but these changes are exacerbated in neurodegenerative diseases including AD and may contribute to the progression of disease. Neuroinflammation arises because of increased activity of the resident immune cells of the brain, the microglia; these cells release inflammatory mediators which can cause neuronal degradation. These inflammatory changes are reflected systemically in the immune cells in the blood, monocytes and macrophages.

Interestingly these cells infiltrate the brain with age and in AD, perhaps because of the increased blood-brain barrier permeability and they can possibility contribute to the pro-inflammatory environment present in the brain.

The aim of my PhD is to develop a biomarker of early cognitive deterioration by further examining the inflammatory changes in the blood of cognitively intact and cognitively compromised individuals. Monocytes positive for CD14 are isolated from whole blood and differentiated into macrophages by incubating in the presence of ImmunoTools rh GM-CSF. The cells will be challenged with pro- and anti-inflammatory stimuli including lipopolysaccharide (LPS), amyloid-β, and a combination of the anti-inflammatory cytokines interleukin (IL)-4 and IL-13 supplied by ImmunoTools. The use of ImmunoTools flow cytometry antibodies would greatly help in analysing the cell surface expression of CD11b, CD14 and CD45. Cytokine release will be measured through ImmuoTools ELISA kit for IFNγ, IL-6, IL-8, IL-10, IL-12p40 total, and TNFα, which will also be valuable in assessing levels of these cytokines present in plasma isolated from whole blood. It is anticipated that cognitively compromised individuals in the cohort examined will exhibit an increased pro-inflammatory profile with a heightened response to inflammatory stimuli and an increase in cytokine concentrations. The markers identified will be examined at a two-year follow-up assessment and correlated with cognitive function where it is hypothesised that the inflammatory markers will be indicative of early cognitive decline. The ImmunoTools special award would prove to be a great asset to enable me to carry out this study.

References

Downer, E. J., Jones, R. S., McDonald, C. L., Greco, E., Brennan, S., Connor, T. J., Robertson, I. H. & Lynch, M. A. (2013). Identifying early inflammatory changes in monocyte derived macrophages from a population with IQ discrepant episodic memory. *PLOS ONE, Vol(8),* 5, 1-8.

ImmunoTools *special* AWARD for **Hannah Wolfe** includes 25 reagents

FITC - conjugated anti-human CD11b, CD45,

PE - conjugated anti-human CD14,

APC - conjugated anti-human CD14,

human IFN-gamma ELISA-set for 96 wells, human IL-6 ELISA-set for 96 wells, human IL-8 ELISA-set for 96 wells, human IL-10 ELISA-set for 96 wells, human IL-12p40total ELISA-set for 96 wells, human TNF-alpha ELISA-set for 96 wells, (each 3 reagents),

recombinant human cytokines: rh GM-CSF, rh IL-4, rh IL-13

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