Fane Mensah: PhD student supported by IiME

Title of Project:

"Immunoregulation in patients with ME/CFS:

Investigating B cell metabolism to understanding disturbed immune function in patients with ME/CFS"

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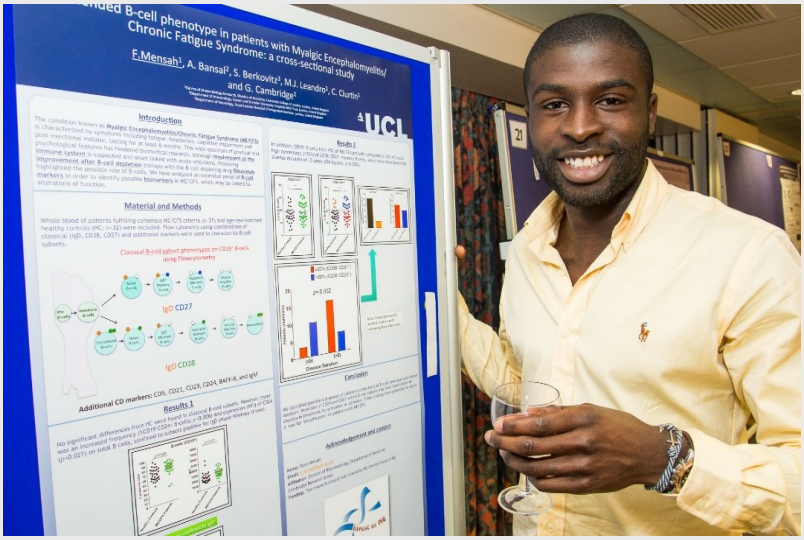

In the first data paper published by Fane from UCL, he described abnormal expression of a molecule on B cells (CD24). 'New' B cells exit the bone marrow in large numbers every day (10^9) before undergoing a complex cycle of differentiation and maturation to become mature memory B cells or commit to producing antibodies. This whole process is coordinated by regulated cycles of growth, cell death and very precise interactions with other immune cell types and the environment. Therefore, the study of B cells allows us to investigate the dynamics of possible disruptions in checkpoints or pathways which may be altered in disease and thus impact immune functioning. The molecule (CD24) which Fane found to be up-regulated on B cells in patients

with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) compared with age-matched healthy controls (HC) at certain stages of their maturation was therefore thought worthy of further investigation. CD24 is expressed on the earliest B cells in the bone marrow and plays an important role in B development. Despite also being expressed at later stages of development, its function in these latter stages has not been investigated. Fane proceeded to investigate the relationship between CD24 expression and B cell maturation.

Cultured, isolated B cells were therefore stimulated in various ways to follow the dynamics of CD24 positivity during differentiation in relation to cycles of proliferation and metabolism using phospho-flow (phosphorylation of AMPK-pAMPK) and Mitotracker Far-red (Mitochondrial mass-MM). In cells cultured for 5 days, in the absence of stimulation, we also showed a significant difference between B cells from ME/CFS patients and HC. There was also a positive relationship between %CD24+ B cells remaining in unstimulated cultures and age in HC ($R2=0.84$; $p<0.01$) but this relationship was NOT present in B cells from ME/CFS, which tended to have an 'older' phenotype. The other striking and novel finding was the relationship between CD24 and the activation of a stress-induced regulating molecule (pAMPK) on B cells in later stages of differentiation. These findings suggest that altered expression of CD24 during B cell differentiation reflects the differential needs of naive versus memory B cells. We concluded that CD24 expression may regulate energy metabolism to maintain B cell homeostasis and dysregulation of its expression may therefore be associated with ME/CFS. The manuscript based on this research is under review by Frontiers in Immunology (International high impact factor peer-reviewed journal.

As part of a collaboration also funded by a Ramsey Award (SolveME,USA) with Dr Christopher Armstrong, Melbourne University, Australia, Fane has established in vitro techniques to investigate the metabolites used/generated in cultured B cells following exposure to different agonists/antagonists and growth conditions as a model for energy metabolism in patients with ME/CFS. They have documented metabolite differences including a reduced use of glycolysis in ME/CFS patients and increased utilisation of amino acids for ATP production (manuscript in preparation).

In addition to working with Christopher in Australia for 4 weeks, Fane was selected to present his work in an Oral Presentation at the British Society of Immunology in Brighton in December, 2017 – a very high achievement for ME/CFS-related research.

Fane's work has produced novel findings which points to ways to develop useful biomarkers by which to identify metabolic changes in ME/CFS cells. He has also established a platform (B cell culture) enabling testing of different pathways of intervention (agonists/antagonists) to restore homeostasis.

G.Cambridge, UCL, Supervisor.