Novel TCR Sequences to Treat Epstein-Barr Virus Associated Diseases

Background

Epstein-Barr virus (EBV), a member of the herpesvirus family, has infected 90-95% of adults at some point during their lives. Although generally asymptomatic, EBV can cause acute mononucleosis in adolescents and adults. More importantly, EBV has been directly implicated in a number of chronic and potentially fatal diseases including nasopharyngeal carcinoma, post-transplant lymphoproliferative disorder, gastric cancer, some lymphomas and multiple sclerosis. Because of its role in many chronic diseases, EBV has become a target for T cell immunotherapies currently in clinical trials.

T cell immunotherapy involves the collection of lymphocytes from the patient (or donor), followed by in vitro activation and proliferation. These activated T cell are then infusion back into the patient where they aid the immune system in fighting diseases such as tumours and viral infections. Genes that encode for T cell receptors (TCRs) can be transfected into T cells, giving rise to T cell therapies that are specific for certain tumour or viral antigens.

Technology

Human leukocyte antigens (HLAs) on the surface of EBV-infected cells are known to present peptide antigens from viral proteins such as LMP2, LMP1 and EBNA1. Researchers from QIMR Berghofer have now identified a number of TCR sequences that recognize HLA-presented peptide fragments from the LMP2 protein. These epitopes are presented by HLA alleles that are highly prevalent in Asian populations, where EBV-associated nasopharyngeal carcinoma (NPC) can affect some 20-30 per 100,000 people. These epitopes are:

- Epitope IEDPPFNSL presented by HLA-B*40:01 (13 TCR sequences)
- Epitope SSCSSCPLSK presented by HLA-A*11:01 (12 TCRs)
- Epitope TYGPVFMSL presented by HLA-A*24:02 (9 TCRs)

Our researchers have also identified TCR sequences that recognize epitope YLLEMLWRL from the LMP1 protein, which is presented by HLA-A*02; an allele that is far more common in Caucasian populations. A select number of TCR sequences have been transfected into Jurkat T cells to confirm their affinity for cells presenting EBV-derived peptides. Transfection of these highly specific TCR sequences into patient T cells will provide a valuable therapeutic tool for the treatment of EBV-associated diseases.
**Competitive Advantage**

TCR gene therapy offers several advantages over conventional adoptive T cell therapy. The non-specific expansion of patient T cells following (or prior to) TCR gene transfer is easier and more likely to produce a T cell line with significant antigen reactivity, compared with using antigen-specific stimulation to expand the extremely low numbers of antigen-specific T cells from patients prior to conventional adoptive T cell therapy. T cell lines produced through TCR gene therapy are also highly potent, and only low cell numbers are often required for treatment. The recent FDA approval of two autologous CAR T cell therapies has now paved the way for the adoption of gene therapy as a vital treatment for certain tumours. Unlike CAR T therapies which can only recognize antigens expressed on the cell surface, TCR-based therapy can recognize peptide epitopes from intracellular or extracellular proteins.

**EBV-Associated Disease Market**

The global market for multiple sclerosis (MS) treatments is worth an estimated $22 billion annually. The reported prevalence is higher in developed nations, making MS the most commercially viable EBV-associated disease for a TCR-based therapy. Solid tumours (such as NPC and gastric carcinomas) and lymphomas will also expand the commercial market for TCR sequences specific for EBV peptide antigens.

**Partnering opportunity**

The TCR sequences are the subject of a provisional patent application, filed in Australia. We are now seeking licensing or investment partners with experience in T cell immunotherapy to co-develop and commercialise this technology.

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**Lead researcher**

Professor Scott Burrows has been a key leader in the Epstein-Barr virus field for nearly three decades. His early studies investigating the immune response to Epstein-Barr virus has now led to successful clinical trials of new therapies for the diseases caused by this virus. His more recent work has greatly contributed towards our understanding of the molecular basis of how T cells of the immune system recognise and kill virus-infected cells. Professor Burrows is an inventor on a number of patents and has published a total of 185 scientific papers, cited over 11,500 times.

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