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PhD Project - Targeting the p38 MAPK signalling pathways in Glioblastoma

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High-grade Glioma/Glioblastoma (HGG/GBM) are rare brain tumours in children, have an extremely poor prognosis and so contribute to brain tumours as the leading cause of cancer deaths in children [1, 2]. Treatments for children older than 3yr parallel approaches adopted in adult HGG/GBM using chemo-radio therapy. However, progress has been stubbornly slow, and mortality remains high because of a number of contributing factors including; a) the biological differences for HGG/GBM arising in very early life, b) their rarity in the population, c) the very limited evidence of the impact of Temozolomide chemotherapy in the young age group, d) the slow adoption of Gliadel interstitial therapy [3] and e) the neurotoxic risks of cranial radiotherapy [4-7]. New treatments are urgently needed. Immunotherapy is currently being investigated in combination with surgery, chemo- and radio-therapy in adult HGG/GBM [6, 7]. Recent clinical trials in common malignancies have established the value of immune checkpoint blockade to limit the termination of immune responses [8] and these are now ongoing in HGG/GBM [NCI]. Despite advances with checkpoint blockade to "take the brakes off" the immune system when activated against cancer, dendritic cells (DC) are nevertheless required to initiate immune responses [9]. However, the function of DC is commonly suppressed in advanced cancer [10, 11]. The prospect of tailoring DC-based immunotherapy has great potential for paediatric HGG/GBM, especially if it can in future be combined effectively with checkpoint blockade. **This proposal aims to understand circulating DC function in paediatric HGG/GBM patients, and restore DC immune function by inhibiting the p38-MK2 intracellular signalling pathway.**

This PhD project test two main hypotheses:

1. The frequency of circulating DC subsets are significantly decreased in children with HGG/GBM. However, as children have more myeloid DC than adults, the number of mDC1 in paediatric HGG/GBM will be sufficient for future isolation and adoptive immunotherapy.
2. The function of circulating mDC1 cells is suppressed in children with GBM and can be enhanced *ex vivo* by inhibiting the p38 MAPK pathway.

Specifically, you will:

1. Determine the abundance circulating DC subsets in children with GBM.
2. Assess the extent of functional deficiency in mDC1 cells from paediatric GBM patients.
3. Enhance mDC1 function by inhibiting the p38-MK2 MAPK pathway.

By addressing these we will advance our understanding of DC biology in paediatric GBM and pave the way for a next generation adoptive immunotherapy with "enhanced" circulating DC.

The successful student would join the Host-Tumour Interactions Group co-directed by Dr Andrew Jackson and Professor Poulam Patel. The group currently comprises PhD students, clinical research fellows and technicians, and has an international standing in the field. The group is based on the City Hospital Campus in laboratories shared with other immunology and cancer biology research groups.

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