Development of a human monocyte-derived microglial model for identifying modulators of neuroinflammation

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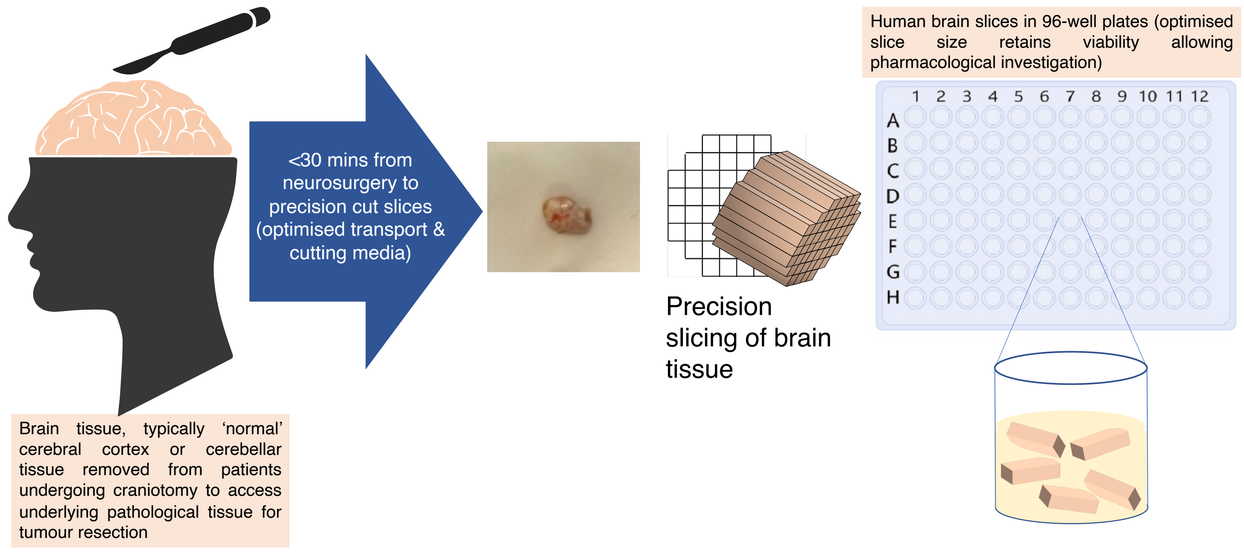
ABSTRACT

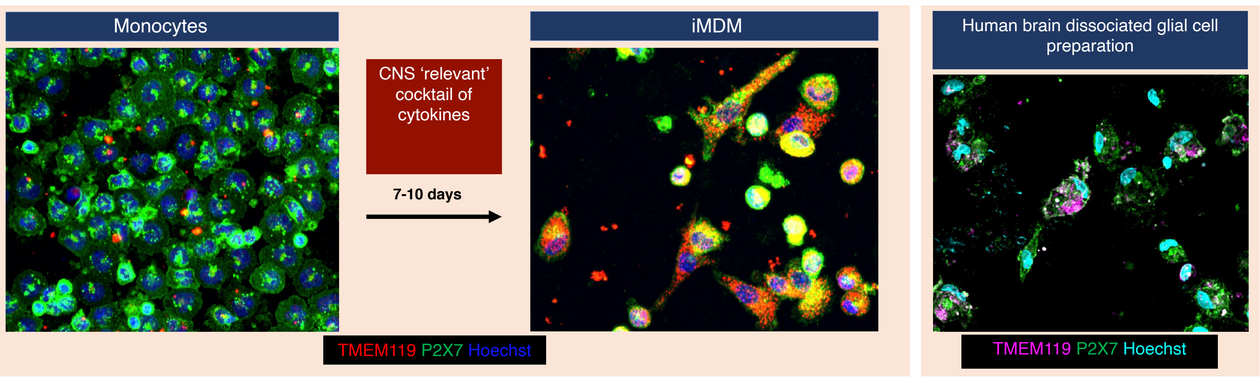
Neuroinflammation is now generally accepted as a major contributor to both neurodegenerative and psychiatric disorders. 'Myeloid' associated genes (e.g. TREM2, CD33, ABCA7 and CR1) are associated with neurodegeneration and point to an important role for microglia in mediating pathology. Testing of potential therapeutic molecules in human microglia is challenging because of the difficulty of accessing and isolating sufficient numbers of cells from human brain tissue. While iPSC microglial models provide an option for drug discovery they display a number of limitations so we sought to develop a complementary approach using human monocytes. One of the primary goals was the arising cells allowed the rapid testing of molecules on cells derived from multiple patients.

Exposure of monocytes to a cocktail of CNS-associated cytokines transformed the cells to express the phenotypic markers associated with microglia leading us to term the cells induced microglia derived from monocytes (iMDM). Following iMDM stimulation of purinergic receptors, a receptor family strongly associated with neuroinflammation, pro-inflammatory cytokines such as IL-1β and IL-18 were released. Model antagonists including those inhibiting the P2X7 receptor and the NLRP3 inflammasome reduced this cytokine release. The assay system was further validated by displaying a comparable function and pharmacology with human fresh brain slices. iMDM also exhibited phagocytic activity against a range of cargos including human myelin-basic protein. To further demonstrate the utility of the iMDM platform, we induced iMDM from patients with schizophrenia demonstrating the system could be used for the study of disease-derived material. In summary, iMDM provide a system for testing potential therapeutic agents in a model that recapitulates multiple aspects of microglial biology.

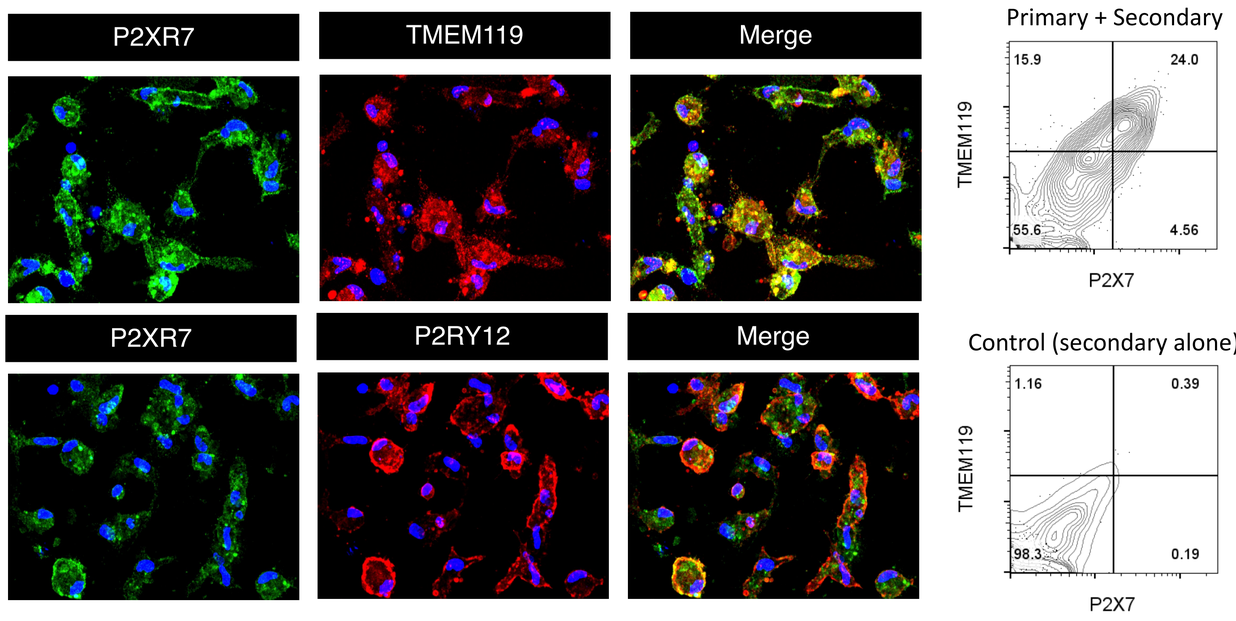
Precision cut human brain sections



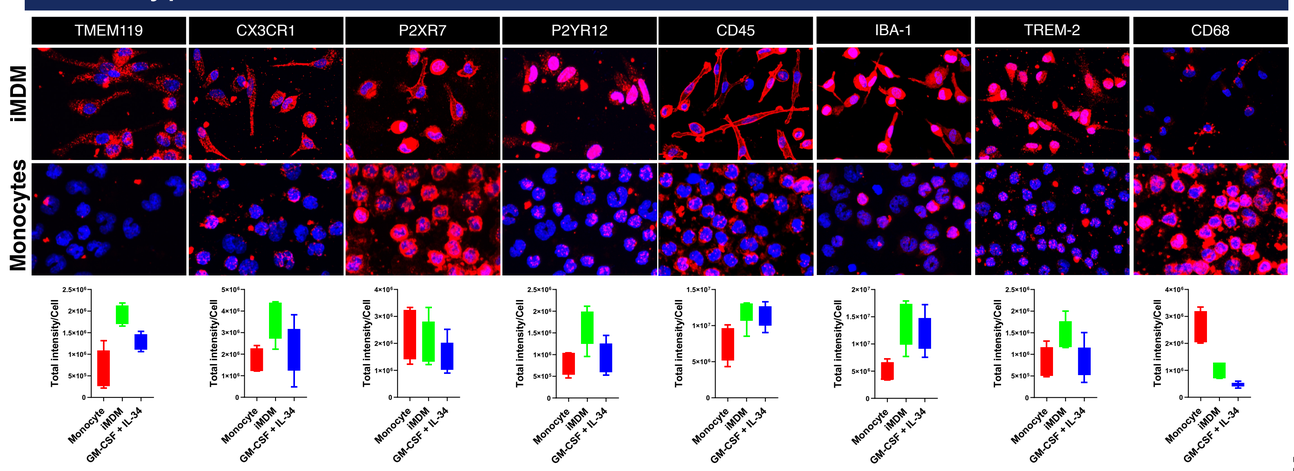
Induced microglia from human monocytes (iMDM)



Validation of P2X7 receptor antagonist action on human brain sections



Phenotypic characterisation of iMDM



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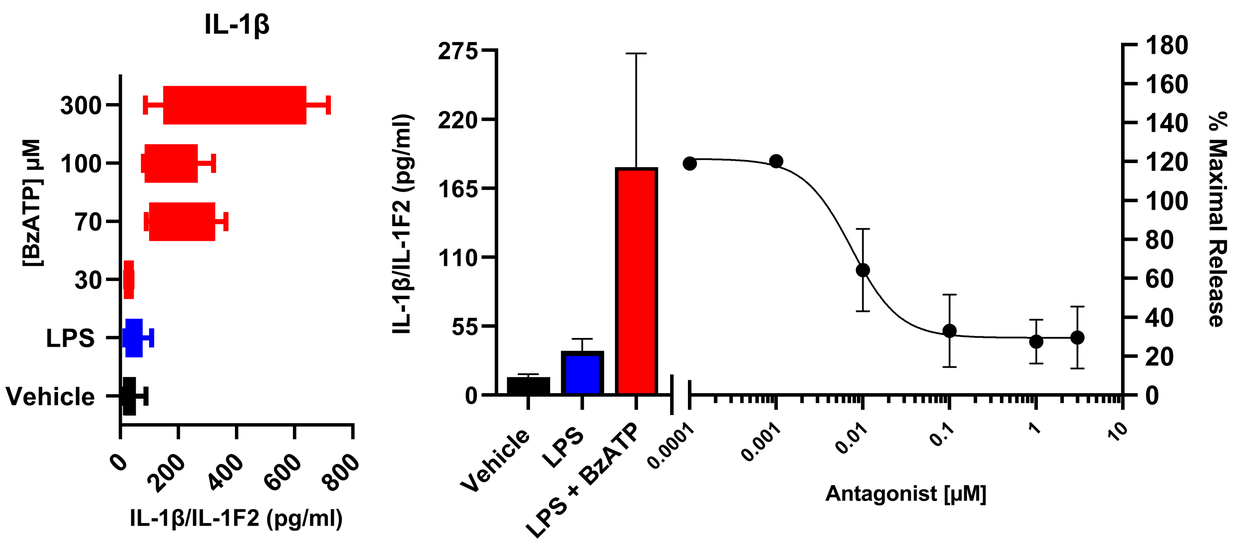
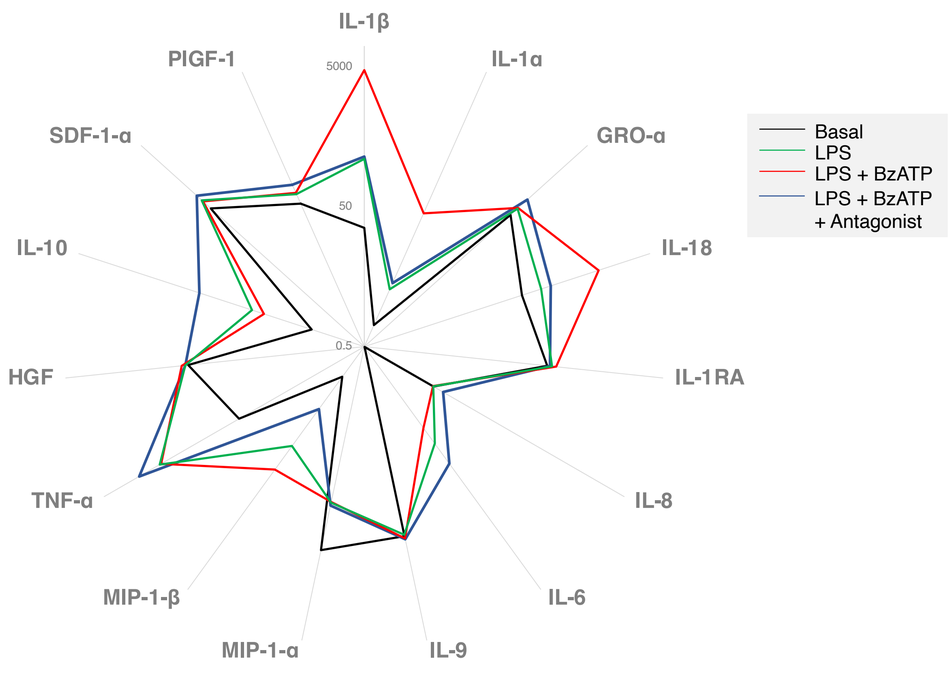
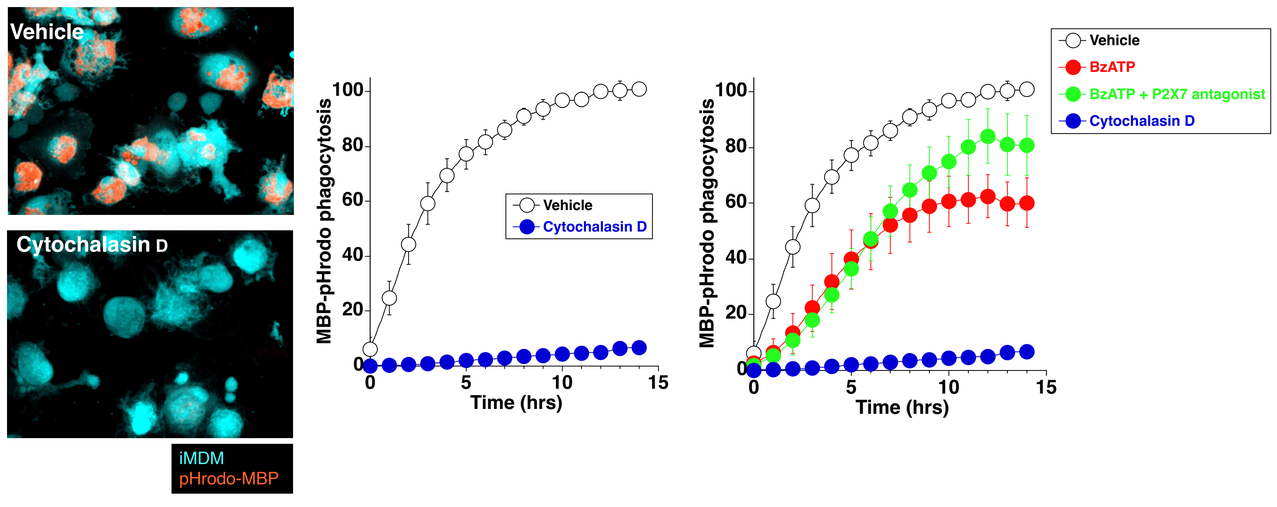
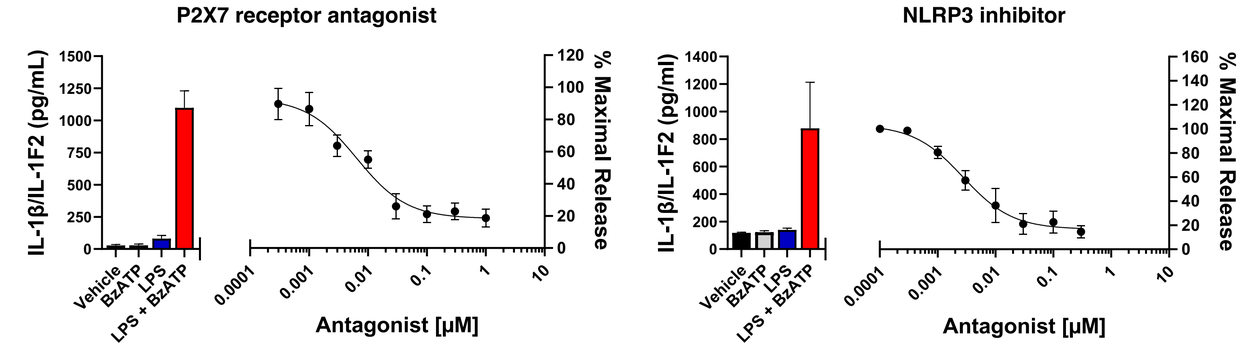


P2X7 receptor-mediated cytokine release from iMDM



Modulation of phagocytosis of a myelin-basic protein cargo





Acknowledgements

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