Prof. Guy C. Brown
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Title of talk:
How to stop the brain eating itself in neurodegeneration

Abstract:
Microglial phagocytosis shapes neuronal networks during development, and protects the mature brain by removing extracellular pathogens, debris and amyloid. However, microglial phagocytosis is unregulated by inflammation, and chronic inflammation may result in excessive microglial phagocytosis of synapses and neurons. Many genes regulating microglial phagocytosis are linked to Alzheimer's disease (AD) risk and/or are unregulated in microglia in AD. For example, one copy of the R47H variant of TREM2 increase AD risk four fold. We find that microglia with R47H TREM2 have increased Syk activation by phosphatidylserine and increased phagocytosis of phosphatidylserine-exposing synapses and neurons, suggesting that R47H TREM2 increases AD risk by increasing phagocytosis. We find that microglia activated by amyloid beta, tau or lipopolysaccharide (LPS) phagocytose live, stressed neurons that reversibly expose phosphatidylserine, and this neuronal loss/death can be prevented by blocking the phagocytosis in culture. The P2Y6 receptor is required for microglial phagocytosis of neurons, and we found that inhibition or knockout of this receptor, prevented LPS-induced neuronal loss in culture and in mice. Injection of amyloid beta into mouse brains induced microglial phagocytosis of neurons and lose of neurons and memory that was prevented by P2Y6 receptor knockout. Crossing P2Y6 receptor knockout mice with P301S TAUopathy mice prevented loss of neurons and memory. P2Y6 receptor knockout mice were also protected against the loss of synapses and memory induced by natural ageing. Thus, excessive microglial phagocytosis of synapses and neurons may contribute to ageing and neurodegeneration, and blocking this phagocytosis in particular ways may be beneficial.

Biosketch:
Professor Guy Brown received his Ph.D. in 1986 from the Biochemistry Department at Cambridge, then had a College Research Fellowship from St Catharine's College for 3 years. He then moved to the Department of Physiology, University College London, and after 18 months transferred to a Royal Society Research Fellowship at the Department of Biochemistry at UCL. In 1994 he returned to Cambridge with the Royal Society Research Fellowship, and is now a Professor of Cellular Biochemistry at the Department of Biochemistry, University of Cambridge. His research has been funded by: the Medical Research Council, the Biotechnology & Biological Sciences Research Council, the European Union, the Wellcome Trust, the British Heart Foundation, AstraZeneca, Ely Lilly, and Alzheimer's Research UK.