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PRE-CLINICAL ANALYSIS OF THE FEASIBILITY OF TUMOUR INFILTRATING LYMPHOCYTE THERAPY FOR PAEDIATRIC BRAIN TUMOURS

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Background: Brain tumours are the most common solid malignancy of childhood, accounting for >20% of all paediatric cancers. Collectively, they remain the leading cause of cancer-related death and long-term morbidity in children. Infant lesions fare poorly since intensifying potentially effective conventional therapy causes overwhelming toxicity without conferring significant survival advantage. Tumour infiltrating lymphocyte (TIL) therapy consists of extracting immune cells from surgically removed tumours and growing them in the lab. This not only allows immune cells to be switched back on, but increases their total number. In this study we are investigating whether applying tumor-infiltrating leukocytes (TIL) therapy to paediatric brain tumours is feasible.

Objectives: We seek to assess, if there are significant T-cell infiltrates in high grade paediatric brain tumours. Whether these cells can be efficiently expanded ex vivo and the anti-tumor reactivity of expanded TILs against autologous tumor ex vivo.

Methods: We report initial evidence that there is a significant presence of TILs in 4 high grade paediatric brain tumour patients with cell type and phenotype analyzed by time of flight cytometry (cyTOF) upon dissociation after resection and after three weeks expansion in interleukin-2 (IL-2).

Results: Initial samples have displayed up to 1300-fold expansion of TILs upon three weeks of culture and cyTOF analysis has shown that expanded cells have an increased capacity to secrete effector cytokines compared to peripheral blood lymphocytes cultured in the same conditions. Crucially, multiplex analysis of supernatant following co-culture of with autologous tumour and tumour lines shows that expanded cells possess anti-cancer activity.

Conclusions: These promising results suggest that TIL therapy for paediatric brain tumours may be feasible. Analysis of an increased number of samples will be required to substantiate this, along with optimization of methodology to produce clinically relevant numbers of cells.

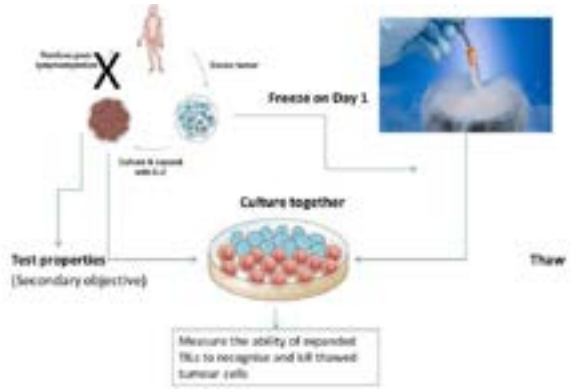

Figure 1: Overview of work process: TIL therapy consists of collection of tumour samples, expansion of TIL ex vivo then re-infusion into the host after lymphodepletion. This work process followed a similar pattern, collecting brain tumour samples, freezing a portion of disaggregated tumour on day 1, expanding TILs ex vivo then analyzing their phenotype and ability to react to thawed autologous tumour cells.

Recent Publications

1. Kueberuwa G, Kalaitsidou M, Cheadle E, Hawkins R E, Gilham D E (2017) CD 19 CAR T cells expressing IL-12 eradicate lymphoma in fully lymphoreplete mice through the induction of host immunity. Molecular Therapy Oncolytics 8:41-51
2. Kueberuwa G, Gornall H, Alcantar Orozco E M, Bouvier D, Kapacee Z A, Hawkins R E and Gilham D E (2017) CCR7+ selected gene-modified T cells maintain a central memory phenotype and display enhanced persistence in peripheral blood *in vivo*. Journal for ImmununoTherapy of Cancer 5:14.

3. Dyer A, Di Y, Calderon H, Illingworth S, Kueberuwa G, Tedcastle A, Jakeman P, Chia S L, Brown A, Silva M A, Barlow D, Beadle J, Hermiston T, Ferguson D J P, Champion B, Fisher K D and Seymour L W (2017) Oncolytic Group B Adenovirus Enadenotucirev Mediates Non-apoptotic Cell Death with Membrane Disruption and Release of Inflammatory Mediators. Molecular Therapy Oncolytics (4):18-30.

Biography

Gray Kueberuwa PhD is a Doctor of Oncology working in the Clinical and Experimental Immunology Group within the Department of Cancer Sciences at the University of Manchester, UK. His research interests include chimeric antigen receptor (CAR) T-cell therapy of cancer, tumor infiltrating lymphocyte (TIL) therapy of cancer and the production of immune regulatory agents from within therapeutic cells.

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