A MUTATED PROSTATIC ACID PHOSPHATASE (PAP) ACTIVE IMMUNIZATION AGAINST HUMAN PROSTATE CANCER. We have previously shown that a 15 amino acid (AA) PAP sequence of 15 AA long to increase the CD4 + and CD8+ response.

Materials and Methods The presence of PAP-135–143 epitope-specific CD8+ T cells in the blood of patients with prostate cancer (PCa) was assessed by flow cytometry using Sipuleucel-T. We propose the use of mutated NY-ESO-1/HAGE/WT1 peptides in combination with CAF09b for the treatment of GBM, PCa and TNBC at a stage where no tumour cells can be detected to prevent or delay relapse in these malignancies.

Conclusions We propose the use of mutated NY-ESO-1/HAGE/WT1-derived peptides in combination with CAF09b for the treatment of GBM, PCa and TNBC at a stage where no tumour cells can be detected to prevent or delay relapse in these malignancies.

Disclosure Information C. Puig Saenz: None. D. Christensen: A. Employment (full or part-time); Significant; Croda Pharmaceuticals. S.E.B. Mc Ardle: None.

A MUTATED PROSTATIC ACID PHOSPHATASE (PAP) PEPTIDE-BASED VACCINE INDUCES PAP-SPECIFIC CD8+ T CELLS WITH EX Vivo CYTOTOXIC CAPACITIES IN HHDII/DR1 TRANSGENIC MICE


Background Prostate cancer (PCa) is the second most frequent cancer in men and the fifth most frequent cause of cancer-related deaths in men worldwide. Current treatments for castrate (hormone)-resistant prostate cancer (CRPC) are limited and not curative, with a median survival from diagnosis of 23 months. Sipuleucel-T is the only FDA approved autologous cellular immunotherapy for PCa targeting prostatic acid phosphatase (PAP), showing a 4.1 month survival benefit for metastatic castration-resistant prostate cancer patients. However, its anti-neoplastic responses remain minimal and is cost prohibitive and while PAP is a good target for future prostate cancer vaccine, new, more affordable therapeutic approaches are therefore needed to treat advanced PCa. We have previously shown that a 15 amino acid (AA) PAP sequence-derived peptide could induce strong immune responses and delay the growth of murine TRAMP-C1 prostate tumours. We have now substituted one amino acid and elongated the sequence to include epitopes predicted to bind to several additional HLA haplotypes. Herein, we present the immunological properties of this 42mer-mutated PAP-derived sequence (MutPAP42mer) and the additional use of another PAP-derived sequence of 15 AA long to increase the CD4+ T-cell responses.

Materials and Methods The presence of PAP-135–143 epitope-specific CD8+ T cells in the blood of patients with prostate cancer (PCa) was assessed by flow cytometry using Dextramer™ technology. HHDII/DR1 transgenic mice were immunized with mutated and non-mutated PAP-derived 42mer peptides in the presence of CAF®09 or CpG ODN1826 or 2395 (TLR-9 agonist) adjuvants. WT-hPAP-42mer was also used to immunize syngeneic C57Bl/6 mice. Vaccine-induced immune responses were measured by assessing the proportion and functionality of splenic PAP-specific T cells in vitro.

Results PAP-135–143 epitope-specific CD8+ T cells were detected in the blood of patients with PCa and stimulation of PBMCs from patients with PCa with mutPAP42mer enhanced their capacity to kill human LNCaP PCa target cells expressing PAP. MutPAP42mer peptide was significantly more immunogenic in HHDII/DR1 mice than the wild type sequence, and immunogenicity was further enhanced when combined with the CAF09b™ adjuvant. The vaccine induced secretory (IFNγ and TNFα) and cytotoxic CD8+ T cells and effector memory splenic T cells.

Conclusions The periphery of patients with PCa exhibits immune responsiveness to the MutPAP42mer peptide and immunization of mice induces/expands T cell-driven, wild-type PAP immunity, and therefore, has the potential to drive protective anti-tumour immunity in patients with PCa.


ACTIVE IMMUNIZATION AGAINST HUMAN ENDogenous RETROVIRUS TYPE K (HERV-K) AS AN IMMUNOTHERAPEUTIC STRATEGY AGAINST SOLID TUMORS

10.1136/jitc-2022-ITOC9.31

Background Human endogenous retroviruses constitute 8% of the genome and are distributed among viral families of which HERV-K is the most recently integrated. Endogenous retroviruses are well established, natural targets for immunotherapy. Previously, we observed that encoding an endogenous variant of the murine leukemia virus as a particle-forming transgene in adenoviral vectors, allowed for curative therapy against small established cancers. In addition, immunogenicity could be further improved by point mutations of an immune suppressive domain (ISD) (WO 2019/043127). In humans, HERV-K Gag and Env genes are structurally intact, and while expression is almost absent in healthy tissues, HERV-K proteins are detected in human cancers, including on cell surfaces and exosomes. Functionally, the HERV-K Env genes are implicated in oncogenic signaling pathways, Epithelial Mesenchymal Transition and immune evasion. Consequently, we developed a particle forming HERV-K vaccine incorporating ISD mutations for treatment of cancer with a combined T and B Cell response.

Materials and Methods HERV-K Gag and Env consensus sequences were encoded in human adenovirus type 5 and 19a/64 adenoviral vectors. Expression analyses were performed on human and mouse DCs. Immune responses were analyzed by intracellular cytokine staining and tetramers. Murine colorectal cancer cells were engineered to express the HERV-K Gag and Env antigens. Immunotherapy experiments in tumor-bearing mice were performed by transplantation of selected immune cell populations obtained from vaccinated donor mice.

J Immunother Cancer 2022;10(Suppl 1):A1–A49
Background Intracranial tumours present a significant therapeutic challenge due to their physiological location. Immuno-therapy approaches represent attractive treatments for targeting these intracranial tumours due to their tumour specificity relatively low toxicity. The SCIB1 ImmunoBody® is a DNA vaccine developed by Scancell Ltd. that encodes a human IgG1 antibody with one TRP-2 two gp100 epitopes engrafted into its complementarity determining regions. SCIB1 has been shown to induce a stronger immune response than peptide, whole antigen DNA vaccines and peptide pulsed dendritic cells due to Fc-receptor mediated cross presentation. Taking all of this into account, we decided to examine the efficacy of SCIB1 therapy in combination with anti-PD-1 immune checkpoint blockade for the treatment of intracranial tumours.

Materials and Methods C57BL/6 HHDII/DR1 mice were immunised with SCIB1 ImmunoBody® DNA vaccine and ex vivo ELISpot assays were used to assess the immune response while the frequency of TRP-2 specific T-cells was examined via pentamer staining and subsequent flow cytometry analysis. The efficacy of this vaccine was then tested in mice with B16 HHDII/DR1 tumours implanted intracranially. These cells where knockout for murine beta2m and transfected with the chimeric HLA-A2 (HHDII) construct, and naturally express both the TRP-2 and gp100 antigens making it the ideal target for SCIB1 therapy. These mice also received anti-PD-1 therapy, the survival of these mice was then monitored. Immunohistochemical staining for TRP-2 and gp100 was also performed on human GBM tissue micro arrays to study whether SCIB1 could be applicable to this type of cancer. Furthermore, the expression of PD-L1 on GBM tumour cell lines was measured before and after IFNγ treatment via flow cytometry. This was done to give an indication of the efficacy of combined anti-PD-1 with SCIB1 vaccination in the GBM setting.

Results Here we demonstrate that SCIB1 generates a strong TRP-2 specific immune response in humanised C57BL/6 HHDII/DR1 mice, and this method of vaccination increased the frequency of TRP-2 specific CD8 T-cells. The survival of mice harbouring intracranial B16 HHDII/DR1 tumours was significantly prolonged when SCIB1 ImmunoBody® vaccination was combined with anti-PD-1 immune checkpoint blockade compared to mice that received sham vaccination combined with anti-PD-1 and mice that received sham vaccination combined with an isotype control antibody. Our analyses revealed that GBM patients could benefit from SCIB1 ImmunoBody® therapy due to the expression of TRP-2 witnessed in GBM tumour tissues. GBM cell lines were also shown to express PD-L1 on their surface and the cell lines studied were shown to upregulate PD-L1 on their surface when exposed to IFNγ, providing further evidence for the combination of anti-PD-1 with active immunotherapy such as SCIB1.

Conclusions Combinatorial SCIB1 and anti-PD-1 therapy represents an exciting therapeutic intervention for the treatment of intracranial tumours. Our analysis of GBM tumours reveals that this therapy may be applicable to these types of tumours due to their antigen expression profile, because of these findings the efficacy of this combined treatment is now being tested in the GL261 and CT-2A murine GBM models with the aim of moving this combinatorial therapy forward for the treatment of GBM.

Disclosure Information J.R.D. Pearson: None. V.A. Brentville: A. Employment (full or part-time); Significant; Scancell Ltd.. E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Scancell Ltd. L.G. Durrant: A. Employment (full or part-time); Significant; Scancell Ltd.. E. Ownership Interest (stock, stock options, patent or other intellectual property); Significant; Scancell Ltd.. F. Consultant/Advisory Board; Significant; Scancell Ltd. S.E.B. McArdle: None.