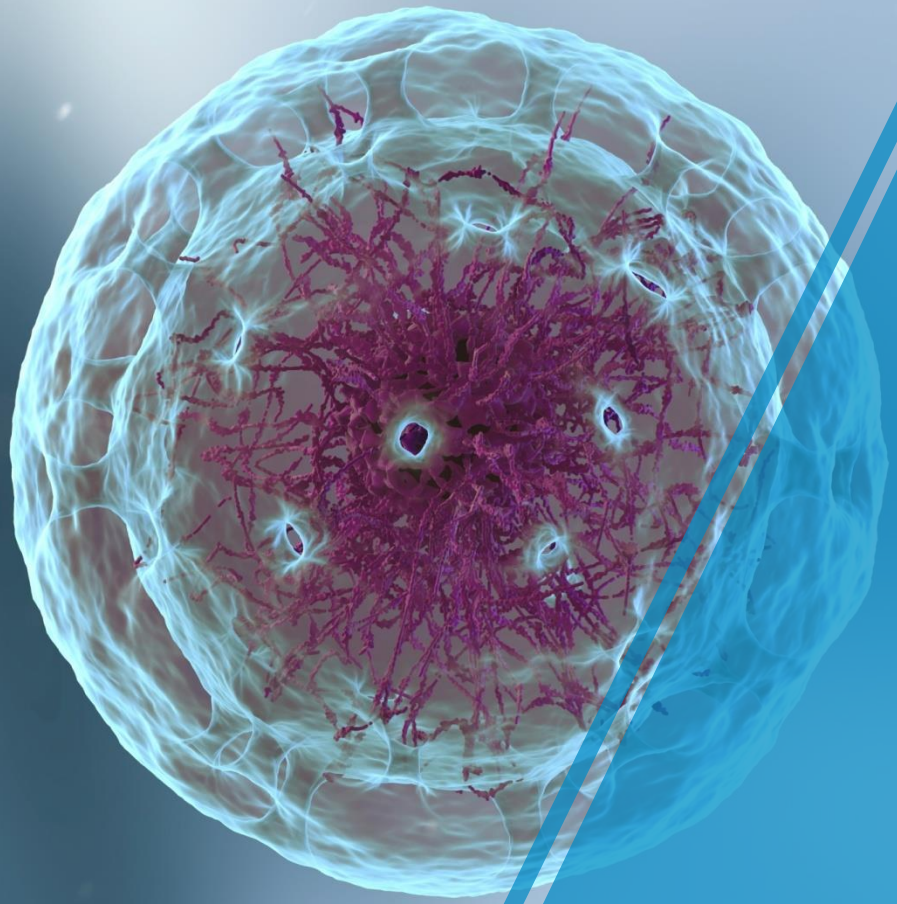

Prescient Therapeutics

OmniCAR

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

Prescient Therapeutics Limited (ASX: PTX)

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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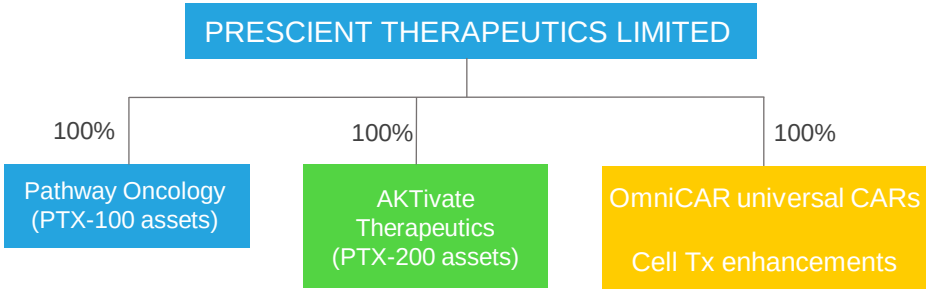
Corporate Snapshot

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

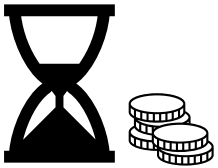
Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Prescient Therapeutics

OmniCAR

Universal, Next Generation CAR-T

Key Challenges Confronting the field of CAR-T



Time and Cost

of delivering treatment

Targets

Finding targets that work;

Antigen heterogeneity - esp. in solid tumours

Safety

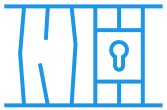
CAR-T can have serious safety concerns

Exhaustion

Persistent stimulation of CAR-Immune cells leads to exhaustion

No Control

Clinicians have no control of cells post infusion



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**

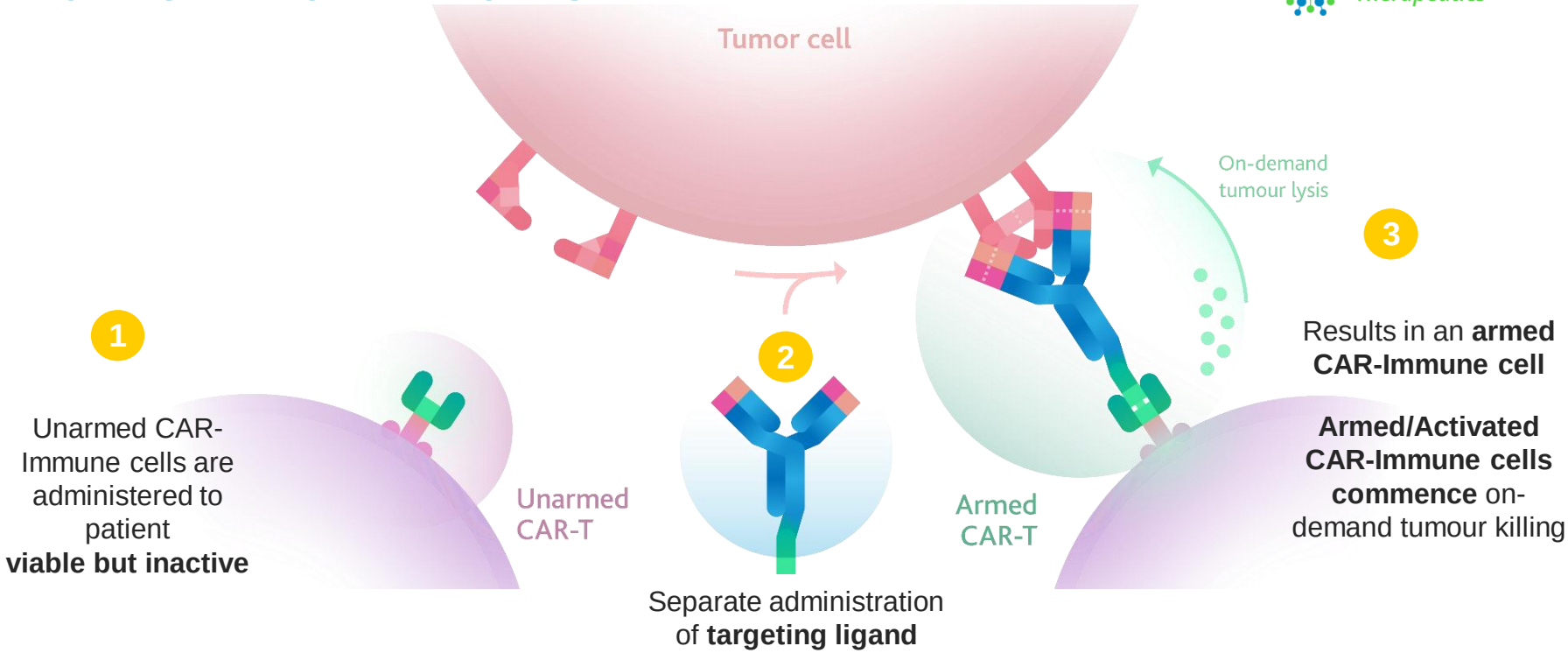
Co-inventors

Associate Professor
Daniel J. Powell, Jr

Professor
Andrew Tsourkas

Powell, DJ et al, JACS; 2020

How OmniCAR works



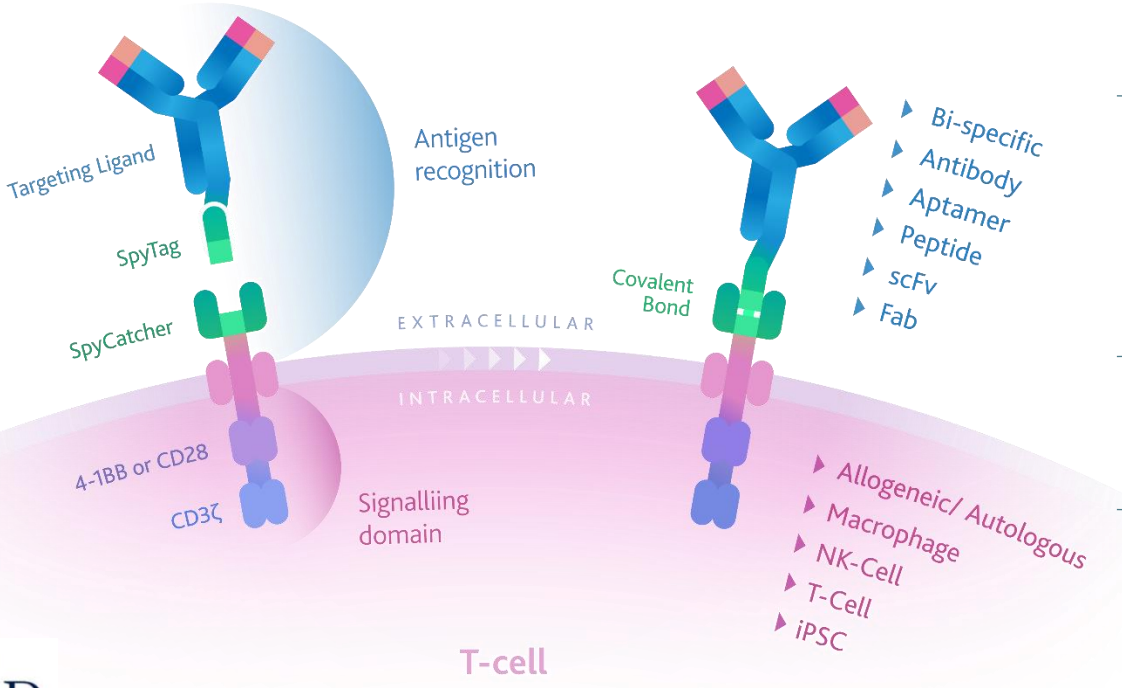
- CAR-Immune Cell activity is **now controllable**
- Target specificity of CAR-Immune Cells can be **switched at will**, by administering a different targeting ligand

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

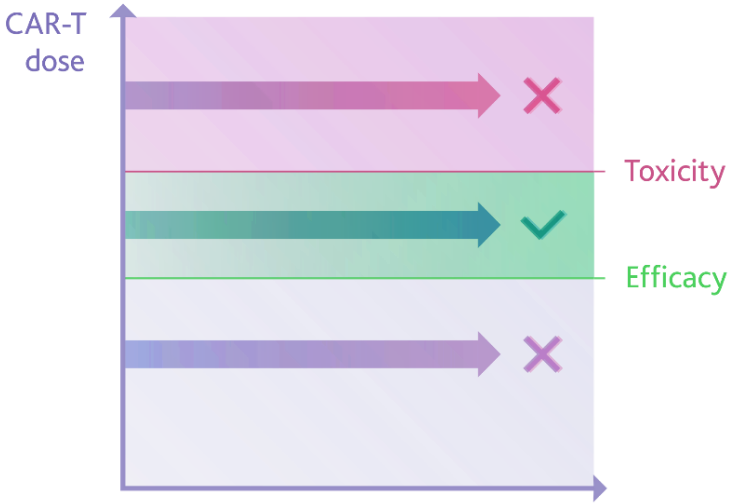
Any Immune Cell → To any Target…

Adapted from Powell, DJ et al, JACS; 2020

Safety: Ability Control Dose & Activity

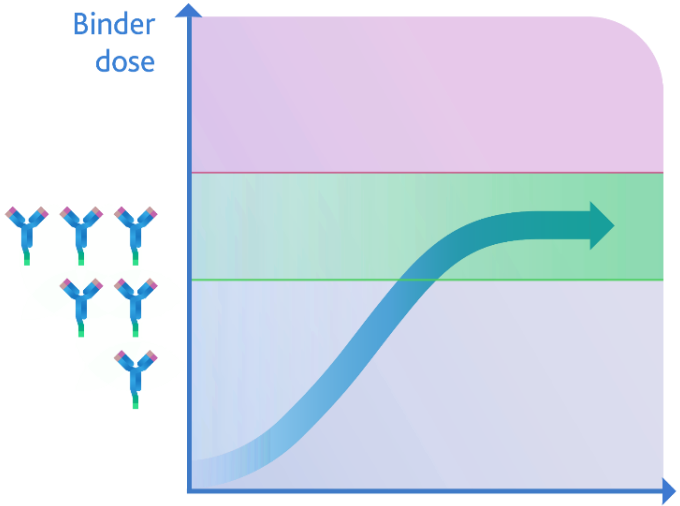
Conventional CAR-T

- 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

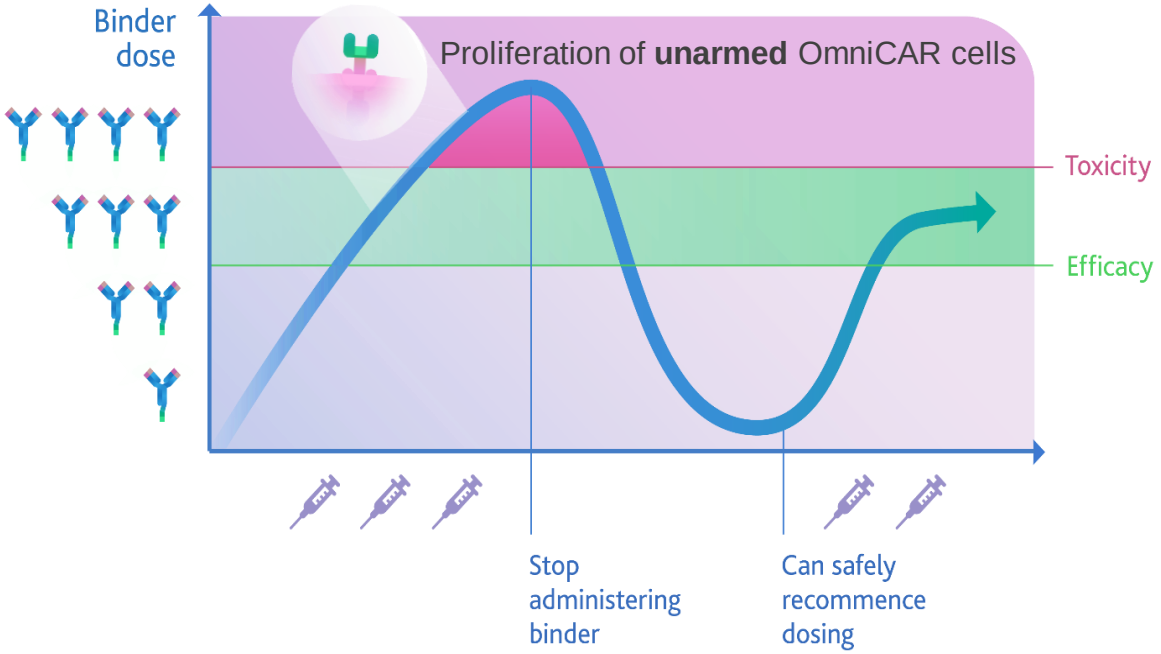
- Clinician control **post infusion**
- Controlling subsequent **dose** of binder controls CAR-T **activity**
- Titrate dose to **safe and efficacious** levels



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

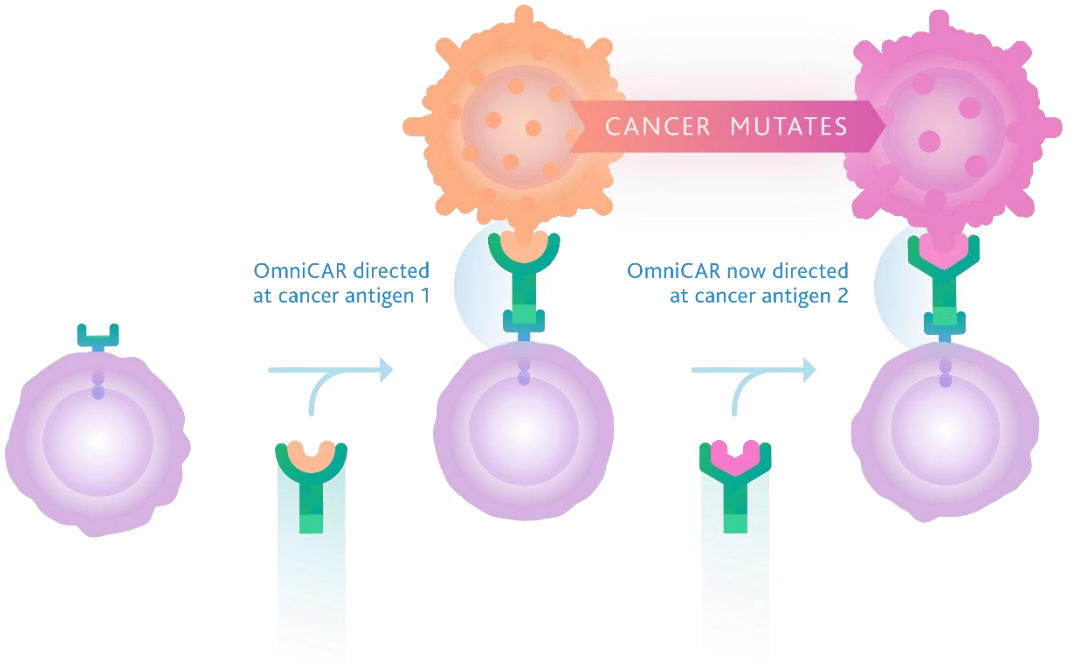
Safety: Built-in on/off switch

- Cell activity can be **switched off at-will**
- Cells remain **viable but inactive**
- OmniCAR can be **safely reactivated**
- No uncontrolled activity
- **Receptor Turnover and Cell Proliferation = Unarmed SpyCatcher**



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

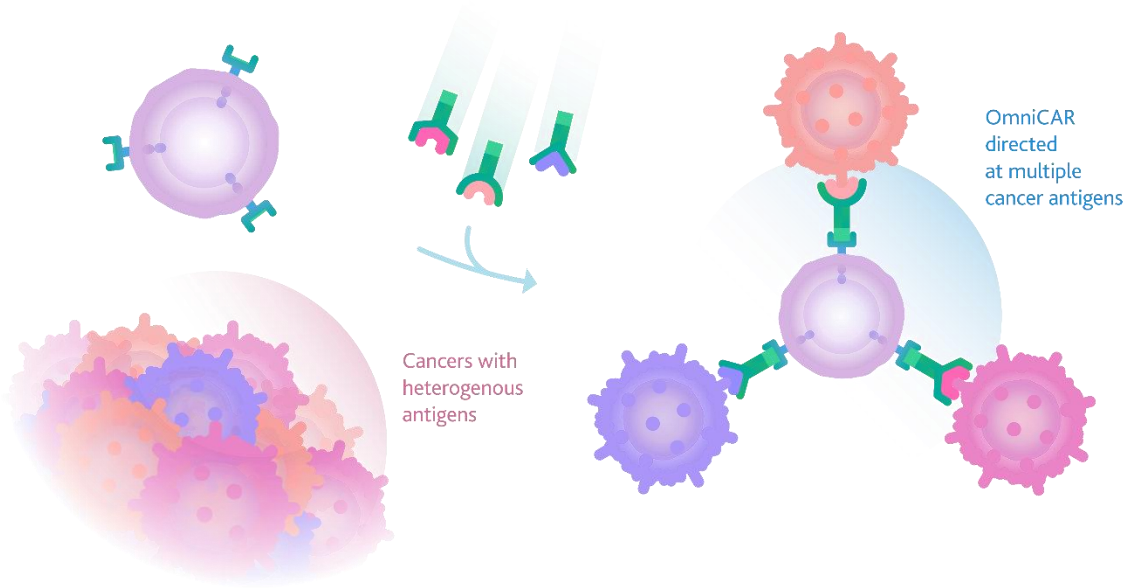
Target Multiple Antigens *Sequentially*



- 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*

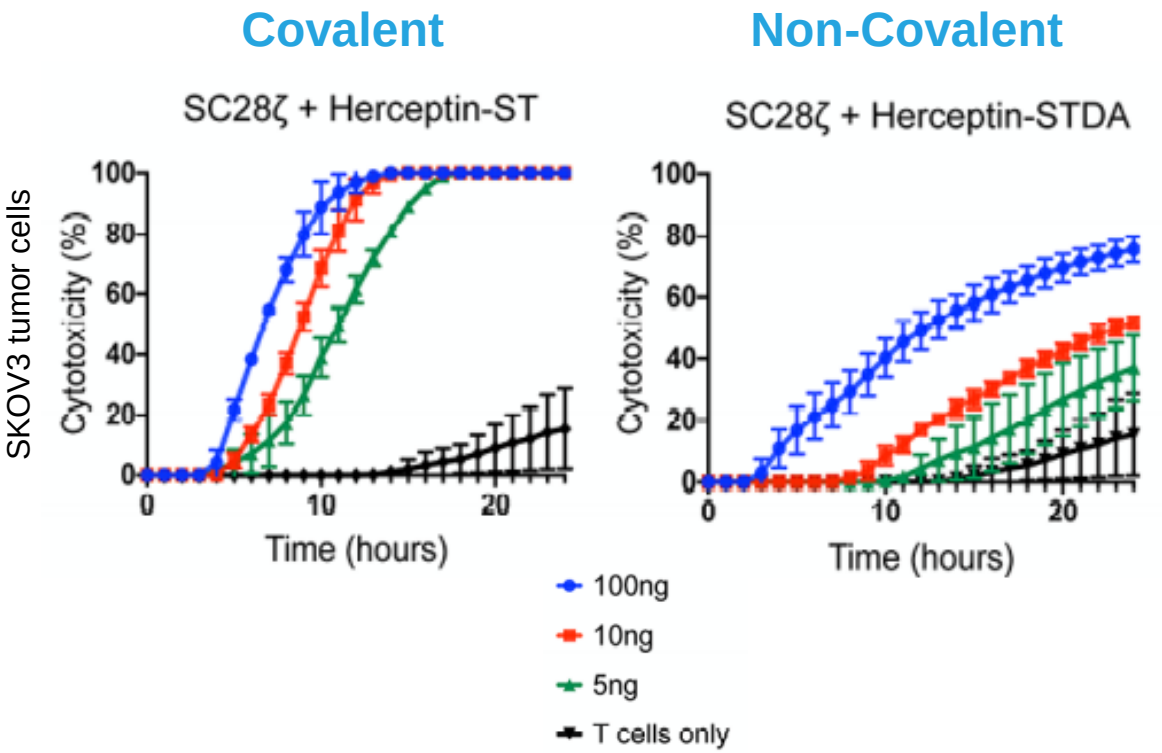


- Multiple antigen targeting with single vector/cell product
- Could broaden anti-tumour immune response
- Prevents escape
- Tailor arming combinations and proportions
- Utility in many solid tumours

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

Covalent Binding:

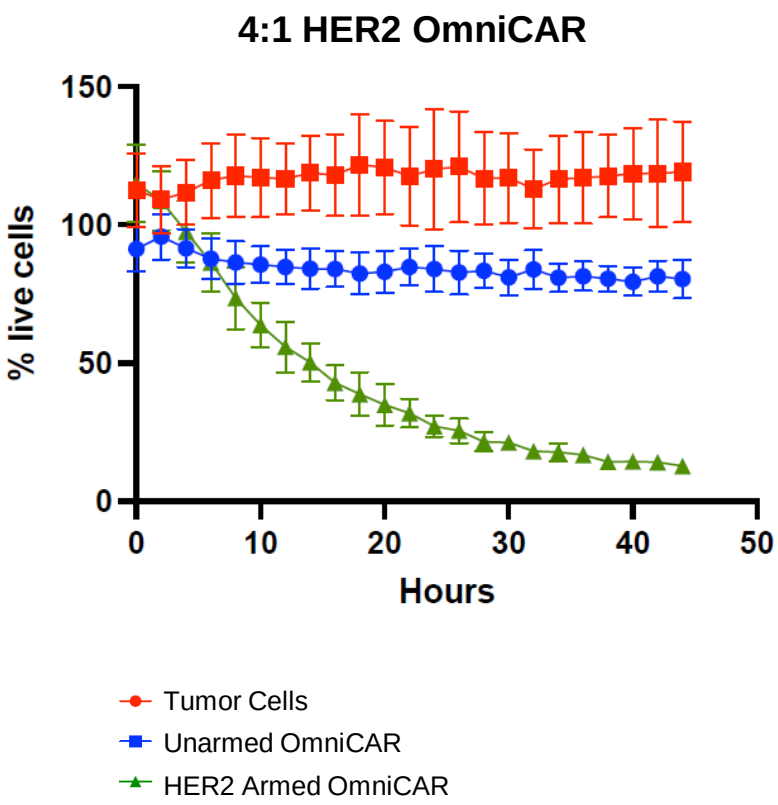
Superior tumor killing & other advantages

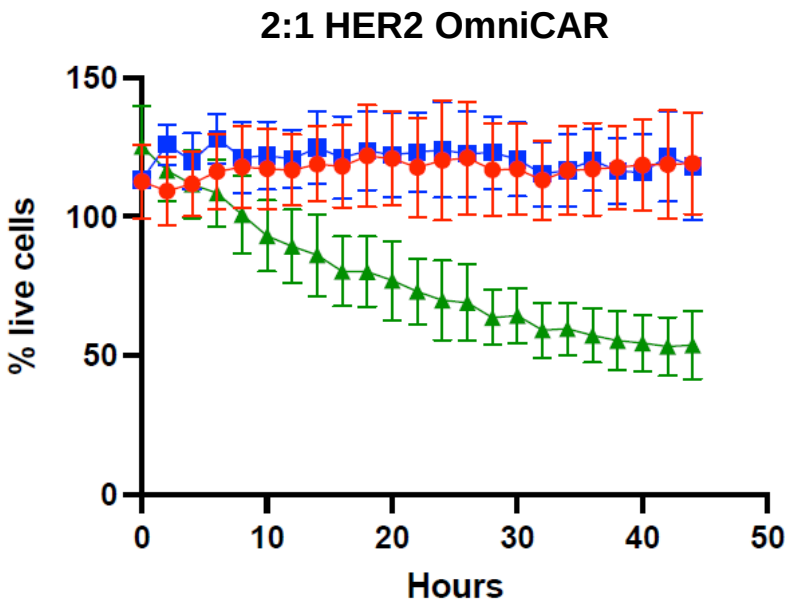


- **Covalent** binding improves SpyCatcher T-cell **loading and tumour cell lysis**
- Covalent binding has additional advantages in:
  - Efficacy
  - Predictability
  - Clinical utility
  - Regulatory considerations

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

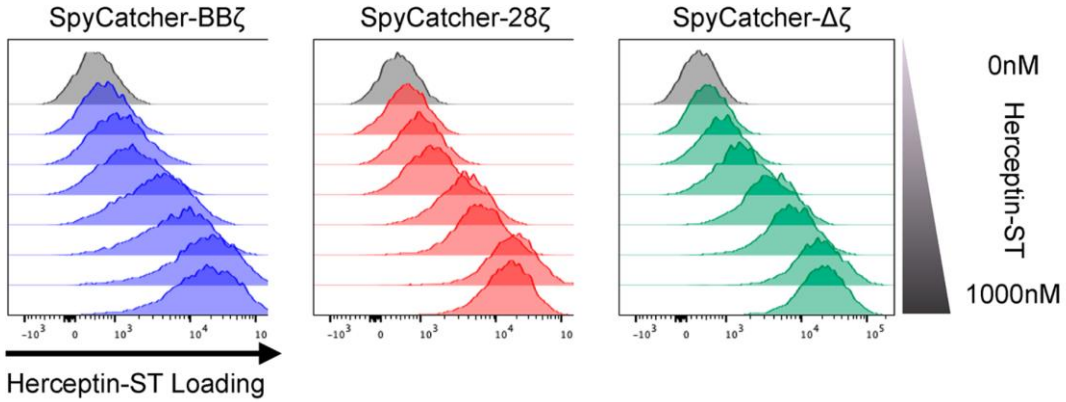




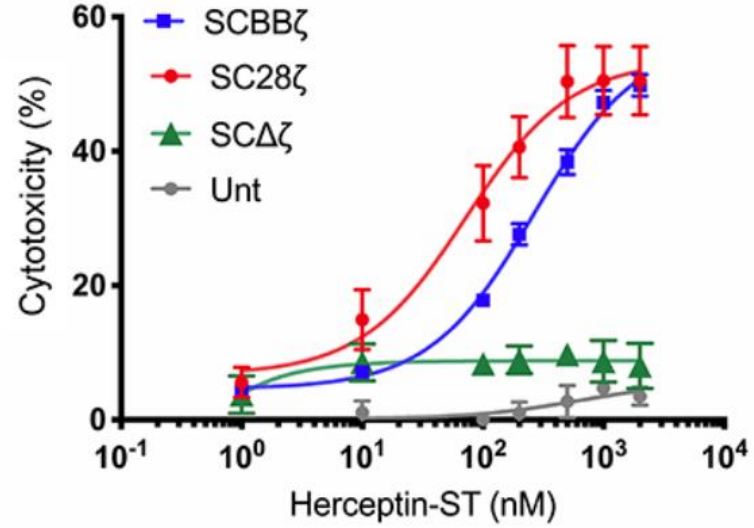
At 2:1, OmniCAR achieves cytotoxicity at a rate that aims to **balance efficacy** whilst **avoiding CRS and exhaustion**

Flexible Loading and Dose-Dependent Lysis

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



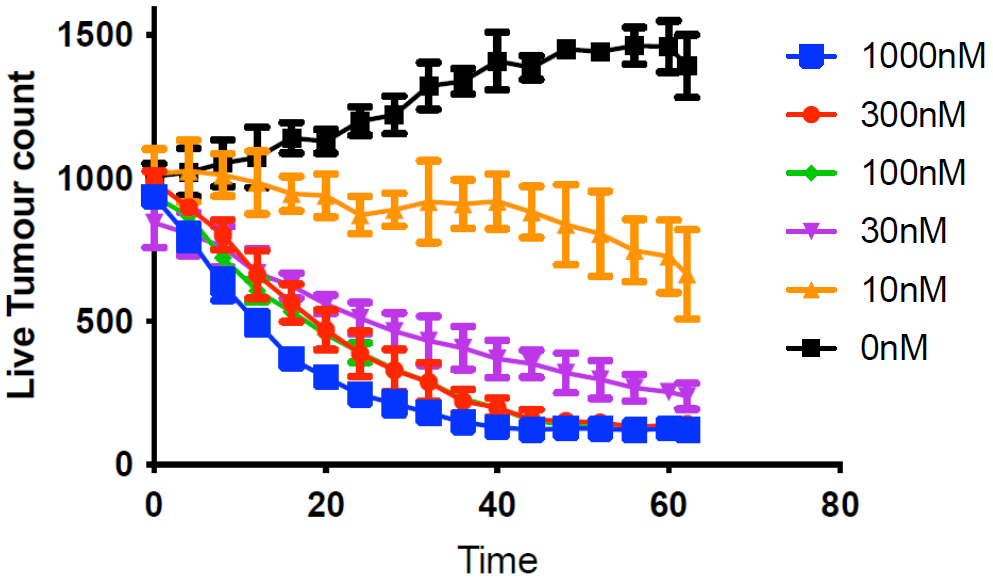
- Increasing targeting ligand concentration results in increased lytic capacity



Powell, DJ et al, JACS; 2020

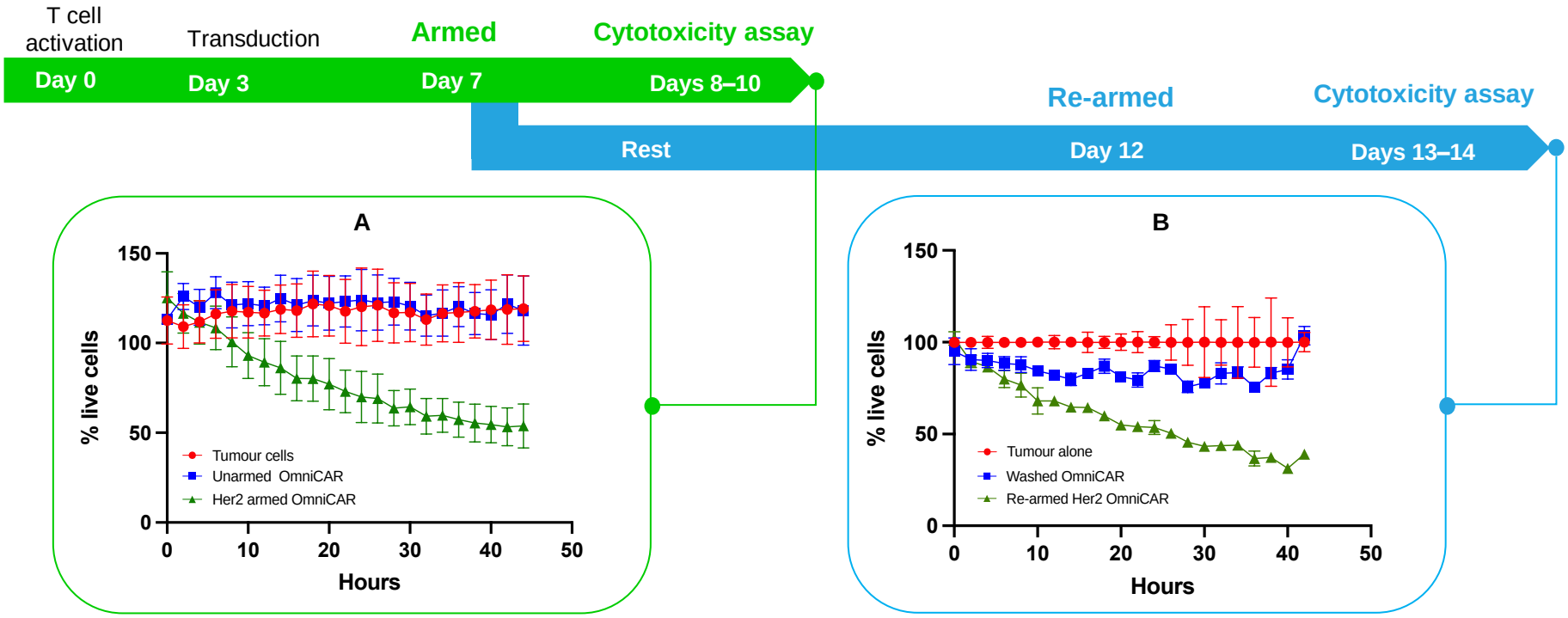
Dose response: High potency with less binder required

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**

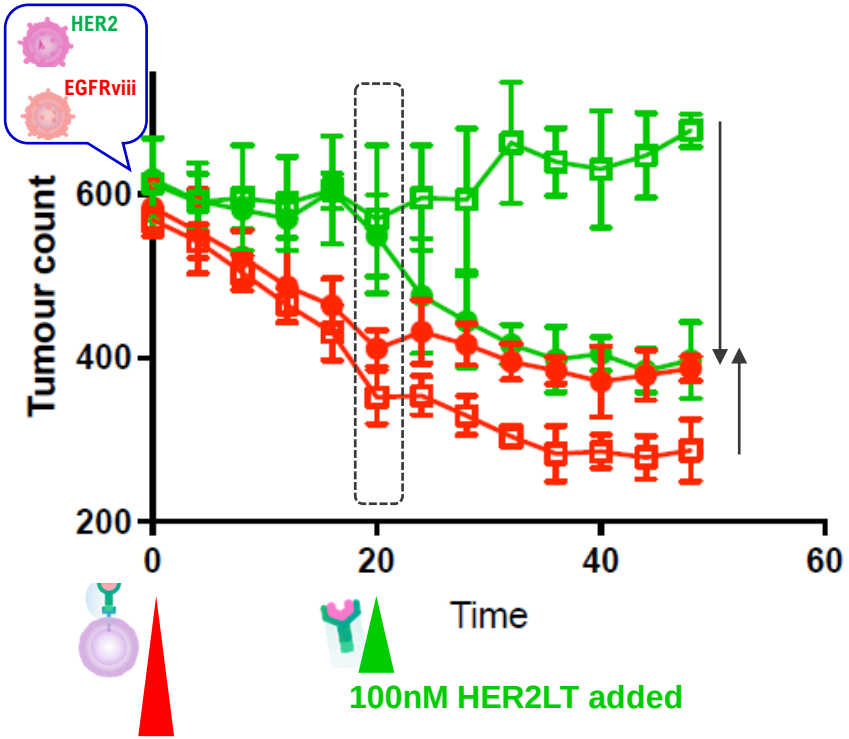
Re-Arming: OmniCAR Her2 can be Re-Armed



- 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

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

Antigen Target Re-direction in Coculture of U251 GBM Cells expressing HER2 or EGFRviii



U251MG-EGFRviii (no switching)
U251MG-HER2 (no switching)
U251MG-EGFRviii (HER2 switching)
U251MG-HER2 (HER2 switching)

- 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**

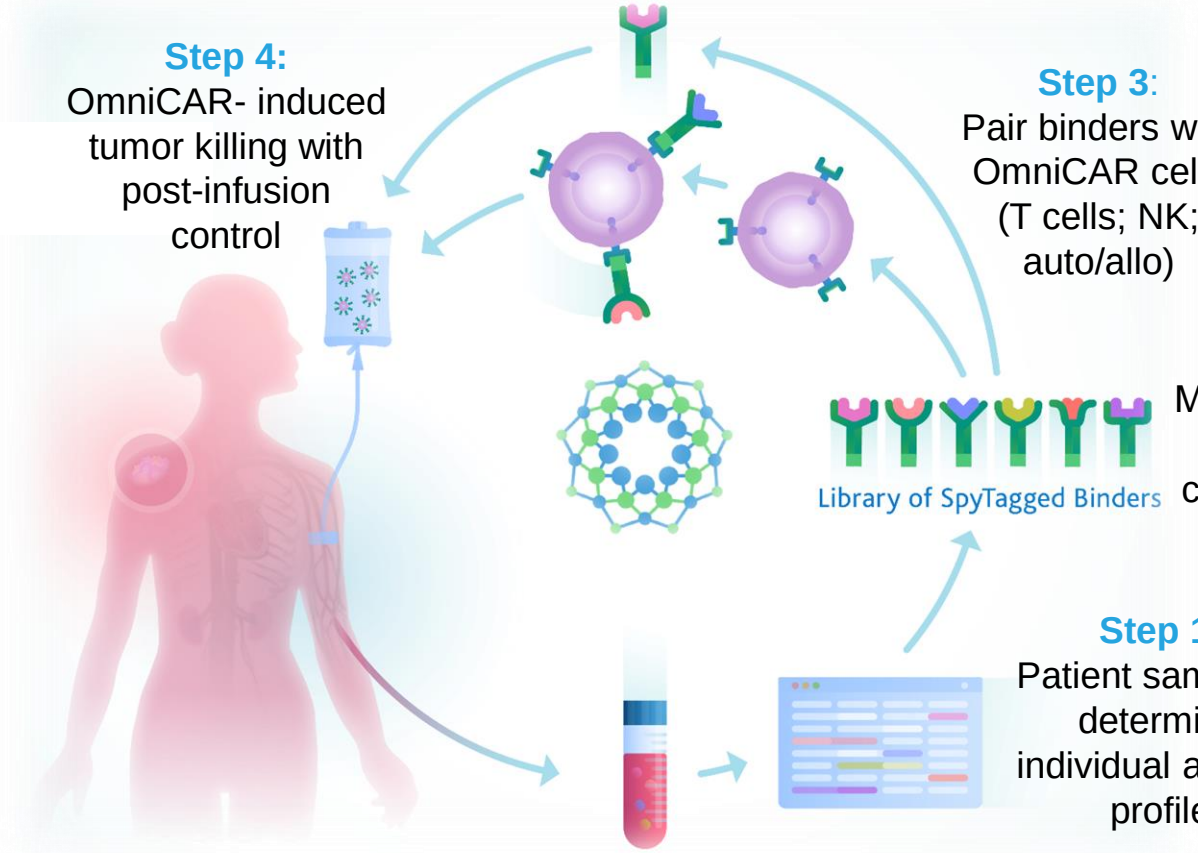
The future of ACT is efficient yet personalized:
OmniCAR cells + “plug & play” binder library

Prescient Therapeutics

Example AML: (28)
ADGRE2 (EMR2)
AIQ–HLA-A2
CD117
CD123
CD13
CD133
CD19
CD25 (IL-2Rα)
CD33
CD34
CD38
CD56 (NCAM-1)
CD70
CD93
CLL-1
EpCAM
FLT3 (CD135, FLK2, STK1)
GMR (CD116/CD131 complex)
GRP78 (HSPA5, BiP)
IL10RB (CRFB4, D21S58, D21S66)
IL1RAP
ILT3 (LILRB4)
Mesothelin
MUC-1
NKG2DL
TIM-3 (HAVCR2)
TPO-R (c-Mpl, CD110)

Step 4:
OmniCAR- induced tumor killing with post-infusion control

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



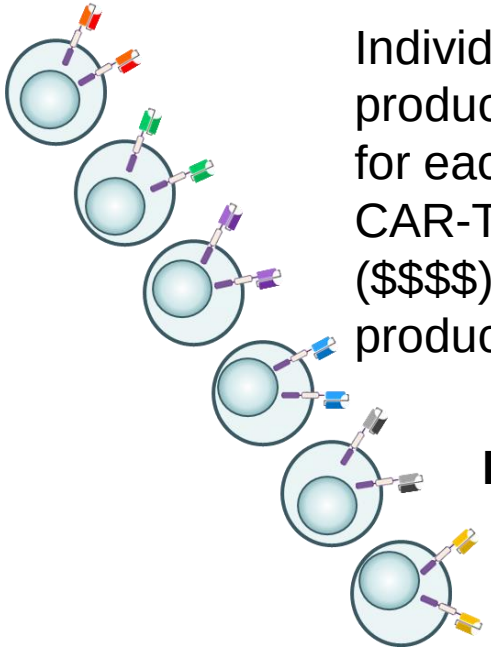
Step 2:
Match patient’s antigens to corresponding binders

Step 1:
Patient sample to determine individual antigen profile

OmniCAR: Enables more efficient, cost-effective, and reproducible manufacturing

Prescient Therapeutics

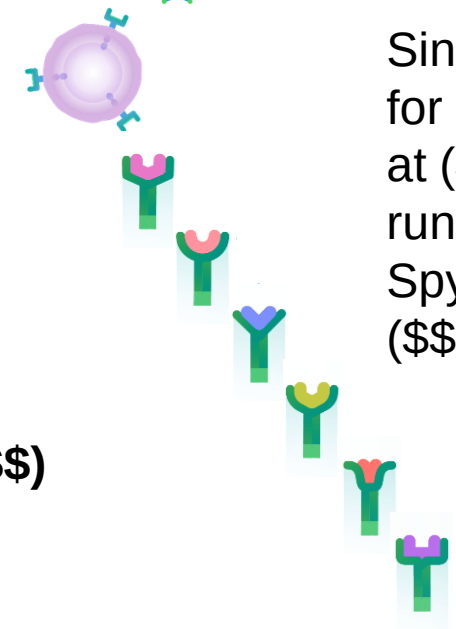
Conventional CAR-T



Individual production runs for each Auto CAR-T product at ($$$$) per production run.

E.g. 6 X ($$$$)

OmniCAR



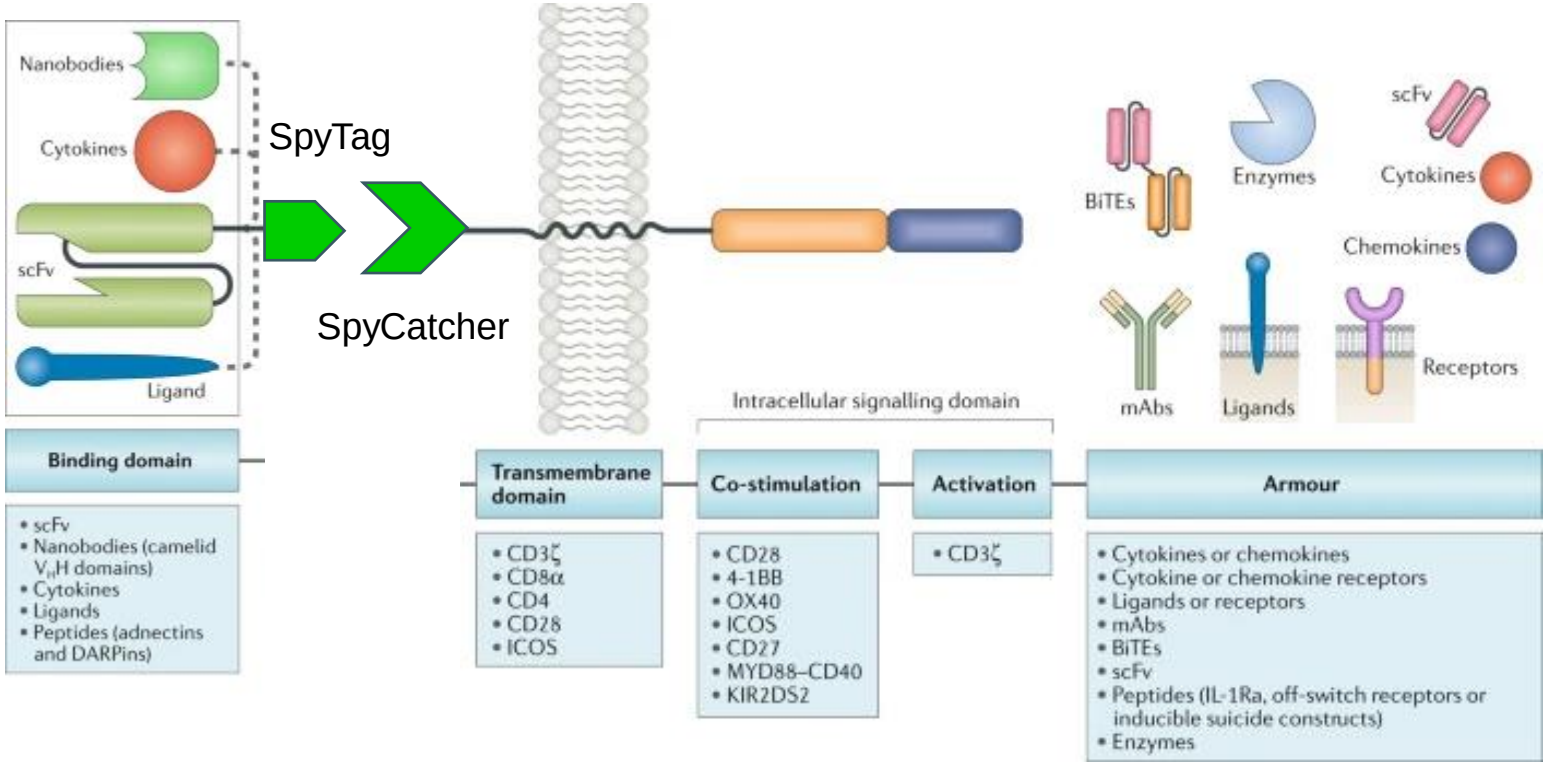
Single production run for SpyCatcher T-cell at ($$$$) and 6 cGMP runs for recombinant SpyTagged Binder at ($$)/run.

E.g. (1 X $$$$) + (6 X $$)

Conclusion: OmniCAR would provide significant cost economics along with control and flexibility compared to conventional CAR-T.

OmniCAR: Integrates Multiple Technologies into a Screening/Therapeutic Ecosystem – Ex: AML

ADGRE2 (EMR2)
AIQ–HLA-A2
CD117
CD123
CD13
CD133
CD19
CD25 (IL-2Rα)
CD33
CD34
CD38
CD56 (NCAM-1)
CD70
CD93
CLL-1
EpCAM
FLT3 (CD135, FLK2, STK1)
GMR (CD116/CD131 complex)
GRP78 (HSPA5, BiP)
IL10RB (CRFB4, D21S58, D21S66)
IL1RAP
ILT3 (LILRB4)
Mesothelin
MUC-1
NKG2DL
TIM-3 (HAVCR2)
TPO-R (c-Mpl, CD110)

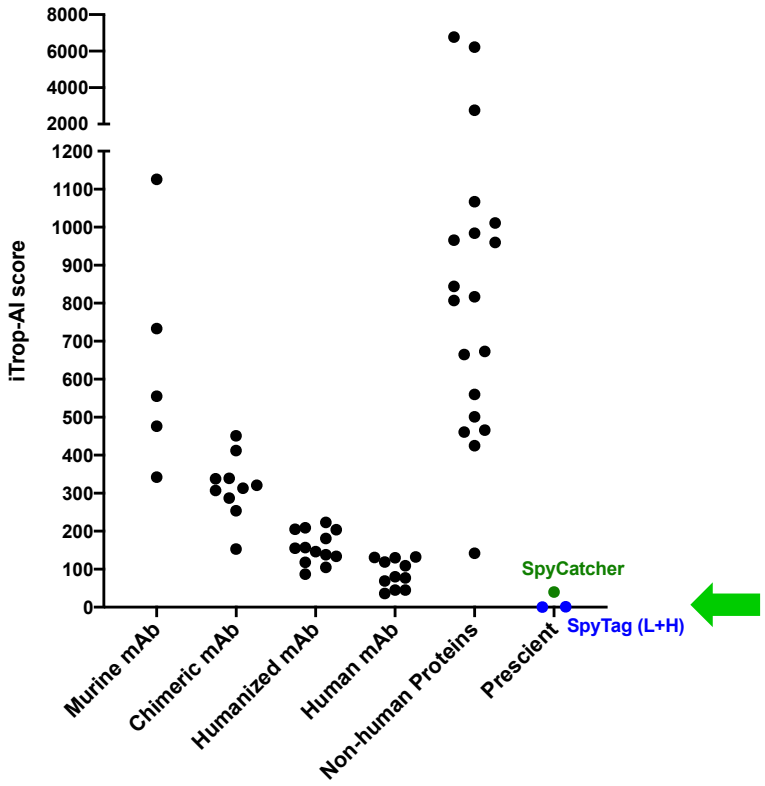


OmniCAR enables high throughput screening of binders/targets and can integrate components into a modular, plug & play **Treatment Ecosystem.**

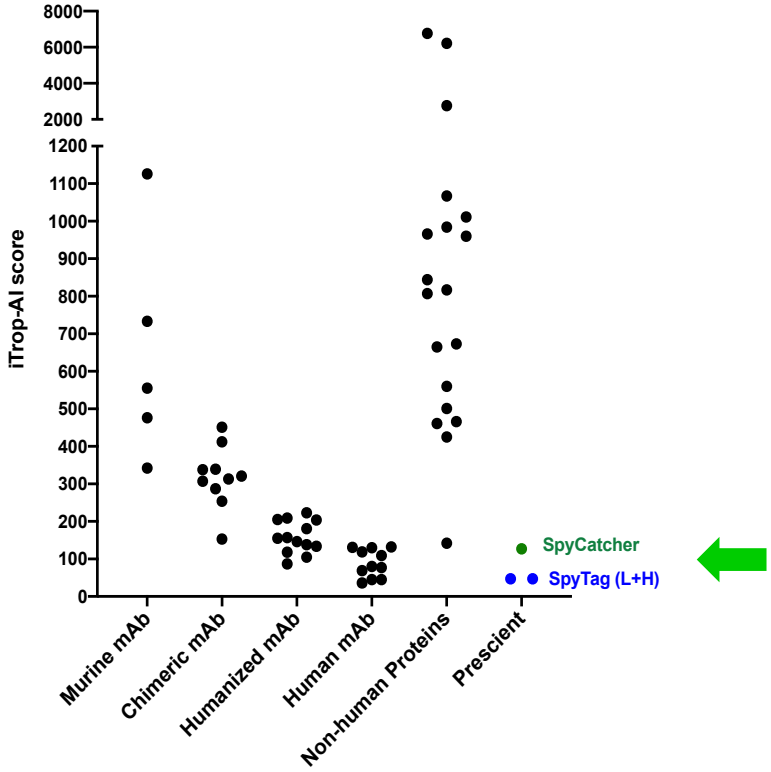
In-silico immunogenicty on par with Human mAbs

Prescient Therapeutics

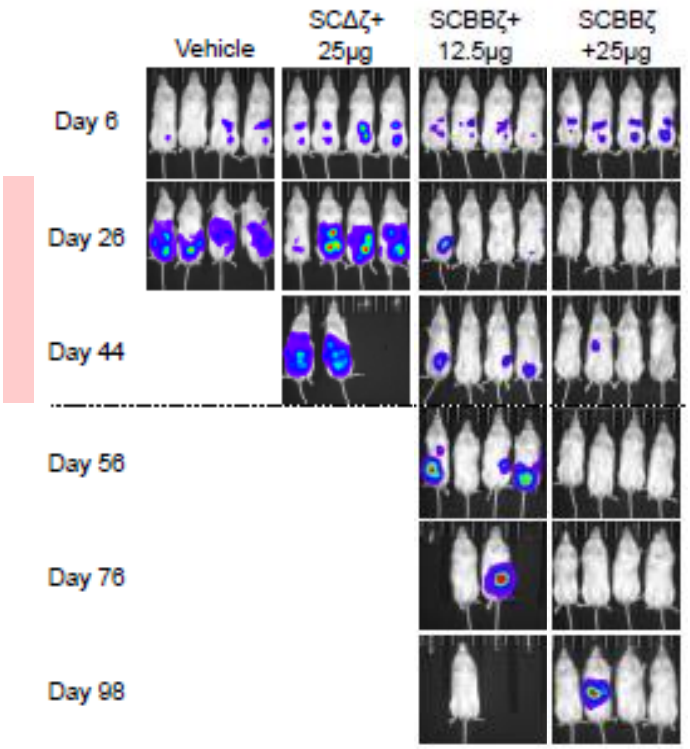
MHC Class 1



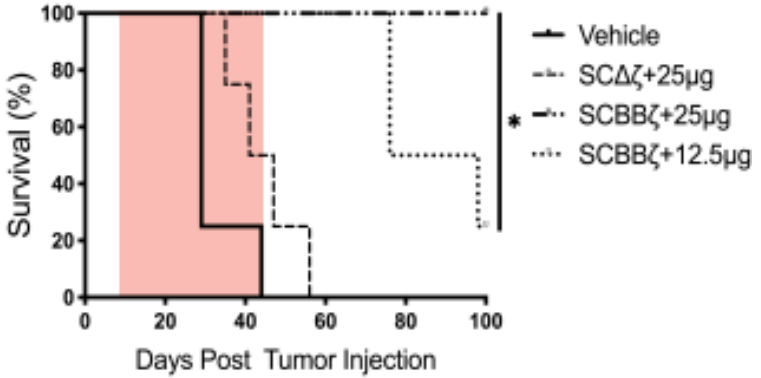
MHC Class 2



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

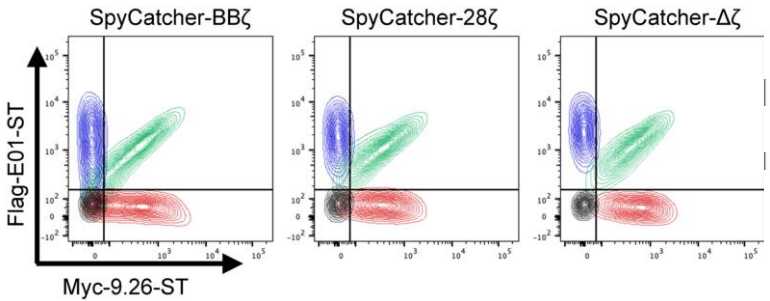


Powell, DJ et al, JACS; 2020

= dosing window of binder

Equal Arming & Equal Tumour Killing

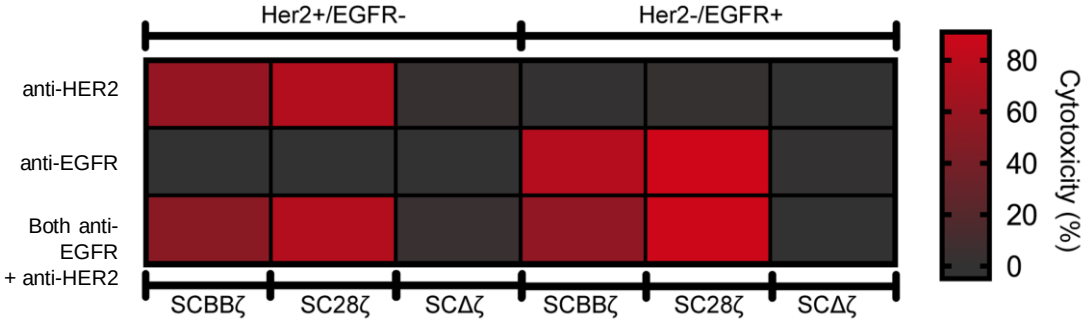
Equal arming



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

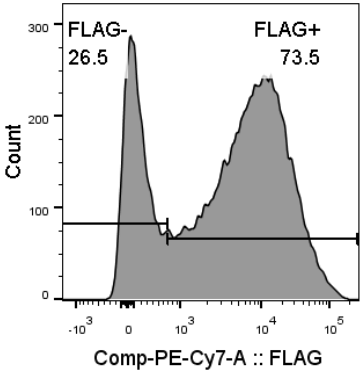
OmniCAR Internal Program Summary

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

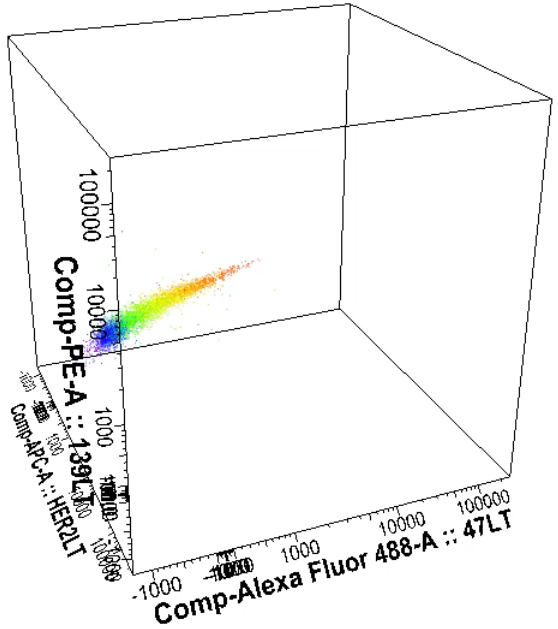
Multi-Arming: Up to 3 Targeting Ligands

Key: Anti-HER2- HER2LT
Anti-EGFRviii- 139LT
Anti-IL13Ra2- 47LT

NFlag003 OmniCAR T cell

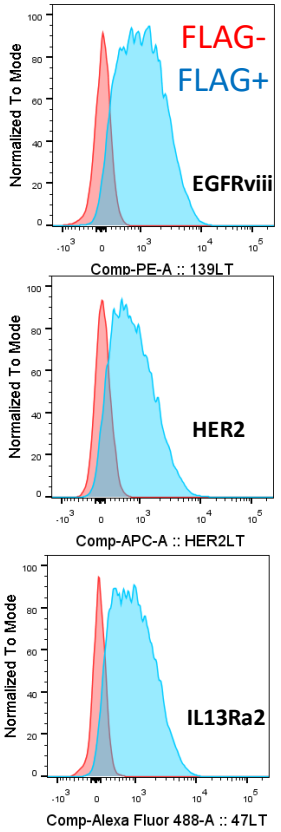


3D FACS plot

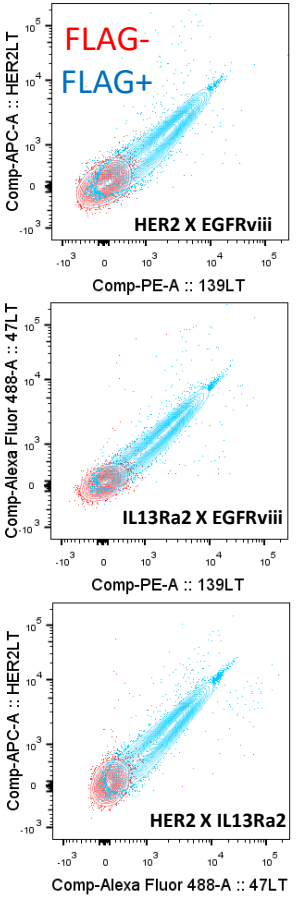


Yellow to Red- high FLAG expression
Green- low FLAG expression
Blue- no FLAG expression

triple arming 33nM+33nM+33nM



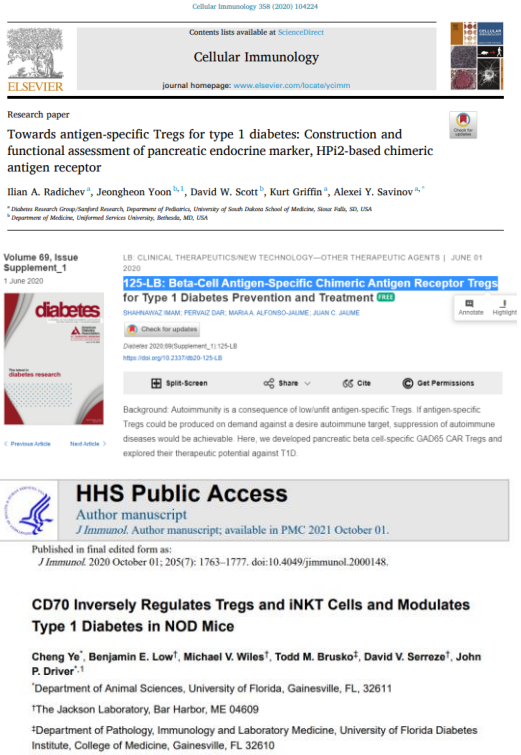
dual arming 50nM+50nM



OmniCAR: CAR-Tregs for Autoimmune disease and T1D

Prescient Therapeutics

- T1D is caused by T cells that become inappropriately activated and kill β cells in the pancreas, resulting in insulin insufficiency and hyperglycemia.*
- CAR-T Regulatory cells could be used to target hyperactivated T-cells, suppressing/reversing destruction of β-cells to treat Type 1 Diabetes Patients.
- Chimeric Antigen Receptor (CAR) expressing a single-chain Fv recognizing the human pancreatic endocrine marker(HPi2).
- GAD65 CAR Tregs were used to prevent/treat diabetes in… humanized mouse model of T1D.
  - Conclusions: GAD65 CAR Tregs were successful in abrogating the diabetes phenotype in T1D mice model. Conceivably, antigen-specific Treg redirection using antigen-specific CAR Tregs and consequent Teff downregulation will allow for recovery and reconstitution of beta cells in humans as well.
- CD27-CD70 costimulation is involved in autoimmunity…
  - Conclusions: A CD27 agonist Ab reversed the effects of CD70 ablation in NOD mice, suggesting that there may be potential to alter the course of T1D by therapeutically targeting CD27.



Cellular Immunology 358 (2020) 104224

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journal homepage: www.elsevier.com/locate/ycimm

Research paper

Towards antigen-specific Tregs for type 1 diabetes: Construction and functional assessment of pancreatic endocrine marker, HPi2-based chimeric antigen receptor

Ilian A. Radichev, Jeongheon Yoon, David W. Scott, Kurt Griffin, Alexei Y. Savinov

Volume 69, Issue Supplement_1
1 June 2020

diabetes

LB: CLINICAL THERAPEUTICS/NEW TECHNOLOGY—OTHER THERAPEUTIC AGENTS | JUNE 01 2020

125-LB: Beta-Cell Antigen-Specific Chimeric Antigen Receptor Tregs for Type 1 Diabetes Prevention and Treatment

SHAHNAWAZ IMAM, PERVAIZ DAR, MARIA A. ALFONSO-JAUME, JUAN C. JAUME

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Background: Autoimmunity is a consequence of low/unfit antigen-specific Tregs. If antigen-specific Tregs could be produced on demand against a desire autoimmune target, suppression of autoimmune diseases would be achievable. Here, we developed pancreatic beta cell-specific GAD65 CAR Tregs and explored their therapeutic potential against T1D.

HHS Public Access

Author manuscript

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CD70 Inversely Regulates Tregs and iNKT Cells and Modulates Type 1 Diabetes in NOD Mice

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*Volfson-Sedletsky V, Jones A, Hernandez-Escalante J and Dooms H (2021) Emerging Therapeutic Strategies to Restore Regulatory T Cell Control of Islet Autoimmunity in Type 1 Diabetes. Front. Immunol. 12:635767. doi: 10.3389/fimmu.2021.635767

OmniCAR: CAR-Tregs for Cardiovascular Disease

- Targeting Cardiac Fibrosis with CAR-T cells emerging as a novel modality.

Molecular Therapy
Commentary

CARdiac Immunotherapy: T Cells Engineered to Treat the Fibrotic Heart

Ronald J. Vagnozzi,[1] Anne Katrine Z. Johansen,[1] and Jeffery D. Molkentin[1,2]

https://doi.org/10.1016/j.ymthe.2019.09.021

Progressive tissue fibrosis underlies numerous disease states, where it can diminish healthy organ function and regeneration after injury.[1] In the adult mammalian heart, excess fibrosis after myocardial infarction (MI) or in the setting of cardiomyopathy worsens cardiac function, leading to hypertrophy and, eventually, heart failure (HF),[2] scar or interstitial fibrosis.[2,6] Despite extensive effort, there is a paucity of therapeutic options currently available to treat cardiac fibrosis clinically.[2] Hence, strategies to directly modulate or target the myofibroblasts to abate pathological cardiac fibrosis are desperately needed.

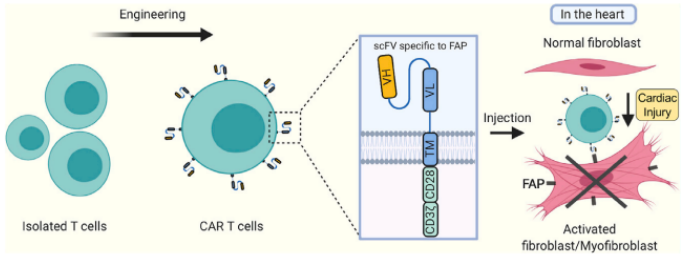


Figure 1. Engineered T Cell Immunotherapy for Cardiac Fibrosis

T cells are isolated and engineered to express a chimeric antigen receptor (CAR), consisting of a scFV fragment recognizing mouse fibroblast activation protein (FAP) that is fused to human CD3ζ and CD28 cytoplasmic domains. CAR T cells are infused and circulate to the heart, where they specifically target activated fibroblasts (myofibroblasts) that express FAP for cytotoxic killing, abrogating fibrosis. TM, transmembrane domain; scFV, single-chain variable fragment; VH, immunoglobulin heavy chain; VL, immunoglobulin light chain.

RESEARCH

CELL AND GENE THERAPY

CAR T cells produced in vivo to treat cardiac injury

Joel G. Rurik[1,2,3], István Tombácz[4]†, Amir Yadegari[4]†, Pedro O. Méndez Fernández[1,2,3], Swapnil V. Shewale[2], Li Li[1,2], Toru Kimura[4]‡, Ousamah Youness Soliman[4], Tyler E. Papp[4], Ying K. Tam[5], Barbara L. Mui[5], Steven M. Albelda[4,6], Ellen Puré[7], Carl H. June[6], Haig Aghajanian[1,2,3]*, Drew Weissman[4]*, Hamideh Parhiz[4]*, Jonathan A. Epstein[1,2,3,4]*

Fibrosis affects millions of people with cardiac disease. We developed a therapeutic approach to generate transient antifibrotic chimeric antigen receptor (CAR) T cells in vivo by delivering modified messenger RNA (mRNA) in T cell–targeted lipid nanoparticles (LNPs). The efficacy of these in vivo–reprogrammed CAR T cells was evaluated by injecting CD5-targeted LNPs into a mouse model of heart failure. Efficient delivery of modified mRNA encoding the CAR to T lymphocytes was observed, which produced transient, effective CAR T cells in vivo. Antifibrotic CAR T cells exhibited trogocytosis and retained the target antigen as they accumulated in the spleen. Treatment with modified mRNA-targeted LNPs reduced fibrosis and restored cardiac function after injury. In vivo generation of CAR T cells may hold promise as a therapeutic platform to treat various diseases.

CAR-T cells directed against FAP have been demonstrated both via ex-vivo generation and by mRNA generation of in-vivo CAR-T cells.

However, both of these approaches lack the ability of OmniCAR to modulate dosing and the ability to turn off the therapy in the event of any adverse event.

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

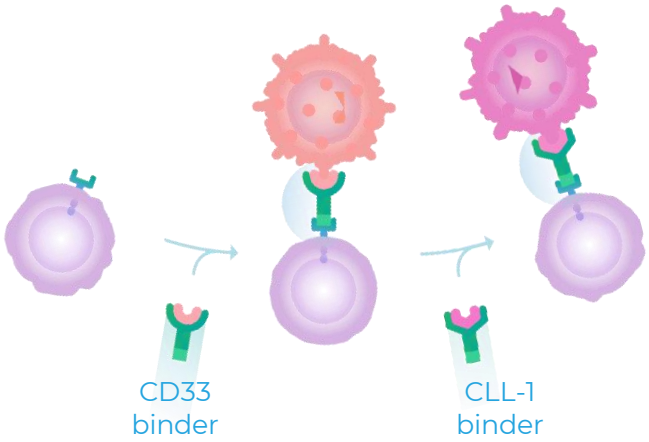
- CD33
  - Validated target in AML with approved anti-body drug conjugate (gemtuzumab ozogamicin, or Mylotarg)
  - CD33 is constantly expressed on both normal and malignant myeloid cells
  - CD33 expressed on >90% adult and childhood AML blasts and on leukemia stem cells, which have the ability to indefinitely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

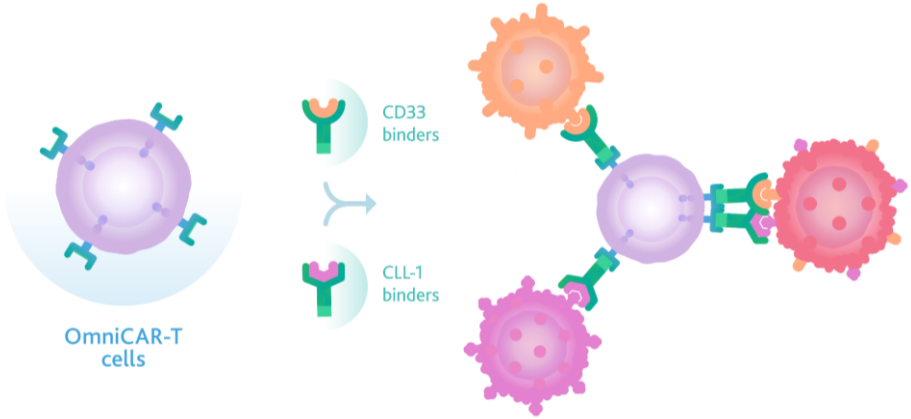
Targeting Multiple Antigens *Sequentially* OR *Simultaneously*

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
3. Luo, H et al, The prognostic value of HER2 in ovarian cancer: A meta-analysis of observational studies. *PLoS ONE* 13(1) 2018
4. Bang YJ, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-97.

GBM

OmniCAR HER2/EGFRviii

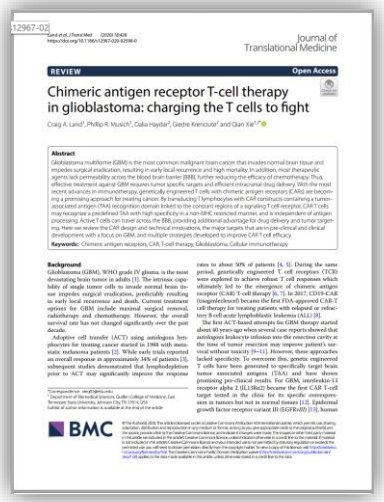
CAR-T challenges in GBM: single antigen targeting

- 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*


12967-02

Journal of Translational Medicine

REVIEW Open Access

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

Craig A. Land[†], Phillip R. Musich[†], Dalia Haydar, Gaelre Krenciute[*] and Qian Xie[*†]

Abstract

Glioblastoma multiforme (GBM) is the most common malignant brain cancer that invades normal brain tissue and impedes surgical eradication, resulting in early local recurrence and high mortality. In addition, most therapeutic agents lack permeability across the blood brain barrier (BBB), further reducing the efficacy of chemotherapy. Thus, effective treatment against GBM requires tumor specific targets and efficient intracranial drug delivery. With the most recent advances in immunotherapy, genetically engineered T cells with chimeric antigen receptors (CARs) are becoming a promising approach for treating cancer. By transducing T lymphocytes with CAR constructs containing a tumor-associated antigen (TAA) recognition domain linked to the constant regions of a signaling T cell receptor, CAR T cells may recognize a predefined TAA with high specificity in a non-MHC restricted manner, and is independent of antigen processing. Active T cells can travel across the BBB, providing additional advantage for drug delivery and tumor targeting. Here we review the CAR design and technical innovations, the major targets that are in pre-clinical and clinical development with a focus on GBM, and multiple strategies developed to improve CAR T cell efficacy.

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

Background

Glioblastoma (GBM), WHO grade IV glioma, is the most devastating brain tumor in adults [1]. The intrinsic capability of single tumor cells to invade normal brain tissue impedes surgical eradication, predictably resulting in early local recurrence and death. Current treatment options for GBM include maximal surgical removal, radiotherapy and chemotherapy. However, the overall survival rate has not changed significantly over the past decade.

Adoptive cell transfer (ACT) using autologous lymphocytes for treating cancer started in 1988 with metastatic melanoma patients [2]. While early trials reported an overall response in approximately 34% of patients [3], subsequent studies demonstrated that lymphodepletion prior to ACT may significantly improve the response rates to about 50% of patients [4, 5]. During the same period, genetically engineered T cell receptors (TCR) were explored to achieve robust T cell responses which ultimately led to the emergence of chimeric antigen receptor (CAR) T-cell therapy [6, 7]. In 2017, CD19-CAR (tisagenlecleucel) became the first FDA-approved CAR-T cell therapy for treating patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) [8].

The first ACT-based attempts for GBM therapy started about 30 years ago when several case reports showed that autologous leukocyte infusion into the resection cavity at the time of tumor resection may improve patient's survival without toxicity [9–11]. However, these approaches lacked specificity. To overcome this, genetic engineered T cells have been generated to specifically target brain tumor associated antigens (TAA) and have shown promising pre-clinical results. For GBM, interleukin-13 receptor alpha 2 (IL13Rα2) became the first CAR T-cell target tested in the clinic for its specific overexpression in tumors but not in normal tissues [12]. Epidermal growth factor receptor variant III (EGFRvIII) [13], human

BMC

Land, CA, et al; Chimeric antigen receptor T-cell therapy in glioblastoma; *J Transl Med;* 2020

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

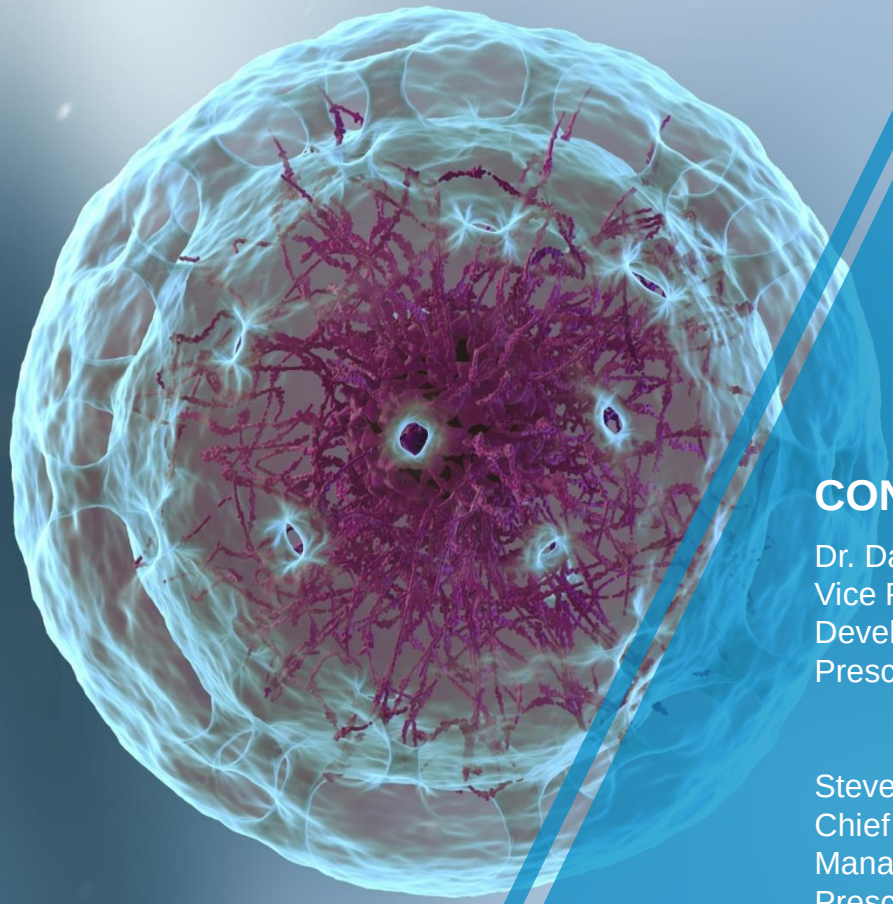
- HER2 occurs in 80% of GBM
- Linked with poor survival

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

Zh*ang*, 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
Land, CA, et al; Chimeric antigen receptor T-cell therapy in glioblastoma; *J Transl Med* 2020
Hegde M, et al. Tandem CAR T cells targeting HER2 and IL13Ralpha2 mitigate tumor antigen escape. *J ClinInvest*. 2016

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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