

Welcome to Immunocore

Immunocore is a privately owned biotechnology company focused on the development of engineered monoclonal T-cell Receptors (mTCRs) as the next evolutionary step after monoclonal antibodies.

Unlike conventional monoclonal antibodies, Immunocore's mTCRs are not restricted to targeting cells via their membrane proteins. Instead, mTCRs use the power of the body's own immune surveillance system, the T-Cell Receptor, as a means of targeting cells differentially expressing any protein, including intracellular ones. This platform technology opens up the ability of targeting cells based upon numerous known and well validated molecular targets unsuitable for monoclonal antibodies, thus removing a key bottleneck to the future development of effective biological therapeutics.

Immunocore is developing a broad platform of mTCR-based therapeutics for the treatment of a range of cancers, type I diabetes and HIV.

Strategy and vision

Vision

Immunocore aims to become the world's leading mTCR-based company. Within five years, Immunocore expects to have several clinical programmes and be supported by partners.

Mission

Immunocore will develop new drugs to benefit patients in cancer, autoimmune disease and viral disease.

Strategy

Immunocore will achieve its mission by:

- Focusing on mTCRs and creating a pipeline of drugs
- Striking partnerships to strengthen the business and create further opportunities to build the portfolio and spread risk
- Maintaining excellence in research
- Focusing on adding value through its core expertise in mTCRs

mTCR Technology Overview

The rationale behind the development of the mTCR platform is to target cells that cannot be reached by conventional monoclonal antibodies – while monoclonal antibodies have revolutionised the treatment of a range of diseases, their continued expansion is severely limited by the lack of new protein targets. This is because antibodies are designed to target cellular surface proteins, which represent only a small percentage of known disease-relevant targets. The majority of disease-relevant proteins are either secreted (i.e. released from the cell) or remain within the cell (Intracellular proteins): neither of which allow the cell to be targeted by monoclonal antibodies. The body, however, has a second mechanism by which the immune system can scan cells for intracellular alterations such as those found in cancer or viral infection. This mechanism is known as the HLA-TCR recognition system.

In this system each cell actively presents small peptide epitopes derived from all of its proteins at the cell surface via Human Leukocyte Antigen (HLA) proteins. Passing T-cells then scan these presented peptides using T-Cell Receptors (TCRs) looking for non-self derived epitopes. Like antibodies, these TCRs are extremely specific for an individual epitope, allowing them to be successfully used to target cells expressing a disease-related protein of interest.

Immuncore's core technology enables the engineering of disease specific TCRs into soluble, high-affinity variants that actively target the desired cells *in vivo* as a means to deliver potent therapeutics in a targeted manner. These TCRs are called monoclonal TCRs or mTCRs.

Making mTCRs

Immuncore has developed robust systems for the routine creation of high affinity mTCRs specific for well validated, disease-relevant targets.

The first step is to identify and validate a T-cell clone specific for the desired epitope; this can either be generated in house or in-licensed as appropriate. The T-Cell Receptor (TCR) from the clone is then isolated and re-engineered into a soluble format through the introduction of a new inter-chain disulphide bond that is buried within the core of the TCR, leaving the TCR's external surfaces completely native. This stabilised protein is truncated at the transmembrane domains to generate a soluble, low affinity (micromolar) affinity mTCR.

Like antibodies, TCRs contain 6 hypervariable complementary determining regions (CDRs) which form the binding epitope contact surface. Immuncore engineers these CDR regions to increase the affinity of the mTCR for its target while maintaining specificity, typically resulting in mTCRs with low pM affinities and long target residence times. The final step is to generate and validate fusions to the desired effector function. Immuncore's mTCRs have four attachment points for fusion partners, allowing a great deal of flexibility in choice of therapeutic payload.

- Boulter *et al.*, (2003). Stable, soluble T-cell receptor molecules for crystallization and therapeutics. *Protein Engineering* **16** (9) pp. 707-711
- Yi *et al.*, (2005). Directed evolution of human T-cell receptors with picomolar affinities by phage display. *Nature Biotechnology* **23** (3) pp. 349-354
- Dunn *et al.*, (2006). Directed evolution of human T cell receptor CDR2 residues by phage display dramatically enhances affinity for cognate peptide-MHC without increasing apparent cross-reactivity. *Protein Science* **15** pp.710-71
- Ashfield & Jakobsen (2006). Making high-affinity T-cell receptors: A new class of targeted therapeutics. *IDrugs* **9** (8) pp.554-559

mTCRs versus mAb comparison

The physical characteristics and targeting mechanism of Immunocore's mTCRs imparts them with several significant advantages over monoclonal antibodies.

	mTCRs	mAbs	Notes
Targets intracellular proteins	Yes	No	<i>~75% of known targets are intracellular</i>
Targets membrane proteins	Yes, both cytosolic & exterior faces	Yes, but exterior faces only	
Targets secreted proteins	Yes, but only the secreting cell	Yes, but only once secreted	
Typical affinity	1-100pM	100pM-10nM	mTCRs exhibit extremely long (8-58hrs) residence time when bound to target
Specific targeting <i>in vivo</i>	Yes	Yes	
Molecular weight	~75kDa	~150kDa	<i>mTCRs are ideal size for good tumour penetration</i>
Inherent killing function	No	ADCC/CDC mediated cell killing	<i>mTCRs can be safely targeted to any cell type</i>
Fusion to alternative effector function	Yes	Yes	mTCRs successfully fused to a number of therapeutic/diagnostic moieties
Manufacturing system	<i>E. coli</i>	Mammalian expression	<i>mTCRs may have cost advantage</i>

Pipeline Overview

Immunocore's mTCRs are biological targeting proteins with binding affinities very similar to monoclonal antibodies, but with the advantage of being able to target cells based on intracellular protein targets. However, unlike traditional antibodies, soluble mTCRs do not possess an in-built killing function; Immunocore expresses its mTCRs as fusion proteins to known potent biological effector functions, such as anti-CD3 binding domains for cancer or cytokines for autoimmune disease. In this regard, they can be thought of as similar to antibody drug conjugates. Overall, this ability to target tissues with a variety of effector function payloads means that mTCRs can be used to treat a disparate range of indications using the same core platform technology.

Cancer programme overview

Unlike traditional antibodies that typically require many thousands of cell surface epitopes to kill cancer cells, Immunocore's mTCR cancer drugs only require around 50. This dramatic difference is because Immunocore's mTCR cancer drugs do not kill the cancer cell directly but instead redirect the body's T-cells to recognise and destroy the cancer.

To achieve this, Immunocore employs an effector function that binds to, and activates the CD3 receptor on T-cells in a cross-linking specific manner, i.e. binding of the mTCR-anti-CD3 drug to T-cells in the circulation does not activate them directly, T cells are only activated when the high-affinity mTCR end concurrently binds the target cancer cell, ensuring a large therapeutic window. This anti-CD3 cross-linking strategy has been well validated in the clinic using traditional antibodies but Immunocore's drugs represent its first use for novel cancer epitopes not suitable for antibody targeting.

mTCRs in development

Immunocore has a range of mTCRs in its portfolio, which target well known and validated intracellular cancer epitopes for both haematological cancers and solid tumours.

mTCR Target	Suitable Indications	Status
NY-Eso	Multiple Myeloma, NSCLC, Prostate, Breast, Bladder, Ovarian	High affinity, (26pM) mTCR –anti-CD3 fusion complete
Melan A	Melanoma	High affinity, (10pM) mTCR –anti-CD3 fusion complete
gp100	Melanoma	High affinity, (11pM) mTCR –anti-CD3 fusion complete
Mage A3	NSCLC, Bladder, Melanoma	High affinity, (100pM) mTCR –anti-CD3 fusion complete
WT-1	NSCLC, Breast, Colorectal, Ovarian, Renal Cell, All Leukaemia's	mTCR engineering programme ongoing

Following on from these Immunocore has a number of additional mTCRs in early development, including mTCRs directed towards survivin, p53, p450 and Bcl-2

Type I Diabetes

Type I diabetes is an autoimmune disease in which the body's T cells aberrantly recognise insulin producing pancreatic beta cells as foreign and destroy them, leading to a life-long dependence upon injected insulin.

To date, it has not been possible to develop beta cell-specific monoclonal antibodies due to the lack of suitable membrane protein targets. However, there are a number of known and well validated intracellular beta cell-specific protein targets, such as PreProInsulin, GAD65 and IGRP.

In partnership with the Juvenile Diabetes Research Foundation, Immunocore has developed a beta cell-targeting mTCR (murine) specific for an insulin derived epitope presented on H-2Kd. The high-affinity (7pM) mTCR has been successfully fused to the immuno-modulating cytokines IL-4 and IL-13, retaining their full biological activity. These cytokines are known to be effective in switching autoreactive T-cells from a destructive TH1 type phenotype to a more protective TH2 type phenotype and already demonstrated effective in the industry standard NOD model. Immunocore is investigating whether, by actively targeting these cytokines to the pancreas, their activity can be improved.

Immunocore's murine beta cell specific mTCRs are currently undergoing *in vivo* efficacy testing in the NOD model with human beta cell specific versions following on.

HIV

HIV, like many viruses, often manages to escape complete destruction by the immune system through mutation of the peptide antigens presented by surface HLA proteins. These 'escape mutants' are poorly recognised by the T cells that controlled the original infection, allowing the mutated virus time to replicate and spread.

In a collaborative effort involving Cardiff University Medical School, the University of Pennsylvania School of Medicine and Immunocore, a highly unusual T cell clone specific for an immunodominant HIV antigen was isolated from an individual who had managed to control HIV infection for many years without the need for anti-retroviral therapy. Characterisation of the TCR from this clone showed not only an exceptionally high natural affinity for the wild-type HIV antigen (150nM) but also a broad recognition profile covering the common HIV escape mutants, leaving the virus nowhere to hide.

Engineering of this TCR by Immunocore has resulted in a soluble, picomolar affinity mTCR that retains the broad recognition profile of the parent TCR. Subsequent fusion of this mTCR to an anti-CD3 effector function has resulted in an exceptionally potent biological therapy that actively targets HIV epitope presenting cells and efficiently redirects a polyclonal cytotoxic T cell response against them.

Vaccine Validation

Many of today's vaccines, either protein or virus-based, require intracellular processing and presentation via HLA for their activity. However, the requirement for several sequential biological processes (such as protein endocytosis or viral infection, protein cleavage, peptide loading of nascent HLA proteins) and their subsequent presentation on the cell surface results in a great deal of uncertainty as to the amount of antigen being actively presented to the immune system. This has consequences for both programme risk going into the clinic and for demonstrating batch-to-batch consistency of the vaccine.

Immuncore's high affinity mTCRs, however, make it possible for the first time to quantify accurately the amount of peptide epitope being presented at the surface of the cell after processing. Immuncore has developed a number of robust and reproducible assays and techniques which can: • confirm the active presentation of the desired epitope, thus reducing risk before initiating clinical trials, • allow comparison of vaccine formulations to ensure the highest possible epitope presentation • allow monitoring of subsequent batch-to-batch variations.

Immuncore currently has a collaboration on vaccine validation with Sanofi Pasteur. Please contact us if you would like to discuss the application of mTCRs for your vaccine programme.

- Purbhoo *et al.*, (2006). Quantifying and Imaging NY-ESO-1/LAGE-1-Derived Epitopes on Tumor Cells Using High Affinity T Cell Receptors. *J. Immunol.* **176** pp.7308-7316

Company Overview

Immuncore comprises ~35 staff based in its Oxfordshire offices in the UK. Originally known as Avidex, a spin-out from Oxford University formed under the direction of its CSO Dr Bent Jakobsen, the company developed a number of programmes aimed at modulating the immune system, based on the original TCR work carried out by Dr Jakobsen at Oxford University.

Avidex was acquired by the German Biotech company, MediGene AG in 2006; however, following a strategic review in early 2008, MediGene AG decided to concentrate on the development of its late stage assets, the company opted to divest its preclinical assets as a number of technology orientated spin-outs. The first of these spin-outs is Adaptimmune Limited, which specialises in adoptive therapy (see www.adaptimmune.com)

Immuncore is the second spin-out and became operational on 1st October 2008 with investment from a consortium of investors along with MediGene AG to advance the development of soluble engineered T-Cell Receptors.

Company Management**James Noble, CEO**

James Noble is CEO of Immunocore Limited. As the former CEO of Avidex Limited, James has in-depth knowledge of Immunocore's mTCR technology as well as a wealth of prior experience in the international biotech community. Former CFO of British Biotech prior to leading Avidex for 7 years, James also sits as a non-executive director on the boards of GW Pharmaceuticals plc and Evolve Capital plc (both listed on AIM) and of Curagen Corporation (listed on NASDAQ) plus the privately held Axellis Limited. He is also CEO of Adaptimmune Limited.

Dr Bent Jakobsen, CSO

Bent Jakobsen is CSO of Immunocore Limited. As the former founder of Avidex Limited and inventor of the engineered mTCR platform; Bent's scientific leadership provides the unique expertise driving the development of mTCR based targeting reagents forwards. He is also CSO of Adaptimmune Limited.

Intellectual Property

Immunocore's extensive patent coverage of soluble T-Cell Receptors, their engineering into high-affinity forms, fusion to a wide range of effector or detection functions and their subsequent use ensures that all mTCRs resulting from the company's programmes enjoy strong patent protection.

Copies of all Immunocore's patents and patent applications are available upon request, under CDA where appropriate.