| Project Details | |
|---|---|
| Project Code | MRC22IIARCa Gallimore |
| Title | Equipping Antigen-Specific T Cells With the Ability to Remodel the Tumour Microenvironment to Improve Cancer Rejection |
| Research Theme | Infection, Immunity, Antimicrobial Resistance & Repair |
| Summary | The anti-cancer T cell response can drive structural alterations to the tumour microenvironment (TME) which amplify the immune response promoting tumour destruction. This project will determine whether immunotherapy can be enhanced by empowering T cells with the ability to alter the TME, tipping the balance in favour successful T cell driven cancer therapy. |
| Description | Purpose: We have evidence that the anti-tumour T cell response can, under certain circumstances, drive structural alterations to the tumour microenvironment (TME) which serve to amplify the immune response leading to tumour destruction. Our findings indicate that changes to the TME are widespread and are characterized by the development of specialised blood vessels named high endothelial venules (HEV), re-organization of lymphatic vessels and loss of extracellular matrix (ECM). Our preliminary data imply that the cytokine lymphotoxin-alpha (LT-alpha) and the matrix degrading enzyme heparanase, are important for remodelling the ECM in this way. Based on these data, we hypothesise that tumour rejection may be improved by equipping particular antigen-specific T cells with the ability to produce LT-alpha and heparanase; expression of this cytokine and/or enzyme may drive HEV development and loss of ECM respectively. The hypothesis will be tested in this PhD project. Aims: We have identified HLA-A2 and HLA-DR1/4-restricted T cell epitopes from the cancer associated antigens 5T4- and DNAJB7 and have generated T cell lines and clones which recognise these peptides. T cell receptors (TCRs) will be cloned and transduced into mouse splenocytes / human PBMC and co-engineered to express cytokines or matrix-degrading enzymes. The function of these cells will be assessed in organoid co-cultures (matrix degradation) and in HLA-A2 and/or HLA-DR1 transgenic mouse tumour models (matrix degradation and HEV development). Year 1: 1.Cloning of TCRs and optimisation of TCR sequences. 2.Generation of constructs for expression of LT-alpha and heparanase. This will provide the T cell toolkit to test the hypothesis. Year 2: 1.Select and grow human colon cancer organoids expressing relevant HLA class I / II molecules (which interact with the TCRs above). 2.Transduce autologous human PBMC with TCR and heparanase constructs generated in Year 1 and examine organoid-T cell co-cultures by confocal microscopy (opera phenix) and by immunohistochemistry. This will determine whether antigen-specific T cells expressing heparanase degrade organoid matrix and infiltrate organoids more effectively. Year3: 1.Transduce mouse splenocytes with TCRs and LT-alpha and/or heparanase constructs generated in Year 1 and adoptively transfer into tumour-bearing HLA-A2 and/or HLA-DR1 transgenic mice. 2.Measure tumour growth rates and recover tumours for immunohistochemical staining to examine matrix degradation and HEV development. This will determine whether genetically engineered antigen-specific T cells exhibit enhanced tumour rejection capacity. Outputs: This project will determine whether immunotherapy is |

| | |
|---|---|
| | enhanced by empowering adoptively transferred T cells with the ability to digest the ECM and/or to improve endothelial cell function. By altering the TME in this way, it may be possible to tip the balance in favour of the perfect storm even when the T cell response is sub-optimal. Key Recent Papers From Our Lab: 1. Lauder SN et al. Enhanced anti-tumour immunity through sequential targeting of PI3Kδ and LAG3. J Immunother Cancer. 2020 Oct;8(2):e000693. 2. Pires A et al. Immune Remodelling of the Extracellular Matrix Drives Loss of Cancer Stem Cells and Tumour Rejection. Cancer Immunol Res. 2020 Oct 6:canimm.0070.2020. 3.Scurr M et al. Cancer antigen discovery is enabled by RNA-sequencing of highly purified malignant and non-malignant cells. Clin Cancer Res. 2020 Mar 2. pii: clincanres.3087.2019. 4.Colbeck E et al.Treg Depletion Licenses T Cell-Driven HEV Neogenesis and Promotes Tumor Destruction. Cancer Immunology Research 2017 Sep 25. |
| Supervisory Team | |
| Lead Supervisor | |
| Name | Professor Awen Gallimore |
| Affiliation | Cardiff |
| College/Faculty | BLS |
| Department/School | Infection and Immunity, School of Medicine |
| Email Address | gallimoream@cardiff.ac.uk |
| Co-Supervisor 1 | |
| Name | Dr Gareth Jones |
| Affiliation | Bristol |
| College/Faculty | Biomedical Sciences |
| Department/School | School of Cellular and Molecular Medicine |
| Co-Supervisor 2 | |
| Name | Professor Andrew Godkin |
| Affiliation | Cardiff |
| College/Faculty | BLS |
| Department/School | Infection and Immunity, School of Medicine |
| Co-Supervisor 3 | |
| Name | |
| Affiliation | |
| College/Faculty | |
| Department/School | |
| Co-Supervisor 4 | |
| Name | |
| Affiliation | |
| College/Faculty | |
| Department/School | |