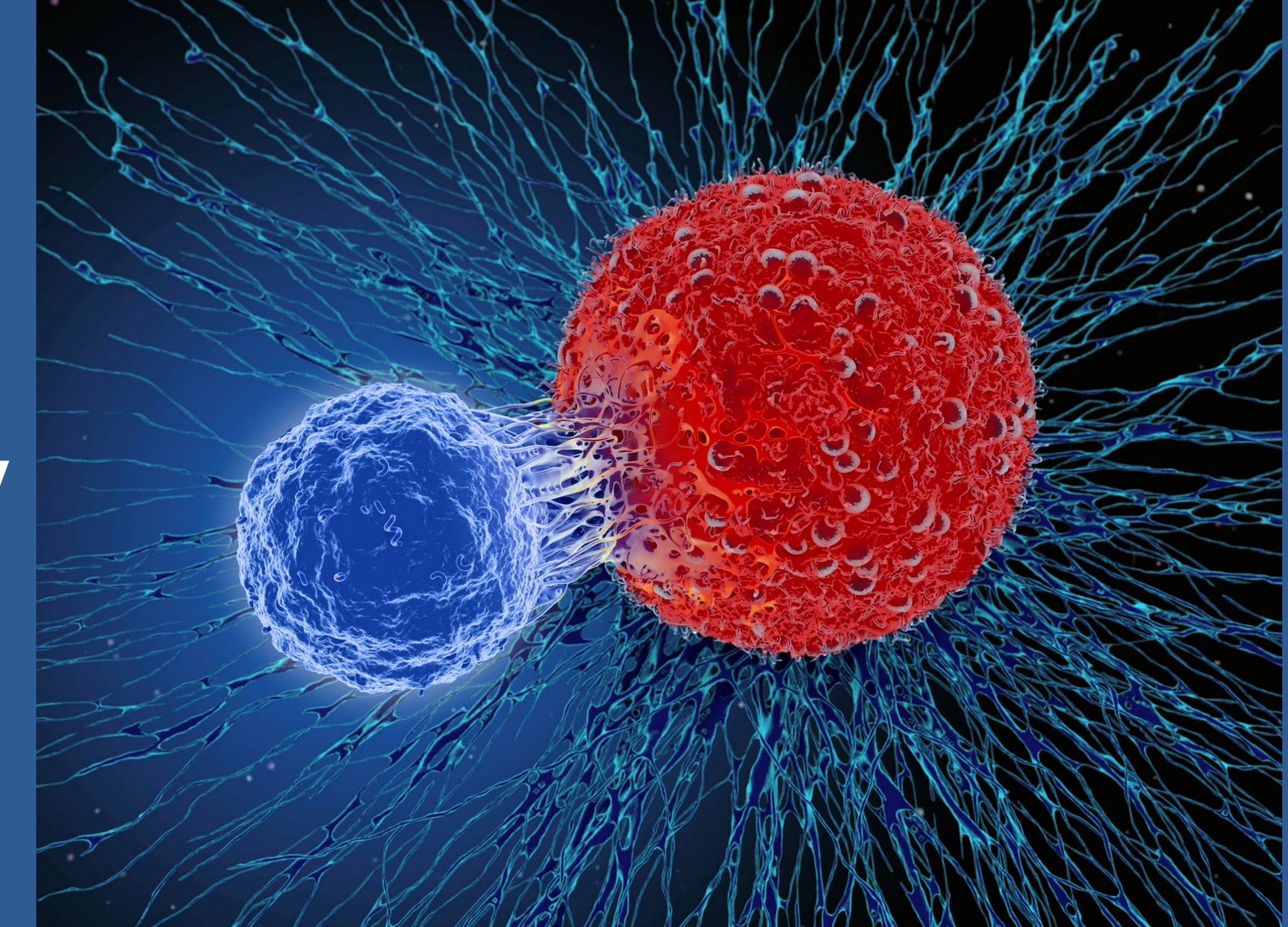# Development of novel cancer immunotherapy by exploring human immunopeptidome using mass spectrometry

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Overview

Adaptimmune is a clinical-stage biopharmaceutical company focused on the development of novel cancer immunotherapy. The company's unique SPEAR (Specific Peptide Enhanced Affinity Receptor) T-cell platform enables the engineering of T-cells to target and destroy cancer, including solid tumors. We use mass spectrometry to identify HLA-associated peptides presented on the surface of normal and malignant human tissue as well as cancer cell lines.
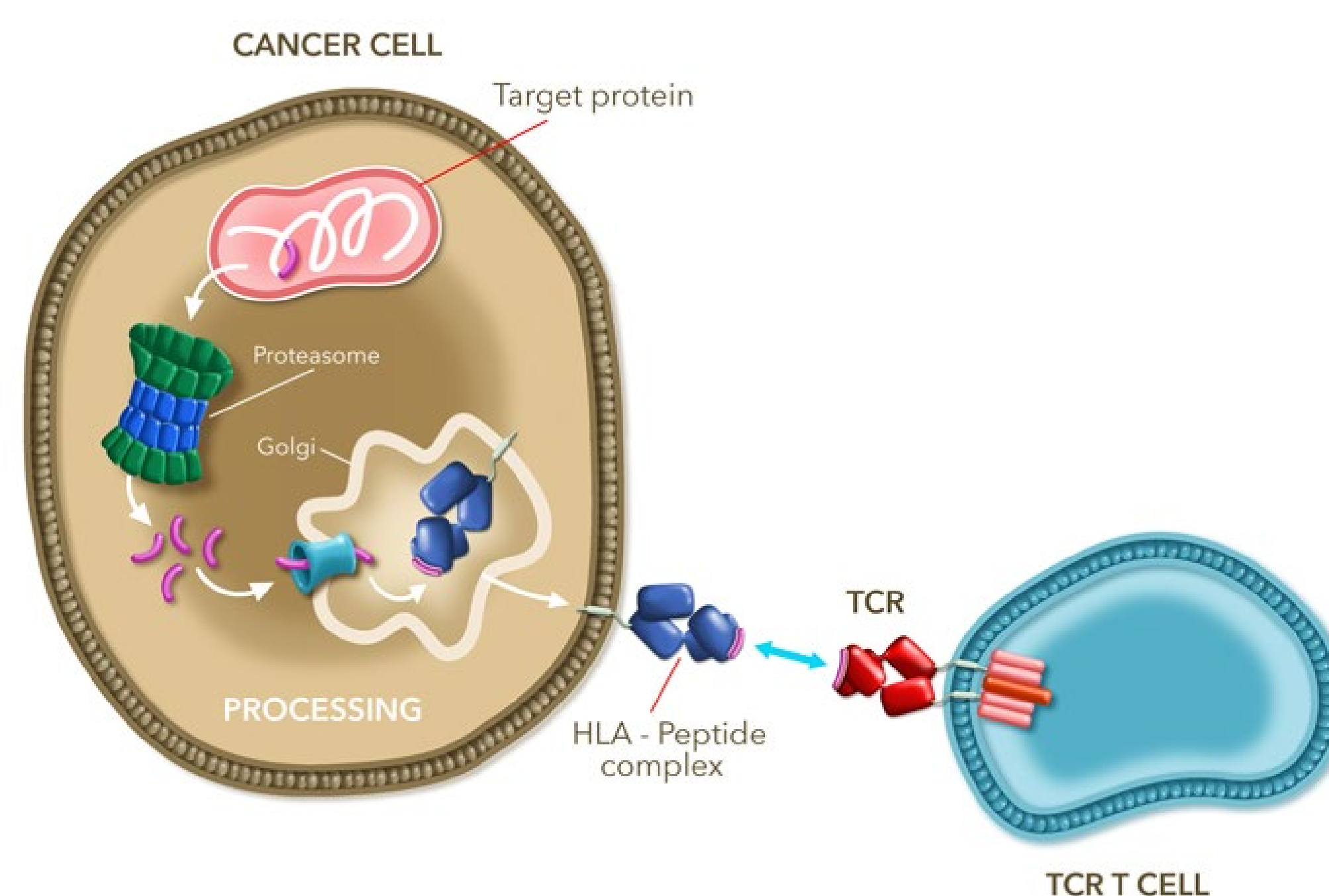
Our work has shown

- Meaningful clinical responses in solid tumors is achievable
- Engineering TCRs can optimize T cell activity (1)
- Molecular mapping of TCR antigen enables optimal TCR selection
- Alloreactivity testing may improve safety
- Engineered T cell persistence correlates with clinical response (1, 2)
- Our platform provides long term repopulating T cells with continued cytolytic function
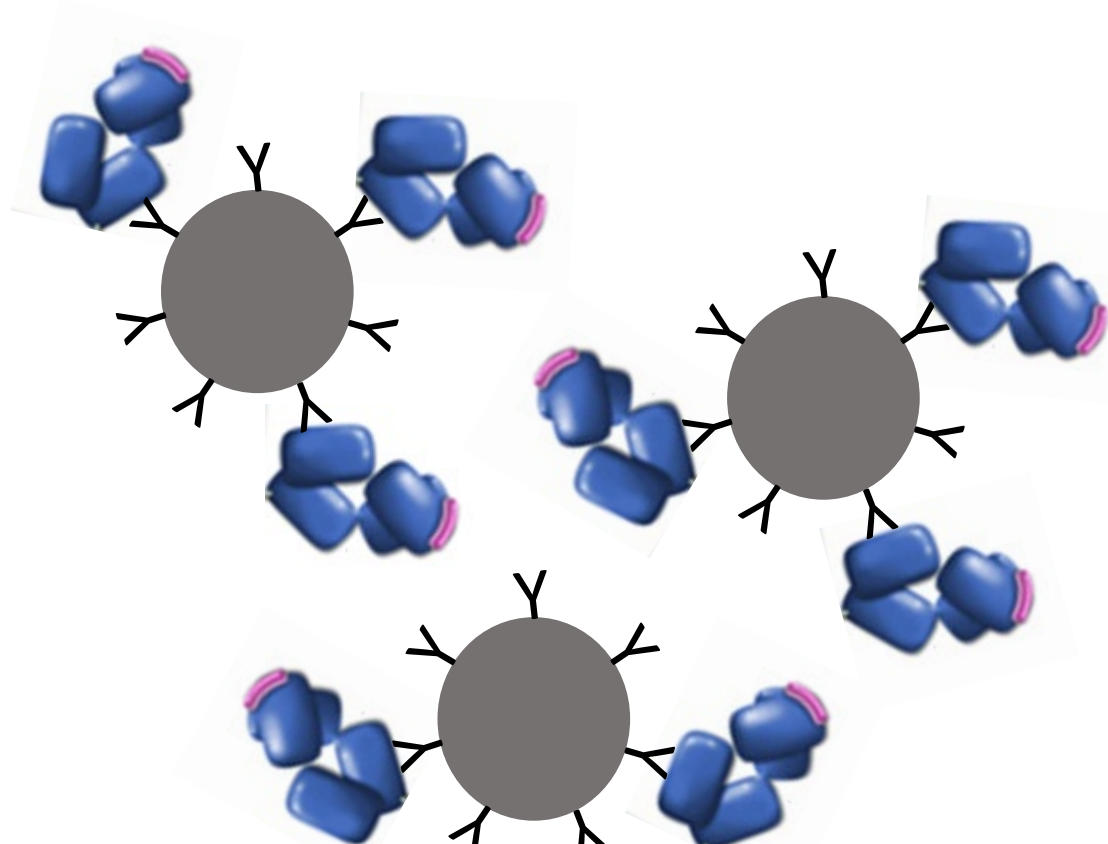
Our workflow

| Immunopurification of HLA-peptide complexes from the cancer cells/ healthy tissue/ tumour tissue | LC-MS/MS identification of HLA peptides followed by selection of a target peptide | TCR identification and engineering | Preclinical safety testing to determine safety and efficacy |

LC-MS/MS Orbitrap Fusion™ Lumos™ Tribrid™ Mass Spectrometer (Thermo Scientific). Image from www.thermofisher.com
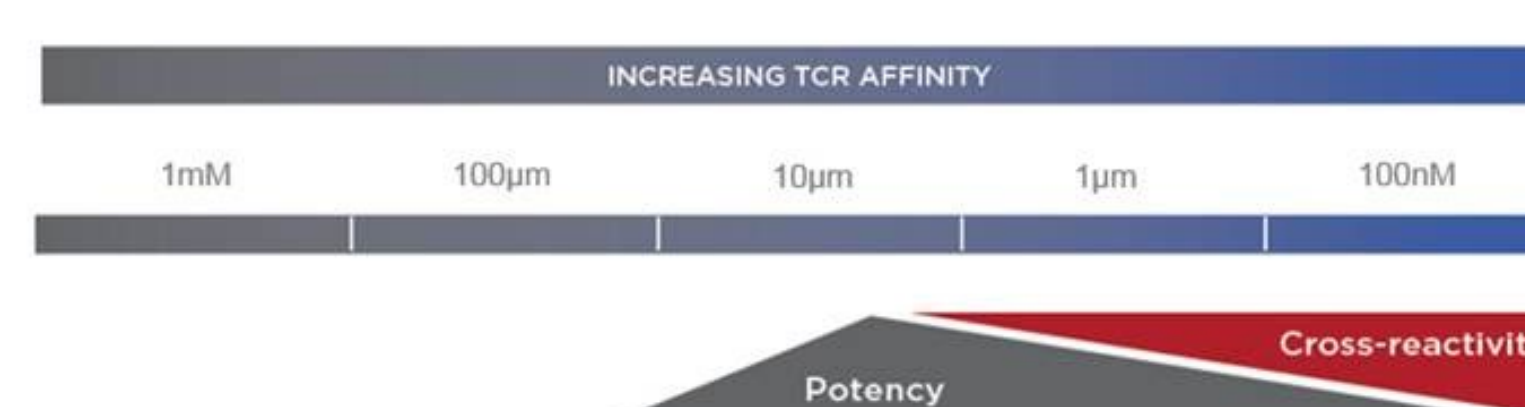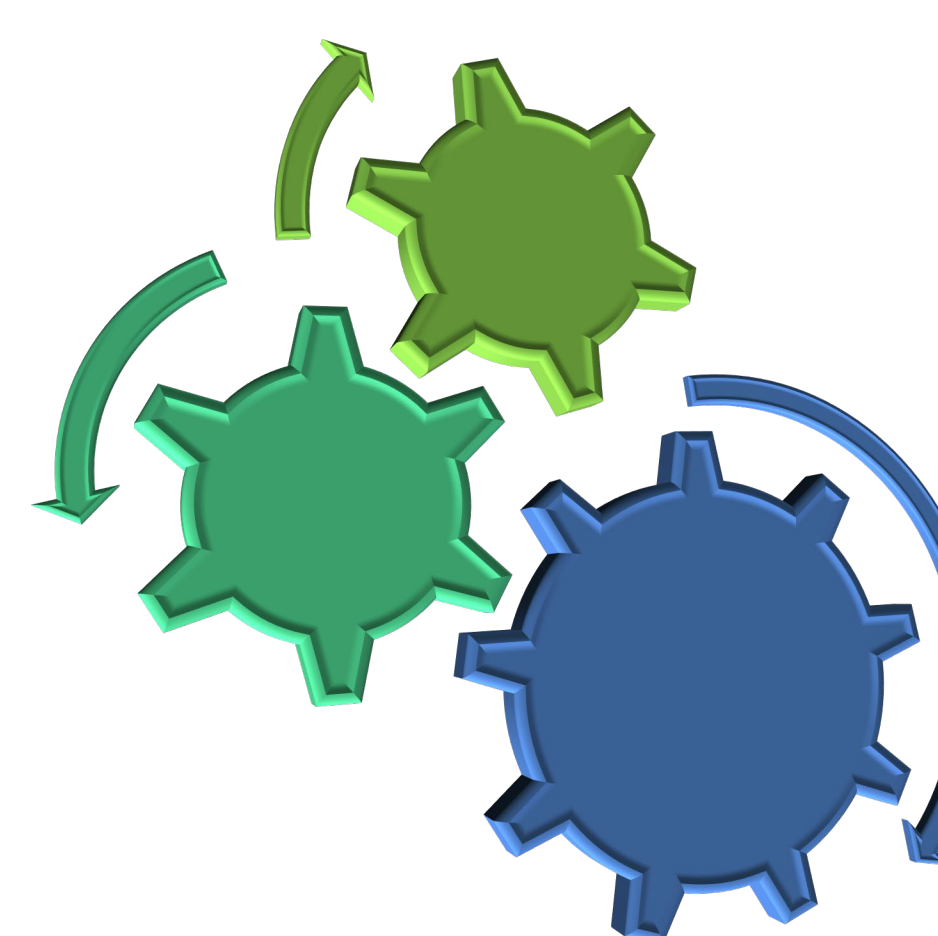
Affinity-enhanced engineered TCR ready for clinical trials

By engineering the sequences that encode the T-cell receptors by which T-cells recognize HLA-peptide complexes we can generate a T-cell therapy which works with a patient's own immune system to target specific cancer peptides. Our technology platform allows us to identify and select the T-cell receptors which are likely to prove the most effective in patients whilst minimising off-target (non-cancer cell) binding recognition.

Naturally occurring T-cell receptors struggle to recognize cancer proteins. This is because the cancer proteins tend to be very similar to proteins expressed by healthy cells. At Adaptimmune we engineer the affinity of the T-cell receptors so that they can recognize cancer proteins and as a result can detect and fight cancer within patients.

Results

SPEAR T-cell therapies targeting MAGE-A10, MAGE-A4, and AFP are progressing through clinical studies in multiple cancer types. Other targets are in research.

References

1. Rapoport AP, et al. Nat Med. 2015 Aug;21(8):914-921
2. D'Angelo SP et al., Cancer Discov. 2018 Aug;8(8):944-957