Jamie Cowley[1, 2], Neale Harrison[1, 2], Ines M. Morano[2], Hujo Chan[2], Elizabeth Jinks[2], Fabiana Corsi-Zuelli[1, 3], Ashley Pegg[1], Haleema Yoosuf Ali[1], Andrew R. Stevens[4,5], Thomas H. Land[6], Zenab Sher[6], Athanasios Zisakis[6], Philip J. O'Halloran[6,7], Ismail Ughratdar[6], Victoria Wykes[6], Antonio Belli[4,5], Rachel Upthegrove[6], Catherine A. Brady[1,2], John Gordon[2], Omar Qureshi[1, 2], Nicholas M. Barnes[1, 5]

[1]Neuropharmacology Research Group, Institute of Clinical Sciences, University of Birmingham B15 2TT UK
[2]Celentyx Ltd, Birmingham B15 2SQ UK
[3]Department of Neuroscience and Behaviour, Division of Psychiatry, University of São Paulo, Brazil
[4]Institute of Inflammation and Aging, University of Birmingham B15 2TT UK
[5]NIHR SRMRC Research Team, Queen Elizabeth Hospital Birmingham, B15 2GW UK
[6]Department of Neurosurgery, Queen Elizabeth Hospital Birmingham, B15 2GW UK
[7]Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin, Ireland
[8]Institute for Mental Health, School of Psychology, University of Birmingham B15 2TT UK

P2X7 receptor mediated cytokine release from human microglia (monocyte-derived) and precision-cut brain slices; implications for patients with TBI and other brain pro-inflammatory conditions

Despite traumatic brain injury (TBI) being the leading cause of death and disability in people in their first four decades of life, there are no pharmacological treatments approved for this indication. Whilst several agents show activity in animal models of disease, achieving human translation remains a major challenge. The excitatory P2X7 receptor, by driving pro-inflammatory cytokine release and cell death, remains a well validated target in mouse models of a number of neuroinflammatory conditions. We therefore investigated the impact of P2X7 receptor inhibition using a P2X7 receptor antagonist, A-804598, in a human monocyte-derived microglial model (iMDM) in which we identified that the P2X7 was co-expressed with the microglial marker TMEM119. Activation of LPS-primed iMDM with the P2X7 receptor agonist BzATP evoked pore formation (as monitored by entry of the fluorescent dye, YO-PRO-1) and release of pro-inflammatory cytokines including IL-1β. P2X7 receptor antagonism reduced cytokine release in a concentration-dependent manner. To obtain further translational validation, using brain tissue from surgical resections, we generated precision cut human brain slices and quantified the impact of P2X7 receptor antagonism on BzATP-evoked cytokine release from LPS-primed slices. Again, A-804598 reduced IL-1β release in a concentration-dependent manner. The present results demonstrate the impact of a P2X7 receptor antagonist in human neuroinflammatory models supporting the hypothesis that P2X7 receptor antagonists may improve the clinical outcomes for patients with TBI. Furthermore, central P2X7 receptor antagonism may benefit patients with other neurological and psychiatric conditions associated with a pro-inflammatory environment in the brain or spinal cord.

Acknowledgements: Funded by the MRC (UK; grant ref MR/R006008/1) and Celentyx Ltd.