



## Scientific Abstract

### SU2C-CRUK Pediatric Cancer New Discoveries Challenge:

#### “Combinatorial Targeting of Oncogene-Driven Childhood Cancer”



Immunotherapy has joined chemotherapy, radiotherapy and surgery as the “fourth pillar” of cancer therapeutics but has had limited success in childhood solid cancers which broadly lack infiltrating immune effector cells as a result of immune evasion, lack of tumour antigens or both. Amongst possible mechanisms of immune evasion to target in childhood cancers we have selected *myc* as a driver oncogene in multiple tumour types, and for which we have developed animal models of body (neuroblastoma; NB) and CNS (medulloblastoma: MB) tumours that are both chemo- and immunotherapy resistant. Moreover, we have developed trial-ready small molecule inhibitors to target *myc* at the transcriptional or protein level, which we hypothesise will subvert immune evasion mechanisms in the models.

Our approach is to combine, within these immune competent animal models, the small molecule inhibitors with 1) CAR-T cells to target a ubiquitous tumour antigen and 2) “in situ vaccine” to allow the emergence of adaptive immune responses at the tumour site with capacity to control metastatic disease. Firstly in pharmacodynamic studies we will identify the capacity of small molecule inhibitors (*myc* inhibitors and, for neuroblastoma ALK inhibitor) within the animal models to subvert immune evasion (Work Package 1 ICR/ICH). Secondly, we will refine our existing CAR-T platform targeting the antigen B7-H3 expressed in NB and MB, with enhanced capability to proliferate and kill in a highly antigen specific manner (Work Package 2 ICH). Thirdly we will build on our existing in situ vaccine data to identify the combinations of agents that can successfully eliminate metastatic disease and large tumour bulk in the immunologically cold NB model (Work Package 3 UW). Finally, in Work Package 4 we will work together to select the emerging agents to evaluate in combination studies and from this we will develop a clinical trials strategy for development in the second phase SU2C/CRUK funding round.

