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Using bispecifics to treat infectious disease

How Immunocore's T cell receptor-based therapies may clear chronic infections.

Immunocore leads the way in T cell receptor-based bispecifics. By enabling a patient's own immune system to identify and kill target cells, the bispecific molecules address major medical needs. Immunocore validated the concept in cancer and is now applying its technology to chronic infectious diseases, including hepatitis B and HIV.

The oncology and infectious disease programs are based on the same platform. Immunocore creates soluble bispecific biologics, called ImmTAX molecules, that consist of a T cell receptor (TCR) and an anti-CD3 effector function. The high-affinity TCR detects a peptide epitope presented on the surface of target cells, even if the antigen is only present at very low levels, and the effector function recruits and activates T cells. In doing so, the bispecifics redirect T cells of any specificity to target cells.

ImmTAX molecules have inherent advantages over other modalities. The molecules recognize peptides derived from intracellular proteins, enabling them to engage a far wider range of targets than antibody-based therapeutics. ImmTAX molecules are off-the-shelf therapies that are simpler to make at scale than cell therapies.

Immunocore validated the platform through an oncology program in metastatic uveal melanoma. The therapy, tebentafusp, is the first potential new treatment for the disease and the first TCR therapeutic to improve overall survival. In phase 3, patients on tebentafusp on average lived longer than their peers in the active control group. The success also made tebentafusp the first bispecific to demonstrate efficacy in solid tumors in a randomized phase 3 study and the first immuno-oncology monotherapy in the setting of cancers with low tumor mutational burden.

Targeting infectious diseases

The ImmTAX technology has the potential to address chronic infectious diseases in which persistent pathogens escape immune detection and establish cellular reservoirs that provide a source of subsequent disease.

Multiple viruses form such reservoirs but Immunocore is initially focusing on hepatitis B virus (HBV) and HIV. The World Health Organization estimates there are more than 250 million people with chronic HBV infection and 38 million people with HIV[1,2].

The T cell response plays a key role in controlling HBV and HIV infection. Yet, the response frequently fails to overcome viral evasion mechanisms, such as mutational escape, virus-specific T cell exhaustion and transcriptional silencing with very low or no antigen expression. T cells need help to defeat viruses that deploy such mechanisms.

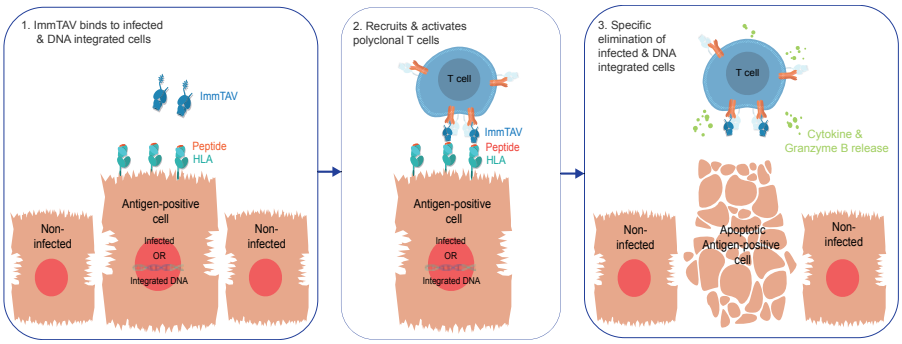

Fig. 1 | Schematic describing the mechanism of action of the virus-targeted ImmTAX molecule (ImmTAV)[3].

ImmTAX molecules can provide the required assistance by redirecting non-exhausted T cells to target and kill cells infected with HBV or HIV (Fig. 2). By detecting low copy numbers of viral peptides on infected cells, ImmTAX bispecifics overcome a major limitation of natural adaptive T cell responses and, by definition, adoptive T cell therapies based on wild-type TCRs.

The Bill & Melinda Gates Foundation recognized the potential of the molecules in infectious diseases in 2017 when it made a strategic investment to support the development of safe, accessible and affordable new therapies against pathogens that affect large patient populations worldwide.

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Validating the technology

Immunocore's work to establish a path from target discovery through proof of concept in oncology is paving the way for infectious disease applications of ImmTAX. The path is enabled by proprietary technologies for target discovery, TCR engineering, in vitro preclinical testing and scalable manufacturing.

Immunocore's drug development process is custom-built for the selection of TCRs with high specificity for viral antigens, including naturally occurring variants. Immunocore is using clinical biomarkers of the activation of T cells and their migration into sites of disease to validate the platform's mechanism of action.

Using the aforementioned platform technologies, Immunocore discovered and developed a potential treatment for chronic HBV. The drug candidate, IMC-I109V, entered phase 1 clinical evaluation on the strength of preclinical data showing that at picomolar drug concentrations it redirects elimination of HBV surface antigen-positive cell lines and HBV-infected cells[3].

Immunocore is now working to take the first soluble TCR bispecific for HIV into human testing. The lead candidate, IMC-M113V, is in CTA and IND-enabling studies. Immunocore is committed to moving forward in HIV after showing ImmTAX molecules redirect the elimination of HIV-infected CD4+ T cells taken from individuals treated with antiretroviral therapy[4].

Beyond HBV and HIV, Immunocore plans to develop its platform to enable the universal application of its ImmTAX molecules by targeting viral and bacterial peptides presented by HLA-E, an invariant HLA class I allele.

Over the next five years, Immunocore aims to demonstrate its technology can transform treatment of infectious diseases and in doing so address the needs of hundreds of millions of people.

1. World Health Organization. Hepatitis B. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b (2020).
2. World Health Organization. HIV/AIDS. https://www.who.int/news-room/fact-sheets/detail/hiv-aids (2020).
3. Fergusson, J. R. et al. *Hepatology* **72**, 1528–1540 (2020).
4. Yang, H. et al. *Mol. Ther.* **24**, 1913–1925 (2016).

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