specific peptides that can be used to create a personalized, targeted T cell therapy for children with high risk medulloblastoma.

IMMU-16. INTRA-TUMOURAL IL-12 DELIVERY ENABLES CAR T-CELL IMMUNOTHERAPY FOR HIGH-GRADE GLIOMA

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Treatment with T-cells redirected to tumour specificity with a chimeric antigen receptor (CAR) may be well suited to treat intracranial tumours due to the ability of T-cells to access the central nervous system and migrate to infiltrative sites of disease. In adult glioblastoma, a case report of local and distant eradication of intracranial and spinal tumour deposits following intraventricular infusion of IL13Ra2-CAR T-cells indicates the potential of this approach. However, in contrast to the sustained complete remissions observed in haematological malignancies, in the majority of patients with glioblastoma CAR T-cell therapy has not resulted in clinical benefit. Tumour heterogeneity and the highly immune inhibitory tumour microenvironment (TME) are likely key barriers to achieving durable anti-tumour immunity. Here use intra-tumoural administration of IL-12 to enable CAR T-cell immunity. We employed CAR-T cells targeting the tumour-specific epidermal growth factor variant III (EGFRvIII). In an immunocompetent orthotopic mouse model of high-grade glioma, we show that CAR-T cells alone failed to control fully established tumour, but when combined with a single, locally delivered dose of IL-12, durable antitumor responses were achieved. IL-12 not only boosted cytotoxicity of CAR T-cells, but also reshaped the TME driving increased infiltration of proinflammatory CD4+ T-cells, decreased numbers of regulatory T-cells (Tregs) and activation of the myeloid compartment. Critically, immunotherapy enabling benefits of IL-12 were achieved with minimal systemic effects. Our findings show that local delivery of IL-12 is an effective adjuvant for CAR-T cell therapy for high-grade glioma. Assessment of application in high-risk childhood brain tumours is ongoing.

IMMU-17. CAR T CELLS TARGETING THE INTEGRIN ALPHA$_V$BETA$_3$ EXHIBIT ROBUST ANTI-TUMOR RESPONSES AGAINST DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) AND GLIOBLASTOMA (GBM)

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Effective therapies for DIPG and GBM are lacking. CD19 chimeric antigen receptor (CAR) T cells are highly effective in patients with refractory B-cell malignancies. We aim to develop novel CARs for high-grade gliomas. The integrin complex alpha$_v$beta$_3$ was selected as a CAR-T cell target due to its expression on gliomas and their vasculature, yet with minimal expression throughout normal tissues, vessels and organs. Indeed, a majority of DIPG and GBM cell lines express surface $\alpha_v\beta_3$. Second-generation CAR-T cells expressing an anti-$\alpha_v\beta_3$ scFv and either a CD28 or 4-1BB co-stimulatory domain and CD3zeta were constructed. Transduced healthy, donor-derived T cells exhibited high level CAR expression, efficient expansion, and representative populations of memory subsets including central, effector, and stem cell-like memory CAR-T cells. $\alpha_v\beta_3$.28z and $\alpha_v\beta_3$.BBz CAR-T cells exhibited antigen-specific *in vitro* cytotoxicity and cytokine production against DIPG and GBM cell lines. Both CARs mediated rapid and robust anti-tumor responses in NSG mice bearing orthotopic DIPG or GBM tumors. 5/13 $\alpha_v\beta_3$.28z and 0/14 $\alpha_v\beta_3$.BBz treated animals died without detectable disease within 2 weeks of infusion suggesting different toxicity profiles and is consistent with faster CAR-T cell expansion in CD28-versus 4-1BB-containing CD19 CAR-T cells seen clinically. Our results demonstrate that $\alpha_v\beta_3$.BBz CAR-T cell therapy may be both highly effective and safe in DIPG and GBM patients. Due to the restricted nature of $\alpha_v\beta_3$ expression in normal tissues, the robust responses seen in tumor-bearing mice, and the slower kinetics of $\alpha_v\beta_3$.BBz CAR-T cell expansion, a first-in-human clinical trial is being planned.

IMMU-18. FAVORABLE OUTCOME IN REPLICATION REPAIR DEFICIENT HYPERMUTANT BRAIN TUMORS TO IMMUNE CHECKPOINT INHIBITION: AN INTERNATIONAL RRD CONSORTIUM REGISTRY STUDY

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Pediatric brain tumors with replication repair deficiency (RRD) are hypermutant and may respond to immune checkpoint inhibition (ICI). We performed a consortium registry study of ICI in recurrent RRD cancers. Clinical and companion biomarkers were collected longitudinally on all patients. Biomarkers included tumor mutational burden (TMB), neoantigens and genetic signatures obtained from whole genome and exome sequencing. Immune inference was obtained by RNAseq and T cell rearrangement was collected in the tumor and in blood throughout treatment. Of the 46 tumors on the study, 32 were brain tumors with glioblastoma in 96%. Rapid, objective responses (>50%) were observed in 50% of glioblastomas. Three year overall survival for the whole cohort was 48+/-8% which compares favorably with historical controls. Brain tumors fared worse with OS of 39+/-10% and late recurrences observed even after 2 years of therapy (p=0.02). Tumor size and acute "flare" constitute poor outcome throughout all cancers. While all tumors are hypermutant, TMB and predicted neoantigens correlated with response to ICI (p=0.02). Specific signatures extracted from SNVs and total mutations predicted response to ICI and favorable outcome (p=0.005). RNA inference and TCR reveal that the FLARE phenotype is mostly acute nonspecific immune response and not true progression. Finally, glioblastomas (n=8) which failed single agent ICI had favorable responses to combinational immunotherapies with prolonged survival of 65%+/-8% at one year after failure vs 0 for other patients (p=0.01). RRD glioblastomas exhibit favorable outcome and responses to ICI. Combinational therapies based on tumor and immune signatures of these cancers are necessary.