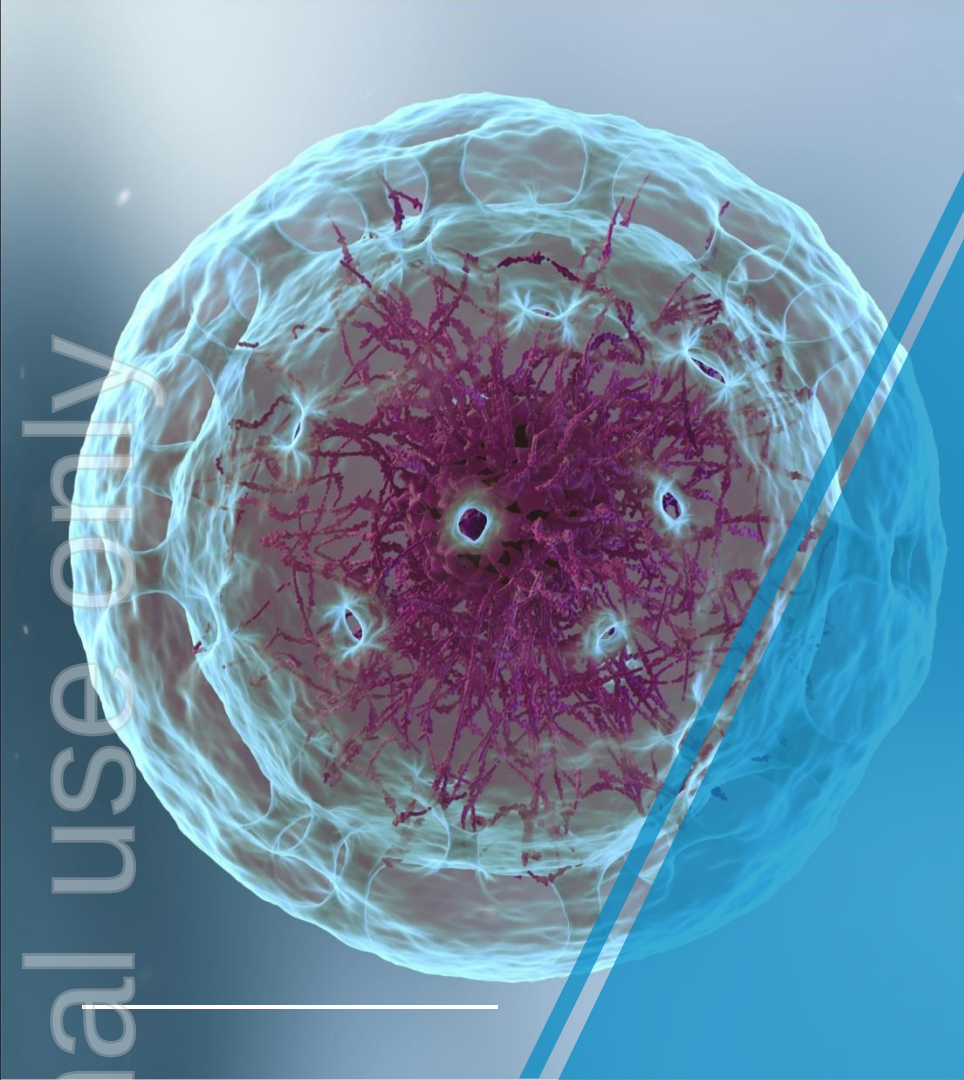



Prescient Therapeutics

OmniCAR

# Creating next-gen cell therapies that are controllable, flexible & adaptable

Prescient Therapeutics Limited (ASX: PTX)

**Cell & Gene Meeting on the Mesa**

**October 2021**

# Disclaimer and Safe Harbor

Certain statements made in this document are forward-looking statements within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These forward-looking statements are not historical facts but rather are based on the current expectations of Prescient Therapeutics Limited ("Prescient" or the "Company"), their estimates, assumptions, and projections about the industry in which Prescient operates. Material referred to in this document that use the words 'estimate', 'project', 'intend', 'expect', 'plan', 'believe', 'guidance', and similar expressions are intended to identify forward-looking statements and should be considered an at-risk statement. These forward-looking statements are not a guarantee of future performance and involve known and unknown risks and uncertainties, some of which are beyond the control of Prescient or which are difficult to predict, which could cause the actual results, performance, or achievements of Prescient to be materially different from those which may be expressed or implied by these statements. These statements are based on our management's current expectations and are subject to a number of uncertainties and risks that could change the results described in the forward-looking statements. Risks and uncertainties include, but are not limited to, general industry conditions and competition, general economic factors, the impact of pharmaceutical industry development and health care legislation in the United States and internationally, and challenges inherent in new product development. Investors should be aware that there are no assurances that results will not differ from those projected and Prescient cautions shareholders and prospective shareholders not to place undue reliance on these forward-looking statements, which reflect the view of Prescient only as of the date of this presentation. Prescient is not under a duty to update any forward-looking statement as a result of new information, future events or otherwise, except as required by law or by any appropriate regulatory authority.

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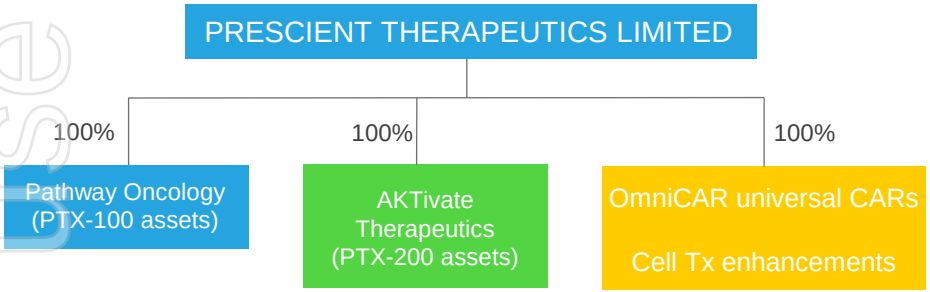
# Corporate Snapshot

## OVERVIEW

- HQ in Melbourne, Australia, with activities in Australia and US
- Est 2014 with assets from Yale (PTX-100) and Moffitt/USF (PTX-200); and UPenn/Oxford (OmniCAR) in 2020
- Programs in US & Australia
- Listed on ASX, with wholly owned private subsidiaries




## METRICS

| | |
|---|---|
| **ASX Ticker** | **PTX** |
| Total Issued Capital | 643 M shares |
| Listed Options | 93.4 M |
| Unlisted Options | 12.1 M |
| Share Price[1] | A$0.27 (US$0.20) |
| **Market Capitalisation[1]** | **A$174 M (US$127 M)** |
| **Market Cap fully diluted[1]** | **A$202 M (US$148 M)** |
| **Cash Position[2]** | **A$16 M (US$12 M)** |
| Top 20 Own | 17% |

1 - AS AT 17 SEPT 2021
2 – AT 30 JUNE 2021

# Innovative Pipeline in Personalised Medicine

Prescient Therapeutics

| Program | Discovery | Screening | Preclinical | Phase I | Phase IB | Phase II |
|---|---|---|---|---|---|---|
| CAR - T | | | | | | |
| OmniCAR CD33 & CLL-1 | AML | | | | | |
| OmniCAR HER2 | Breast, Ovarian & Gastric | | | | | |
| OmniCAR HER2 & EGFRviii | GBM | | | | | |
| Cell Therapy Enhancements | Undisclosed 1 | | | | | |
| | Undisclosed 2 | | | | | |
| TARGETED THERAPIES | | | | | | |
| PTX - 100 | PTCL | | | | | |
| PTX - 200 | AML | | | | | |

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

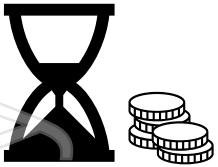
Prescient Therapeutics



# OmniCAR

**Universal, Next Generation CAR-T**

# Key Challenges Confronting the field of CAR-T



## Time and Cost

of delivering treatment

## Safety

CAR-T can have serious safety concerns

## No Control

Clinicians have no control of cells post infusion

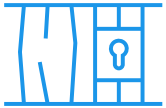
## Targets

Finding targets that work;

Antigen heterogeneity - esp. in solid tumours

## Exhaustion

Persistent stimulation of CAR-Immune cells leads to exhaustion



## Escape

Antigen loss leads to relapse

# OmniCAR Universal Immune Receptor Platform

- Pre-clinical **modularised** universal immune receptor (**UIR)** platform
- Potential best-in class UIR
- Based on multi-disciplinary technology licensed from **Penn**
- Only UIR system with post-translational covalent binding
- Unique, powerful and flexible
  - **Controllable activity**
  - **Flexible antigen targeting**

Penn
University of Pennsylvania

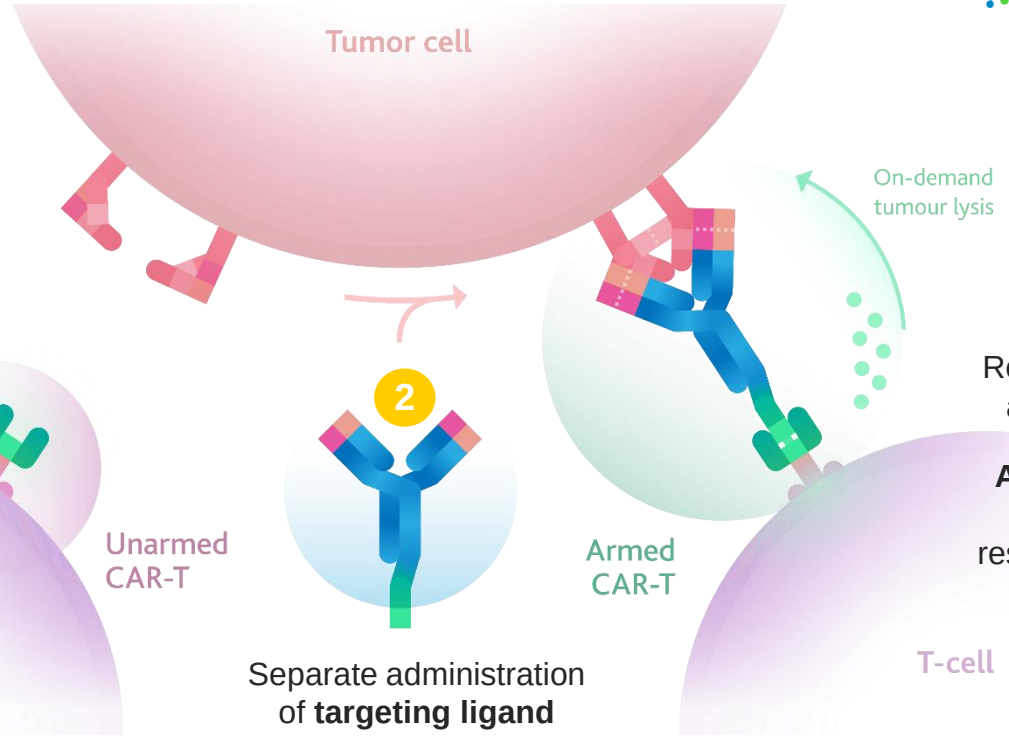
**Co-inventors**

Associate Professor
Daniel J. Powell, Jr

Professor
Andrew Tsourkas

Powell, DJ et al, JACS; 2020

# How OmniCAR works



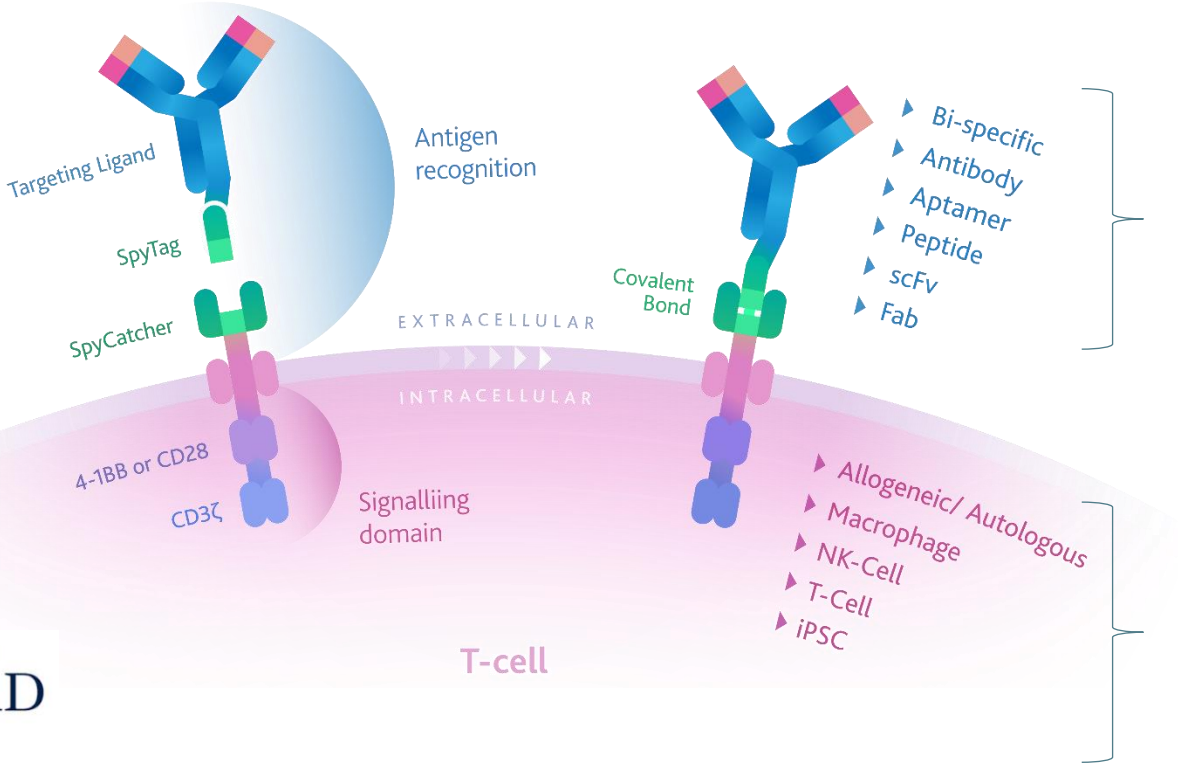

- CAR-T cell activity is **now controllable**
- Target specificity CAR-T cell can be **switched at will**, by administering a different targeting ligand

Concept to be tested in human under well controlled clinical trial(s) in compliance with regulatory requirements.

# An elegant and effective approach

Only UIR with spontaneous, autocatalytic, **covalent** bond formation

Binds targeting ligand to cell signalling domain




OmniCAR can use any type of **targeting ligand…**

**…with any immune cell**

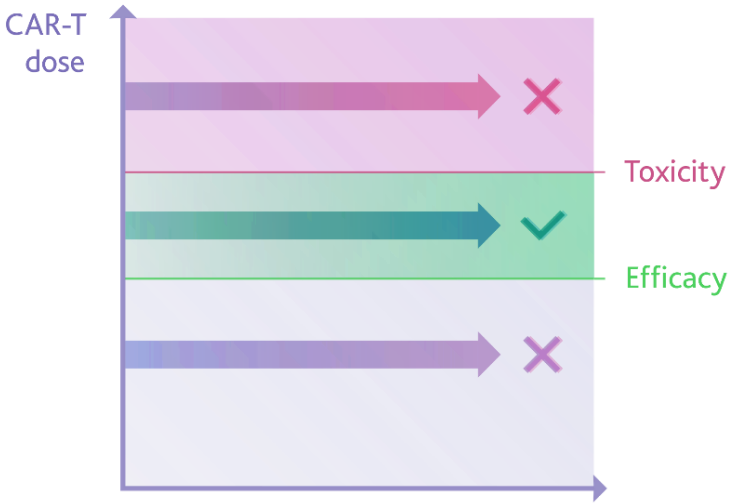
UNIVERSITY OF OXFORD

Adapted from Powell, DJ et al, JACS; 2020

# Safety: Ability Control Dose & Activity

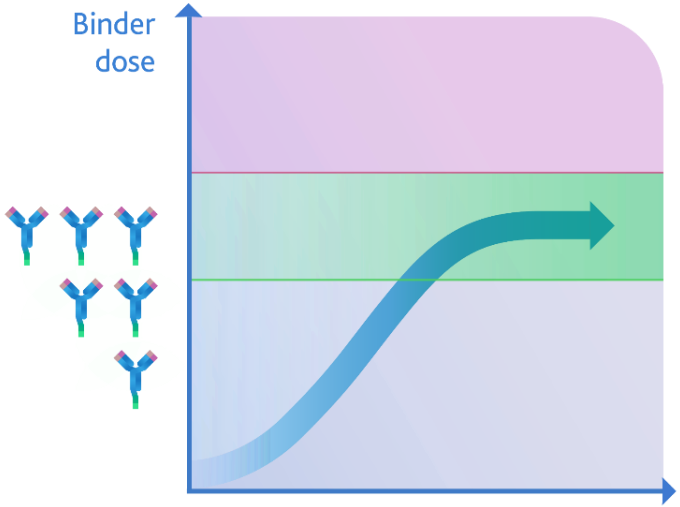
## Conventional CAR-T

- Clinicians have **no control** over CAR-T activity once injected
- Estimate optimal dose **before infusion**
- Half-doses of CAR-T cells provide limited fidelity




## OmniCAR

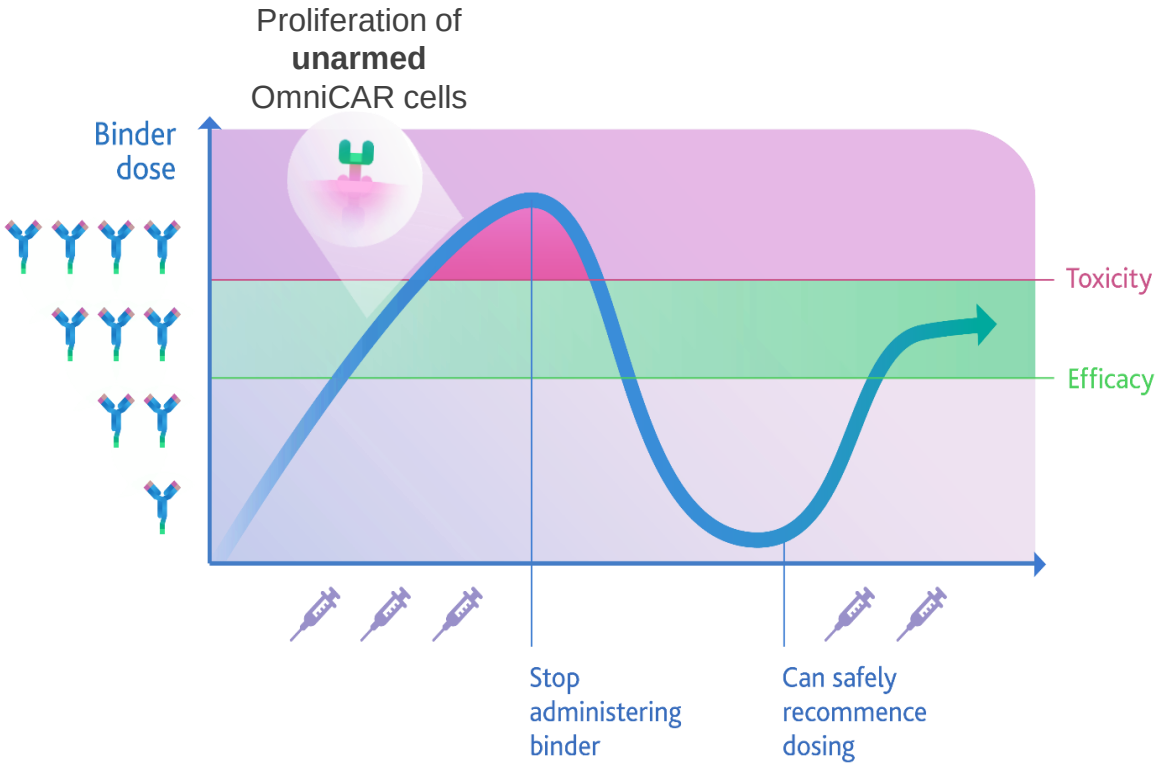
- Clinician control **post infusion**
- Controlling subsequent **dose** of binder controls CAR-T **activity**
- Titrate dose to **safe and efficacious** levels




Concept to be tested in human under well controlled clinical trial(s) in compliance with regulatory requirements.

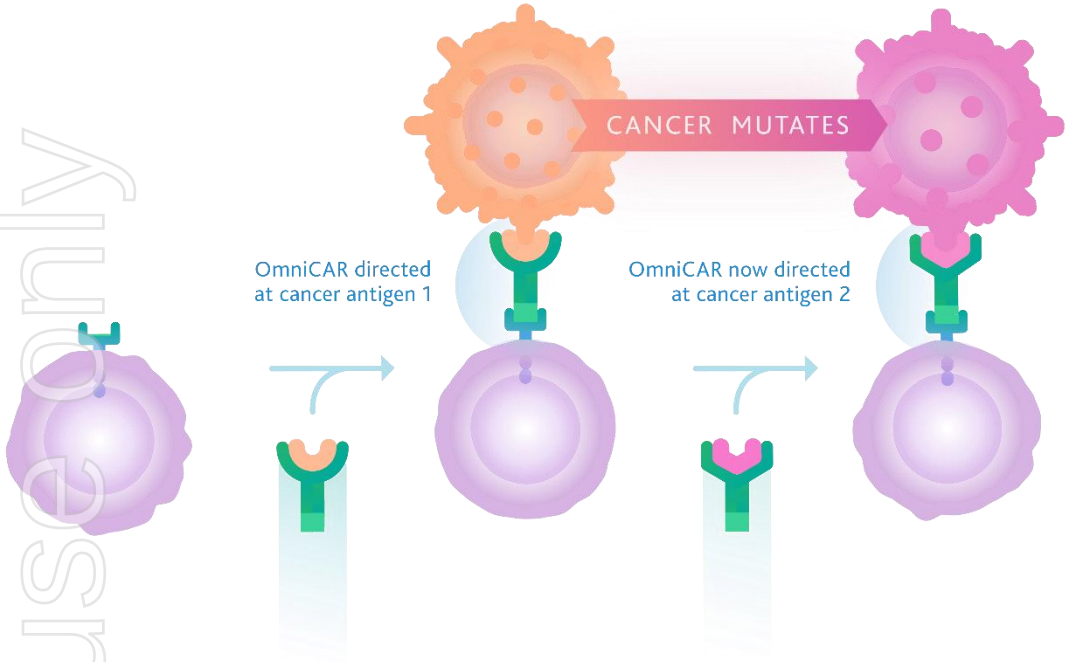
# Safety: Built-in on/off switch

- Cell activity can be **switched off at-will**
- Cells remain **viable but inactive**
- OmniCAR can be **safely reactivated**
- No uncontrolled activity
- **Ongoing stimulation for greater efficacy & persistence**




Concept to be tested in human under well controlled clinical trial(s) in compliance with regulatory requirements.

# Target Multiple Antigens *Sequentially*

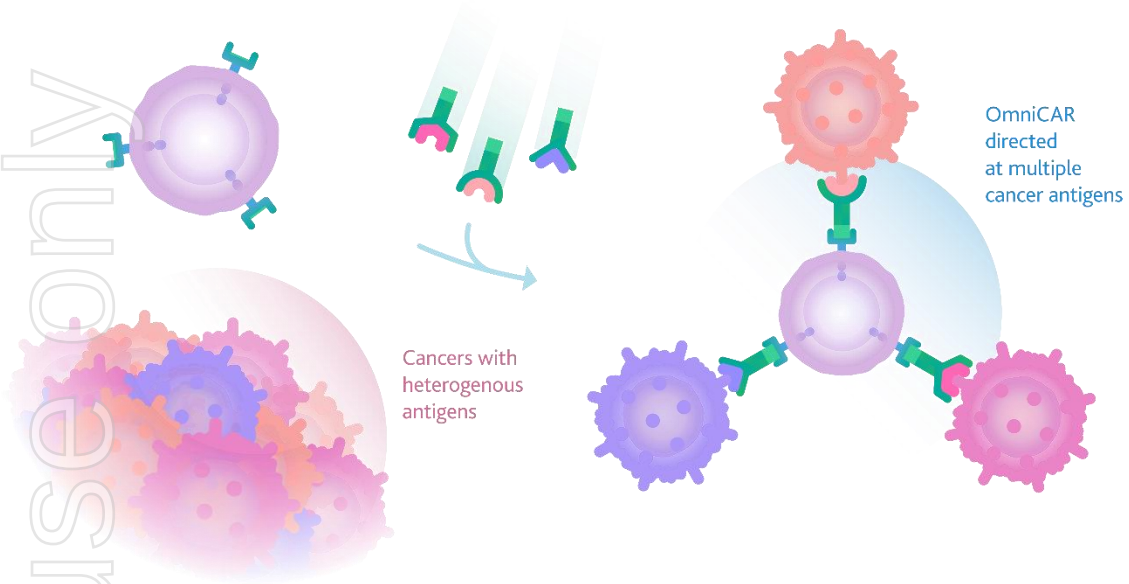



- Switching binder redirects the T-cell
- Uses single vector/cell product
- Addresses escape
- Useful for rapidly mutating cancers, esp those that cannot afford time for another CAR-T production run
  - E.g. AML



Concept to be tested in human under well controlled clinical trial(s) in compliance with regulatory requirements.

# Target Multiple Antigens *Simultaneously*




- Multiple antigen targeting with single vector/cell product
- Could broaden anti-tumour immune response
- Prevents escape
- Tailor arming combinations and proportions
- Utility in many solid tumours



Concept to be tested in human under well controlled clinical trial(s) in compliance with regulatory requirements.

# The future of ACT is efficient yet personalized:
## OmniCAR cells + “plug & play” binder library

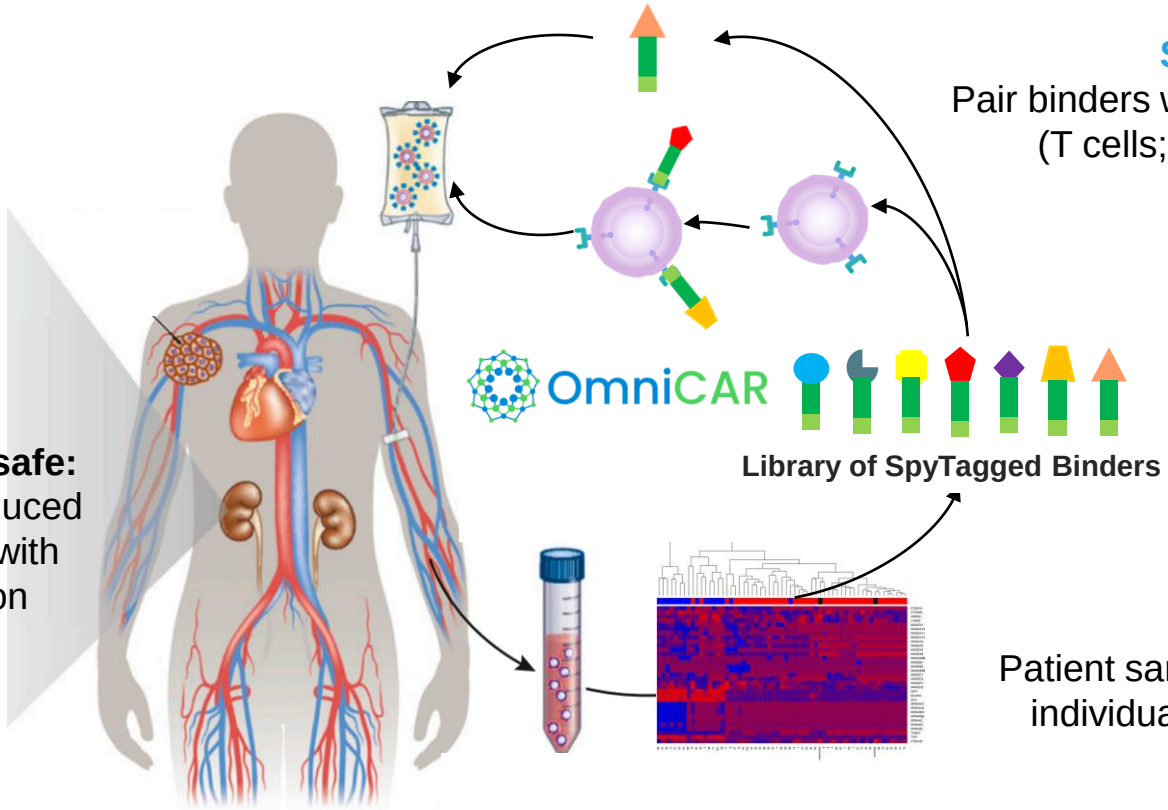
Prescient Therapeutics

**Step 3**:
Pair binders with OmniCAR cells
(T cells; NK; auto/allo)

**Step 2:**
Match patient’s antigens to corresponding binders

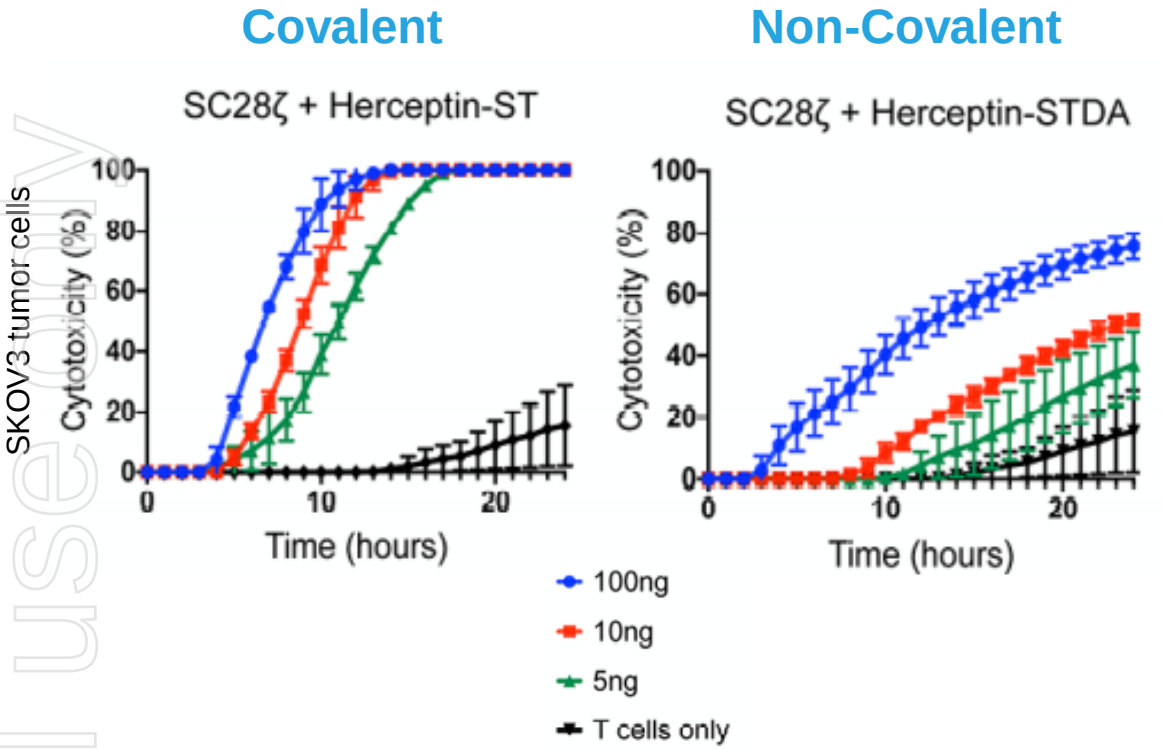
**Step 1**:
Patient sample to determine individual antigen profile

**Step 4:**
**Tailored, optimised & safe:**
OmniCAR- induced tumor killing with post-infusion control



# Covalent Binding:

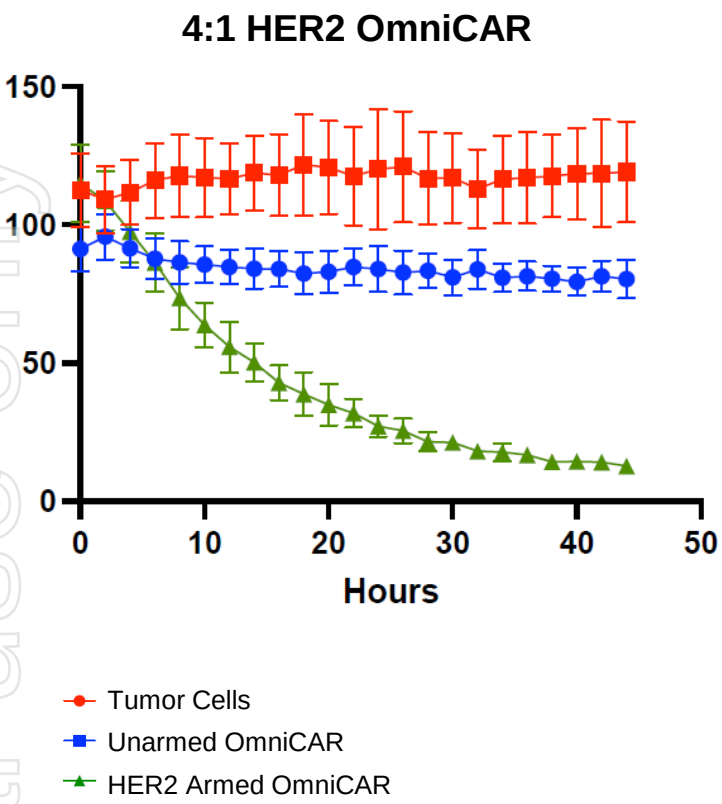
## Superior tumor killing & other advantages

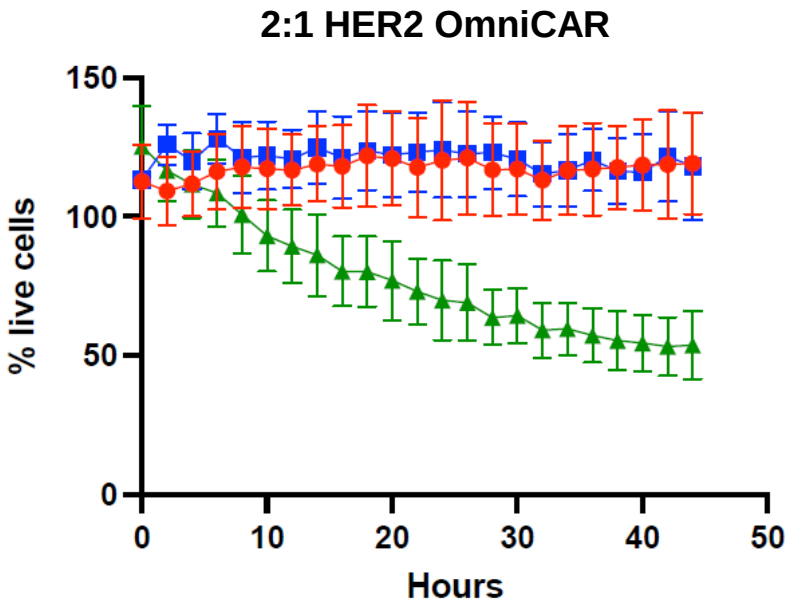



- **Covalent** binding improves SpyCatcher T-cell **loading and tumour cell lysis**
- Covalent binding has additional advantages in:
  - Efficacy
  - Predictability
  - Clinical utility
  - Regulatory considerations

Powell, DJ et al, JACS; 2020
STDA : A SpyTag variant containing an aspartic acid to alanine mutation (SpyTag-DA) abolishes covalent bond formation while allowing formation of a noncovalent complex

# OmniCAR HER2: predictable cytotoxicity

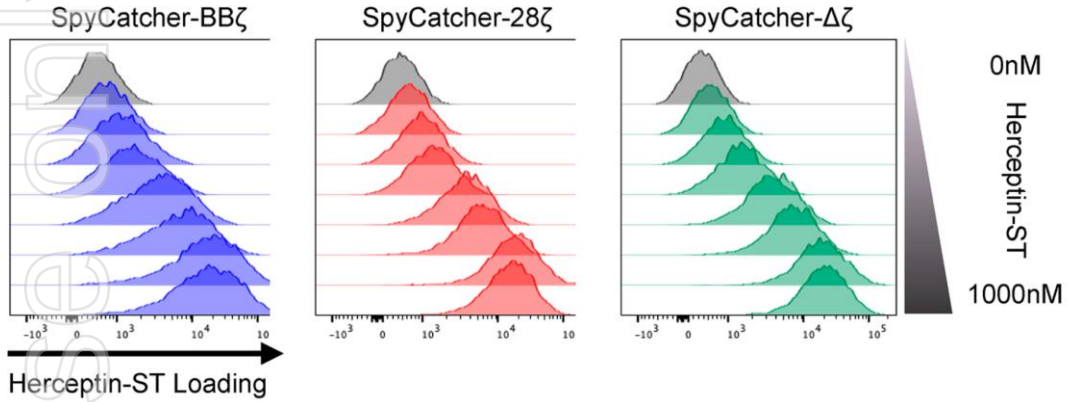


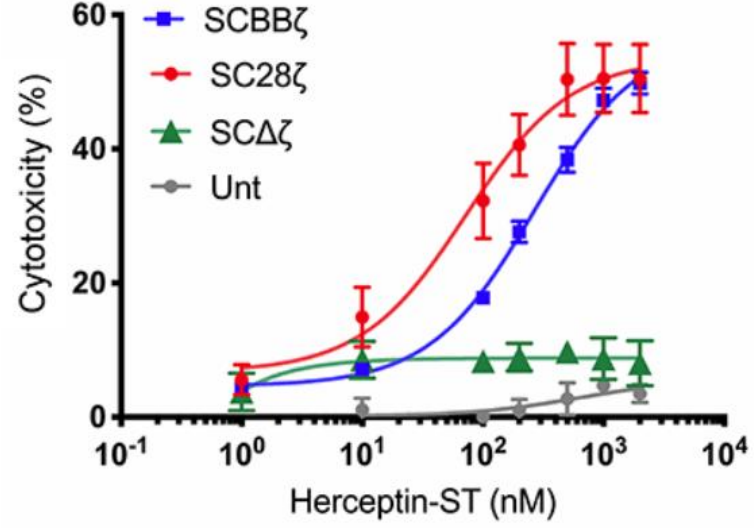

At 2:1, OmniCAR achieves cytotoxicity at a rate that aims to **balance efficacy** whilst **avoiding CRS and exhaustion**

# Flexible Loading and Dose-Dependent Lysis

- OmniCAR T-cells capable of being armed with varying amounts of SpyTagged targeting ligand



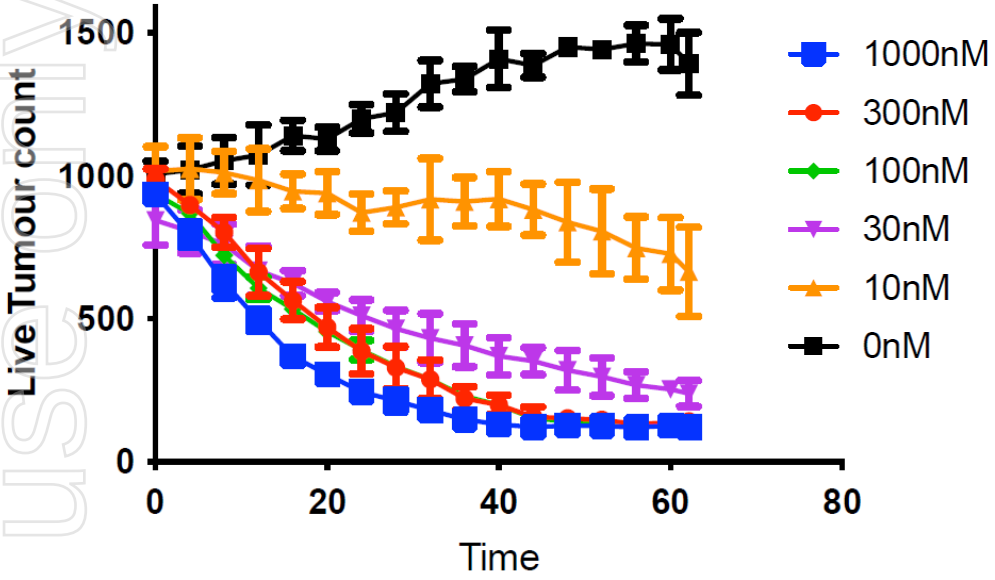

- Increasing targeting ligand concentration results in increased lytic capacity




Powell, DJ et al, JACS; 2020

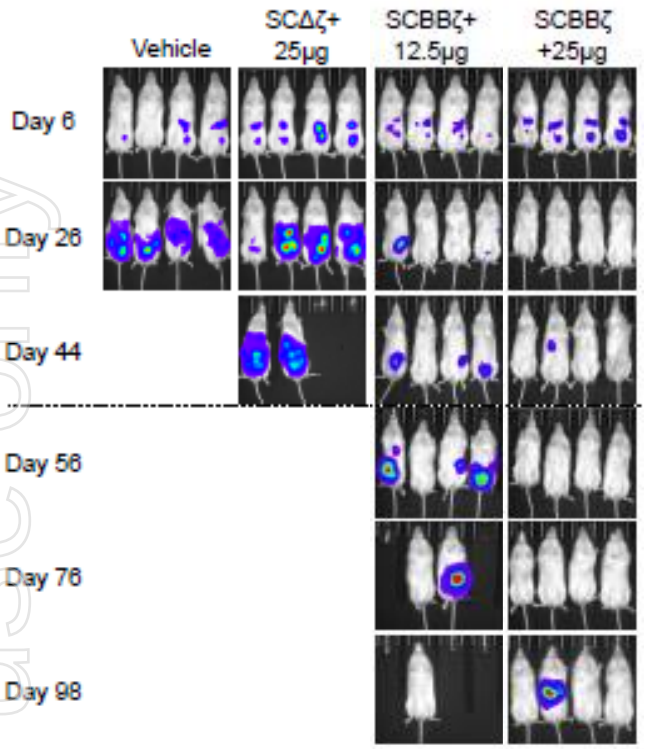
# Dose response: High potency with less binder required

## 2:1 ST-EGFRviii binder vs U251 EGFRviii cells

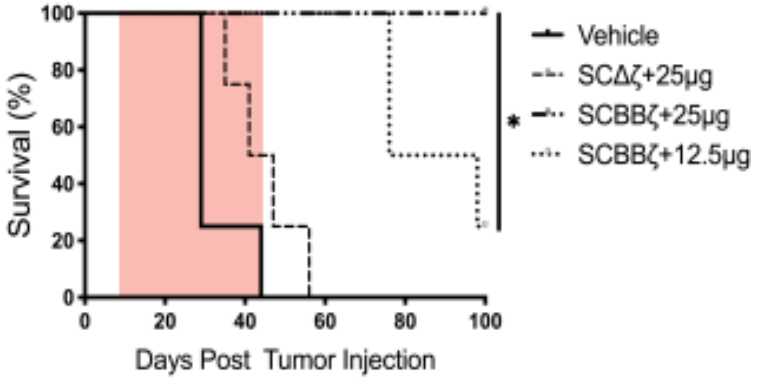



- **Dose-dependent CAR-T activity**
- V3 OmniCAR significantly more potent, and likely safer, than V1 system and competitor UIRs
- Potency with **60 fold less binder** (low nM range)
- Means **improved safety** and **lower cost of goods**

# Control: Dose-dependent CAR-T activity




- Ovarian cancer model, using anti-HER2 OmniCAR
- Loading more binder results in **proportionate killing** of cancer…
- …and **proportionate survival**
- **Lasting effects** even when cease dosing of binder

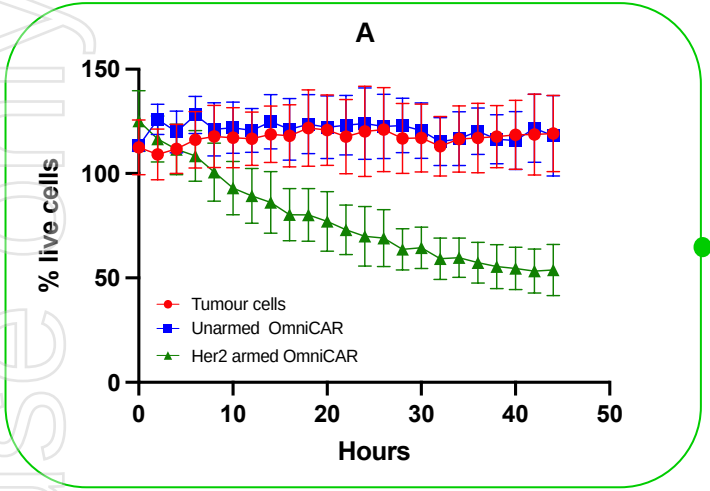


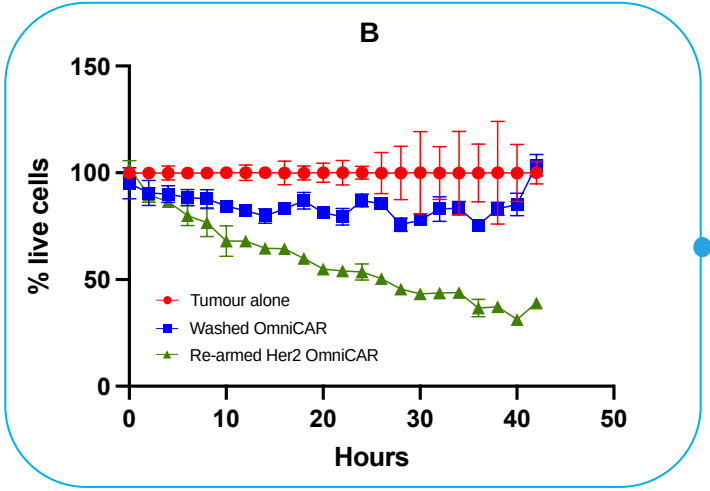

Powell, DJ et al, JACS; 2020

= dosing window of binder

# Re-Arming: OmniCAR Her2 can be Re-Armed

T cell activation
Day 0
Transduction
Day 3
Armed
Day 7
Cytotoxicity assay
Days 8–10
Re-armed
Wash; Rest
Day 12
Cytotoxicity assay
Days 13–14

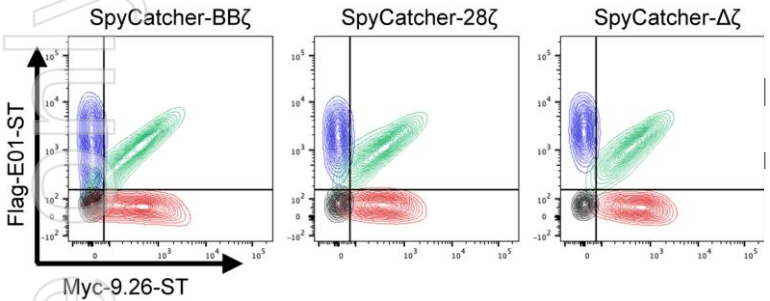



- OmniCAR T cells can be re-armed
- Re-arming results in **same levels and kinetics of cytotoxicity** as pre-armed
- Another example of **flexible** yet **predictable** activity

# Equal Arming & Equal Tumour Killing

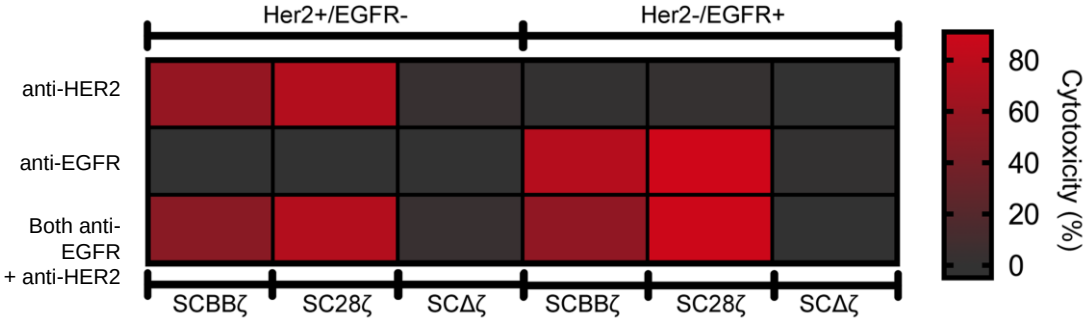
## Equal arming




CAR-T equally armed with:

- Both anti-EGFR + anti-HER2
- anti-EGFR
- anti-HER2
- control

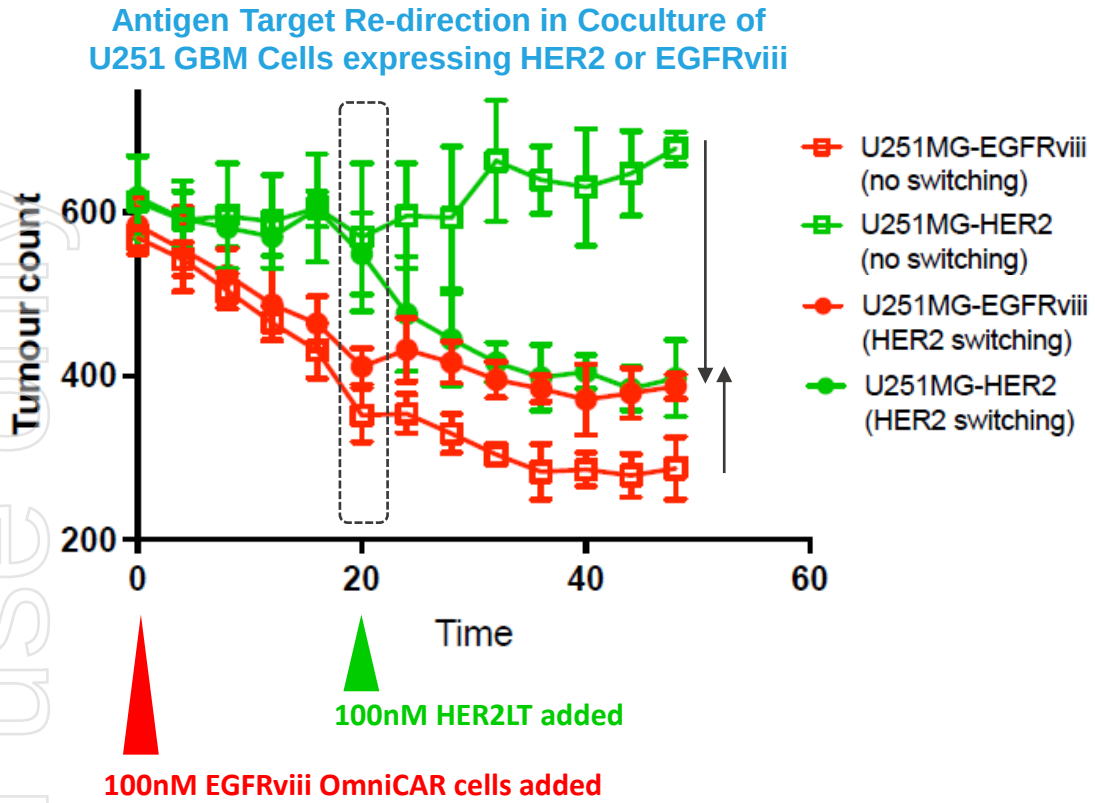
## Specifically directed, at-will killing




- **Only kills cells that the CAR-T is armed against**
- OmniCAR CAR-T cells have similar specific tumour killing capacity, whether **dual**-armed or **single**-armed

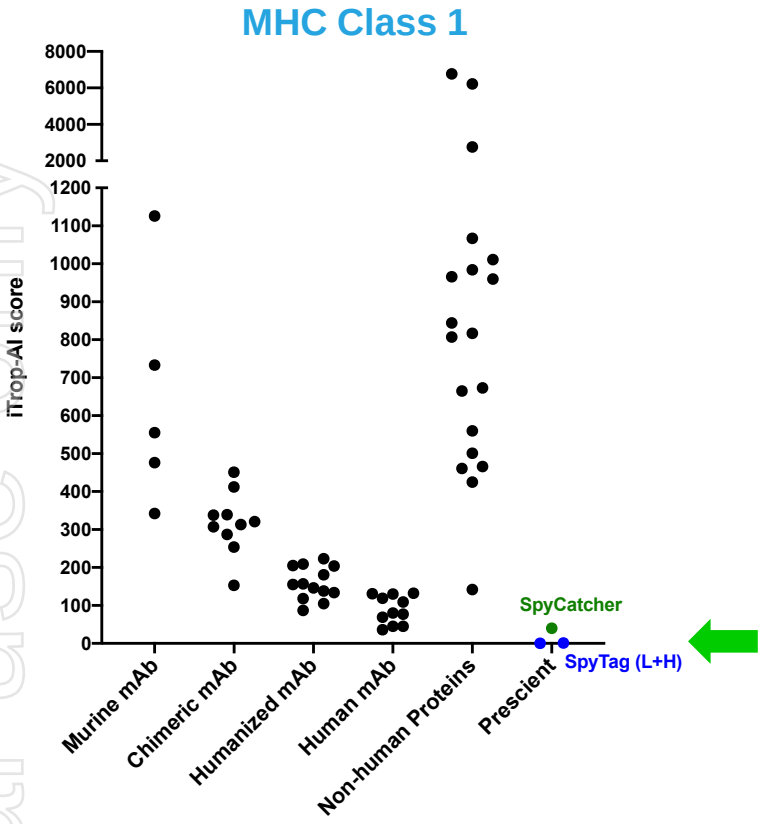
Powell, DJ et al, JACS; 2020

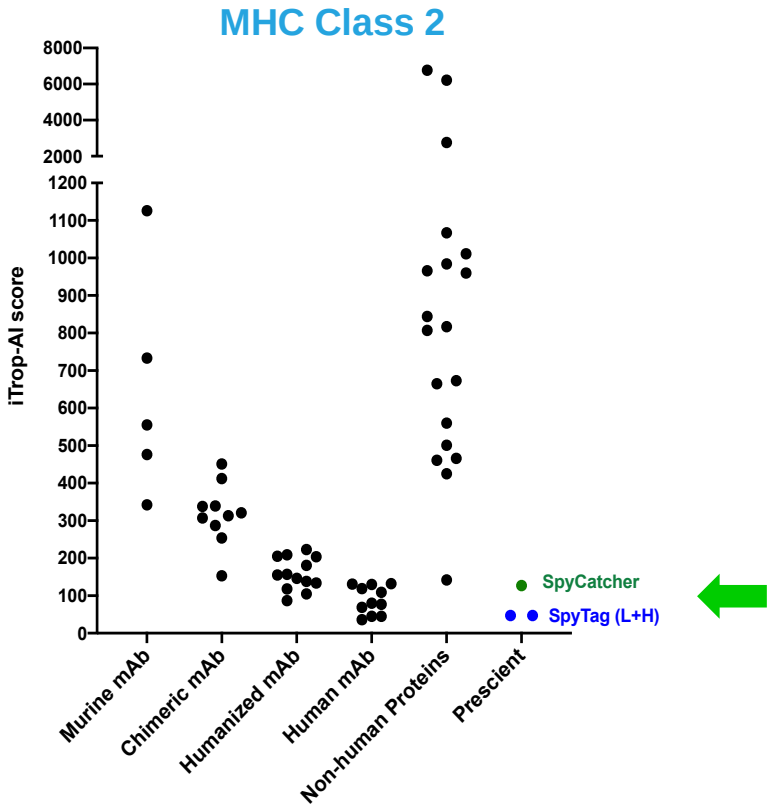
# Redirection: Adding new ST-binder can re-direct cytotoxicity




- Rapid cytotoxicity to EGFRviii
- **Rapid switching and cytotoxicity** against HER2+ tumours upon administration of new binder
- OmniCAR cells can be **re-directed to different antigens** upon administration of a different SpyTagged binder **without new cells**

# In-silico immunogenicty on par with Human mAbs



# OmniCAR Internal Program Summary

| Targets | Indications | OmniCAR features | Comments |
|---|---|---|---|
| **CD33 + CLL-1** | Acute Myeloid Leukemia (AML) | • **Titration** for improved safety<br>• **Co-arming** against CD33 & CLL-1<br>• **Sequential targeting** | • **Validated** targets; expressed on 90%+ of AML blasts & LSCs<br>• **1 of 3 programs worldwide**; the only next-gen program |
| **HER2** | Ovarian; breast & gastric cancers | • **Titration** for improved safety<br>• **Persistent binder dosing** for improved efficacy<br>• **TME** and checkpoint enhancements | • **Most mature** next-gen HER2 CAR-T program<br>• Builds on Penn **pre-clinical PoC** |
| **HER2 + EGFRviii** | Glioblastoma multiforme (GBM) | • **Titration** for improved safety<br>• **Co-arming** against HER2 & EGFRviii<br>• **Persistent binder dosing** for improved efficacy | • **1 of 3 multiple antigen programs in the world**<br>• Single antigen targeting is inadequate in GBM |

# AML

## OmniCAR CD33/CLL-1

# For CAR-T to succeed in AML, it must overcome:

## Safety

AML patients are especially ill with many unable to tolerate vigorous therapies like CAR-T

## Rapid Mutations

AML can mutate mid-therapy, quickly rendering single CAR-Ts ineffective

## Rapid Disease Progression

Even if multiple current generation CAR-T therapies were available, resistant patients are likely to progress before subsequent therapies are manufactured for them

**OmniCAR is uniquely placed to address these challenges for CAR-T in AML**

# CD33 & CLL-1 are excellent AML targets for CAR-T

- CD33
  - Validated target in AML with approved anti-body drug conjugate (gemtuzumab ozogamicin, or Mylotarg)
  - CD33 is constantly expressed on both normal and malignant myeloid cells
  - CD33 expressed on >90% adult and childhood AML blasts and on leukemia stem cells, which have the ability to indefinitely replicate to produce cancerous leukemic cells, leading to relapse

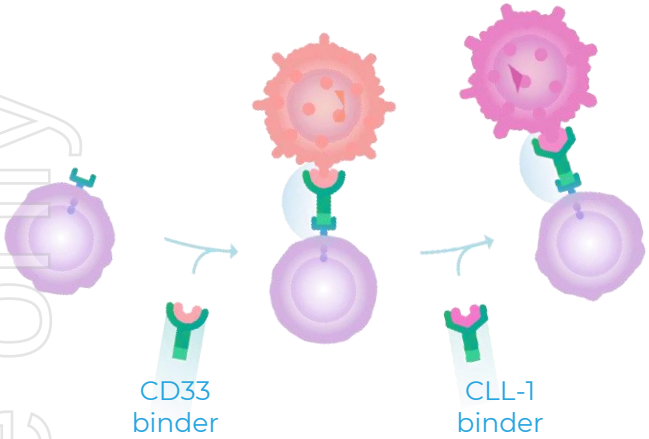
- CLL-1
  - Expressed on 92% of AML cells
  - Absent from normal hemopoietic stem cells
  - Importantly, CLL1 is expressed on leukemic stem cells, which produce subsequent cancer cells leading to relapse



Borot, F,et al; Gene-edited stem cells enable CD33-directed immune therapy for myeloid malignancies; *PNAS*; Jun 2019, 116 (24)
Ma, H., Padmanabhan, I.S., Parmar, S. et al. Targeting CLL-1 for acute myeloid leukemia therapy. *J Hematol Oncol* 12, 41 (2019).

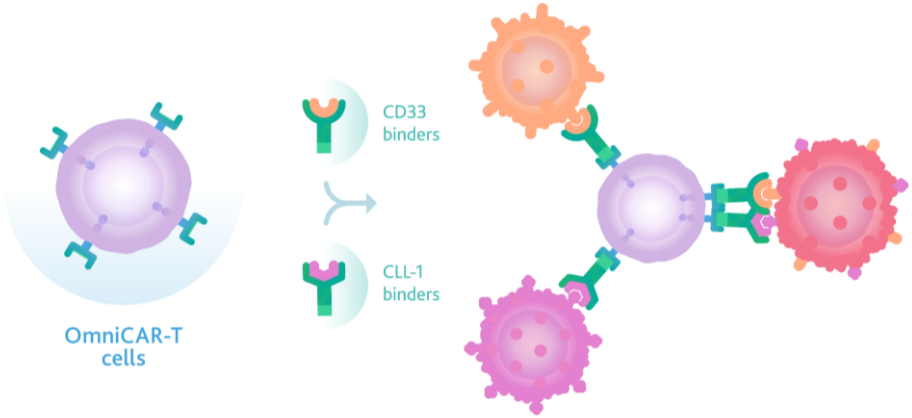
# Targeting Multiple Antigens *Sequentially* OR *Simultaneously*

## Sequentially




- Address antigen escape by redirecting T-cells without new dose of T-cells
- May be a more tolerable approach for sick AML patients

## Simultaneously




- Co-Arming against CD33 & CLL1 on a single T-cell product
- Target several cancer cell populations at once:

  CD33+ | CLL1+ | CD33+ CLL1+

- Could broaden anti-tumour immune response.

# Solid Tumors

## OmniCAR HER2

# Key challenges for CAR-T in solid tumours

**Targets**

Limited targets that are cancer-specific

Leads to on-target, off-tumour effects

**Safety**

Ability to titrate doses safely and switch off in the event of adverse events

Especially important for on-target, off-tumour activity

**Trafficking**

Inability of T-cells to reach tumour sites and penetrate physical barriers

**TME**

Overcoming an immunosuppressive Tumour Microenvironment once they get there

**OmniCAR's features enable it to address these challenges for CAR-T in solid tumours**

# Huge market opportunities for HER2+ cancers

| | New cases/year worldwide[1] | Proportion that are HER2+ [2,3,4] | New HER2+ cases/year |
|---|---|---|---|
| Ovarian Cancer | 300,000 | 29% | 87,000 |
| Breast Cancer | 1,700,000 | 20% | 340,000 |
| Gastric Cancer | 952,000 | 22% | 209,440 |

- OmniCAR T cells armed against HER2
- Builds upon the encouraging work already undertaken by UPenn with HER2
- Makes OmniCAR HER2 the most advanced next-generation HER2 CAR-T program
- Prescient will take a “basket study” approach to HER2+ cancers
- Even when failing HER2 therapies, tumours can still express HER2, making these patients potential candidates for anti-HER2 CAR-T therapy




1. World Cancer Research Fund
2. Shang AQ, et al. Relationship between HER2 and JAK/STAT-SOCS3 signaling pathway and clinicopathological features and prognosis of ovarian cancer. *Cancer biology & therapy*. 2017:1–9
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Prescient Therapeutics

# GBM

## OmniCAR HER2/EGFRviii

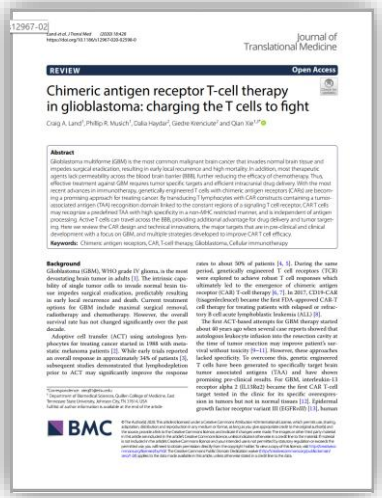
# CAR-T challenges in GBM: single antigen targeting

- Composition of GBM, and its ability to rapidly mutate, limits the effectiveness of CAR-Ts only targeting a single antigen
- Targeting a single antigen targeting can result in relapse

*"A major limitation of a single-antigen targeting in GBM is the inherent heterogeneity and plasticity of the tumor cells, allowing some cells to* ***escape CAR-T*** *cell killing due to the* ***loss of the targeted antigen****…"*

*"…****single antigen-targeting*** *CAR-T cells* ***fail to completely eradicate*** *brain tumors resulting in antigen negative* ***relapses****"*

- By contrast, CAR-Ts targeting multiple antigens have demonstrated **anti tumor responses** and **more importantly prevented antigen escape** *in vivo*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Journal of Translational Medicine

REVIEW Open Access

Chimeric antigen receptor T-cell therapy in glioblastoma: charging the T cells to fight

Craig A. Land[1], Phillip R. Musich[1], Dalia Haydar[2], Gedre Krenciute[2] and Qian Xie[1,3*]

Abstract

Keywords: Chimeric antigen receptors, CAR, T-cell therapy, Glioblastoma, Cellular immunotherapy

Background

BMC

# Two targets are better than one in GBM

- Single antigen targeting has been inadequate in GBM
- By contrast, **combination** of HER2 and other antigen targeting shows early promise in overcoming relapse
- Prescient will also explore other targets for GBM


- HER2 occurs in 80% of GBM
- Linked with poor survival


- EGFRviii occurs in 45% of GBM
- Importantly, EGFRviii is only present on GBM and **is not found on healthy tissues**



Zhang, L et al; HER2-targeted recombinant protein immuno-caspase-6 effectively induces apoptosis in HER2-overexpressing GBM cells in vitro and in vivo; *Oncology Reports*; Sept 2016
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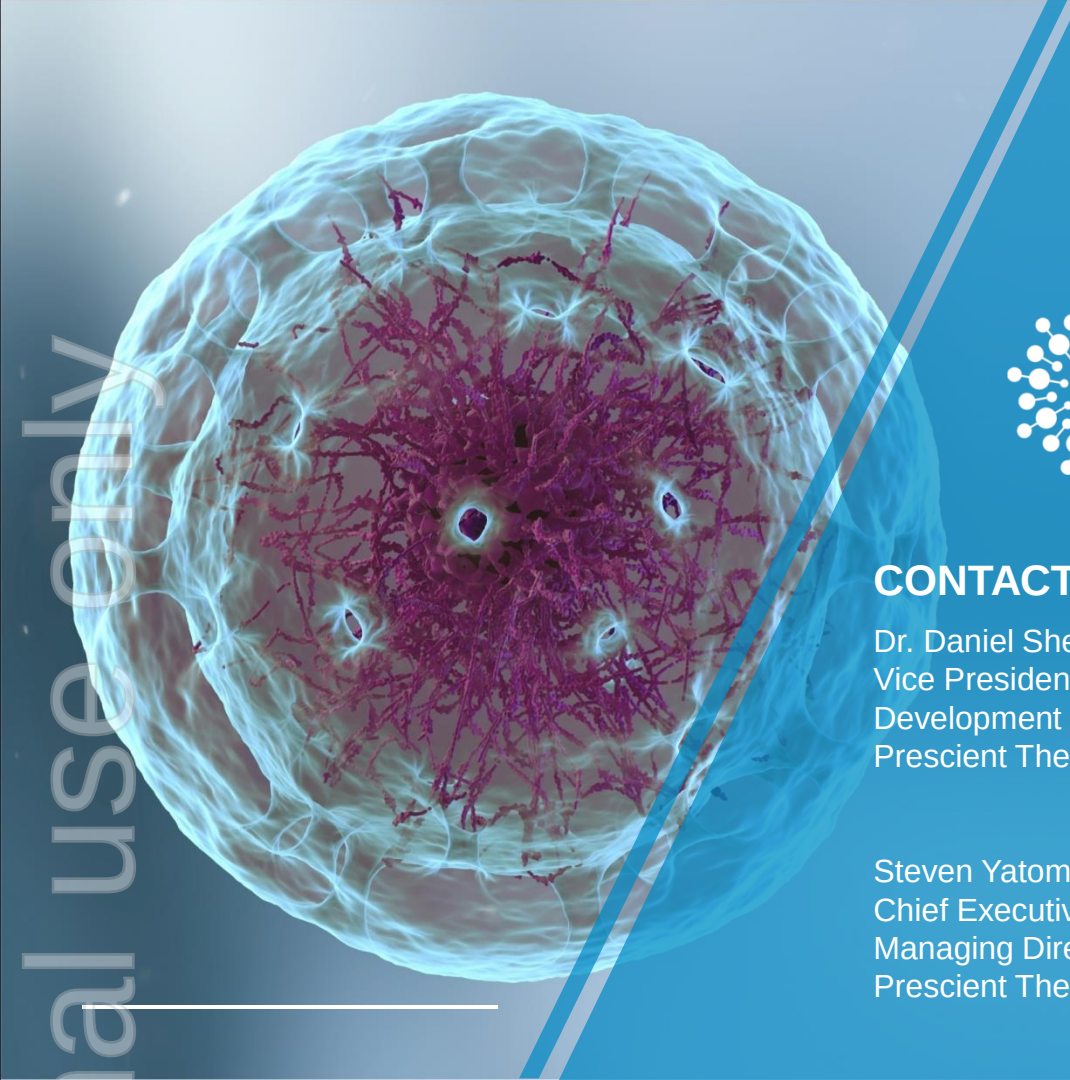
# Summary

- OmniCAR addresses problems encountered by current generation CAR-T
- 3 in-house OmniCAR programs, all highly differentiated and representing large opportunities
  - CD33/CLL-1 for AML
  - HER2+ solid tumours
  - HER2/EGFRviii for GBM
- Prescient is open to licensing and collaboration. OmniCAR can enhance the safety, flexibility and efficacy of third-party CAR programs
  - Agnostic on targets; indication; cell type





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