

Preclinical Safety Testing Of Enhanced-Affinity TCRs

Andrew 'Jez' Gerry

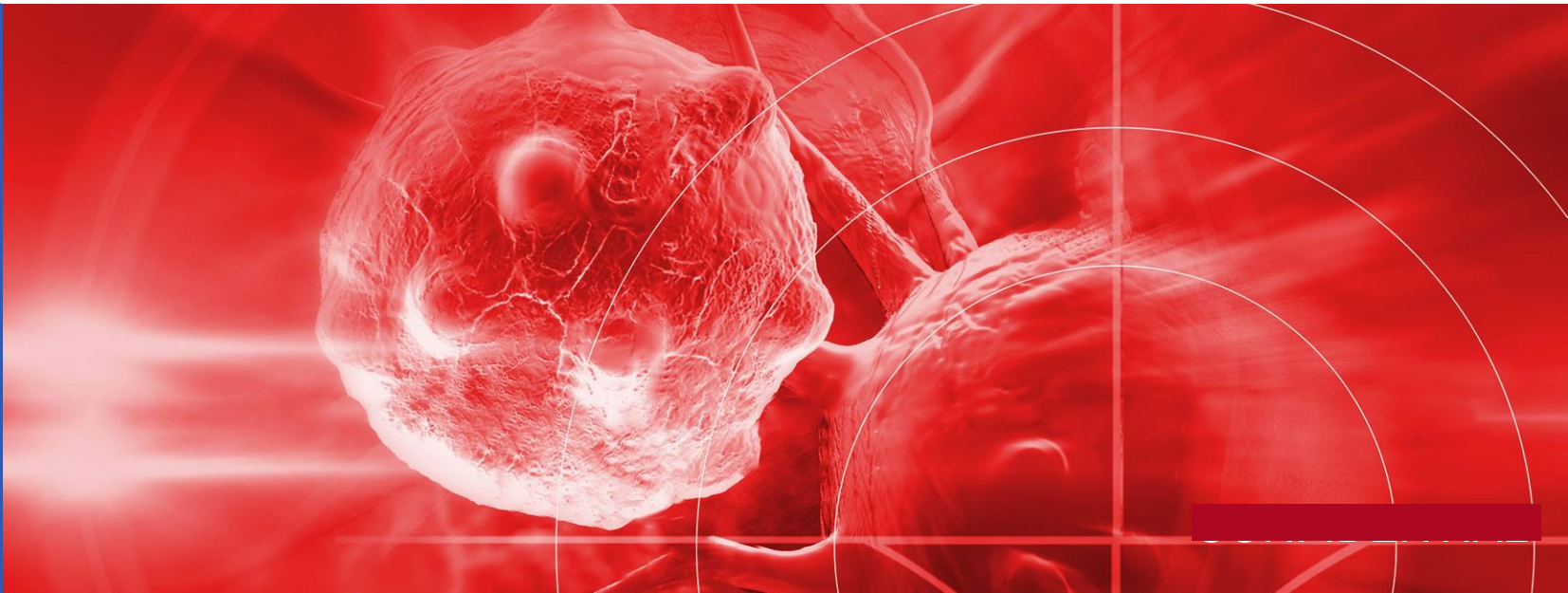
Director of Preclinical Research

EMA, 15-16 Nov 2016



Adaptimmune

TRANSFORMING T CELL THERAPY



DISCLAIMER

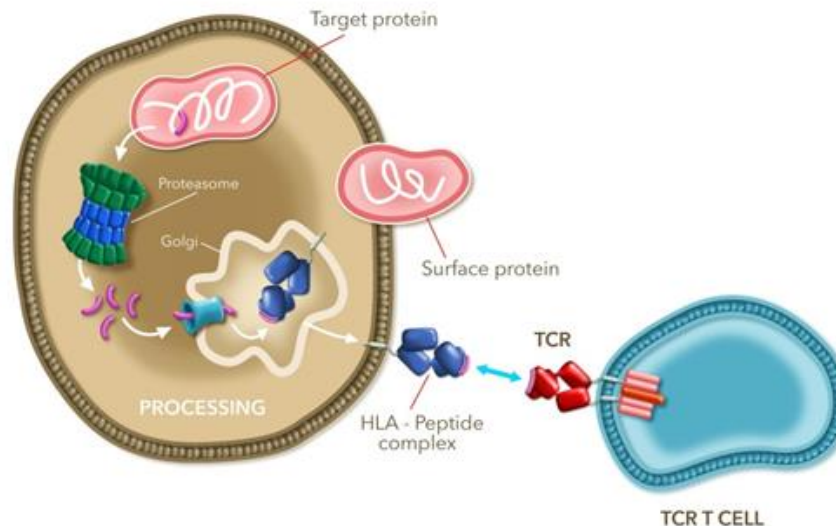
This presentation contains “forward-looking statements,” as that term is defined under the Private Securities Litigation Reform Act of 1995 (PSLRA), which statements may be identified by words such as “believe,” “may,” “will,” “estimate,” “continue,” “anticipate,” “intend,” “expect” and other words of similar meaning. These forward-looking statements involve certain risks and uncertainties. Such risks and uncertainties could cause our actual results to differ materially from those indicated by such forward-looking statements, and include, without limitation: the success, cost and timing of our product development activities and clinical trials; our ability to submit an IND and successfully advance our technology platform to improve the safety and effectiveness of our existing TCR therapeutic candidates; the rate and degree of market acceptance of T-cell therapy generally and of our TCR therapeutic candidates; government regulation and approval, including, but not limited to, the expected regulatory approval timelines for TCR therapeutic candidates; and our ability to protect our proprietary technology and enforce our intellectual property rights; amongst others. For a further description of the risks and uncertainties that could cause our actual results to differ materially from those expressed in these forward-looking statements, as well as risks relating to our business in general, we refer you to our Quarterly Report on Form 10Q filed with the Securities and Exchange Commission (SEC) on August 8, 2016 and our other SEC filings.

We urge you to consider these factors carefully in evaluating the forward-looking statements herein and are cautioned not to place undue reliance on such forward-looking statements, which are qualified in their entirety by this cautionary statement. The forward-looking statements contained in this presentation speak only as of the date the statements were made and we do not undertake any obligation to update such forward-looking statements to reflect subsequent events or circumstances. We intend that all forward-looking statements be subject to the safe-harbor provisions of the PSLRA.

TCRs recognize intracellular cancer antigens

Adaptimmune focuses on developing the best affinity enhanced T cell therapies for autologous T-cell therapeutics

- The TCR is the natural mechanism for T-cells to distinguish a diseased cell from a healthy cell
- All proteins, including intracellular ones, are processed and presented as HLA-peptide complexes which are recognized by TCRs
- Many cancer targets are intracellular – TCR therapeutics can access these targets





Engineering Better T-Cells

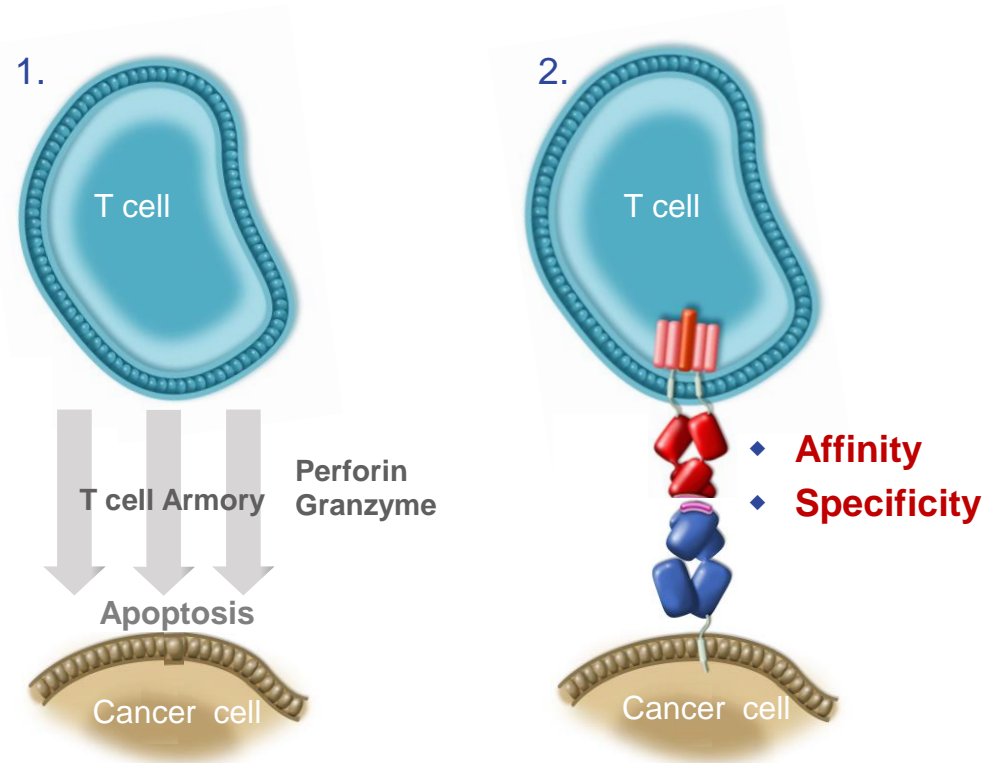
Challenges With TCR Therapy

ADOPTIVE T CELL - Most powerful unit in Immunotherapy

Challenges with TCR Therapy

Four components to an effective adoptive therapy:

1. T cell must recognize a cancer cell via a **guiding receptor**
2. The guiding receptor must have two important aspects
 - ◆ **Affinity**
 - ◆ **Specificity**

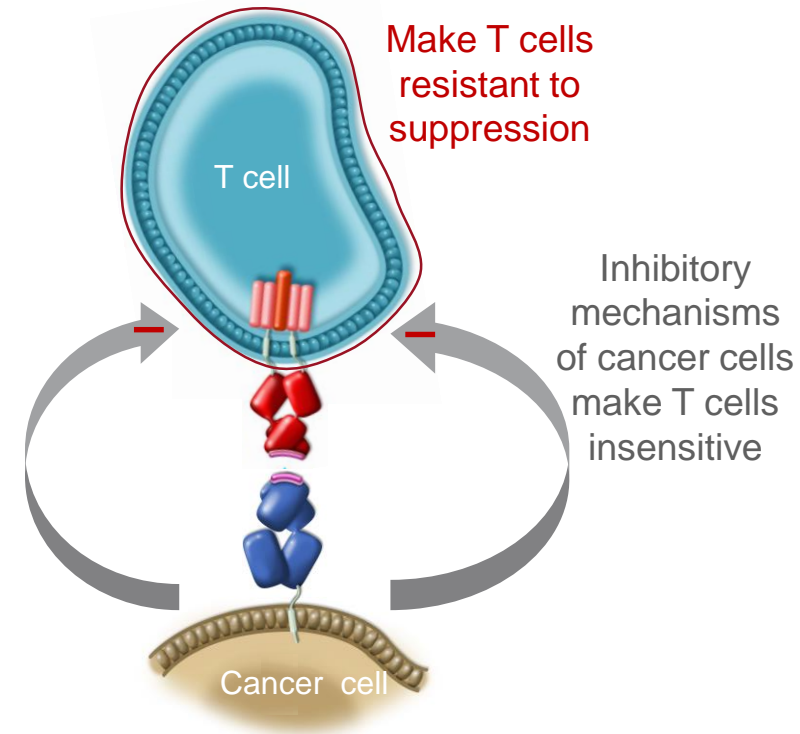


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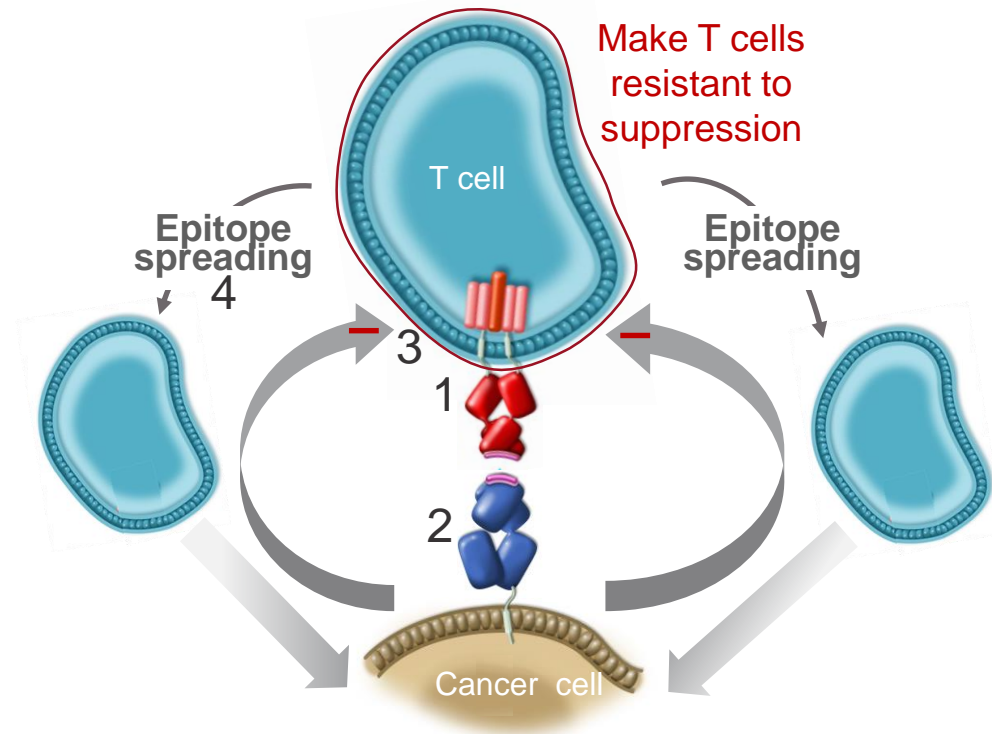


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Challenges with TCR Therapy

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4. The T cell (either alone or via other mechanisms) needs to **'break cancer immune tolerance'**

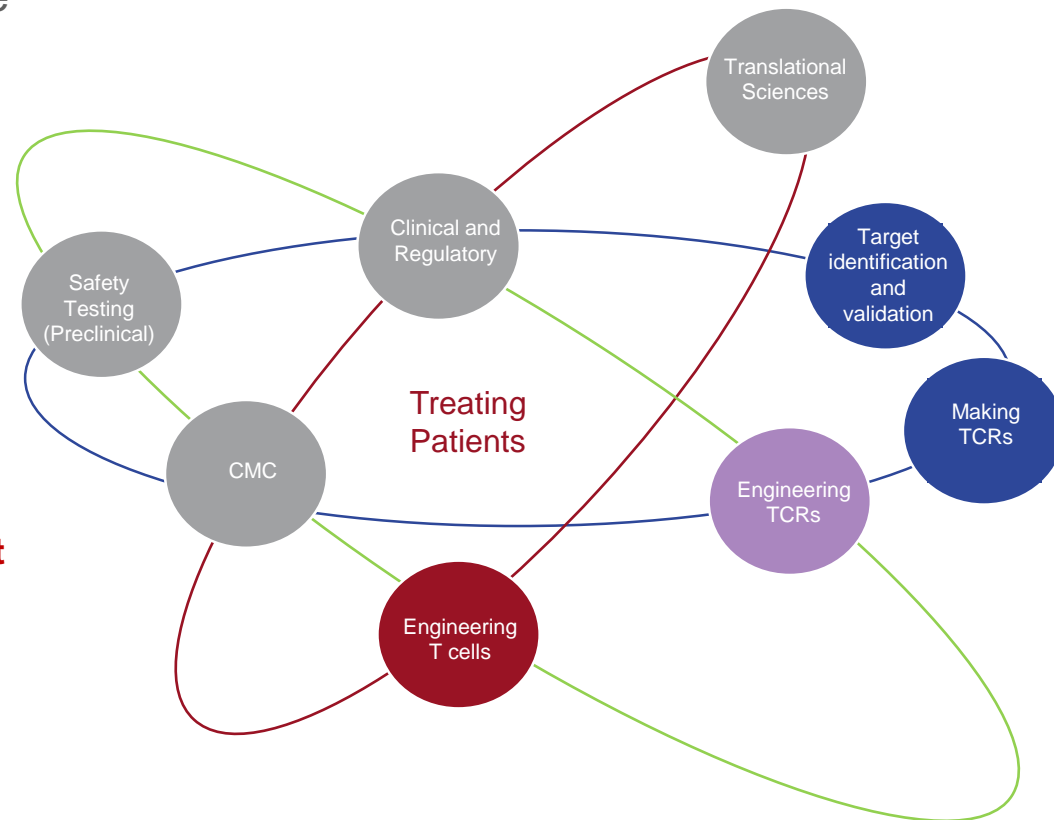


Integrating TCR research and development

Alignment of Multiple disciplines

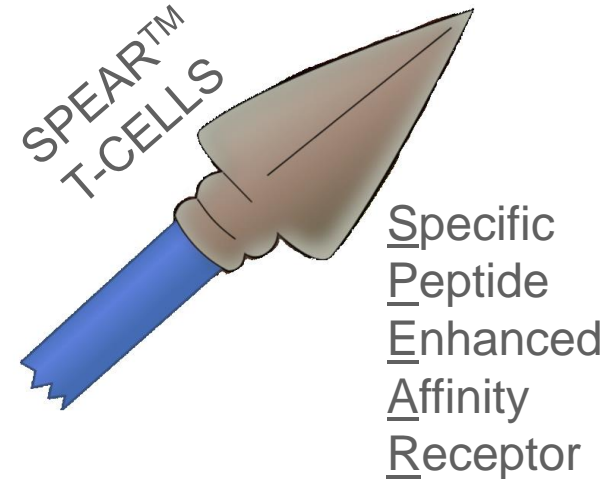
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ADAPT IMMUNE SPEAR™ T-cell PLATFORM

uniquely overcomes these hurdles



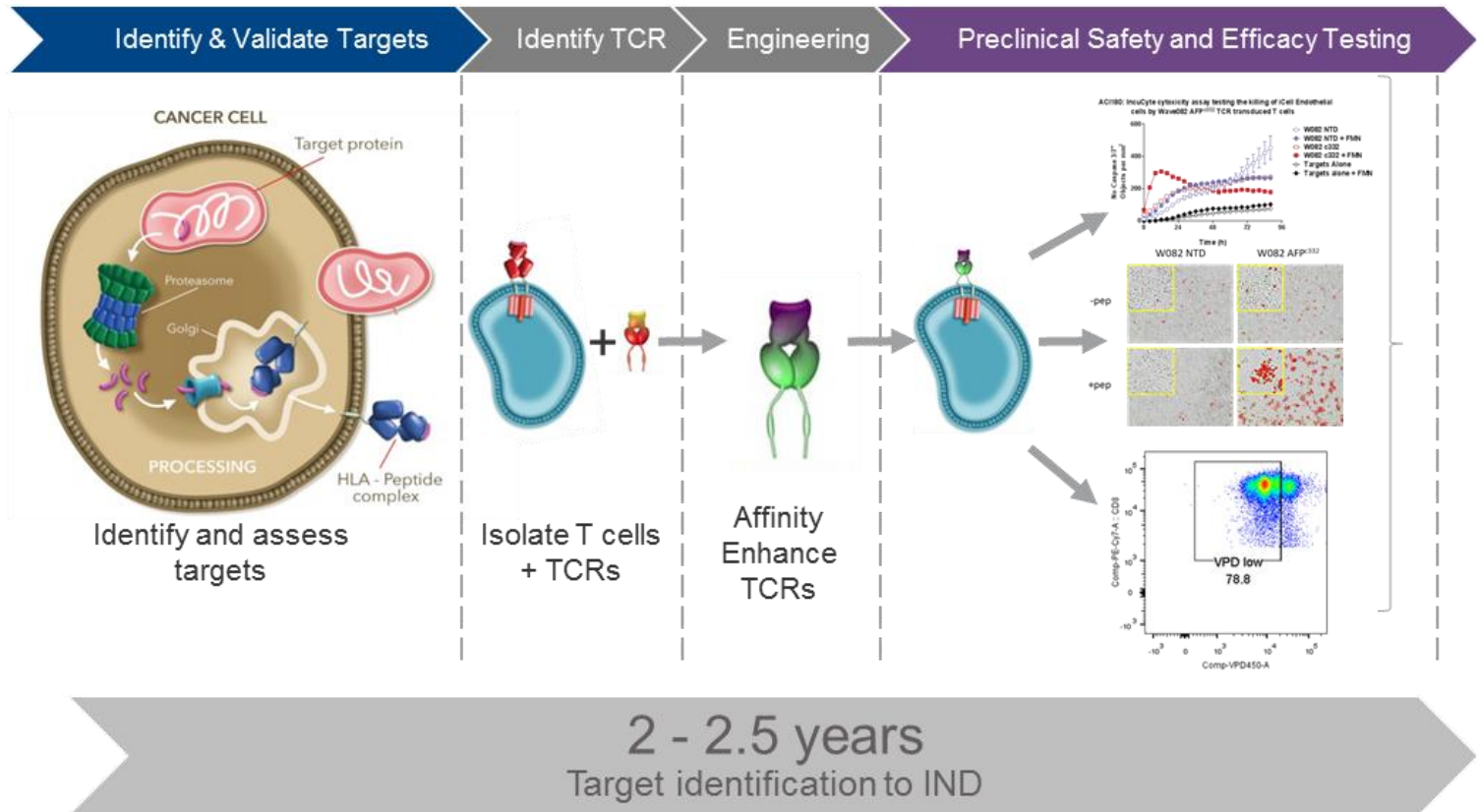
- Target Identification
- TCR Identification
- TCR Engineering – Optimized Affinity
- TCR Safety Testing
- Generation 2 T cells



Engineering Better T-Cells Platform Technology

Research Pipeline

Research Pipeline



Engineering Better T cells

T Cell Receptor (TCR) Engineering

Identify and Validate Targets

Identify TCR

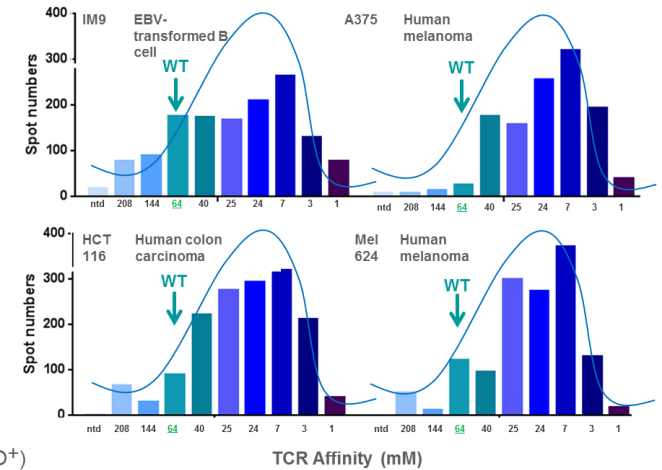
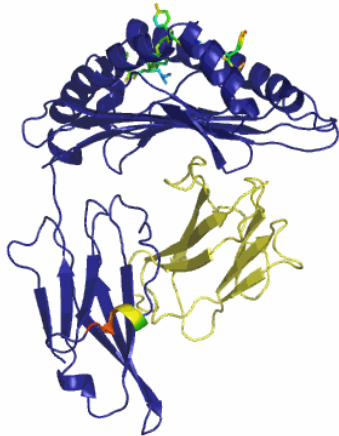
Engineering

Clinical Safety and Efficacy Testing

TCR

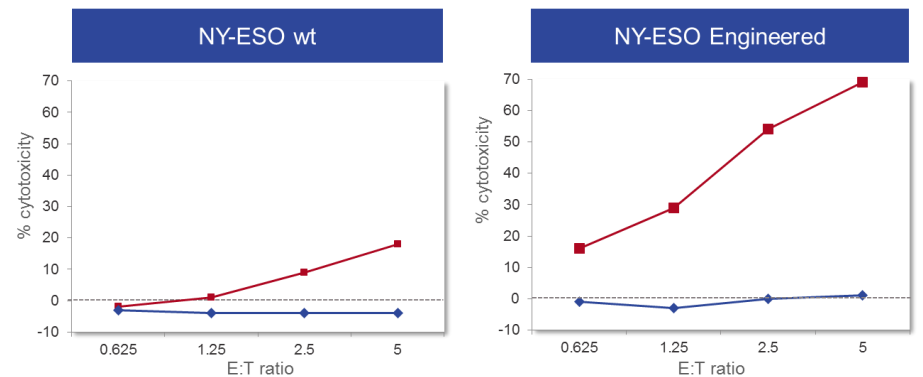
Peptide antigen

MHC



■ IM-9 (NY-ESO⁺)

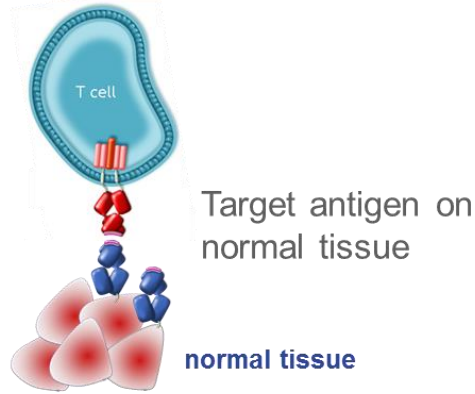
◆ N9 (NY-ESO⁻)



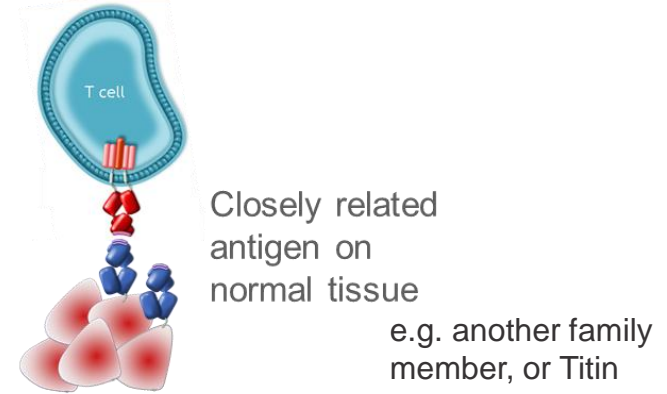
Specificity and non-specificity

Types of safety signal

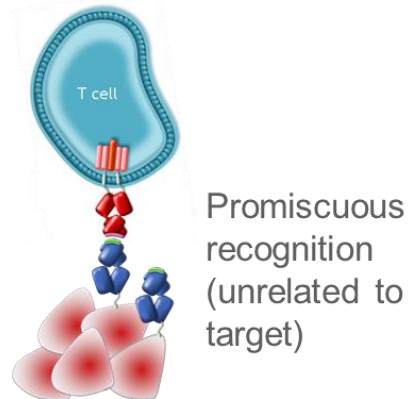
On target



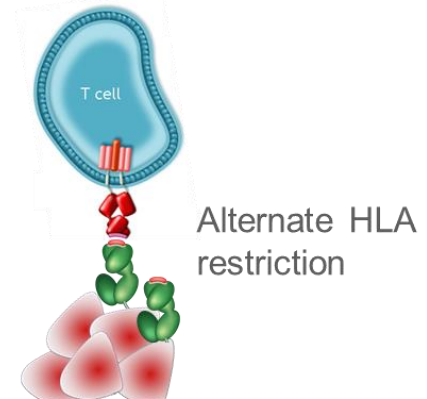
Off target (specific)



Off target (non-specific)



alloreactivity



Adaptimmune's preclinical safety package

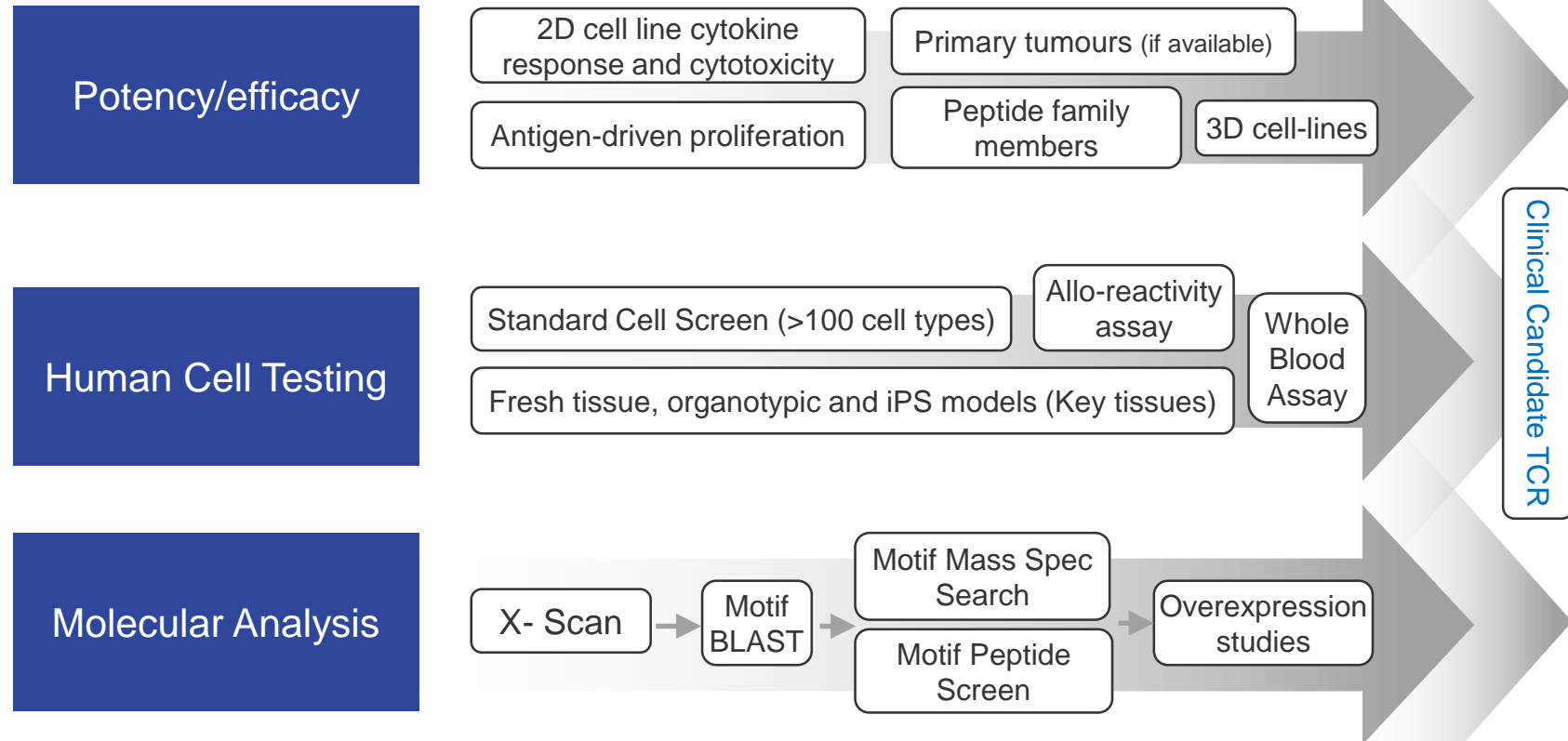
Primary aim to identify potential on- and off-target reactivities

- Preclinical package covers *in vitro* potency, safety and specificity
- In vivo animal models are not informative for assessing TCR specificity and safety for a number of reasons
 - Mainly due to MHC and proteome mis-matches
- Following 2 SAEs on MAGE-A3^{a3a} protocol, we developed a battery of tests that cover parallel approaches to identifying alternate reactivities
 - Molecular characterisation of TCR:peptide binding preferences to generate a motif for searching against the proteome for **potential cross-reactive peptides**
 - Screening cells, tissues and cellular models for **actual cross-reactivities**

[Cameron, Gerry et al, Sci Trans Med, 2013,
Linette et al, Blood, 2013]

Adaptimmune's preclinical safety package

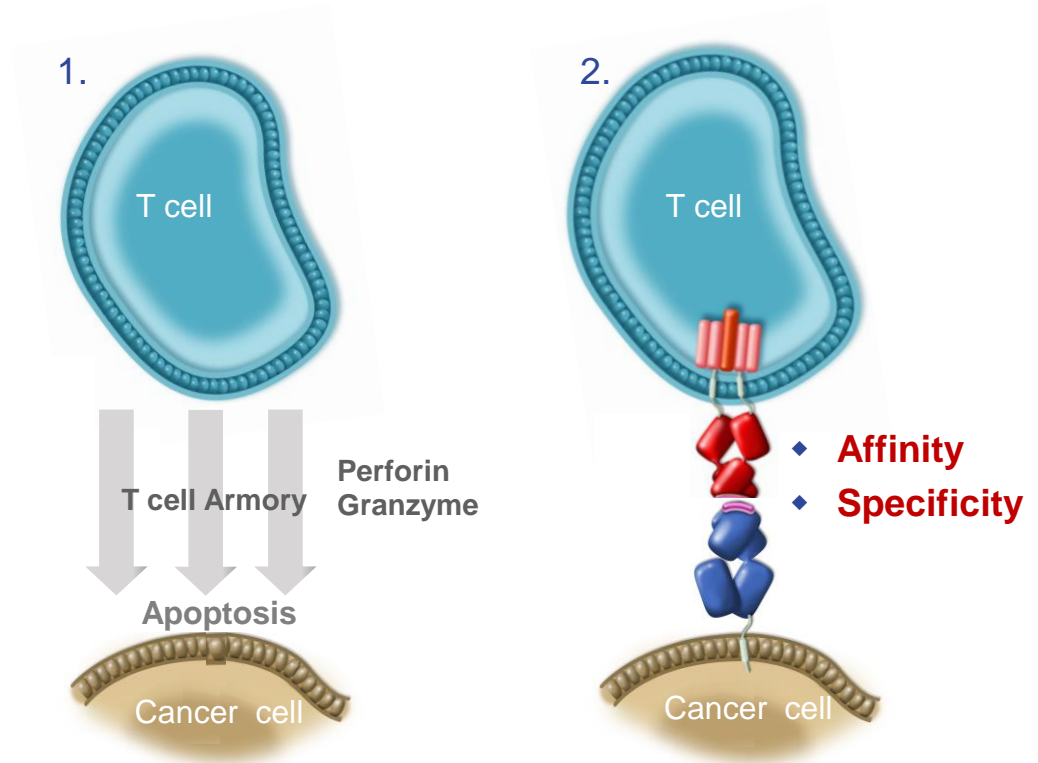
Primary aim to identify potential on- and off-target reactivities



Engineering better T cells

Platform technology

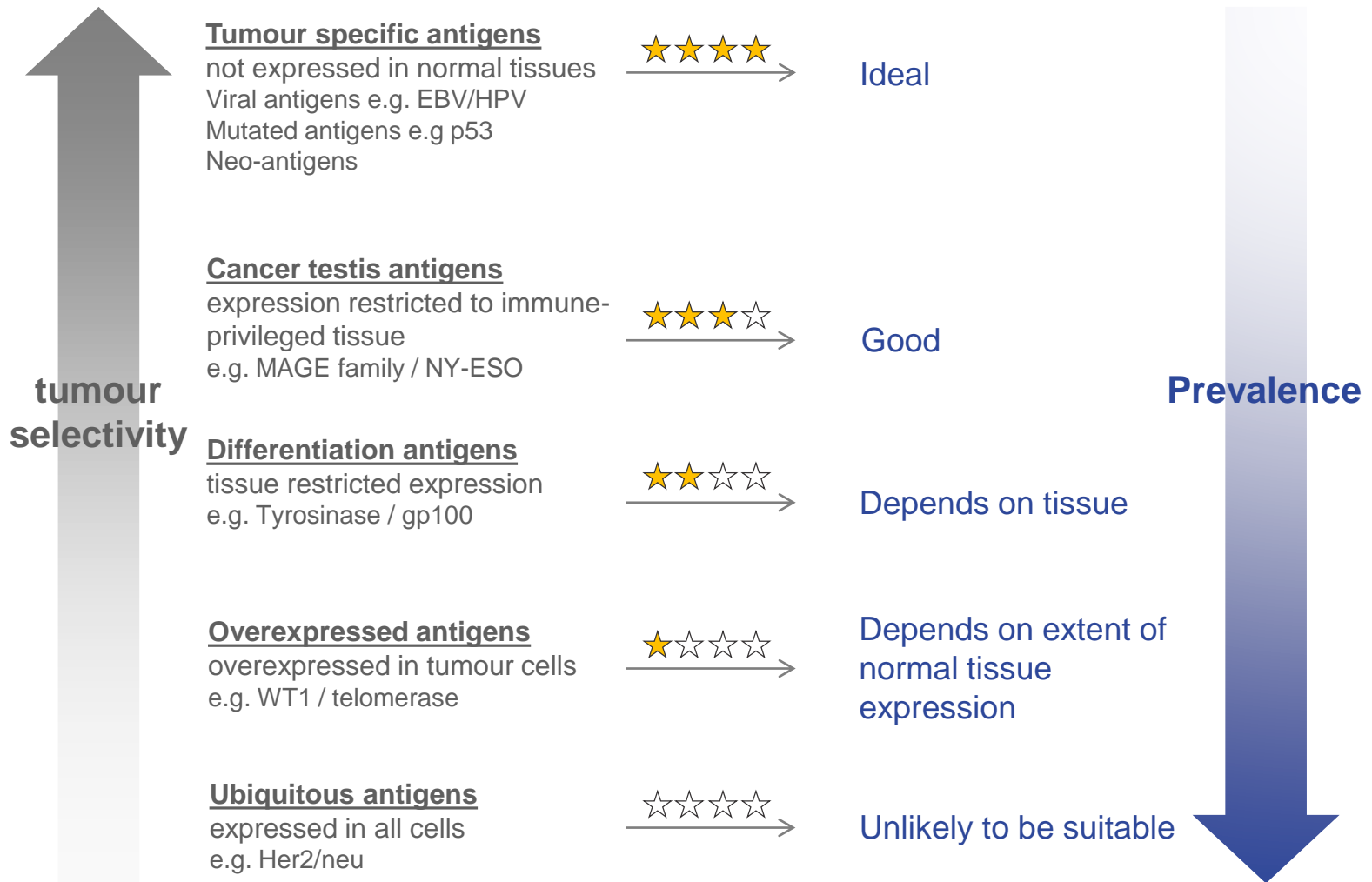
1. T cell must recognize a cancer cell via a **guiding receptor**



1ST select the right TARGETS

Engineering Better T Cells

The spectrum of potential cancer targets for immunotherapy



Engineering Better T Cells

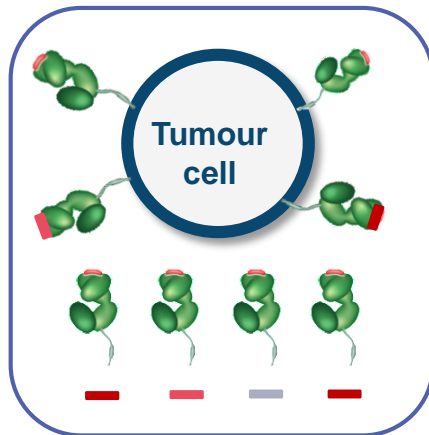
Finding the Right Targets

Identify and Validate Targets

Identify TCR

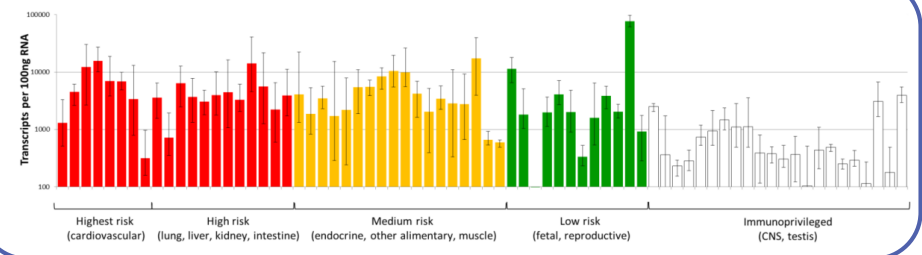
Engineering

Preclinical Safety and Efficacy Testing



Mass
spectrometry

Indication	Frequency
Prostate	100% (inc. androgen independent)
Renal	90%
Lung	88%
Bladder	85%
Breast	83%



Confirms surface expression and expression on tumour cells (i.e. not normal tissue)

Only **low risk targets** selected for TCR programs

Engineering Better T Cells

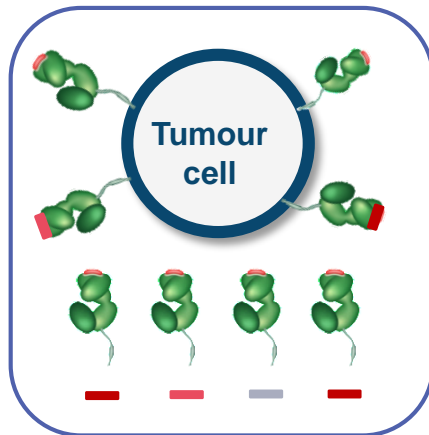
Finding the Right Targets

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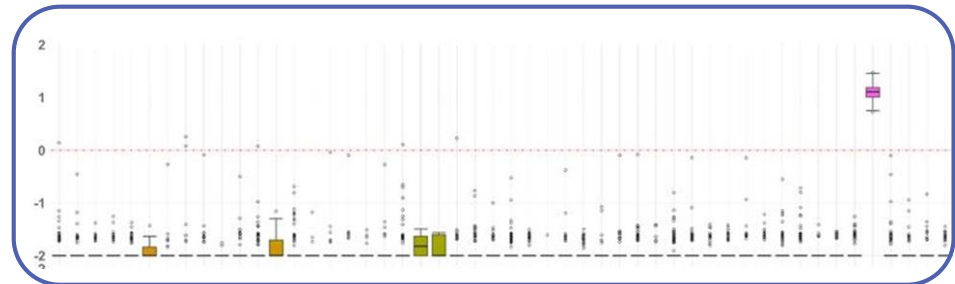
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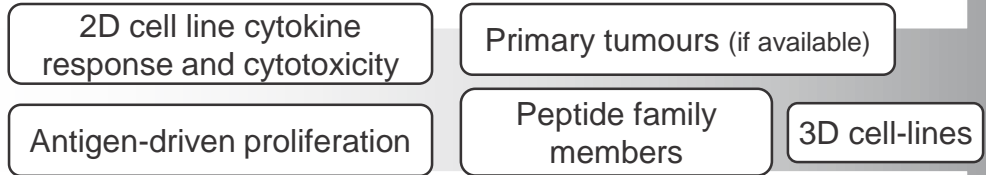
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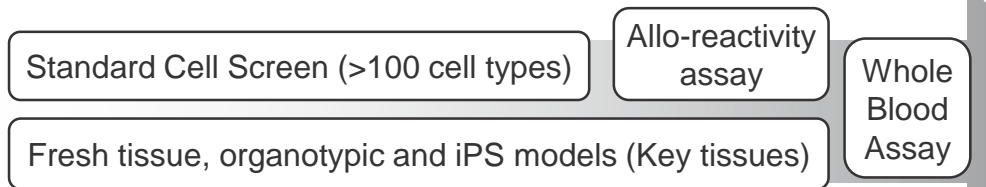
Adaptimmune's standard preclinical package

Assessing safety

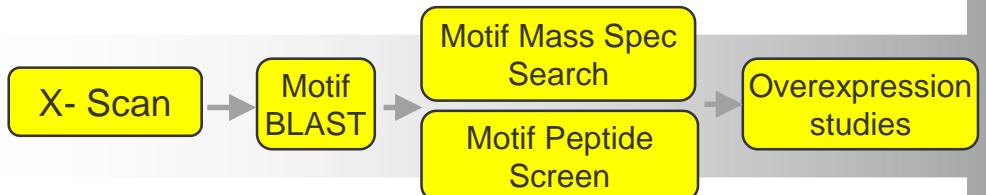
Potency/efficacy



Human Cell Testing



Molecular Analysis



Clinical Candidate TCR

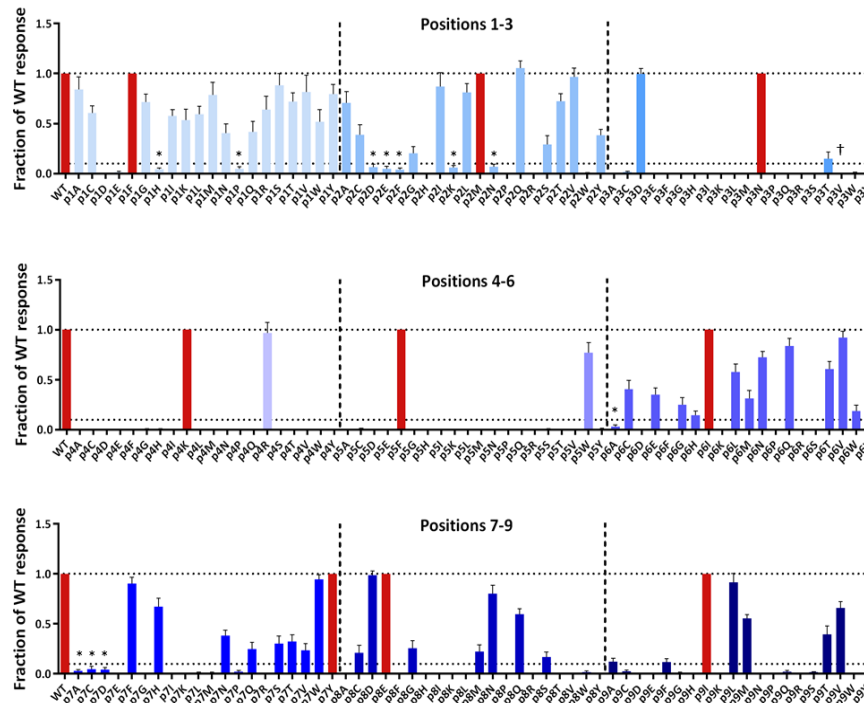
Peptide screening 'X-scan' (AFP SPEAR T-cells)

TCR peptide recognition mapping using combinatorial amino acid substitutions

- Exchange of each aa for all other possibilities to generate a binding motif
- Searching with the motif against the human genome

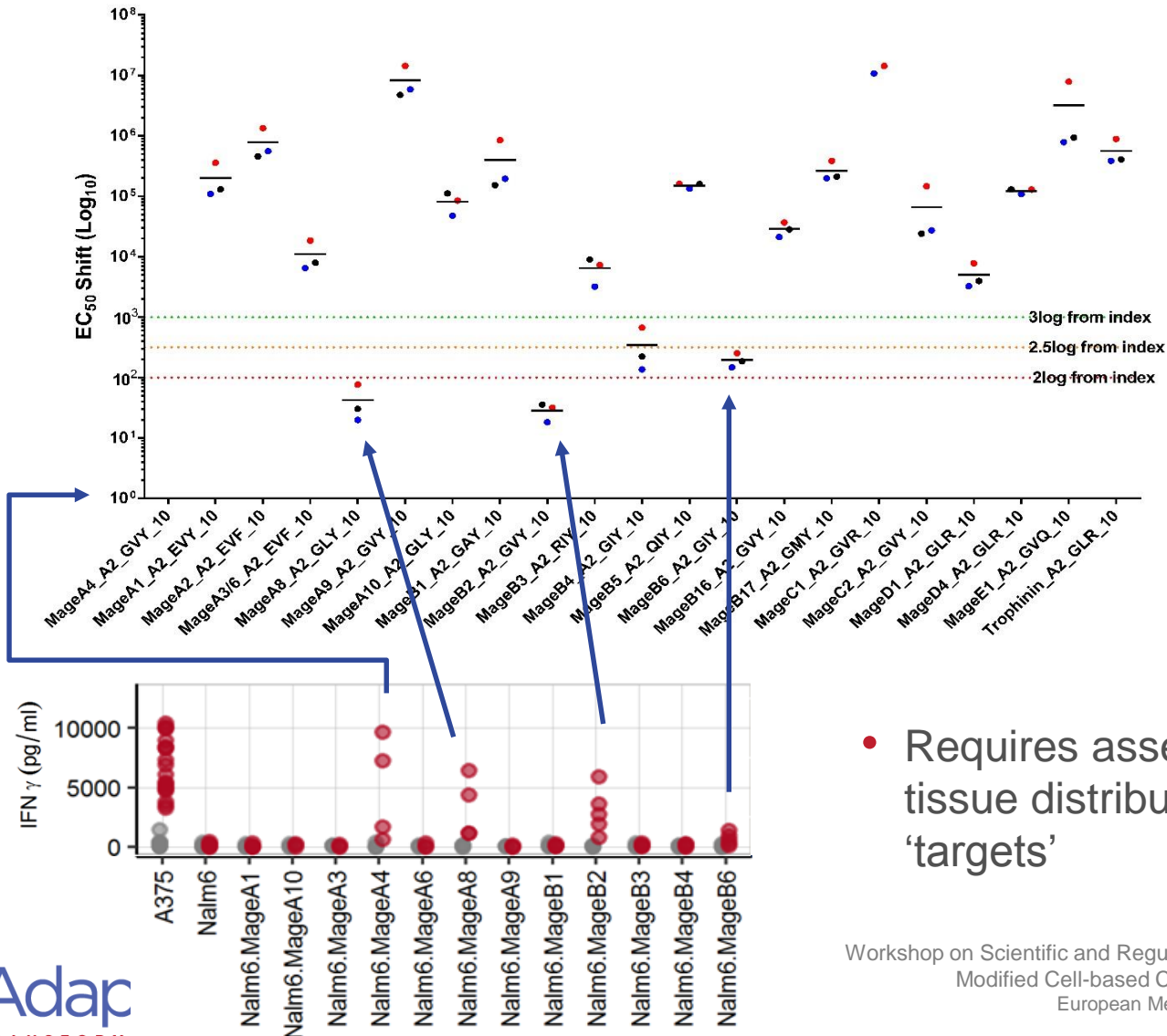
- [ACFGIKLMNQRSTVWY]-[ACGILMQSTVY]-[DNT]-[KR]-[FW]-[CEGHILMNQTVW]-[FHNQSTVWY]-[CDEGMNQS]-[AFILMTV]

p1 p2 p3 p4 p5 p6 p7 p8 p9
XMN**K**FIYEI
FX**N**KFIYEI
 FM**X**KFIYEI
 FMN**X**FIYEI
 FMN**K**XIYEI
 FMN**K**F**X**YEI
 FMN**K**FI**X**EI
 FMN**K**FIY**X**I
 FMN**K**FIY**E****X**



Analysis of peptide recognition – Family members

How well are peptides recognised?



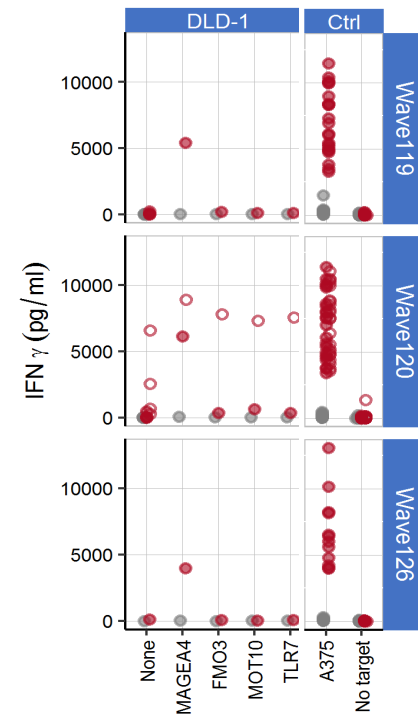
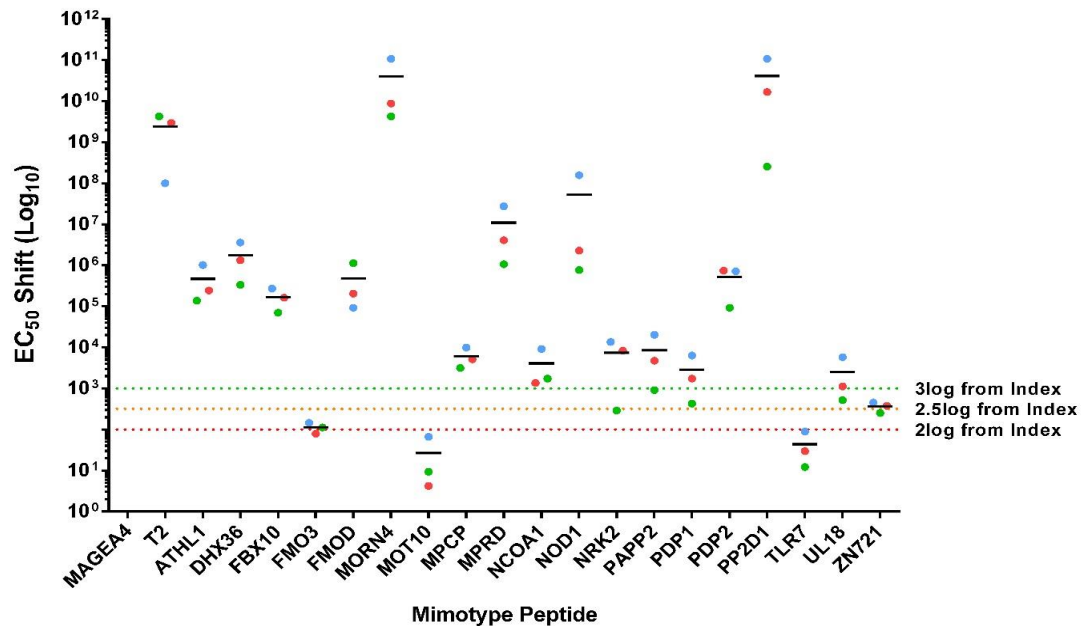
- Requires assessment of tissue distribution of other 'targets'



Analysis of peptide recognition – Mimotypes

How well are peptides recognised?

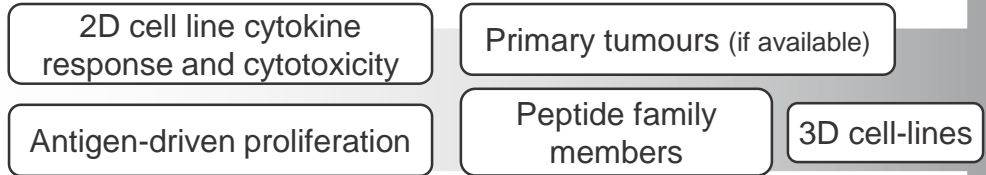
- Non-related proteins derived from X-scan motif proteome search
- Over-express and screen for T cell reactivity
- If other peptides are recognised, a risk assessment is required on those proteins



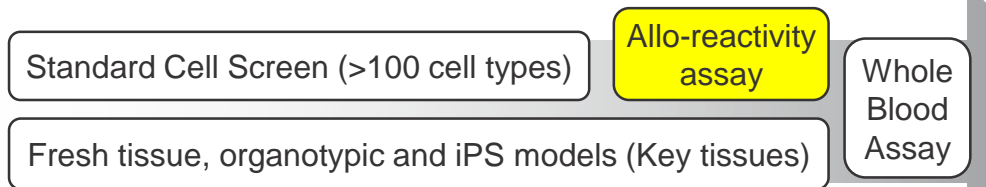
Adaptimmune's standard preclinical package

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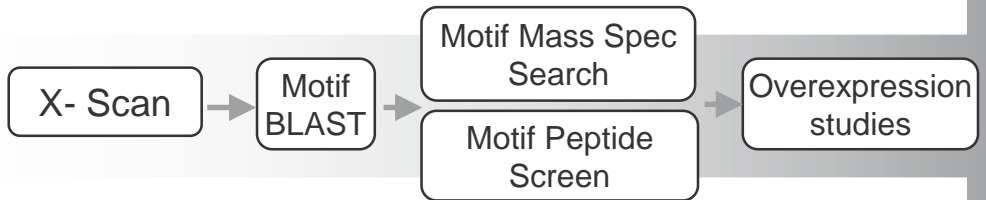
Potency/efficacy



Human Cell Testing



Molecular Analysis

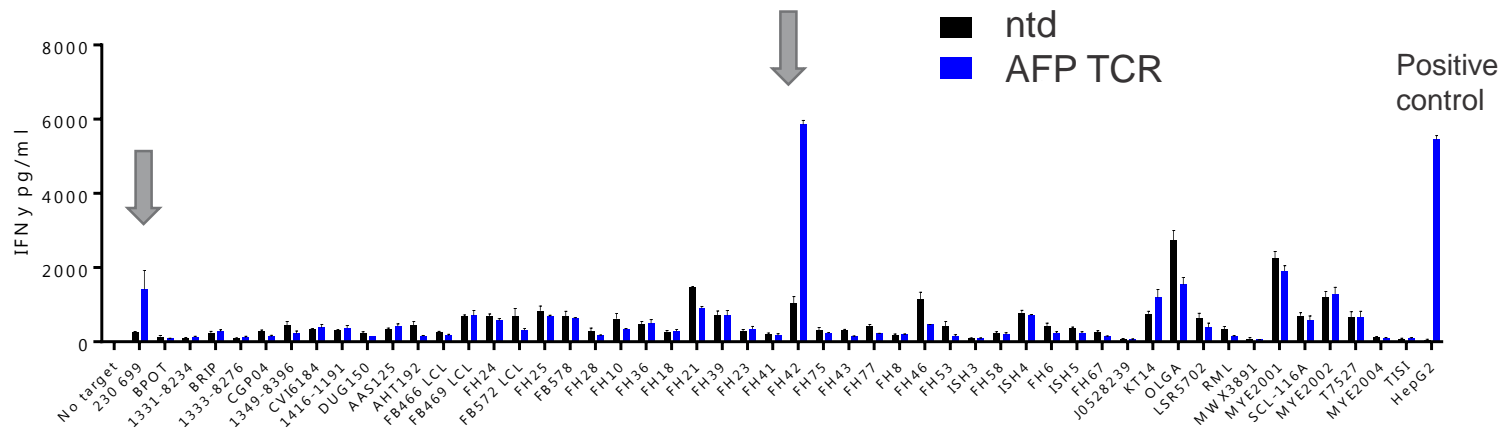


Clinical Candidate TCR

Alloreactivity screen (AFP SPEAR T-cells)

Alloreactivity assay

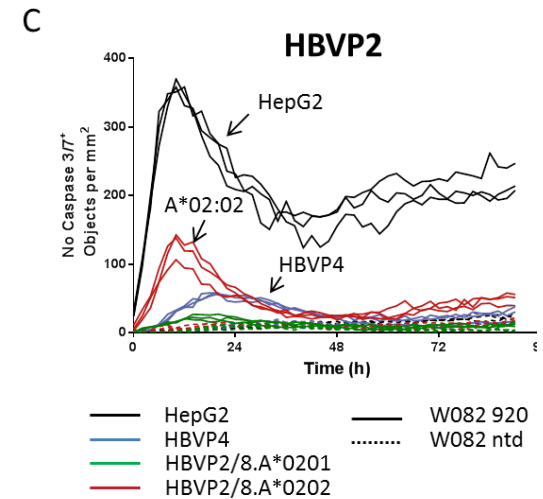
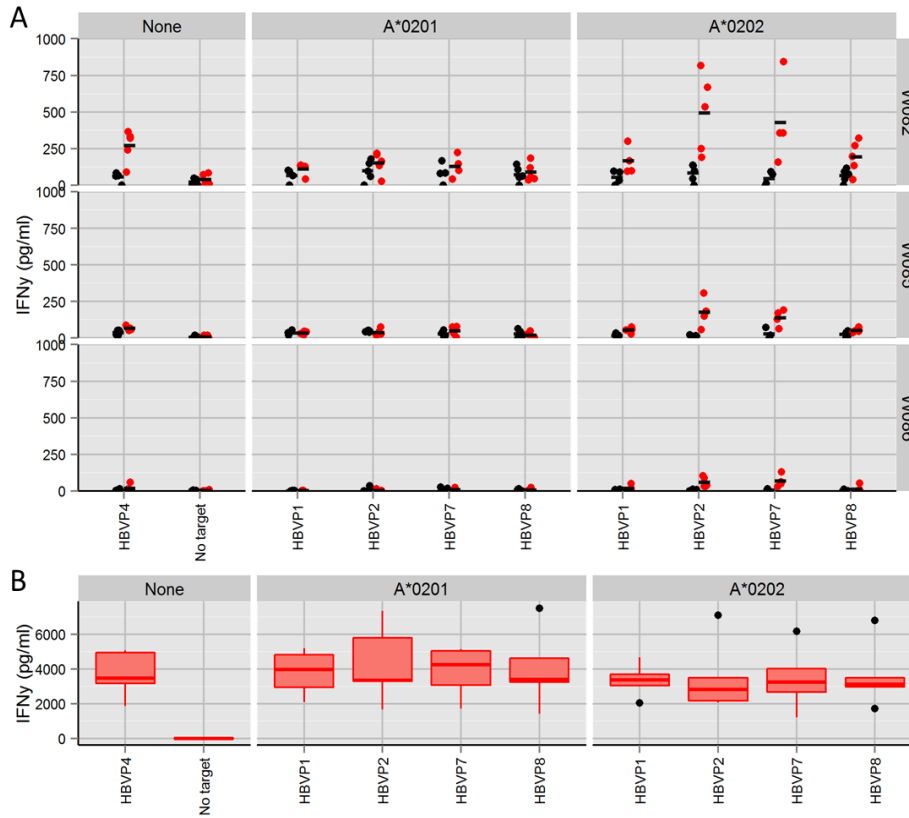
- Looking for response against another unidentified peptide on a different HLA
 - ◆ Screen T cells against panel of 55 EBV-transformed B cells expressing a wide range of different HLAs
 - ◆ 38 HLA-A, 63 HLA-B and 28 HLA-C
- AFP SPEAR T-cells showed response to 2 cell lines
 - ◆ Express unique alleles HLA-B*1501 and C*0404 – clinical exclusions



Alloreactivity screen (AFP SPEAR T-cells)

There may be lineage-specific allereactivities

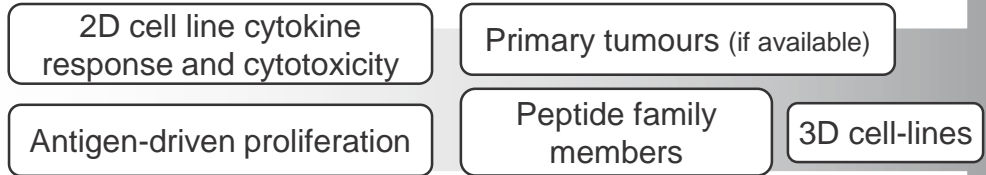
- HLA-A*0202 allereactivity in pericytes



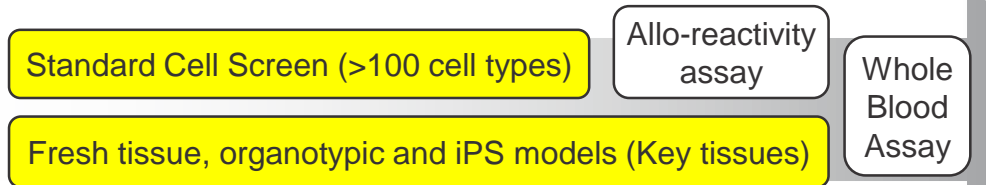
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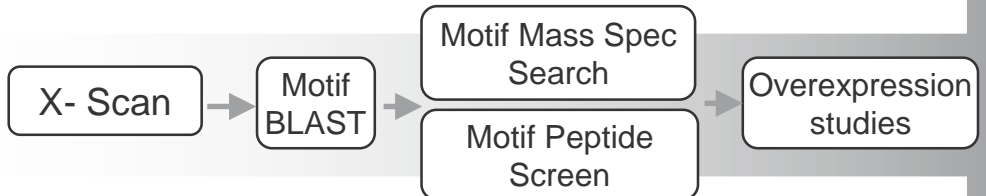
Potency/efficacy



Human Cell Testing



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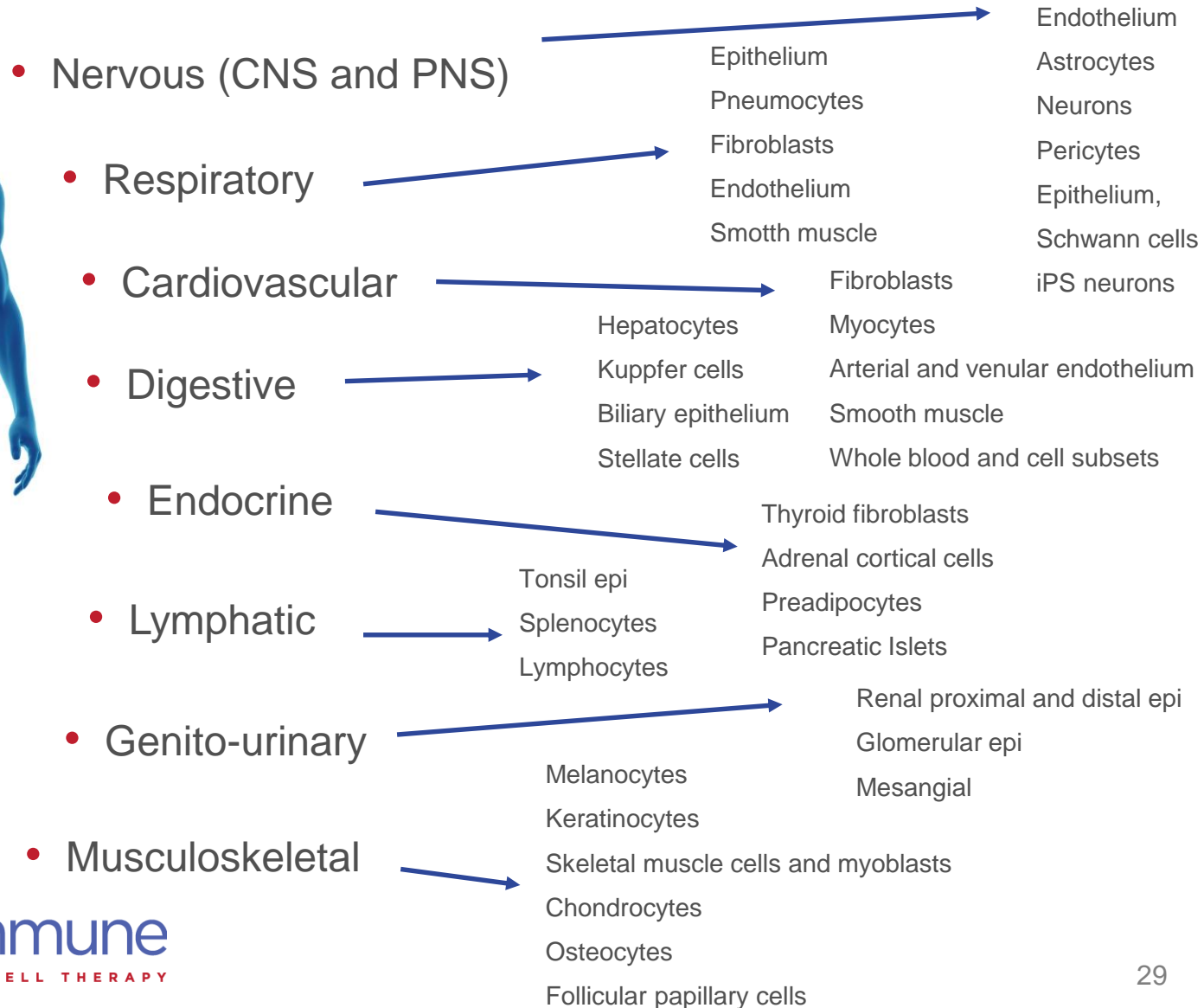
Clinical Candidate TCR

Safety assessment – Cell and tissue screen

- Bank of primary cells, covering multiple organ systems and cell types
 - Over 100 non-fetal cell types (multiple donors sources of each if possible)
 - ◆ Primary normal cells, low passage (2 to ~10)
 - ◆ Tumour lines, generally high passage
 - Coverage is boosted by tumour cell lines, but
 - ◆ Majority are epithelial.
 - ◆ Risk of genetic instability.

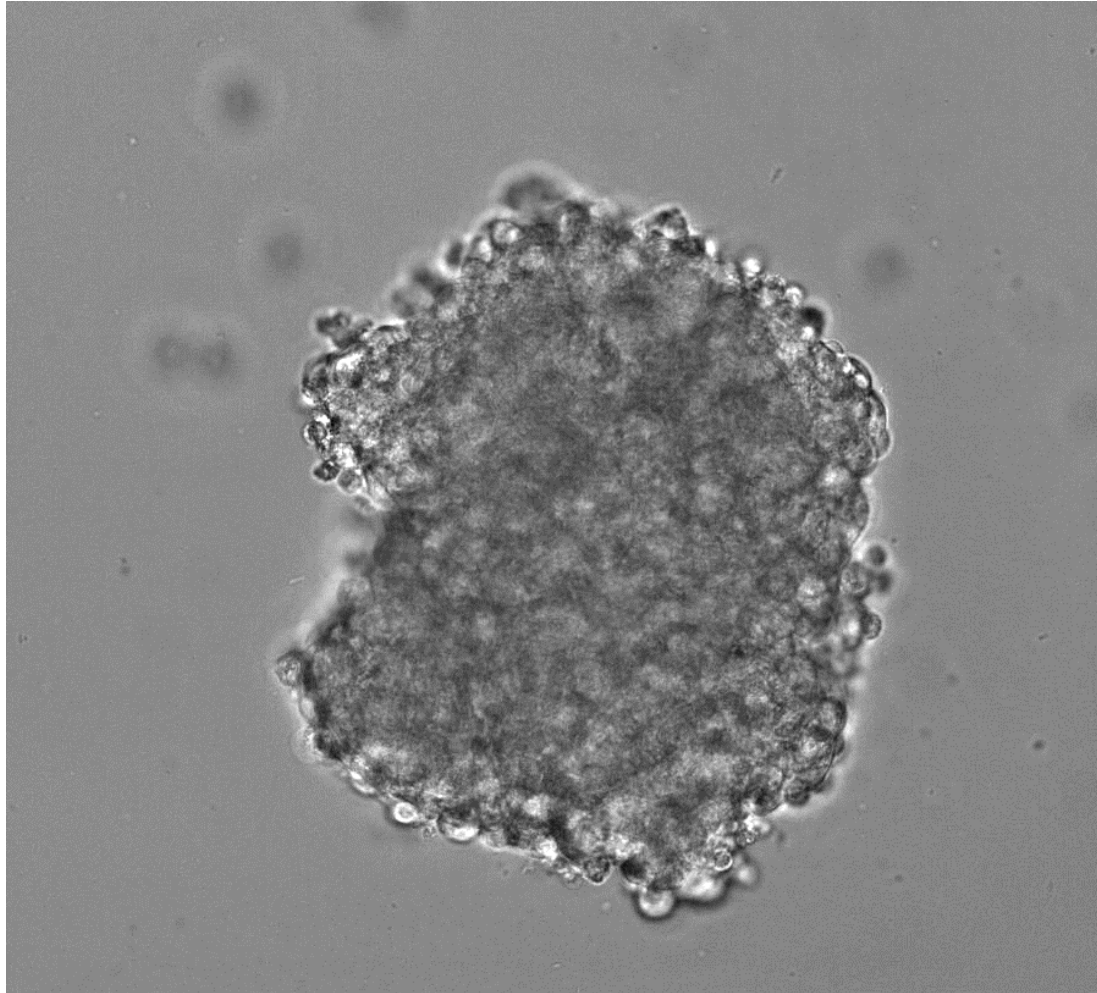
Safety assessment – Cell and tissue screen

Over 100 cells covering multiple key lineages and tissues (selected examples)



Cells, tissues and models - Cardiovascular

iPS CM - Spontaneously electrically active and contractile (beating) myocytes

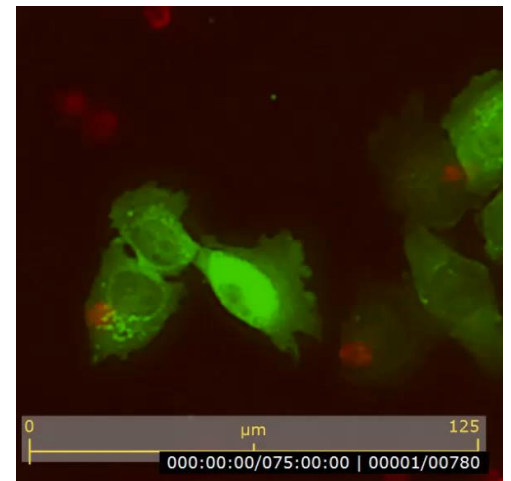
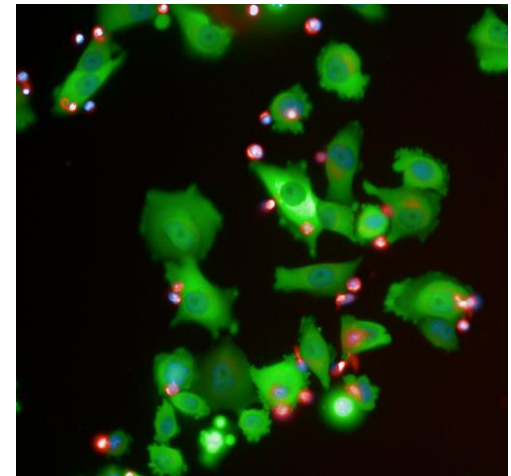


In-vitro 2D Potency and Safety assays are improving

Design the models based upon the science and relevance....

- Improved assay formats and HCS equipment available
- Assess safety *and* potency of TCRs in the same well
 - co-culture and multicolour fluorescently labelled Ag+ cell lines or primary tumour material and Ag- primary cells from the same tissue with T cells **in the same well** eg *Melanoma cultured with Melanocytes and Keratinocytes*
- Other techs – lots becoming available
 - Air-liquid interface
 - Primary tissues
 - Fluid based systems
 - Organs on chips

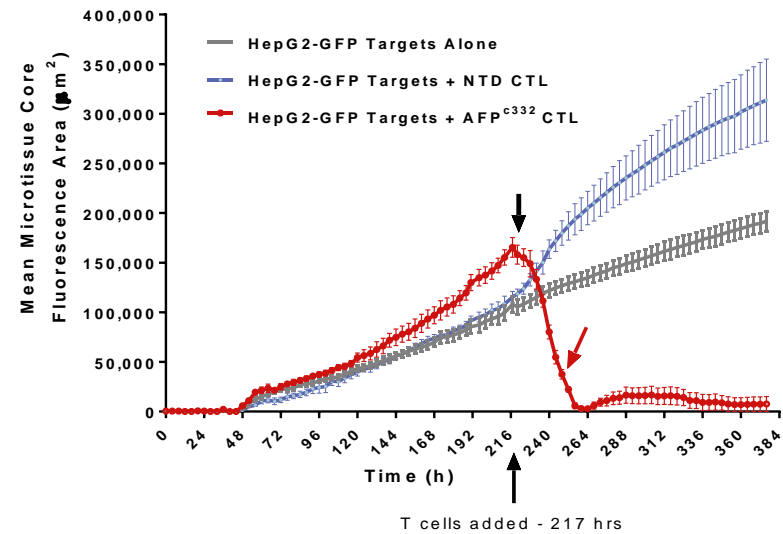
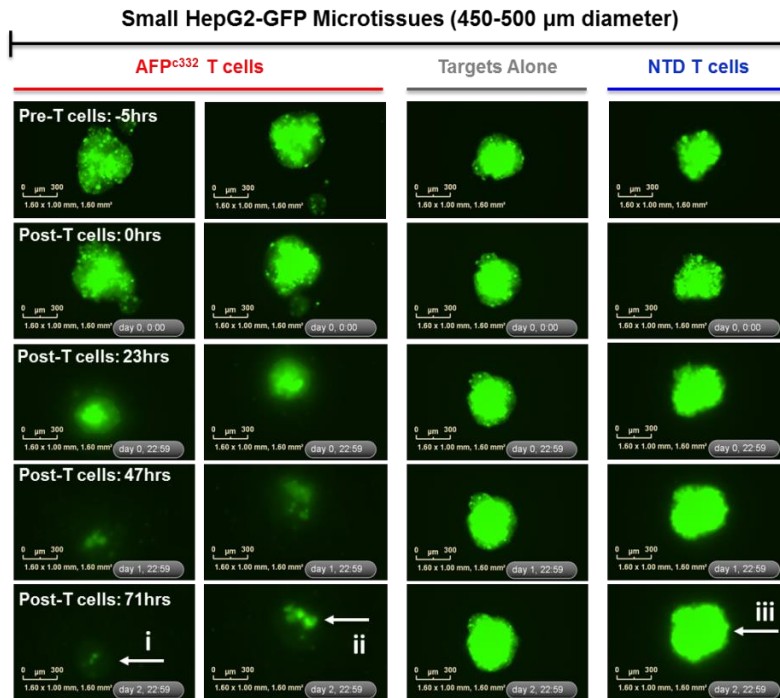
T cells with ADT TCR vs antigen positive Melanoma



Rapid Killing of 3D HCC models by AFP SPEAR T-cells

Can perform similar models with normal cells, co-cultures, iPS cells etc

- Rapid destruction of GFP-labelled HepG2 hepatocellular carcinoma 3D microspheres



Preclinical Safety Testing Of Enhanced TCRs

Summary

- Pick the right target
 - ◆ Favourable expression profile for on-target reactivity (normal vs tumour)
- Identify the right parental TCR
 - ◆ Early cross reactivity profile
 - ◆ Start with multiple parents
- Careful engineering
 - ◆ Step-wise affinity changes from multiple parents to find optimal TCR
- Screening for cross-reactivity in right way
 - ◆ Molecular characterisation, peptide screening and other predictive models
 - ◆ Cell screening
 - ◆ Relevant organotypic models, depends on the target and safety concerns

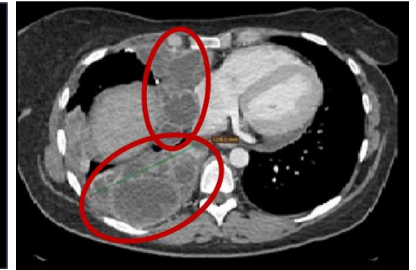
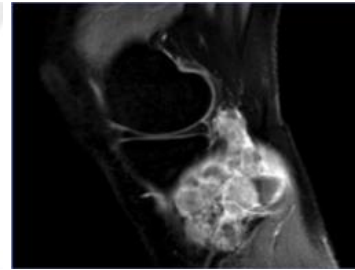
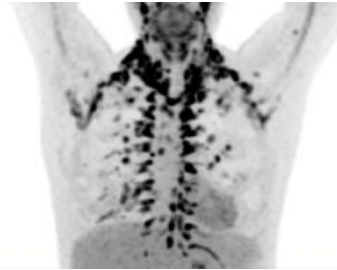


TCR engineering alone is not enough
- need to enhance T cells themselves

Engineering Better T Cells

Tumour Growth in Sarcoma (Pre-treatment)

BEFORE
Treatment

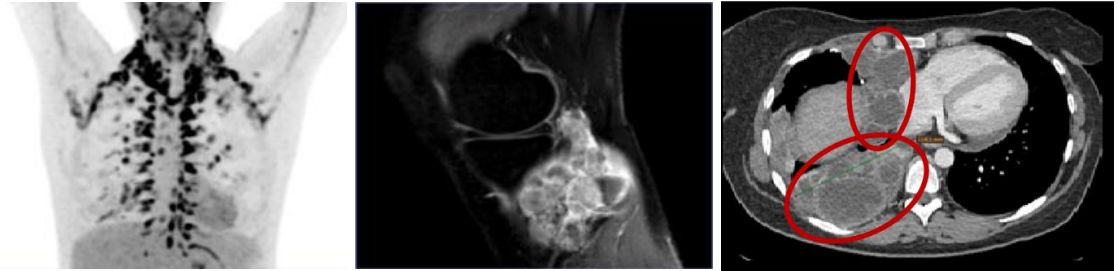


Engineering Better T Cells

Results observed with the Engineering optimal affinity NYESO SPEAR T-Cell

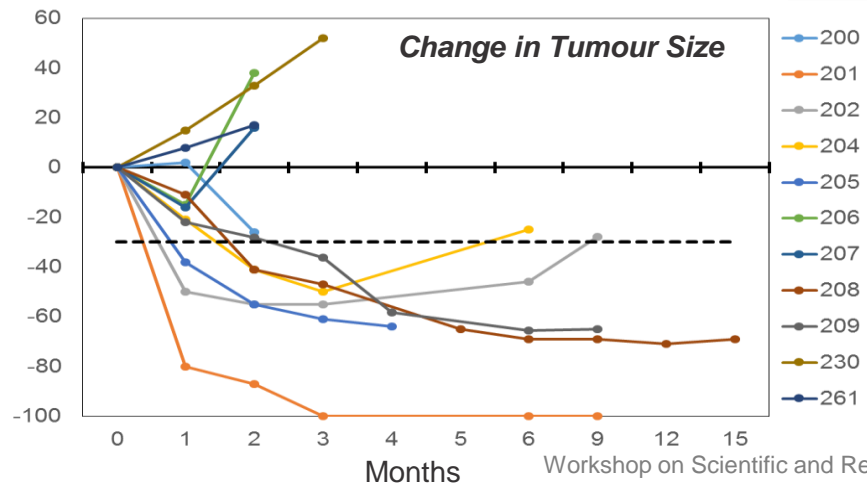
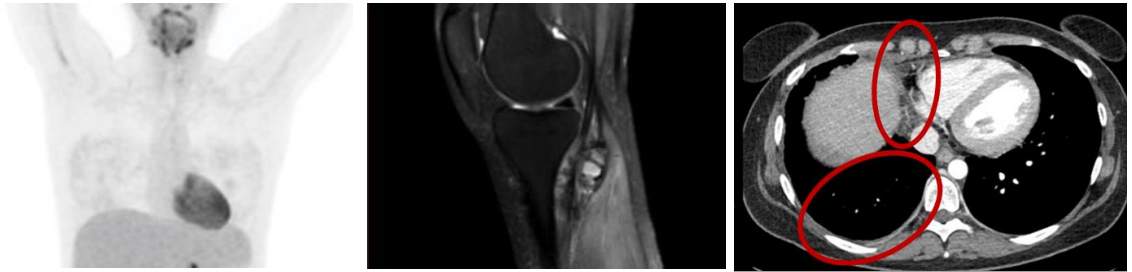
BEFORE

Treatment with NY-ESO
SPEAR T-cell



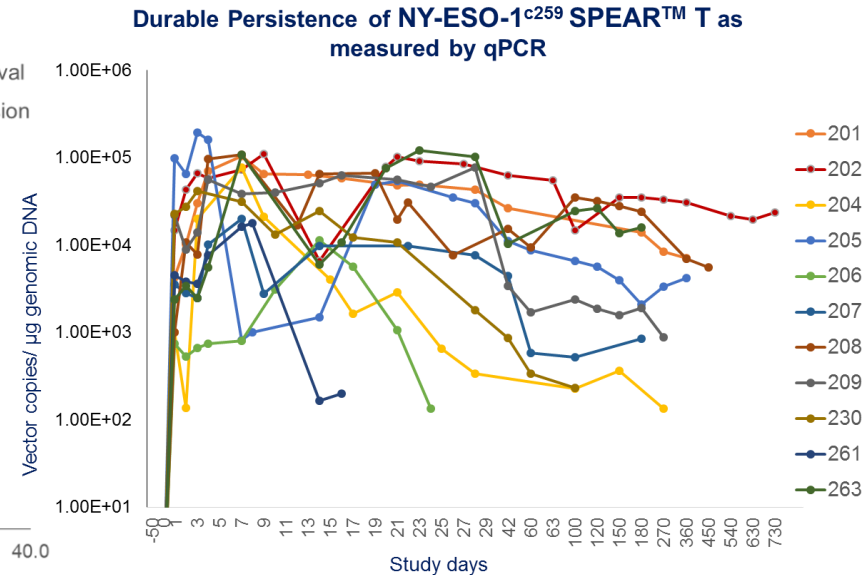
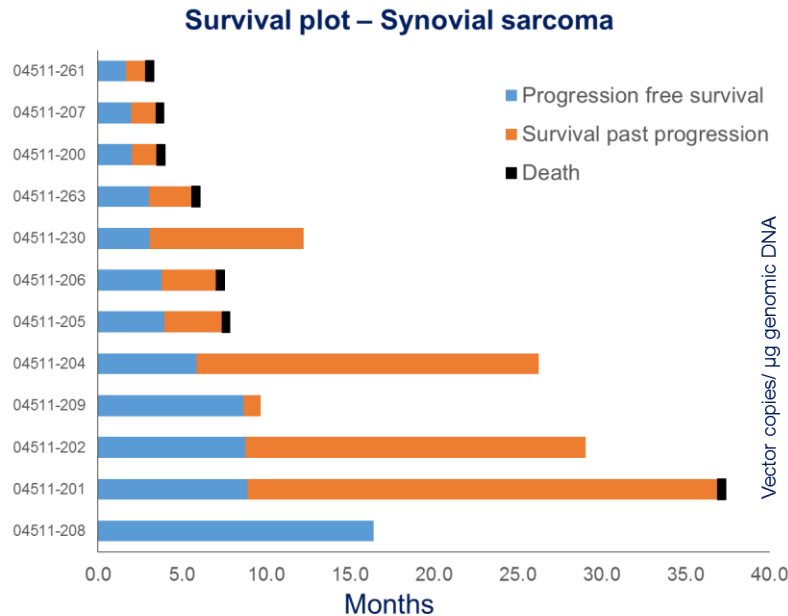
AFTER

Treatment with NY-ESO
SPEAR T-cell



Engineering Better T Cells

Results observed with the Engineering optimal affinity NYESO SPEAR T-Cell



- Have the guiding receptor with optimal affinity and specificity
- Escape mechanisms present which
 - Immune suppression
 - HLA down regulation
 - Antigen escape
 - Reduced Durability

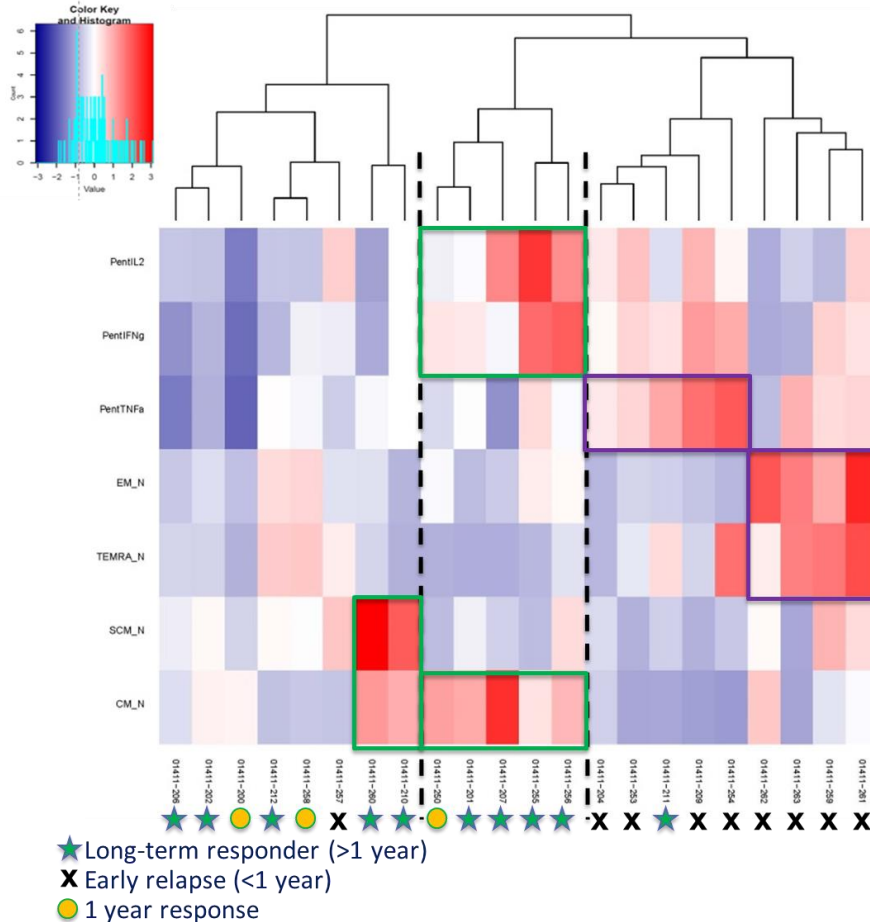


Engineering Better T Cells

Optimal Phenotype of the Cells

Engineering Better T Cells

Lessons from Translational Sciences



- Long term responders are mostly grouped according to a T_{CM} profile with a subset expressing high levels of IFN- γ and IL-2 from CD8 cells (green boxes) after peptide stimulation
- Early relapsers are strongly grouped according to T_{EMRA} and T_{EM} dominated product, or TNF- α producing CD8 NY-ESO-1^{c259T} cells (purple boxes)



Engineering Better T Cells

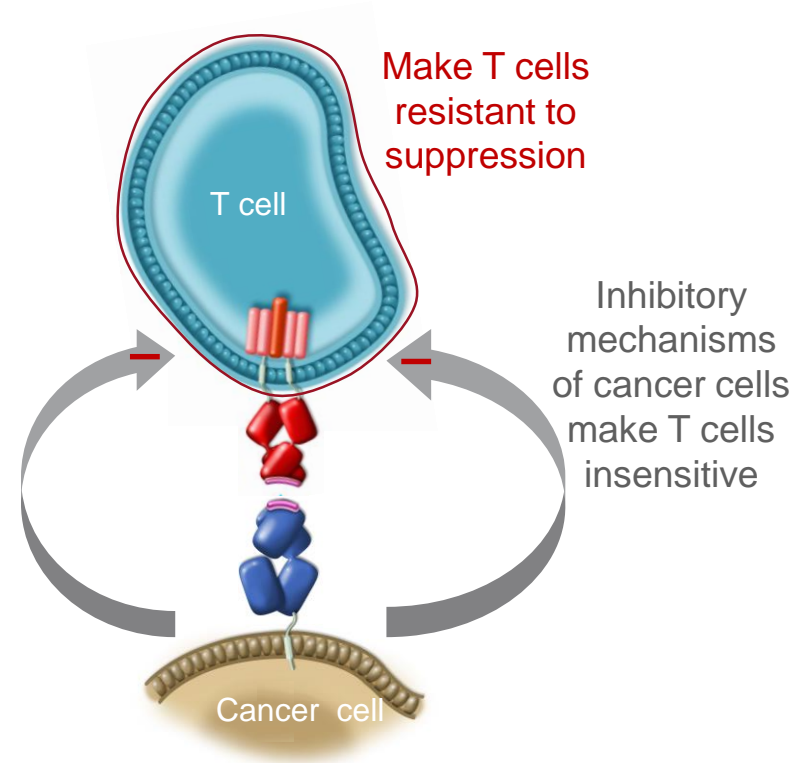
Making T Cells Resistant To Suppression

Engineering better T cells

2nd generation T cells

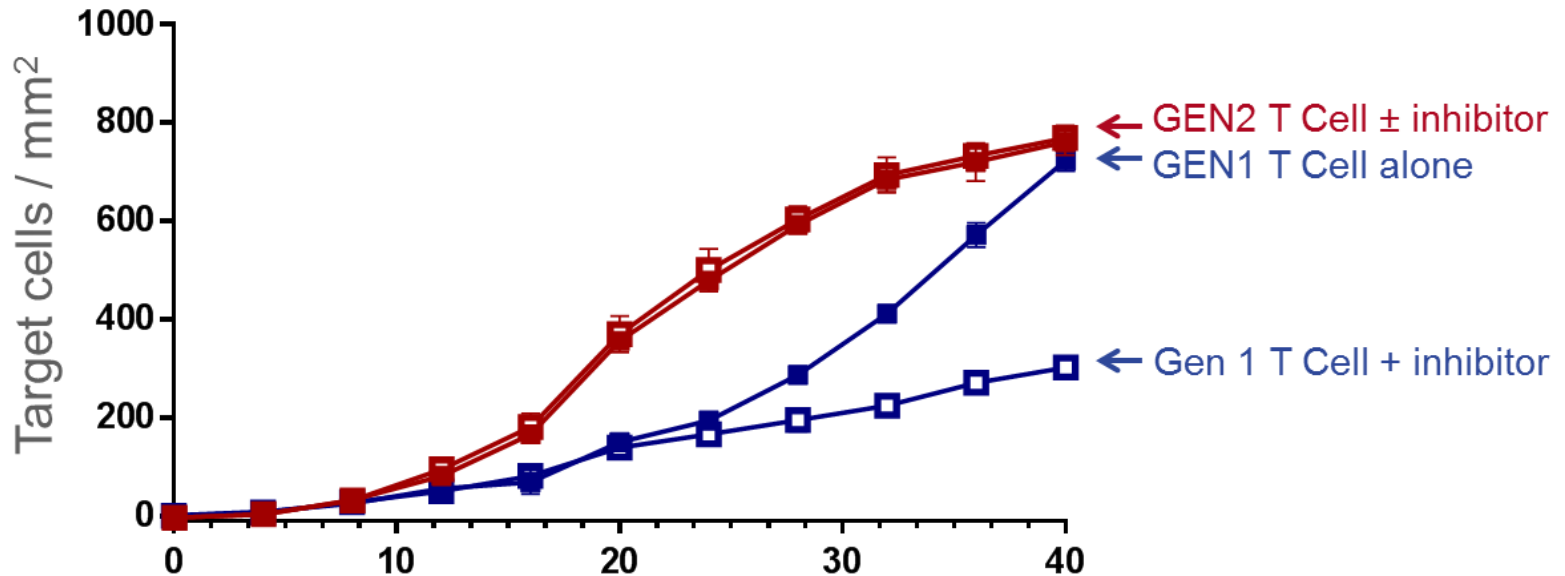
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Engineering Better T Cells

Overcoming inhibition in the tumour microenvironment



Gen 2 T Cells maintain enhanced killing in the presence of inhibitors



Engineering Better T Cells

Summary

Engineering Better T Cells

Summary

- Target choice is critical for efficacy and safety profile
- TCR affinity optimization crucial for best TCR-targeted T cell response
- Specificity crucial for lowest toxicity

TCR specificity can be assessed systematically in vitro

- Several next generation technologies making T cells resistant to tumour microenvironment inhibitory factors
- Several next generation technologies enabling T cells to facilitate breaking immune tolerance to tumour

Next generation approaches need extra consideration, to be driven by the mode of action and the science, and appropriate models designed

SUBTITLE

DATE



Thank you for your attention!