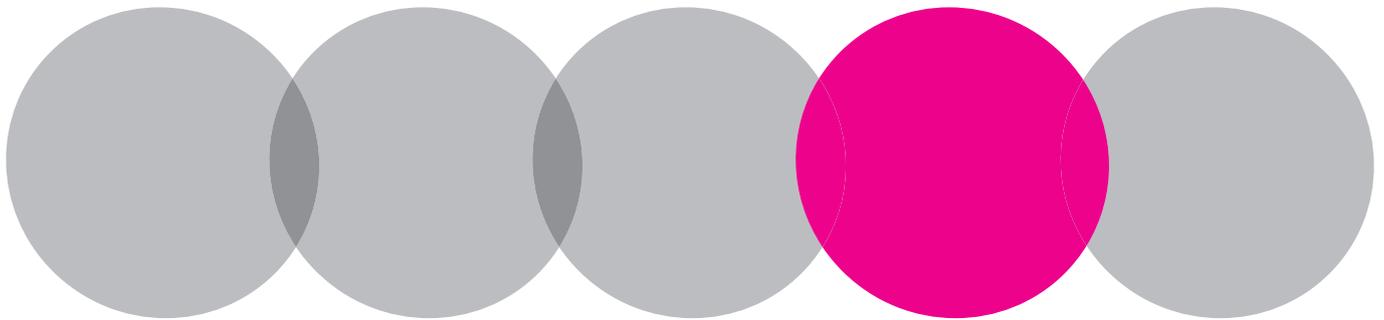


# NOVEL TCR FOR THE TREATMENT OF NASOPHARYNGEAL CARCINOMA



- HLA-A\*1101 restriction makes this LMP2-TCR transduction therapy especially applicable to the Chinese population
- Targeting the LMP2 viral epitope removes concern over on-target toxicity associated with most cell-based therapies
- Gene transfer approach for TCR clones enables significantly faster (48 h) preparation of patient-derived T cells compared to alternative co-culture methods (9 weeks)

## 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.

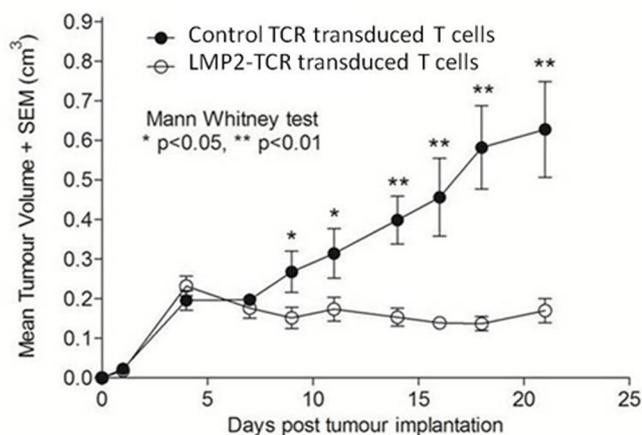
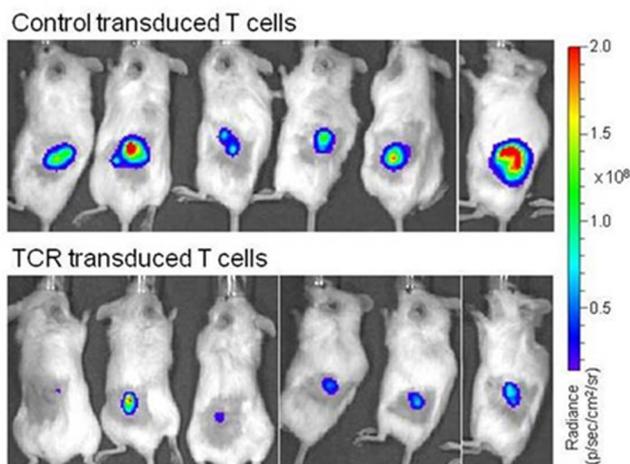
Epstein Barr Virus (EBV) is detected in almost all malignant cells from NPC patients and is strongly associated with NPC pathogenesis. Of all the EBV specific antigens, latent membrane protein 2 (LMP2) induces the largest immunogenic response [8]. Researchers at the University of Birmingham have developed 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.

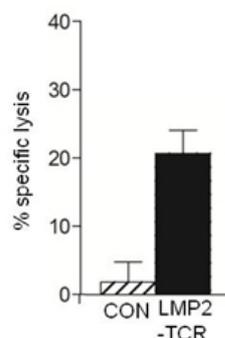
## LMP2-TCR INHIBITS *IN VIVO* TUMOUR GROWTH



**Figure 1 Transduced T-cells expressing the target epitope significantly inhibit tumour growth *in vivo*.** Mice with HLA\*A1101, 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 production<sup>9</sup>. These data indicate that the TCR has potential as a first line and salvage therapy for NPC.



**Figure 2 LMP2-TCR transduced T-cells from NPC patients are cytotoxic to NPC cells.** T cells from two advanced NPC patients were transduced with a control TCR (CON) or the LMP2-TCR and co-cultured with NPC cell lines. Cytotoxicity (% specific lysis) after 5-8 hours was measured with chromium release assay. The graph shows a significant increase in lysis and therefore cytotoxicity in the LMP2-TCR co-cultures.

## 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

1. Ferlay et al., GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013
2. Curado et al., Cancer Incidence in Five Continents, Vol. IX International Agency for Research on Cancer; 2007
3. Cao et al., Familial Nasopharyngeal Carcinomas Possess Distinguished Clinical Characteristics in Southern China (2014) Chin. J. Cancer Res. 26.5: 543-549
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
5. Li et al., Clinical Characteristics of Recurrent Nasopharyngeal Carcinoma in High-Incidence Area (2012) The Scientific World Journal vol. 12
6. Peng et al., Clinical features and prognostic factors in patients with nasopharyngeal carcinoma relapse after primary treatment (2013) Head Neck Oncol. 5(2):21
7. Tian et al., Prognostic model for survival of local recurrent nasopharyngeal carcinoma with intensity-modulated radiotherapy (2014) Br. J. Cancer 110:297-303
8. Lee, Nasopharyngeal carcinoma and the EBV-specific T cell response: prospects for immunotherapy (2002) Semin. Cancer Biol. 6:463-71
9. Zheng et al., Human Leukocyte Antigen (HLA) A\*1101-restricted Epstein Barr Virus-specific T-cell Receptor Gene Transfer to target Nasopharyngeal carcinoma (2015) Cancer Immunol. Res.

## CONTACT

Tommy Rennison, Business Development Executive  
Tommy.Rennison@cancer.org.uk