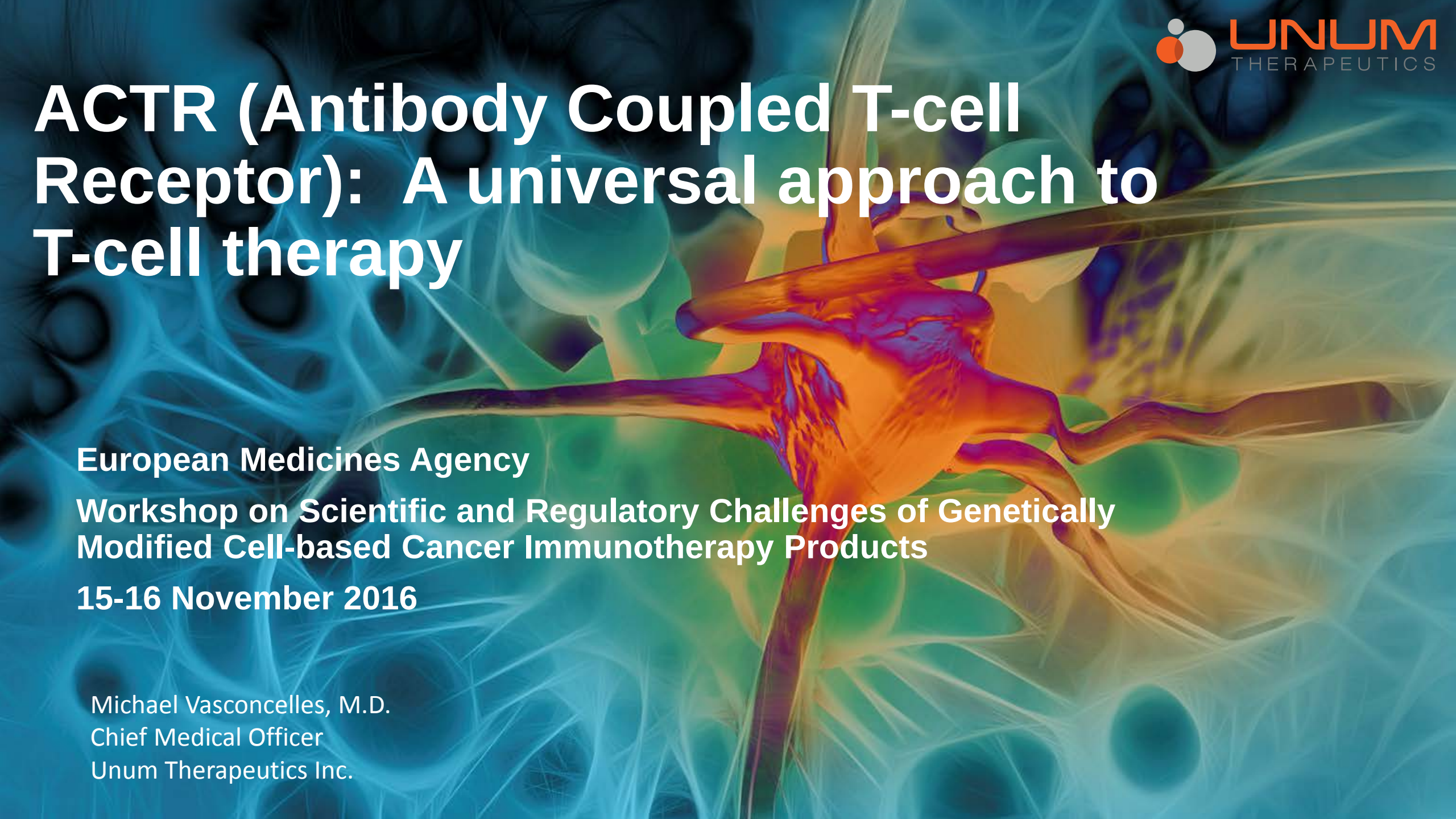
ACTR (Antibody Coupled T-cell Receptor): A universal approach to T-cell therapy



European Medicines Agency

Workshop on Scientific and Regulatory Challenges of Genetically Modified Cell-based Cancer Immunotherapy Products

15-16 November 2016

Michael Vasconcelles, M.D.
Chief Medical Officer
Unum Therapeutics Inc.

The Evolution of Cancer Immunotherapy

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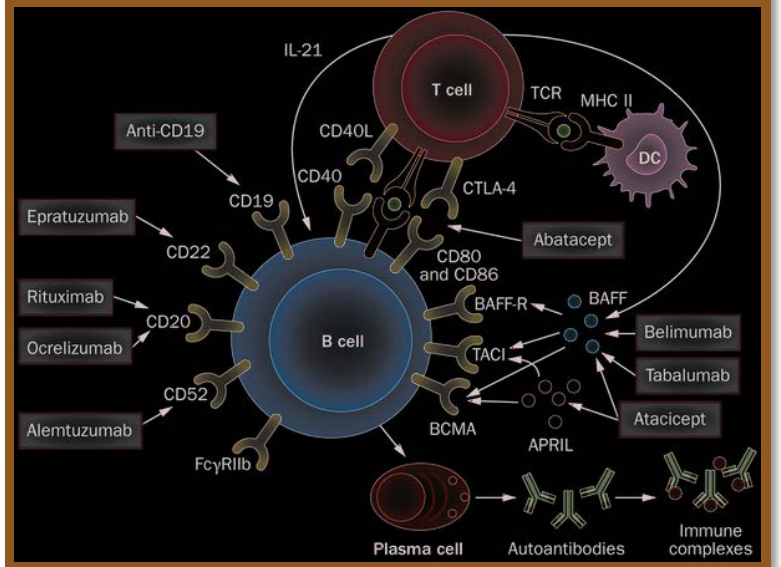
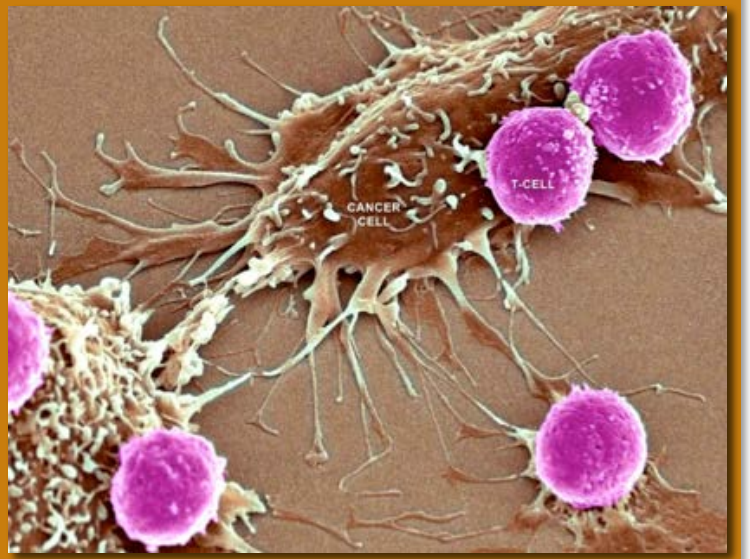
The drug is…

…a molecule normally made by immune cells (e.g., cytokines, monoclonal antibodies)

…an engineered molecule targeting immune cells (e.g., checkpoint inhibitors)



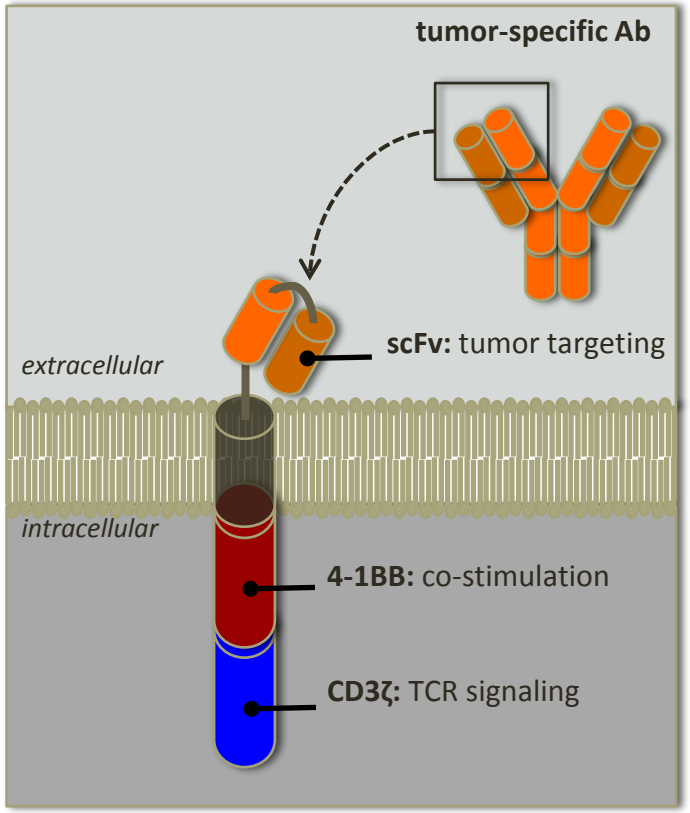
…an immune cell that attacks disease **(cellular immunotherapy)**



Source: New York Times

Chimeric Antigen Receptor (CAR)-expressing Autologous T cells (CAR-T)

- Each CAR requires an optimized antibody fragment for a specific single antigen
- CAR constructs substantially overlap across groups
- Primary foci to date: B cell antigens CD19 and BCMA
  - Acute lymphoblastic leukemia (ALL)
  - Chronic lymphocytic leukemia (CLL)
  - Non Hodgkin lymphoma (NHL)
  - Multiple myeloma (MM)
- CAR construct designs against additional tumor antigens ongoing



CD19+ CAR-T cell outcomes in patients with R/R B cell Acute Lymphoblastic Leukemia

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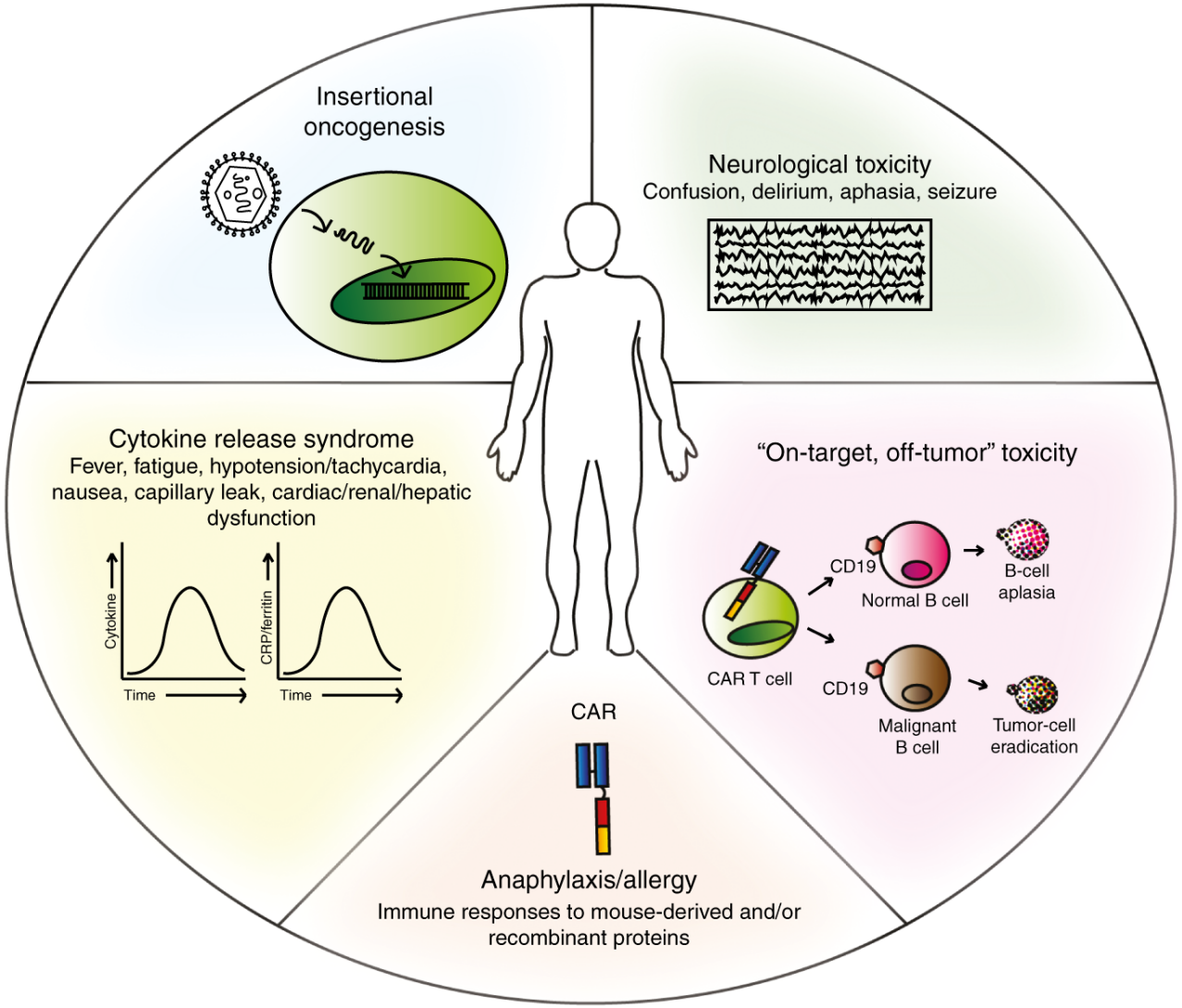
Institution	CAR design	Patient population	Outcome	Toxicities	Reference
MSKCC	CD28, CD3ζ	• *n* = 32 adults • R/R B-ALL	91% CR	• B-cell aplasia • CRS	NCT01044069 (REF. 13)
UPenn/ CHOP	4-1BB, CD3ζ	• *n* = 30 children and young adults • B-ALL	90% CR	• B-cell aplasia • CRS	NCT01626495 (REF. 15)
NCI	CD28, CD3ζ	• *n* = 20 children and young adults • B-ALL	70% CR	• B-cell aplasia • CRS	NCT01593696 (REF. 17)
Fred Hutchinson	4-1BB, CD3ζ	• *n* = 20 adults • B-ALL	83% CR	CRS	NCT01865617 (REF. 18)

Preconditioning chemotherapy was used in all the trials shown in this table. B-ALL, B-cell acute lymphoblastic leukaemia; chemo, chemotherapy; CHOP, Children's Hospital of Philadelphia; CR, complete response; CRS, cytokine-release syndrome; Fred Hutchinson, Fred Hutchinson Cancer Research Center; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; R/R, relapsed and/or refractory; UPenn, The University of Pennsylvania.

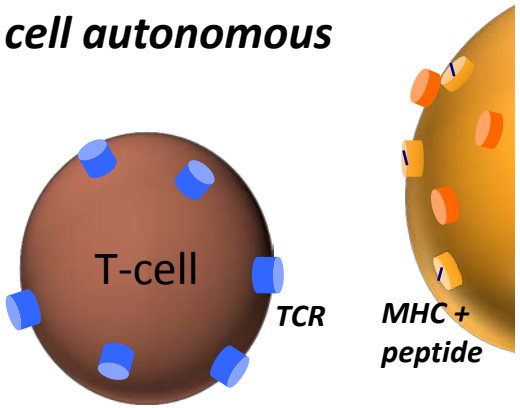
CAR-T cell potential risks



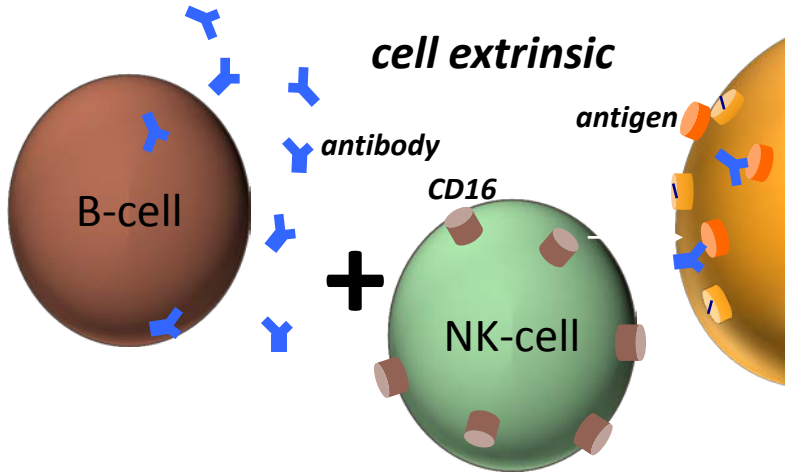
Bonifant, et al. Molecular Therapy-Oncolytics April, 2016.

ACTR T cells + Antibodies: Combining Two Proven Anti-tumor Adaptive Immune Responses

- Distinct, potent and specific mechanisms of immune response to invasion have evolved
- Adaptive immune responses sculpt highly specific recognition of the invader
- Redirecting T cell responses combined with Ab-mediated cellular cytotoxicity maintains specificity while enhancing immune response



one component
(control must be built into the cell)



two component
(control can be outside of cell)

Antibody-Coupled T cell Receptor (ACTR): A Next-Generation Platform

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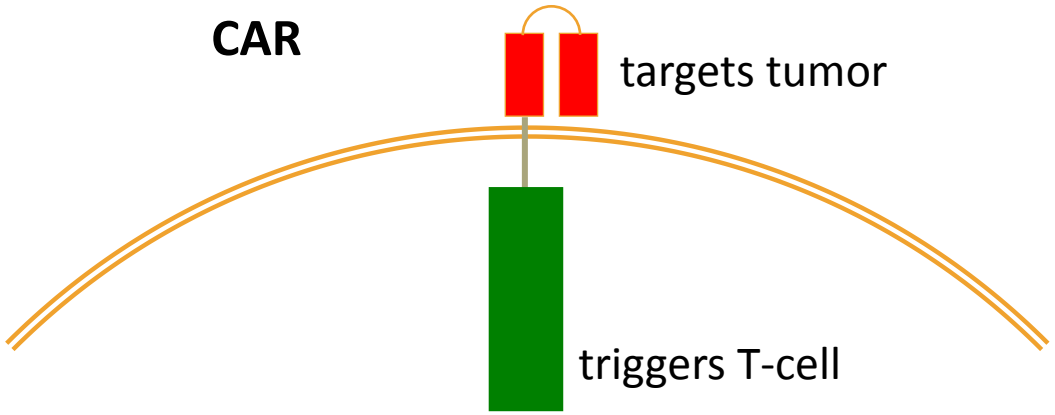
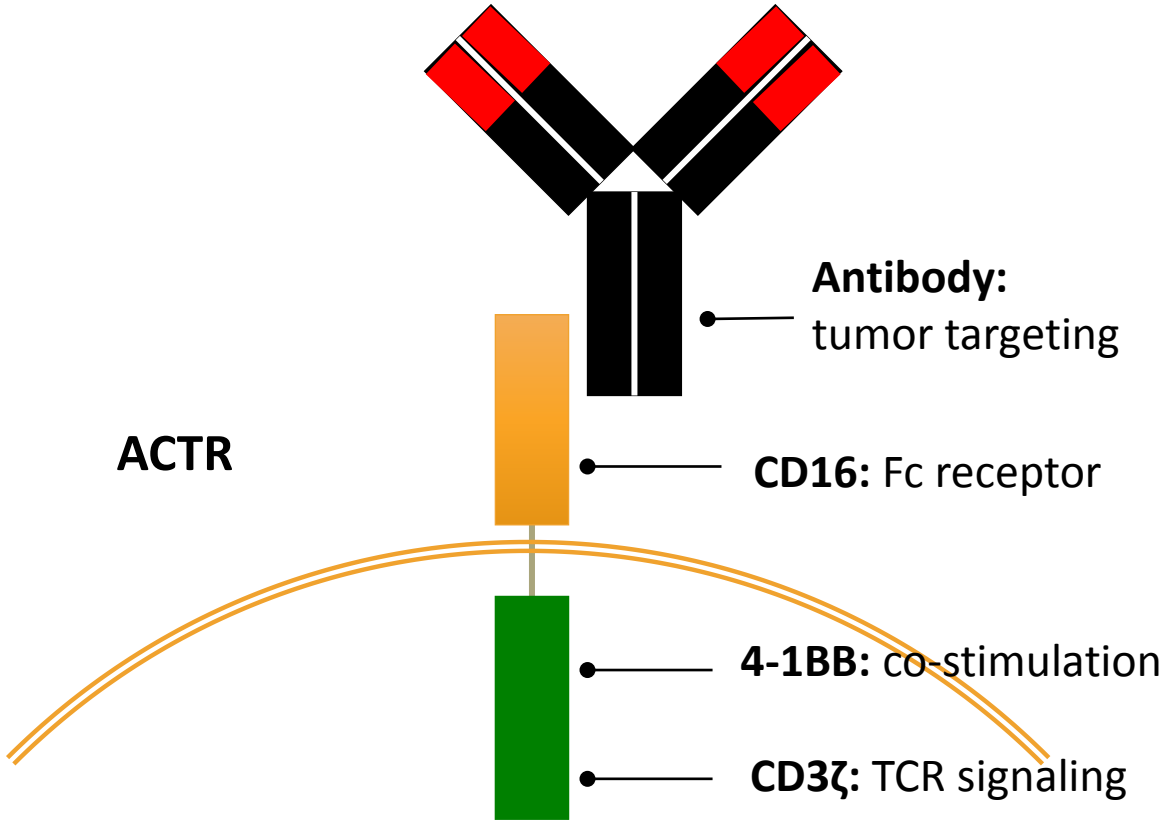
CAR



- Specific for one type of cancer
- Always ‘on’ after infusion into the patient

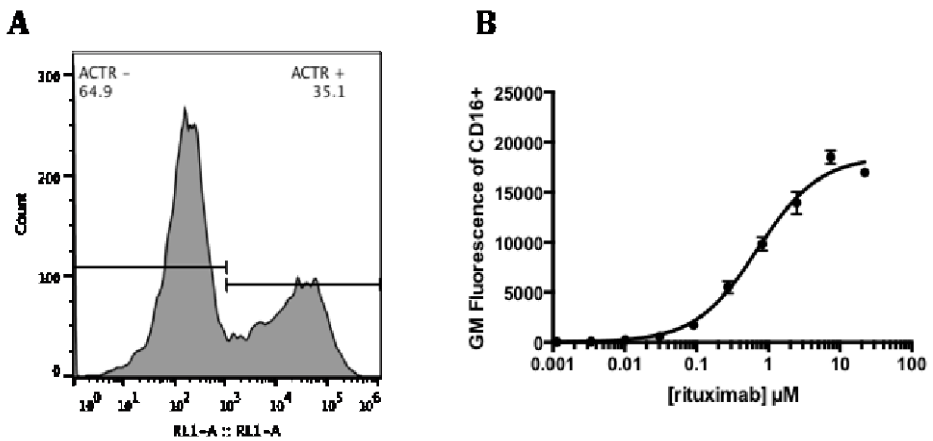
ACTR



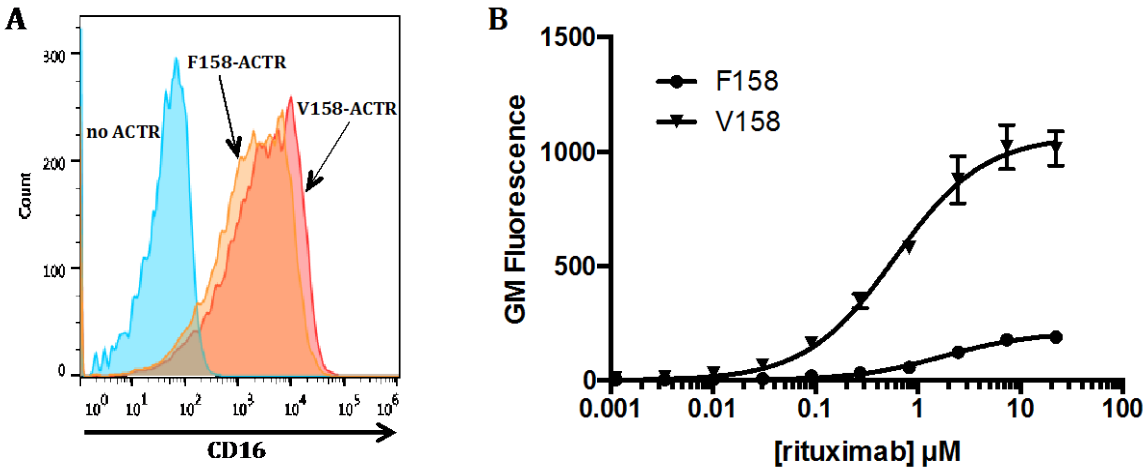
- Universal – ACTR T cell can attack many different cancers
- Activity is controlled by antibody dosing

Rituximab binds ACTR T cells with affinity comparable to endogenous CD16

Example of expression of ACTR-V158 on T cells and binding of rituximab to ACTR-expressing cells



Example of expression of ACTR-V158 and -F158 on Jurkat cells and binding of rituximab to ACTR-expressing cells.



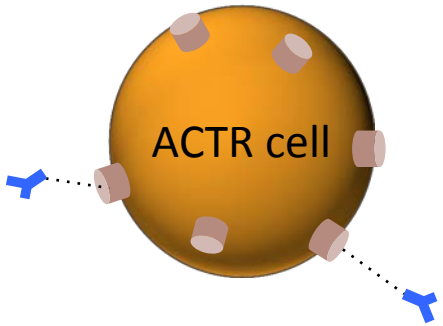
Data for cell expressed ACTR binding to rituximab

	ACTR-V158 (Jurkat cells)	ACTR-F158 (Jurkat cells)	ACTR-V158 (T-cells)
Experiment 1 K_D (nM)	631	1700	598
Experiment 2 K_D (nM)	606	1760	708
Experiment 3 K_D (nM)	596	1610	701
Average K_D (nM)	611	1690	669
Standard deviation of K_D (nM)	18	70	62

- Most wildtype IgG1 antibodies bind CD16 with a monomeric affinity in the range of 200-600 nM
- Published affinity of rituximab for CD16-V158 is 660nM and 2000nM for CD16-F158

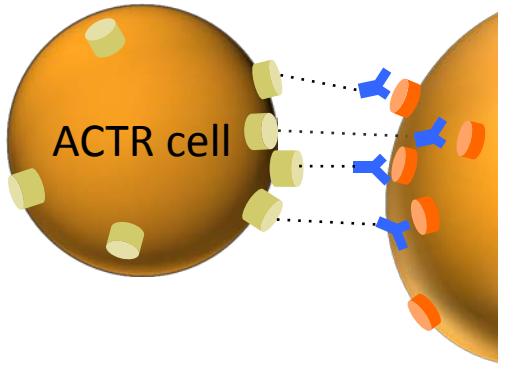
ACTR T cell specificity: Fc-CD16 affinity vs. avidity

Monovalent binding interaction is not productive



Sub μM affinity

Multivalent interactions drive signaling



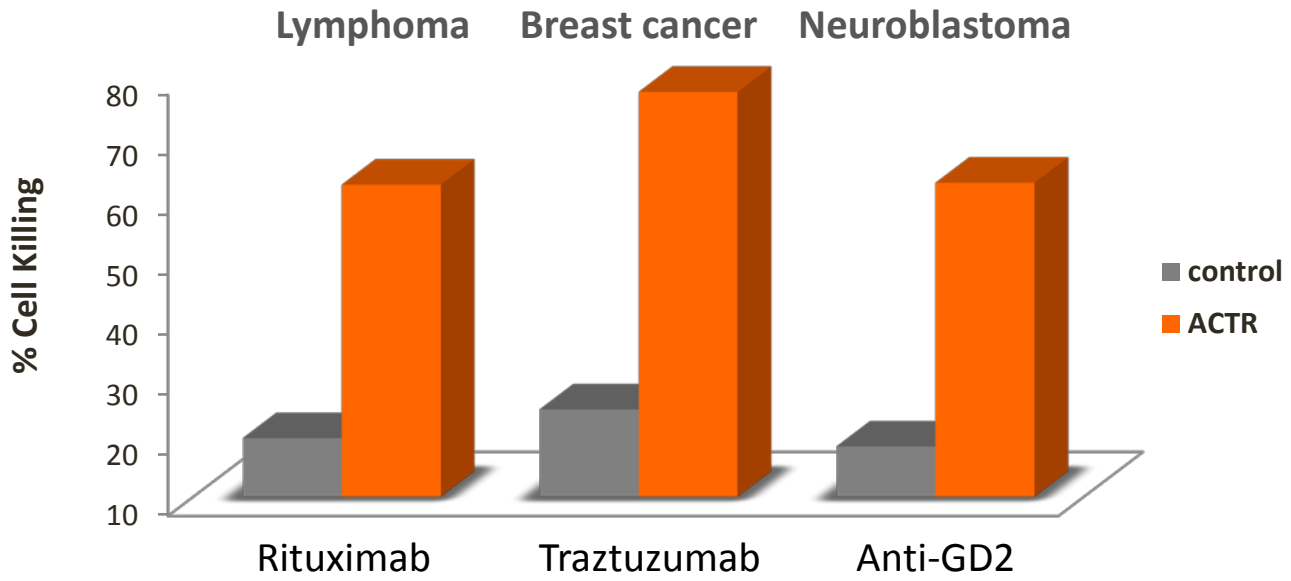
Sub fM avidity

ACTR T cells Kill Tumor Cells *In Vitro*

Cell lines

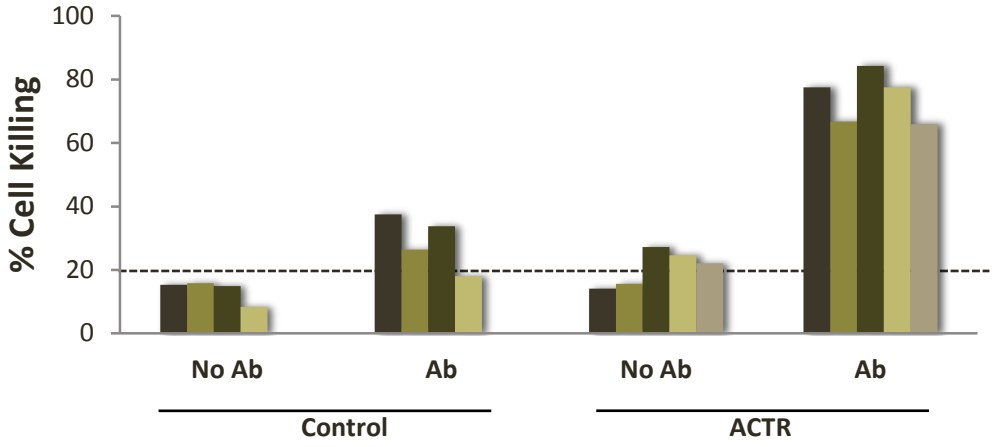
ACTR T cells kill cancer cell lines in the presence of the right targeting antibody

Cell line	Marker	Antibody
Daudi	CD20	Rituximab
SK-BR-3	Her2	Traztuzumab
NB1691	GD2	Anti-GD2



CLL patient cells

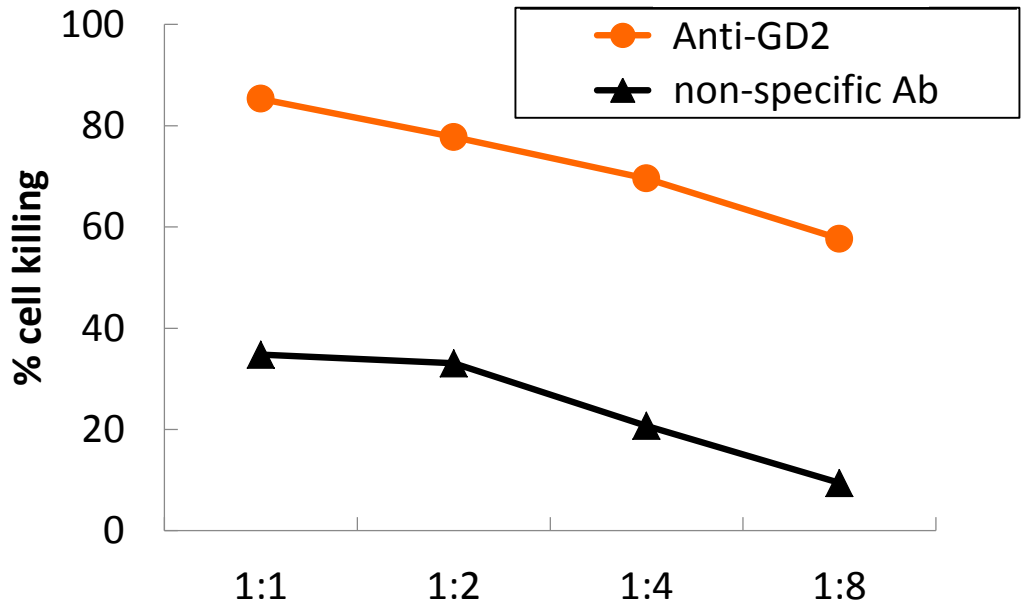
ACTR T cells kill primary cells from chronic lymphocytic leukemia (CLL) patients when combined with Rituxan



Kudo et al., "T lymphocytes expressing a CD16 signaling receptor exert antibody-dependent cancer cell killing," Cancer Res. 74:93-103 (2014)

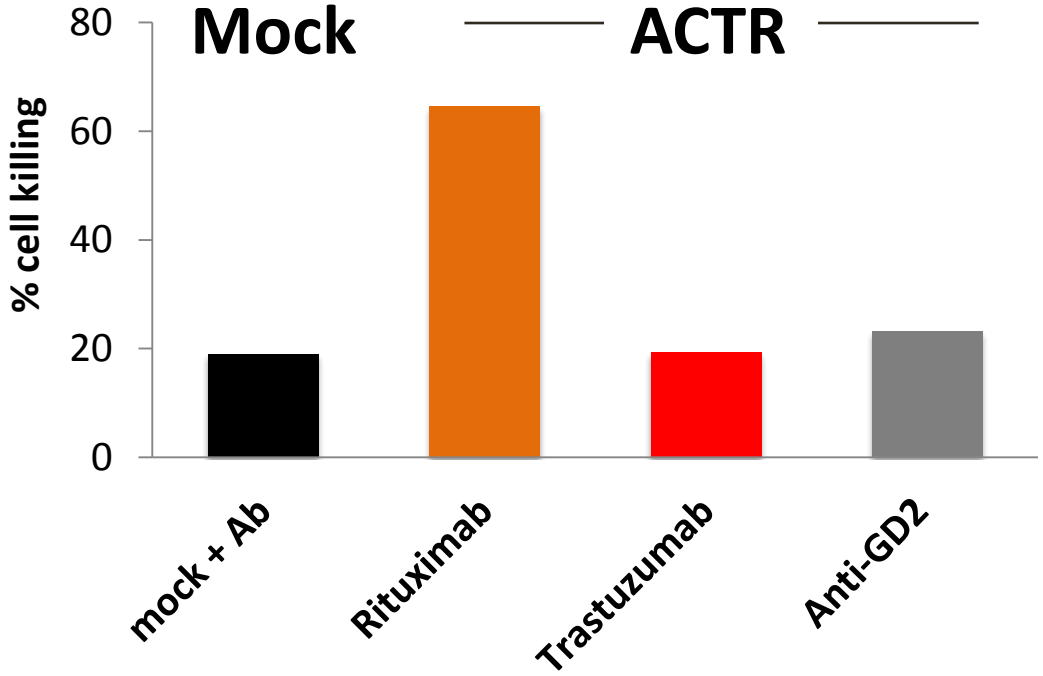
Specificity: Effect of Non-Targeting Antibodies

Non-specific IgG does not trigger ACTR T cell killing



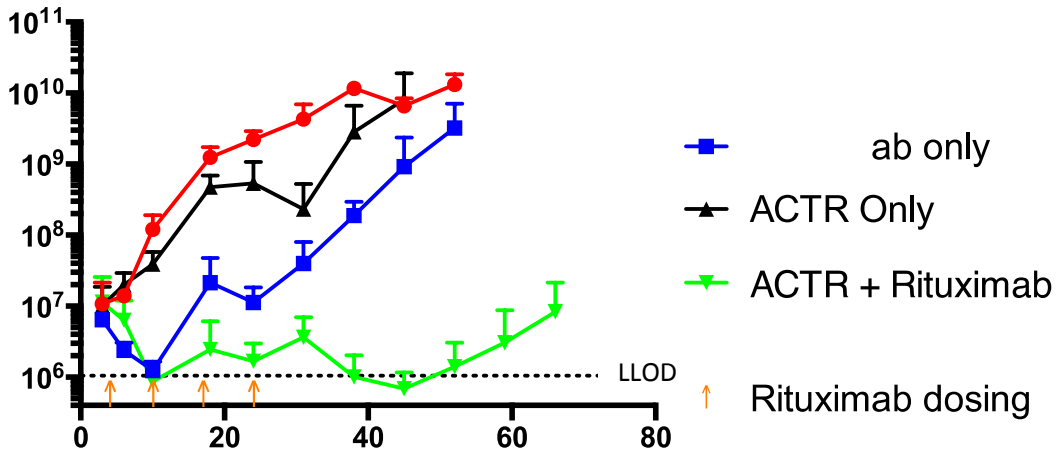
Neuroblastoma cells incubated with ACTR T cells in the presence of either anti-GD2 antibody or nonspecific IgG

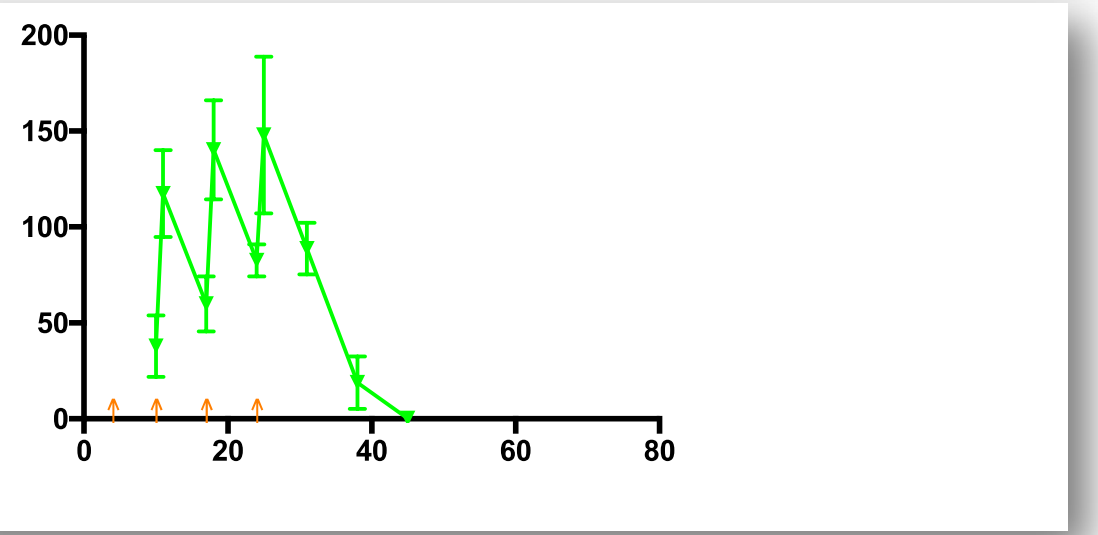
Targeting mAbs do not trigger ACTR T cell killing if the target is not present



Daudi (CD20+) cells incubated with mock T cells + rituximab or ACTR T cells in the presence of rituximab, trastuzumab, or anti-GD2 mAb

ACTR T cells Kill Tumor Cells *In Vivo*



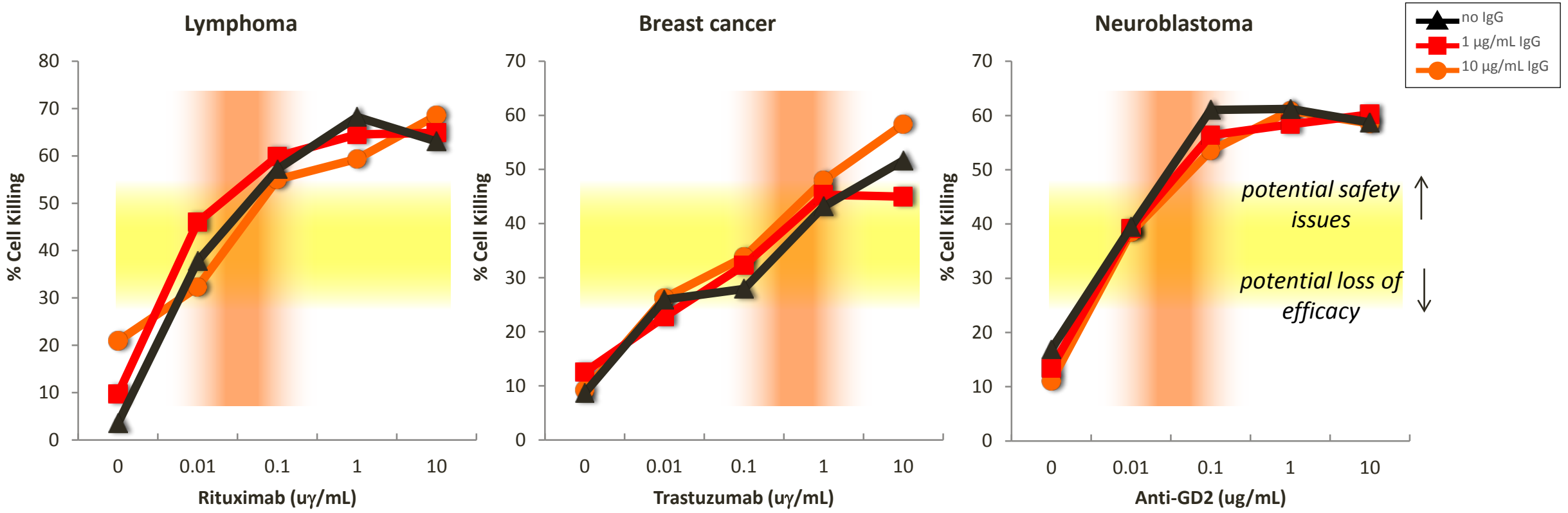


- Daudi cells expressing luciferase were injected in NSG mice on day 0.
- Mice receiving rituximab were injected once weekly for 4 weeks starting on day 4.
- Mice receiving ACTR were injected with ACTR-expressing T cells (2.5 x 10^6) on day 5.

Tuning ACTR Activity

ACTR cell killing can be controlled by adjusting the antibody dose

- Potential to maximize therapeutic index
- Potential to access targets with low levels of off-tumor expression



Ongoing Phase 1 Trial: ACTR T cells + Rituximab (ATTCK-20)

Design

- Safety and feasibility in patients with B-cell CLL or B-cell NHL refractory/relapsed to chemotherapy including rituximab
- ACTR expressed by mRNA electroporation
- Patients receive rituximab one day prior to ACTR T cell infusion; repeat ACTR dosing in recent study amendment
- Dose-escalation (traditional 3+3) with option for intra-patient escalation

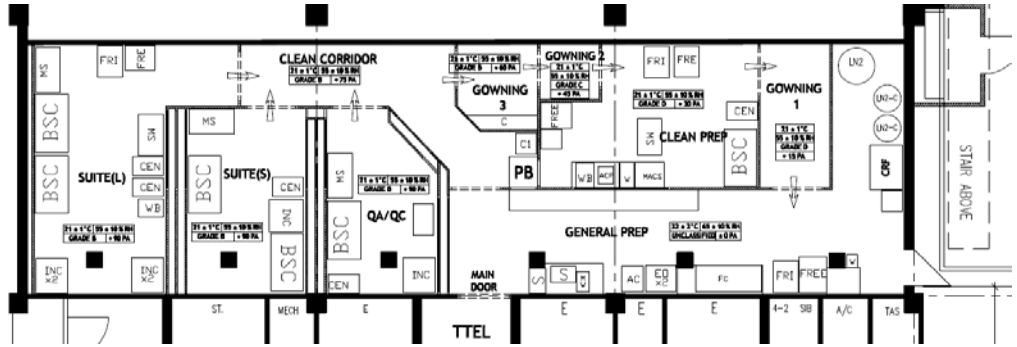
Status

- Enrolling to high, multi-dose cohort

NUH National University Hospital

Singapore General Hospital SingHealth

clinical (large scale) cell selection system & electroporator




multiple stage gowning


biosafety cabinets & incubators

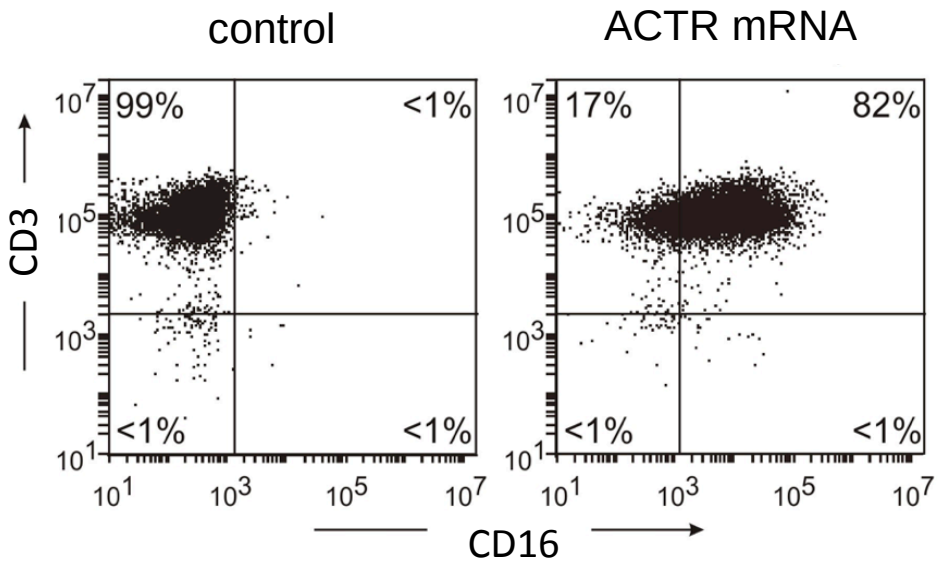

cryopreservation & cell banking


independent culture suites

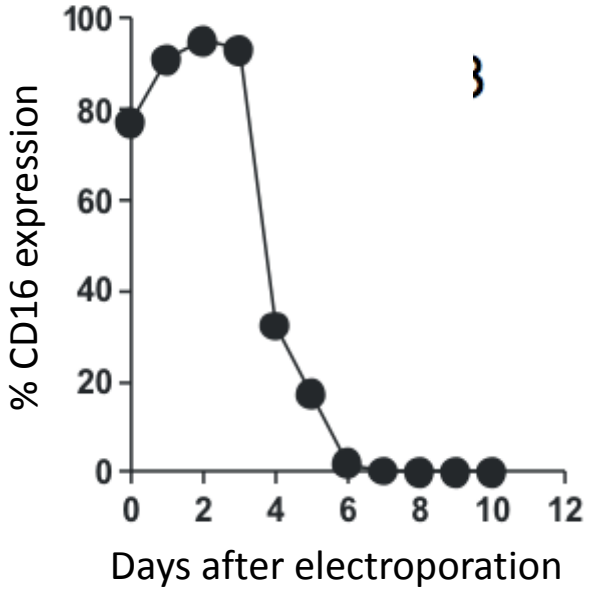
ACTR Construct Can Be Delivered as an mRNA

- ACTR can be transiently expressed as an mRNA by electroporation
- CARs delivered in this way have shown clinical activity

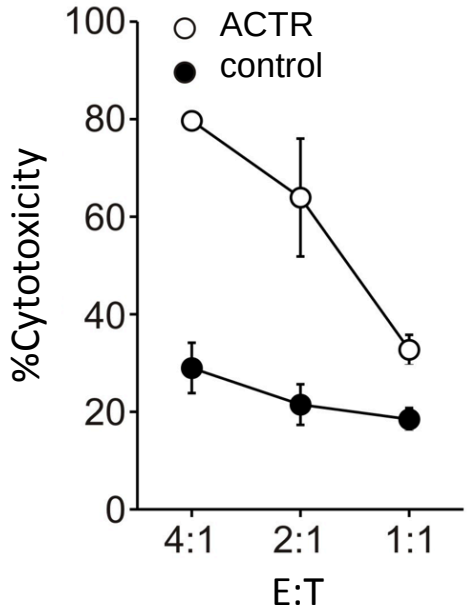
T cells electroporated with ACTR mRNA efficiently express the receptor (assessed 24 h after electroporation by flow cytometry)



T cells electroporated with mRNA express ACTR for about 6 days ex vivo

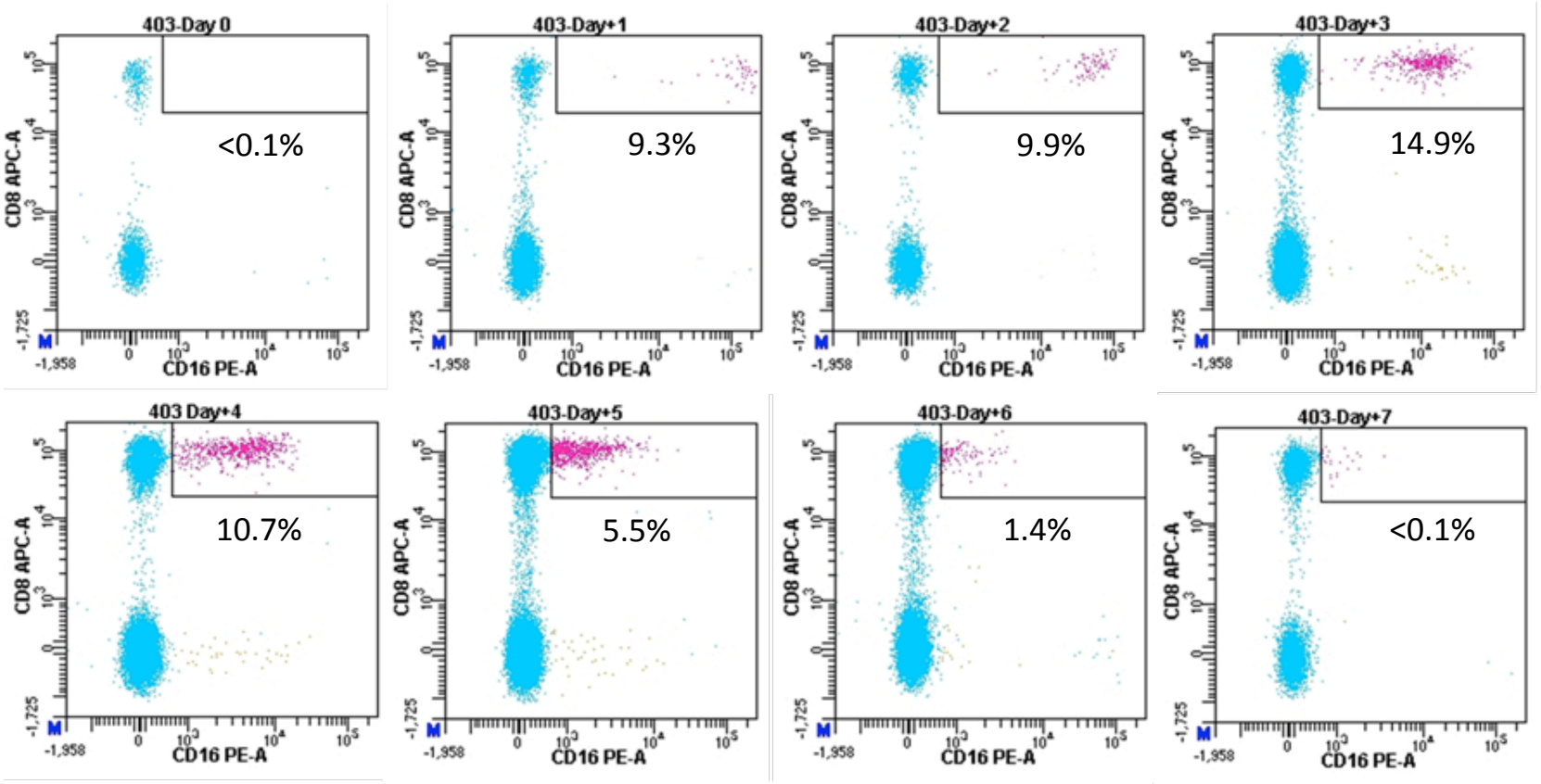


T cells electroporated with ACTR mRNA efficiently kill cancer cells (CD20+) in the presence of rituximab



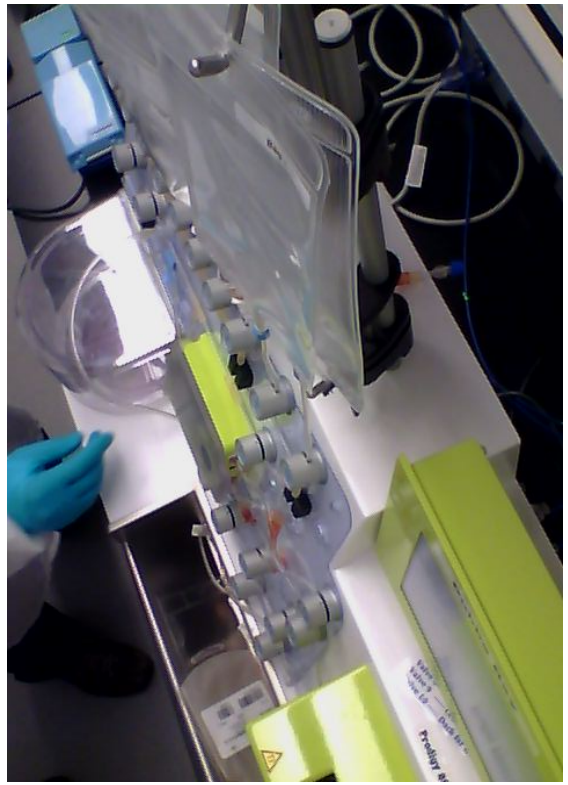
ACTR Pharmacokinetics

- Peripheral blood from ATTCK20 mRNA patient isolated post-infusion and characterized by flow cytometry
- ACTR T cells expand in vivo to ~15% of the total T-cell population by day 3, drop to background by day 7



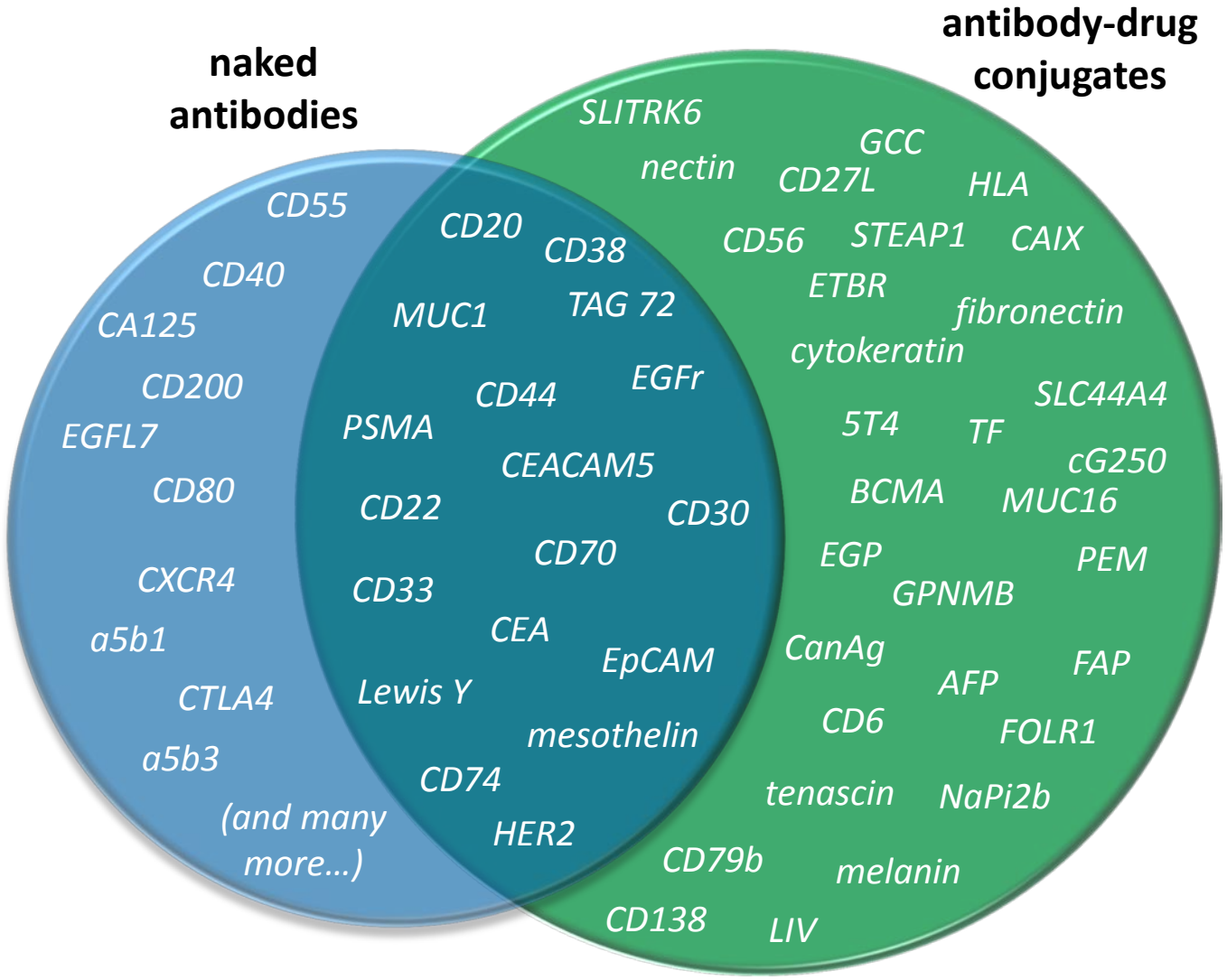
Ongoing Phase 1 Trial (United States): ACTR T cells + Rituximab (ATTCK-20-2)

- Stable ACTR transgene product expression following **viral vector transduction** (vs. mRNA transfection)
- A**utomated, closed T cell manufacturing** system in a centralized facility
- Patient population with **relapsed or refractory CD20+ non Hodgkin B-cell lymphoma** subtypes:
  - diffuse large B-cell lymphoma
  - primary mediastinal B-cell lymphoma
  - mantle cell lymphoma
  - transformed follicular lymphoma
  - Grade 3b follicular lymphoma
- **Multiple rituximab infusions; single ACTR T cell infusion**
  - Flu/Cy lymphodepleting chemotherapy

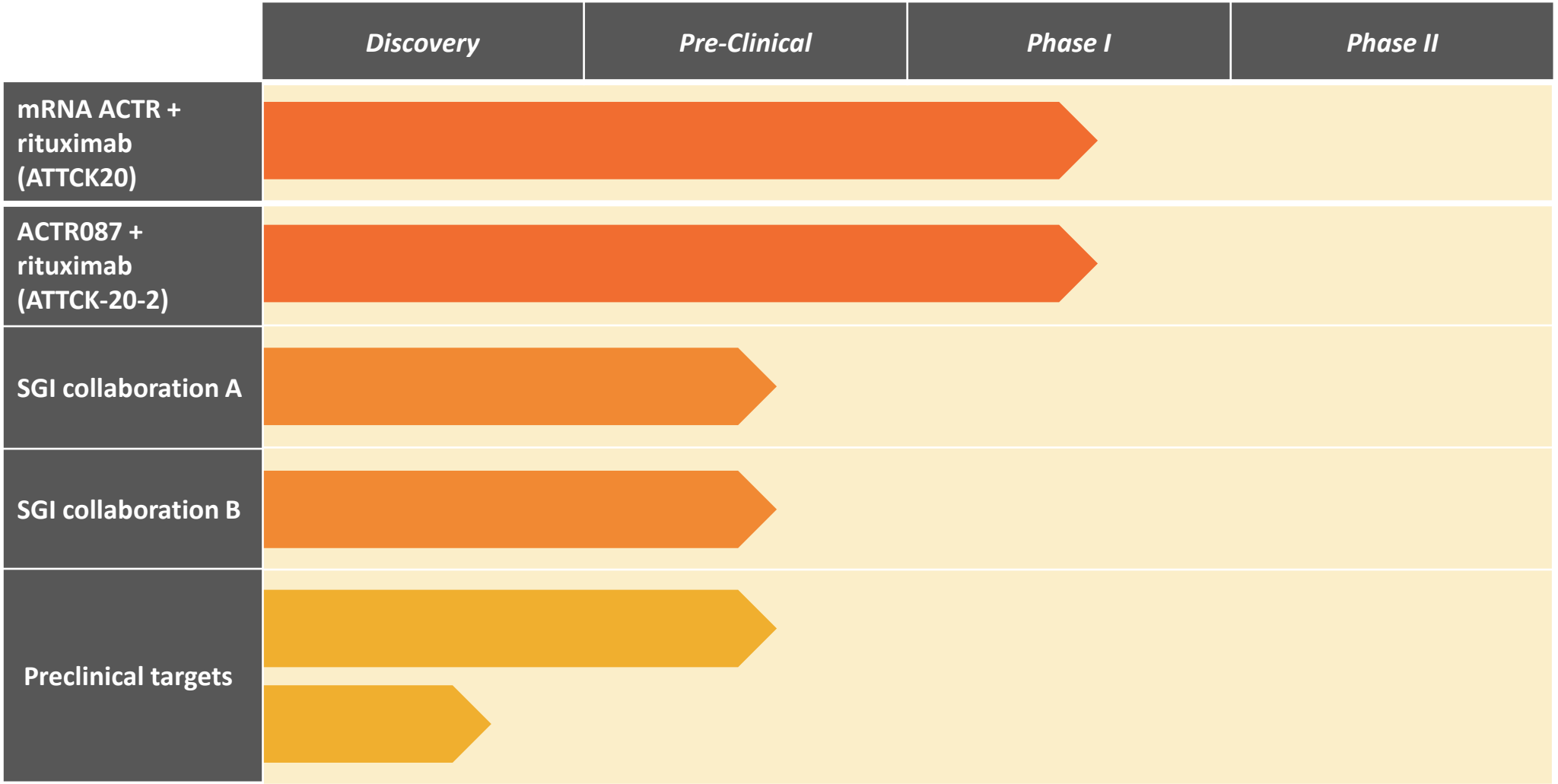


Expanding Unum's Target Space

- A wide range of tumor-targeting antibodies in clinical development
- Combination approach with ACTR provides significant opportunities for to rapid pipeline expansion and accelerated development
- A critical need exists for regulatory mechanisms facilitating early development of novel combinations such as ACTR T cells + Ab



Current Unum Pipeline



ACTR T cell platform: Summary

- Novel immunotherapeutic targets and platforms are transforming oncology

- The ACTR platform combines the potential immunologic benefits of engineered tumor-directed T cells with monoclonal antibodies

- The ACTR platform is distinct from other adoptive T cell therapies (e.g. CAR-T cells), with potential differences in therapeutic index


Thank you!