BACKGROUND
Cancer targeting cell therapies are being widely developed and taken into the clinic where they are proving to be potent treatment modalities to accompany or replace current standard of care. Nasopharyngeal carcinoma (NPC) is unusually common throughout China and Southeast Asia, where it accounts for 63% of the 87,000 NPC cases worldwide [1]. In southern China it is the third most common cancer in men [2]. While radiotherapy is the first-line treatment for NPC, it is often diagnosed late. 60%-90% patients present with late stage disease [3,4] dramatically reducing survival rates. In high incidence regions, relapse following primary treatment occurs in nearly 80% patients and is the leading cause of death from NPC [5,6,7]. Consequently there is a real need for novel approaches to treat NPC.

Epstein Barr Virus (EBV) is detected in almost all malignant cells from NPC patients and is strongly associated with NPC pathogenesis. Of all the EBV specific antigens, latent membrane protein 2 (LMP2) induces the largest immunogenic response [8]. Researchers at the University of Birmingham have developed an optimised T-cell receptor (TCR) clone for NPC-associated EBV protein LMP2 which has demonstrated in vivo efficacy [9]. Rational selection of HLA subtype restriction makes this therapy uniquely applicable to the Chinese NPC population.

THE TECHNOLOGY
Reactivated EBV-specific T-cells from a healthy Chinese donor were screened for reactivity to the EBV protein LMP2 restricted by the HLA-A*1101 allele. The most reactive TCR was cloned into a GMP-compliant retroviral vector and subjected to multiple rounds of optimisation to improve expression and reduce receptor mis-pairing. The HLA-A*1101 allele is found in around 40% of the Chinese NPC population [9], making this optimised T-cell therapy particularly applicable to Chinese population.

The TCR transfer modality gives a significant efficiency improvement over existing adoptive T-cell co-culture approaches. Use of a retroviral vector enables a patient’s T cells to be re-engineered to express the target TCR and tumour antigen within 24 – 48 hours. This therapy demonstrates promising in vivo efficacy in a surrogate xenograft model. Targeting the viral epitope also removes concern over on-target toxicity associated with most cell-based therapies.
LMP2-TCR INHIBITS IN VIVO TUMOUR GROWTH

Figure 1 Transduced T-cells expressing the target epitope significantly inhibit tumour growth in vivo. Mice with HLA-A*1101, LMP2 and luciferase expressing xenografts were treated with T-cells transduced with either a control TCR or the LMP2 TCR and monitored for 3 weeks. Quantification of the tumour volume via luminescence and caliper measurement shows the significant reduction in tumour size in mice treated with LMP2-TCR transduced T-cells compared to control transduced T-cells.

NPC CELLS RESPOND TO LMP2-TCR

Current first line therapy for NPC patients is conventional radio- and chemotherapy which, in concert with patients’ poor health, has a significant negative impact on the condition of T cells. Therefore, it is vital that any emerging cell therapies are efficacious in this challenging clinical setting. In lieu of suitable in vivo NPC disease models, T cells from two advanced NPC patients were transduced with the TCR clone and co-cultured with HLA-A*1101 expressing NPC cell lines. The LMP2-TCR T-cells demonstrated significantly increased cytotoxic activity compared to T-cells with only a control TCR (Figure 2), as well as significantly increased cytokine production9. These data indicate that the TCR has potential as a first line and salvage therapy for NPC.

COMMERCIAL OPPORTUNITY

Cancer Research UK is seeking a partner experienced in the field of cell therapy development and in the Chinese regulatory environment to take this technology through to first in man trials in China. The technology demonstrates in vivo efficacy with no observed toxicities. A patent for the technology and the relevant sequences is currently being prosecuted.

REFERENCES

4. Zhao et al., Positivity of both plasma Epstein–Barr virus DNA and serum Epstein–Barr virus capsid specific immunoglobulin A is a better prognostic biomarker for nasopharyngeal carcinoma (2014) BBA Clinical 2:88-93