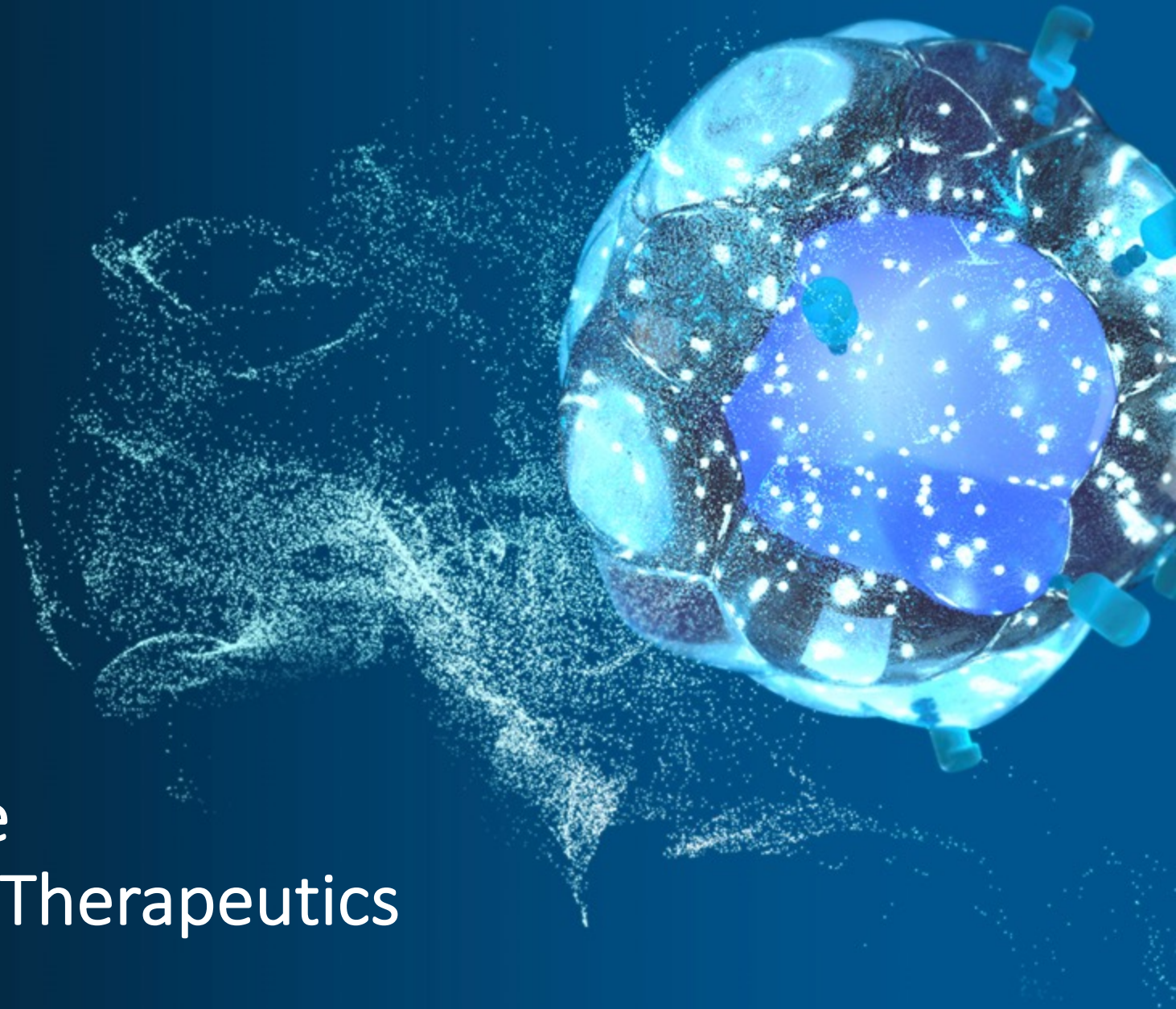
ARCELLX



D Domains:
A De Novo Scaffold for the Development of Targeted Therapeutics

David LaFleur
Sr. Director, Discovery

Presented: PEGS Boston, May 11-13, 2021

Outline

D domain Scaffold

Therapeutic Platforms: ddCAR & ARC-SparX

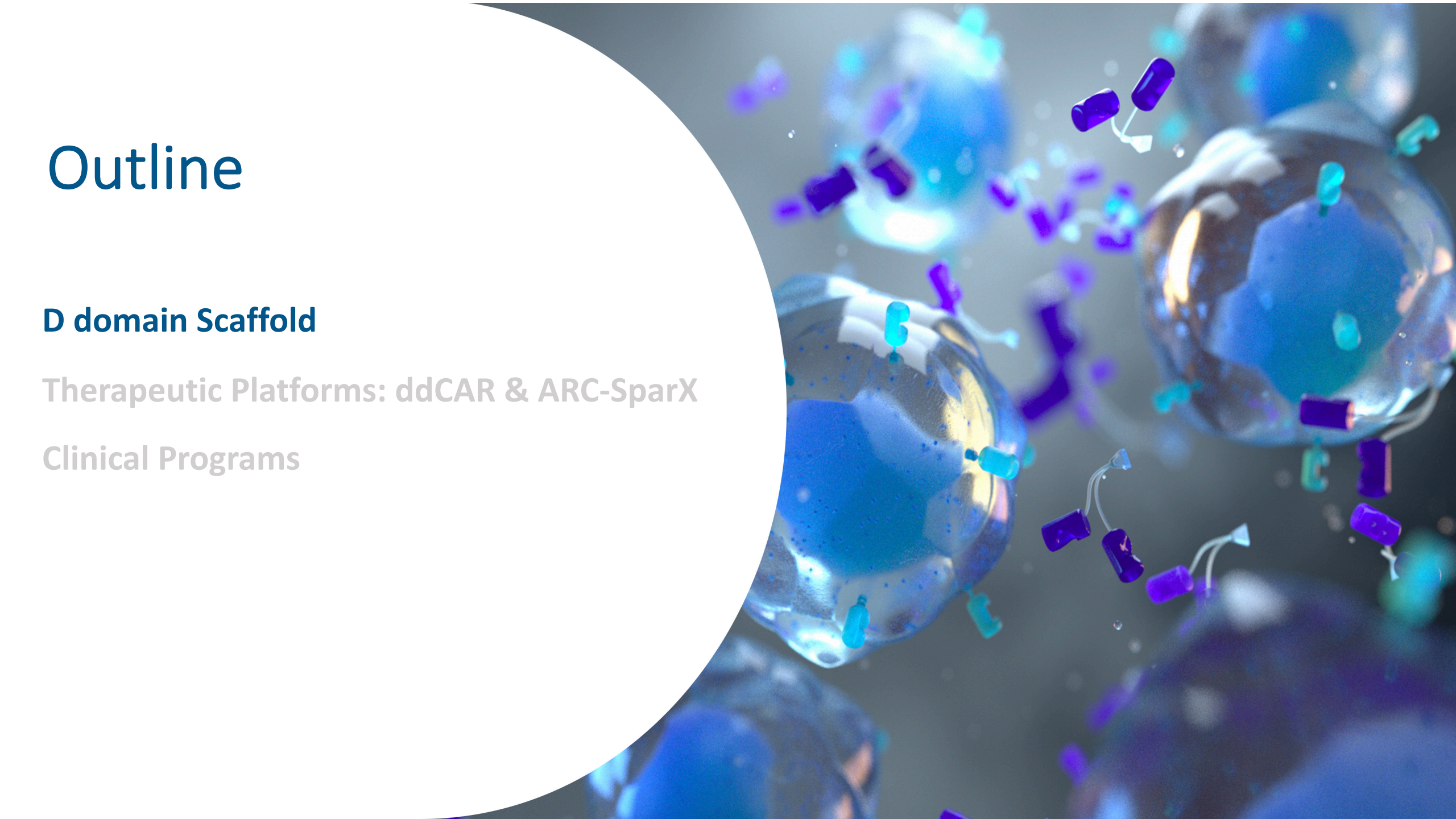
Clinical Programs

Outline

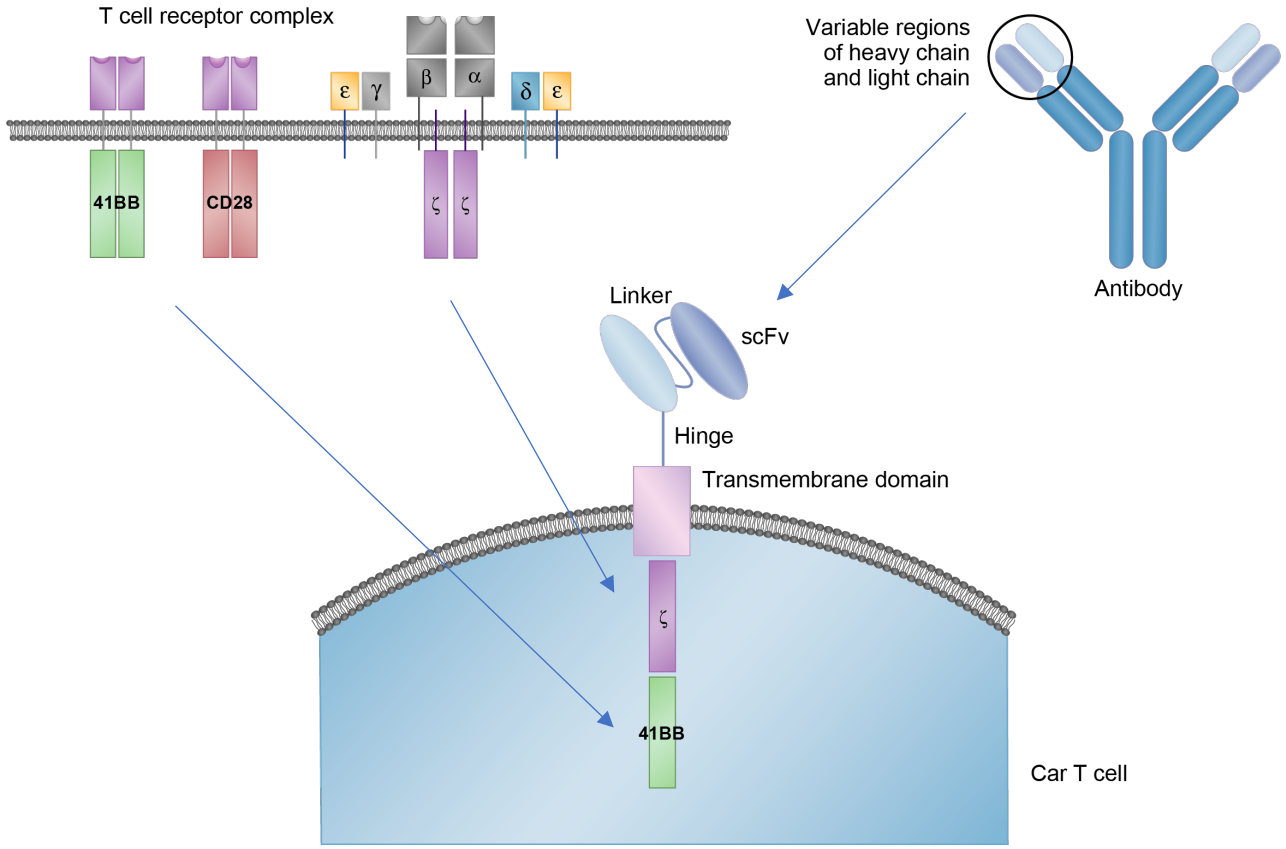
D domain Scaffold

Therapeutic Platforms: ddCAR & ARC-SparX

Clinical Programs



CAR-T Cell Receptor:
Why use an alternative to scFv for targeting?

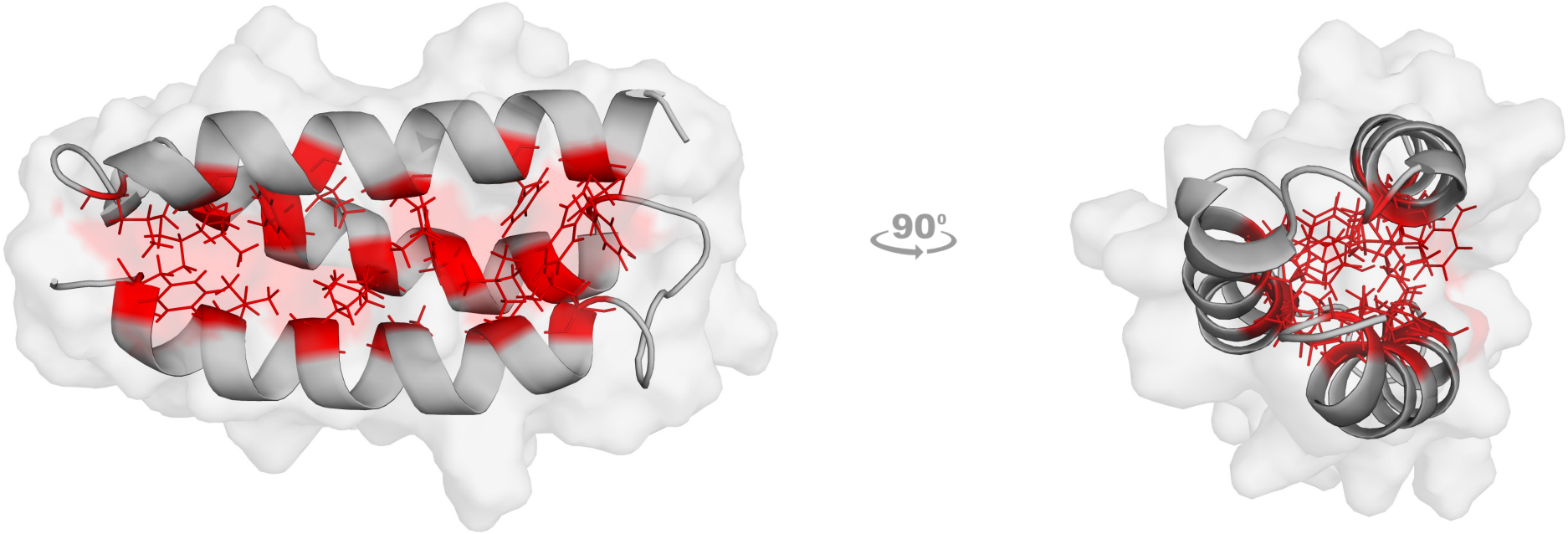


- High affinity not required for CAR-T
- Novel (non-CDR) topologies may bind to novel epitopes
- Creating multi-specific or multi-epitopic chimeras may be less challenging with a less complex domain fold

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 5486–5491, May 1999
Biophysics

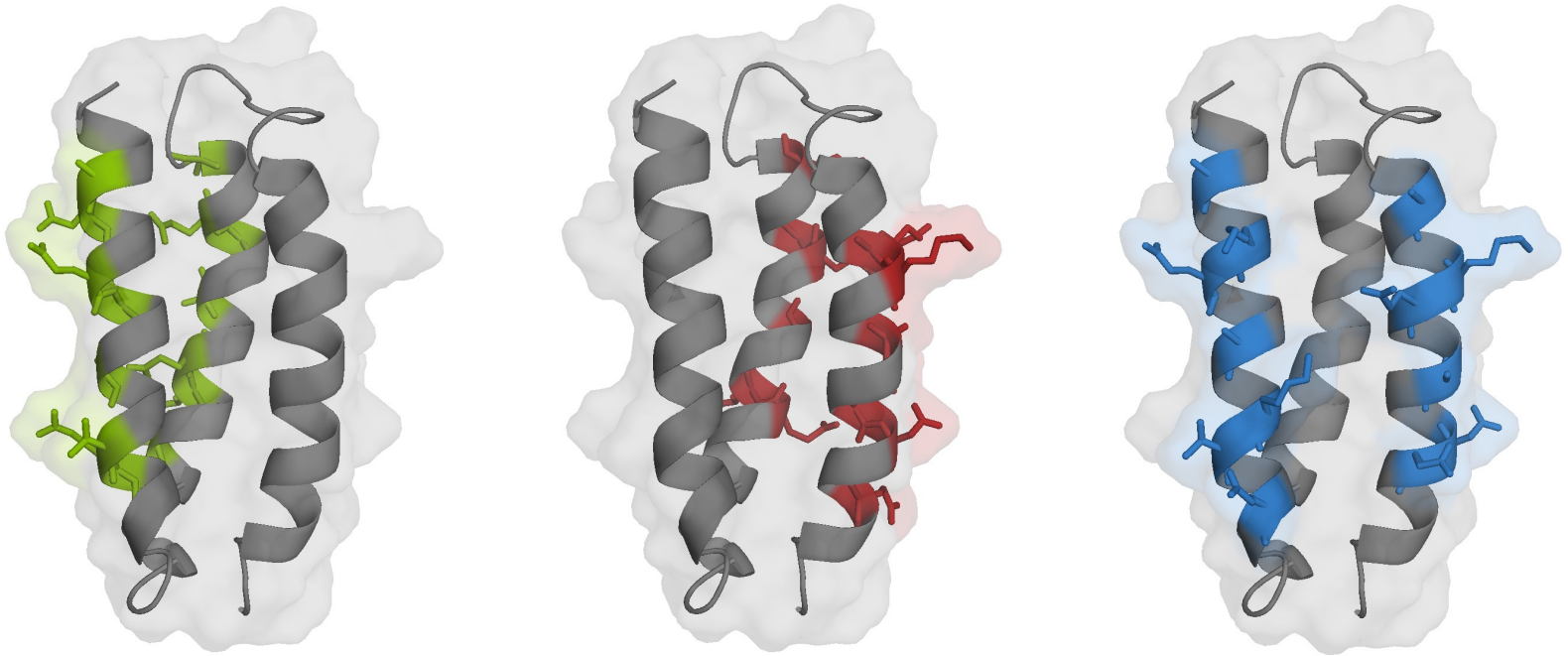
Solution structure and dynamics of a *de novo* designed three-helix bundle protein

Scott T. R. Walsh†, Hong Cheng‡, James W. Bryson§, Heinrich Roder†‡, and William F. DeGrado†¶



- α_3D (PDB 2A3D)
- Single-chain, anti-parallel, three-helix bundle, containing all amino acids except cysteine
- Hydrophobic core (red), surface electrostatics and alpha-helical capping structure in loops
- Exceptional thermal stability and ultra-fast folding (*Zhu etal, PNAS, 2003*)

D domain Library Design



F1 F2 F3

Library	Sequence Profile : X = all amino acid except proline and cysteine
F1	MGSWXXFKXXLAXIKXXLEALGGSEAELAXFEXXIAXFEXXLQXYKGKGNPEVEALRKEAAAIRDELQAYRHN
F2	MGSWAEFKQRLAAIKTRLEALGGSEAELAAFXXEIXAFXXELXAYKGKGNPEVEALXXEAXAIXXELXAYRHN
F3	MGSWXEFXXRLXAIXXRLXALGGSEAELAAFEKEIAAFESELQAYKGKGNPEVEXLRXXAAXIRXXLQAYRHN
C1	MGSWXXFKXXLAXIKXXLEALGGSEAELAAFXXEIXAFXXELXAYKGKGNPEVEXLRXXAAXIRXXLQAYRHN
C2	MGSWXEFXXRLXAIXXRLXALGGSEAELAXFEXXIAXFEXXLQXYKGKGNPEVEALXXEAXAIXXELXAYRHN

- α_3D has no inherent ligand
- Strategy: Randomize contiguous surface exposed positions
- F1, F2 & F3 faces (+2) initial designs
- Used all amino acids except Pro and Cys
- Phage libraries generated with Kunkel mutagenesis and trimer-codon oligos

Pilot Panning Campaign

5 Libraries

Pool of F1, F2 & F3

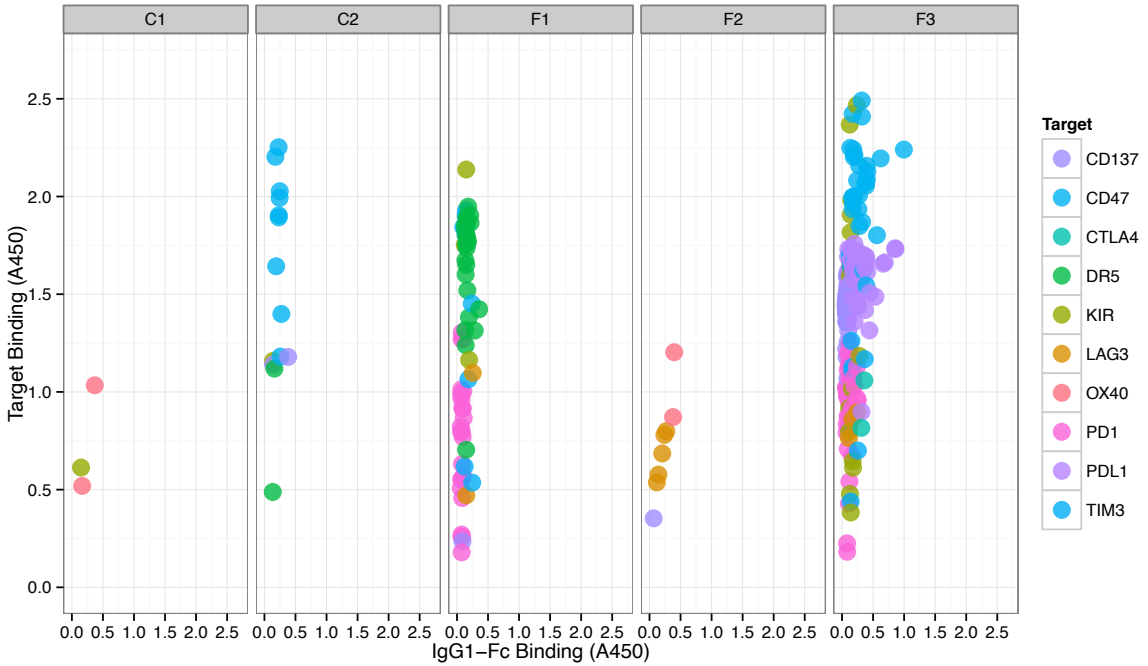
Pool of C1 & C2

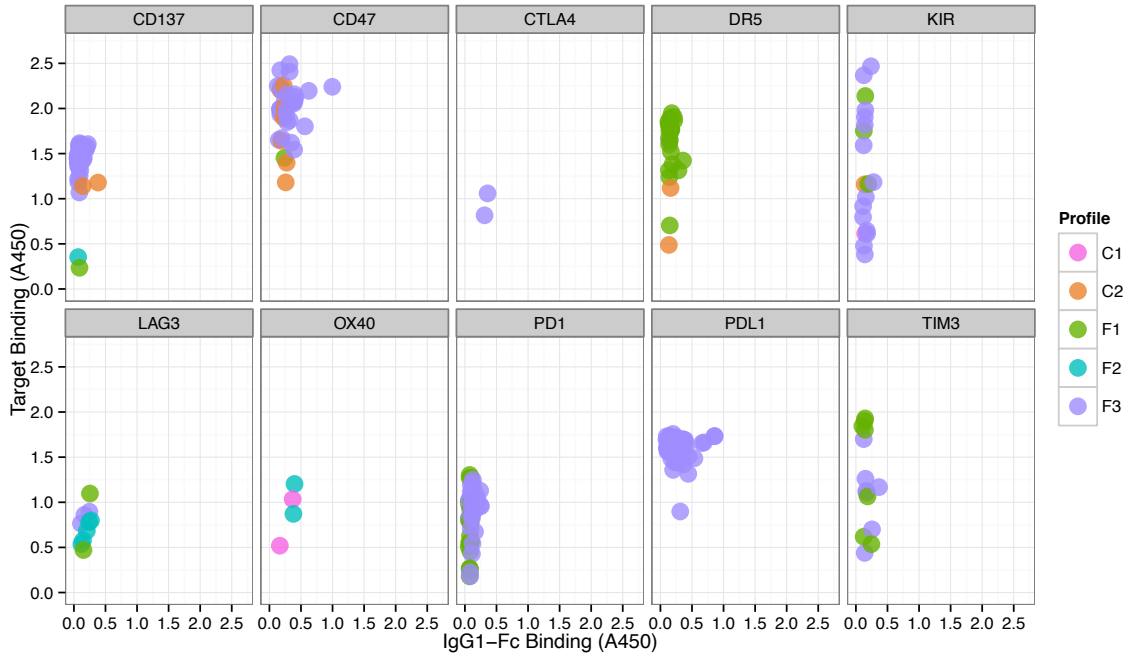
Panned against

10 Targets

CD137 CD47 CTLA4 KIR2DL2

DR5 LAG3 OX40 PD1 PDL1 TIM3

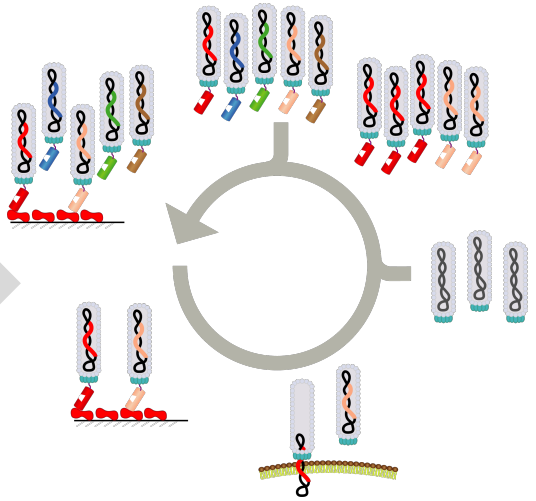




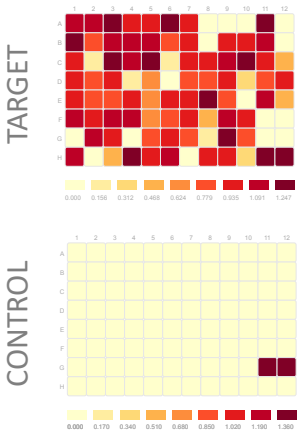
Screening Workflow

Library
(or Library Pools)
+
Antigens

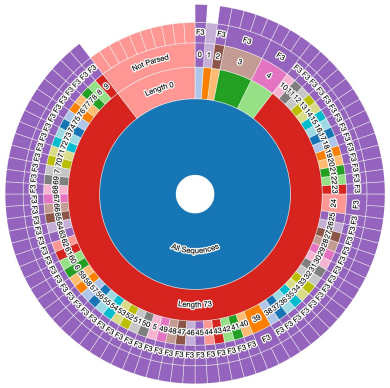
Phase Selection



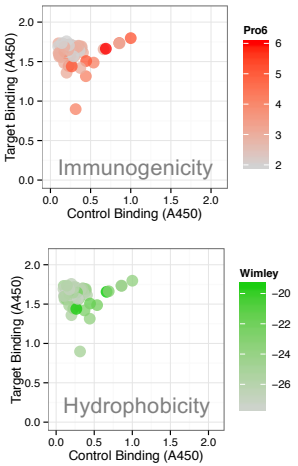
Binding



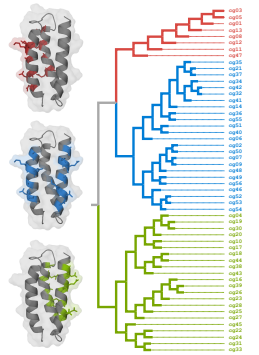
Sequencing & Selection



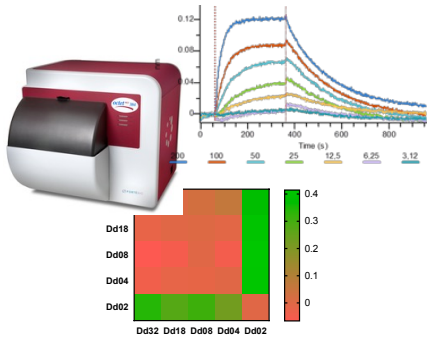
Sequence Attributes & Liabilities



Diverse collection of D domains



Kinetics and Epitopes



Leads converted to ddCAR & SparX

T Cell Biology Assessments

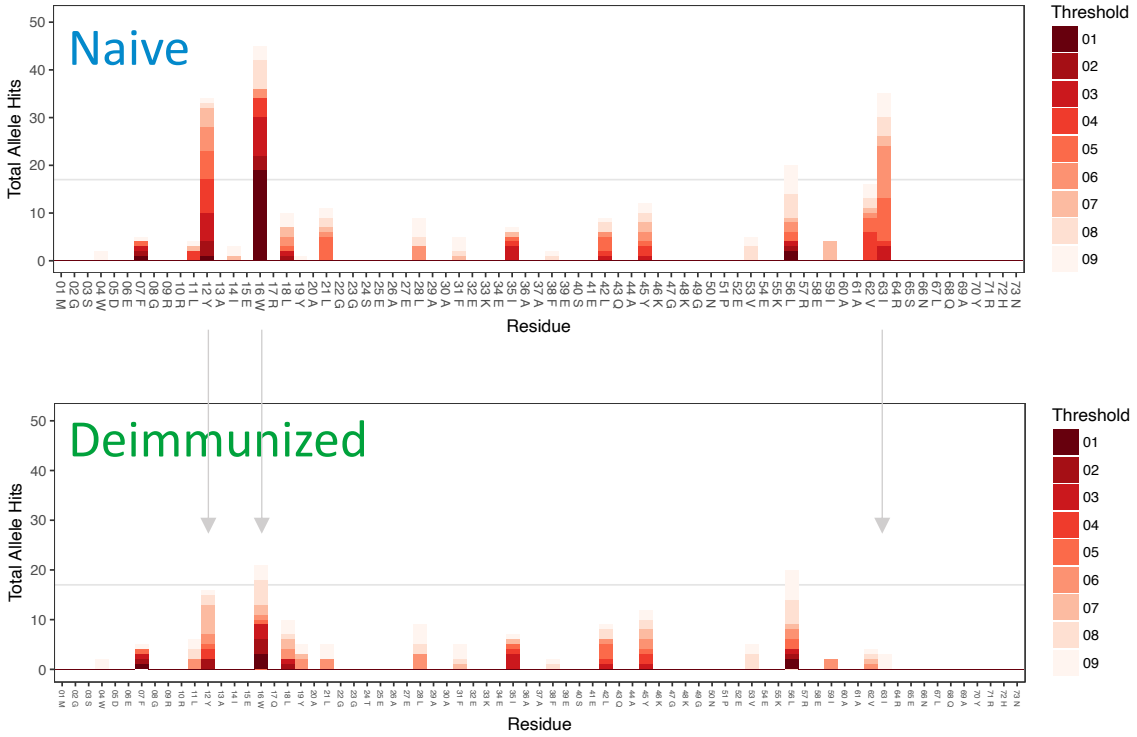
- Activation, Cytotoxicity, Proliferation & Cytokine release

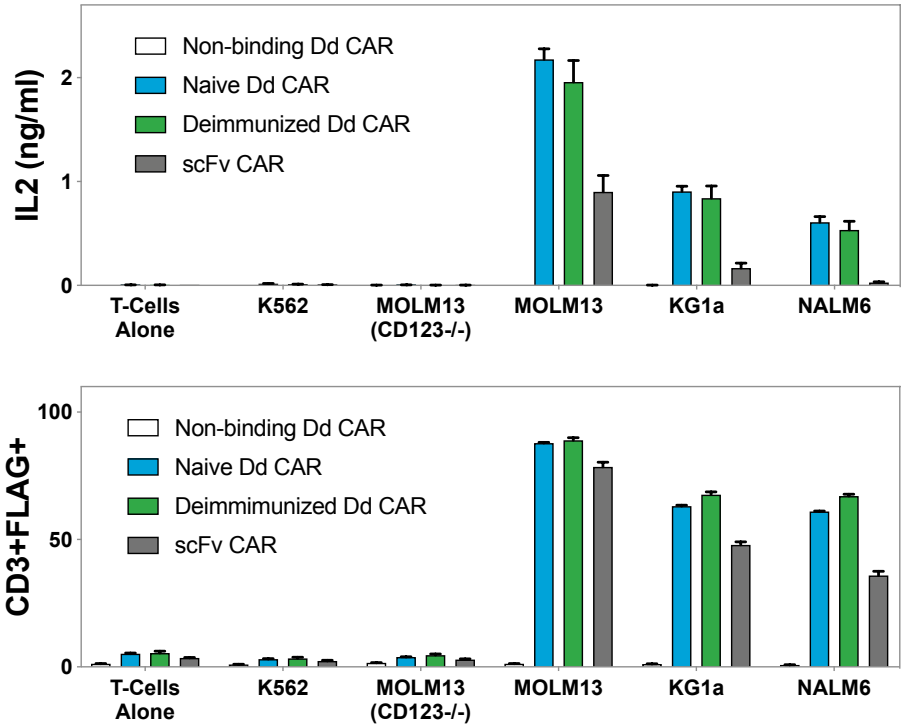
Cross Reactivity

- TCR & Microarray

In Vivo tumor models

Immunogenicity





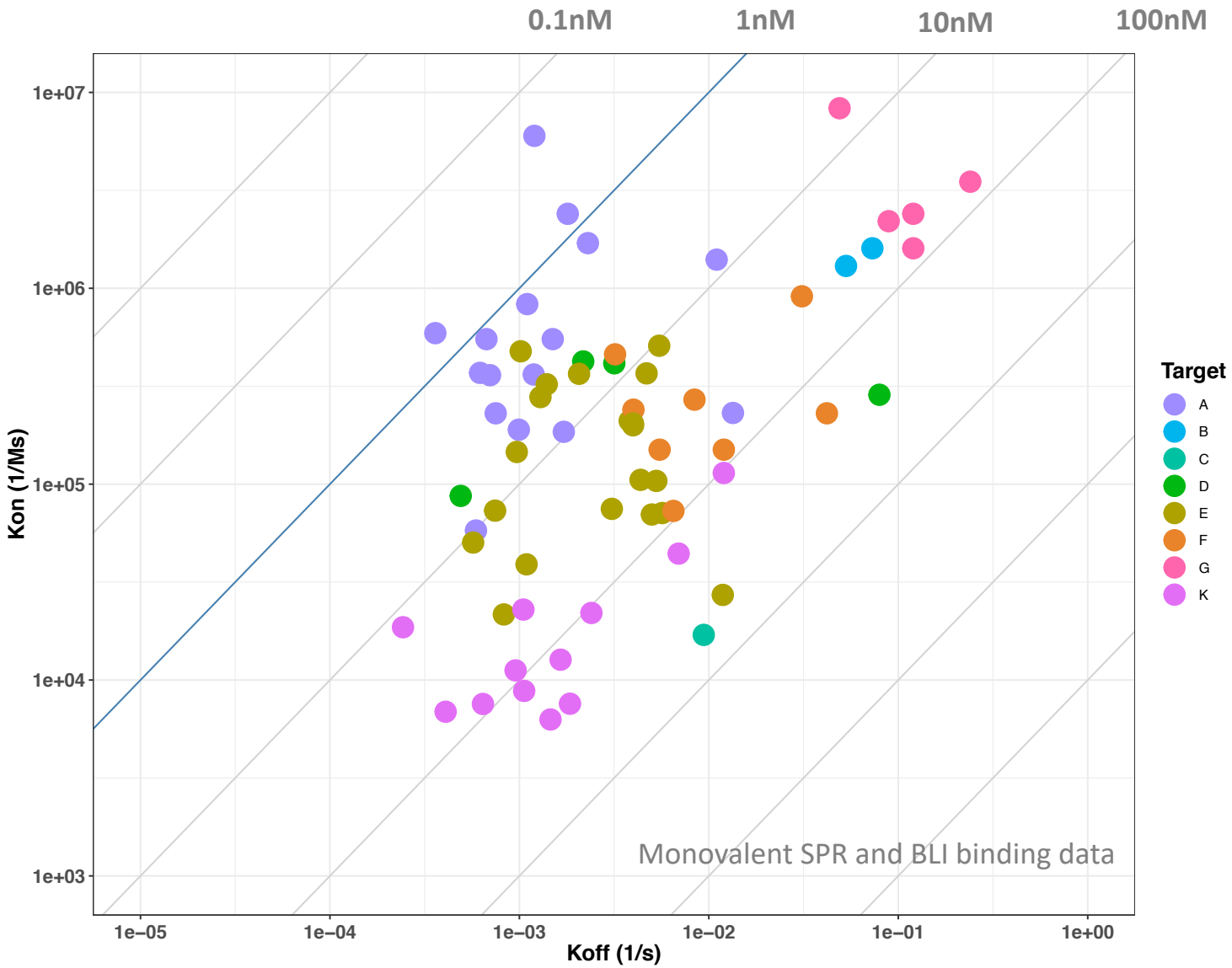
- a_3D inherently low *in silico* immunogenicity score
- D domains with high scores are excluded from development or deimmunized
- *Abzena EpiScreen™*: Assay responses, using donors representing diverse allelic population, are comparable to therapeutics such as trastuzumab

Affinity: Naïve Clones

Kinetics of D domains derived from naïve libraries

Many KDs are 1 to 100nM

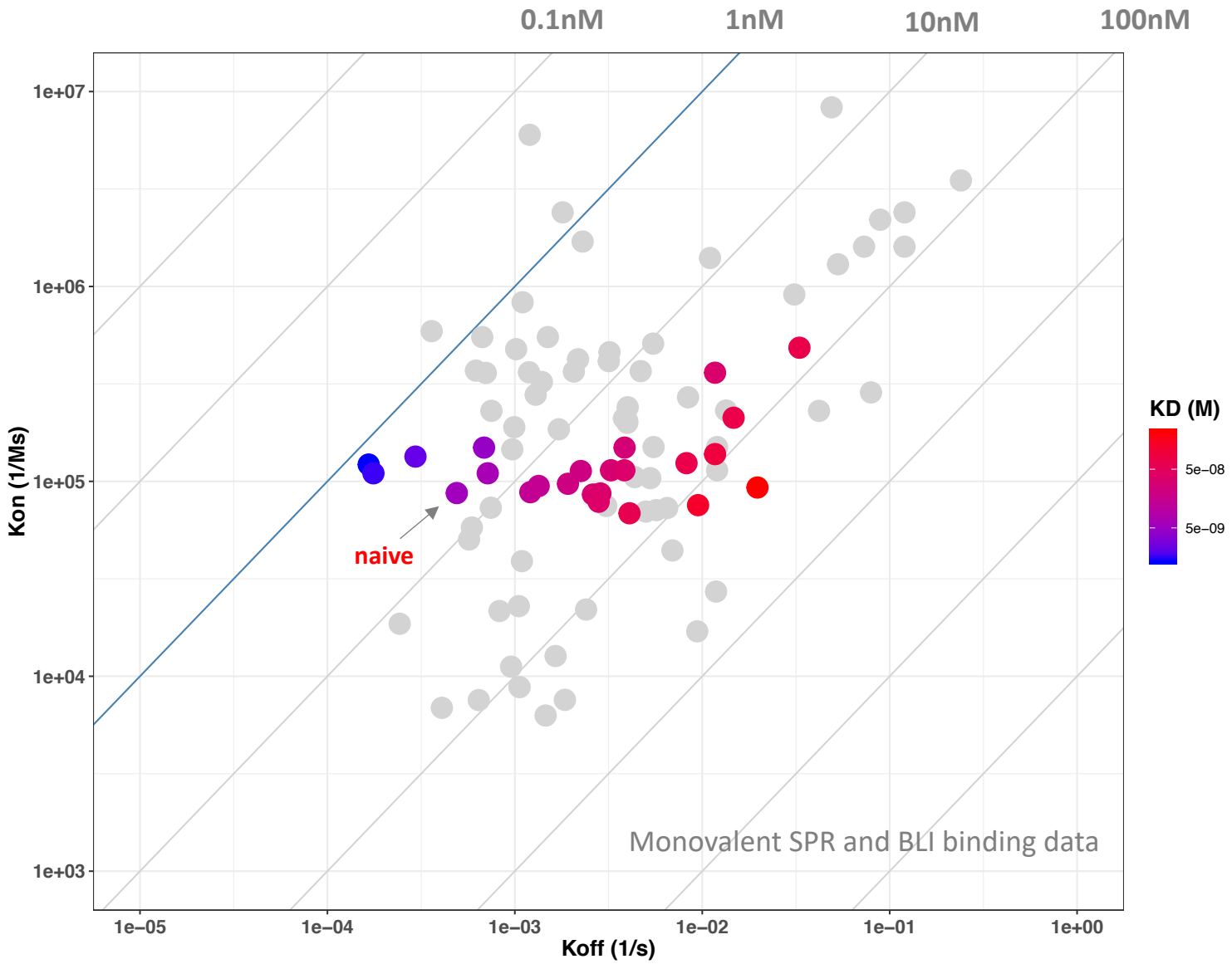
Kinetics are comparable to those derived from naïve antibody libraries



Affinity and Maturation

Single, point mutations to a CD123-binding naïve clone alter affinity over 200 fold range

Combining mutations can achieve sub-nanomolar affinities (not shown)



Outline

D domain Scaffold

Therapeutic Platforms: ddCAR & ARC-SparX

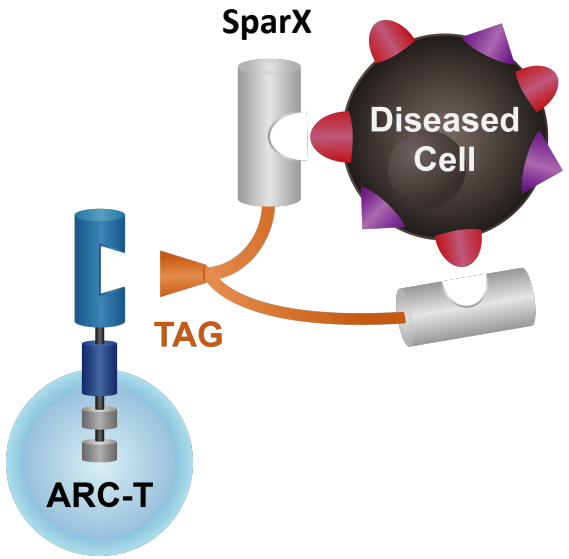
Clinical Programs

ddCAR and ARC-SparX utilize D domains

ddCAR

- D domain CAR
- Target-specific
- Single infusion

ARC-SparX



ARC-T Cell

- ARC-T is a universal cell
- ARC receptor contains D domain that bind to the “TAG” in the SparX protein

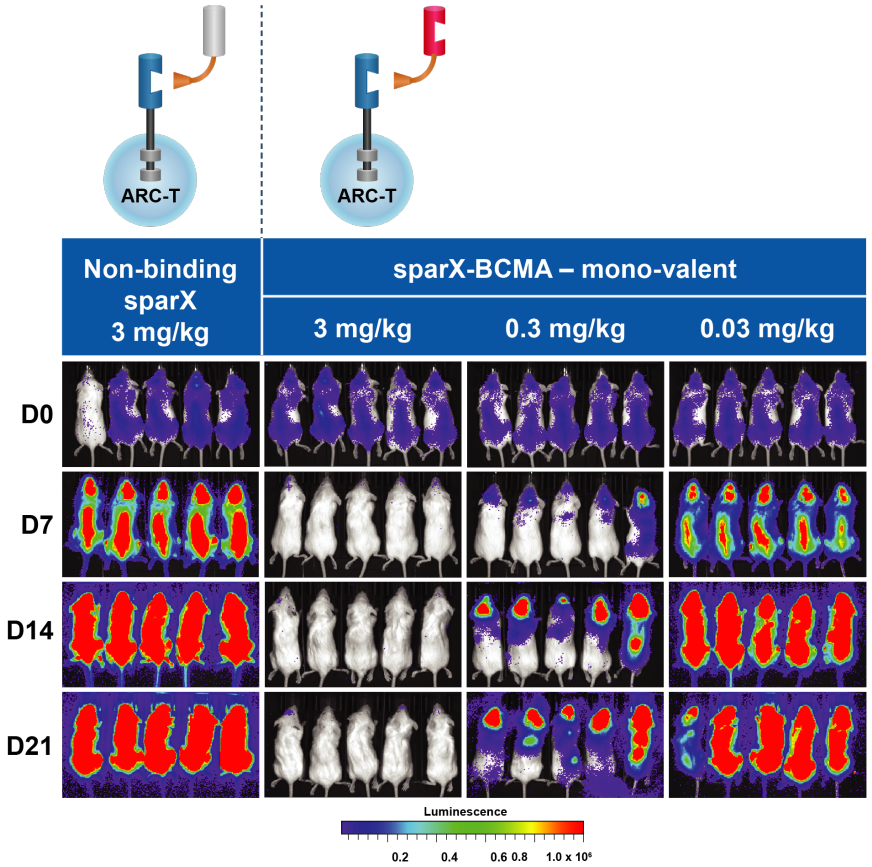
SparX Protein

- “TAG” is a subdomain of human alpha fetoprotein (AFP)
- D domains are target-specific
- Mono/Bi-valent & bi-specific formats

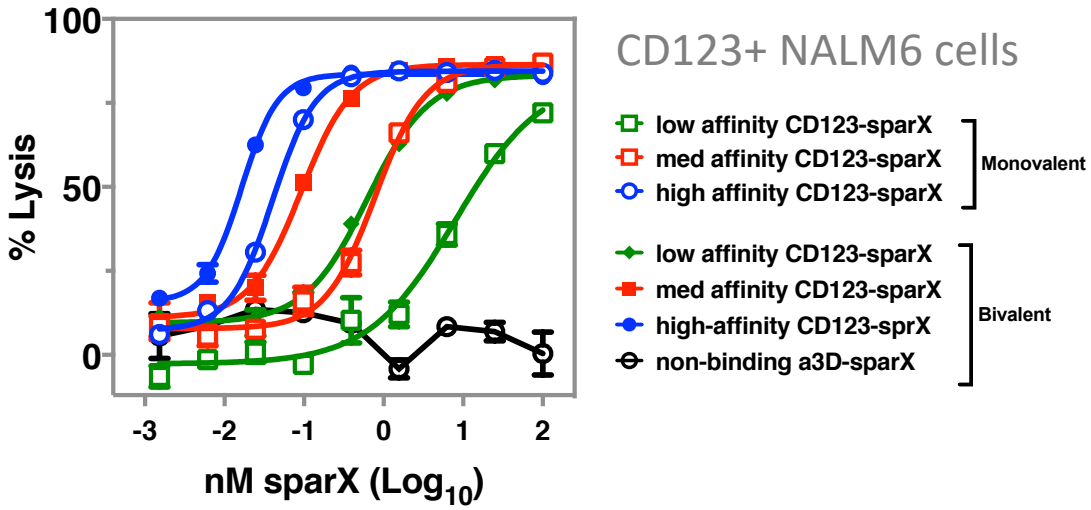
ARC-T Cells *only* activated upon formation of tri-complex: ARC-T + SparX + target cell

ARC-SparX Advantage: Controllable Potency

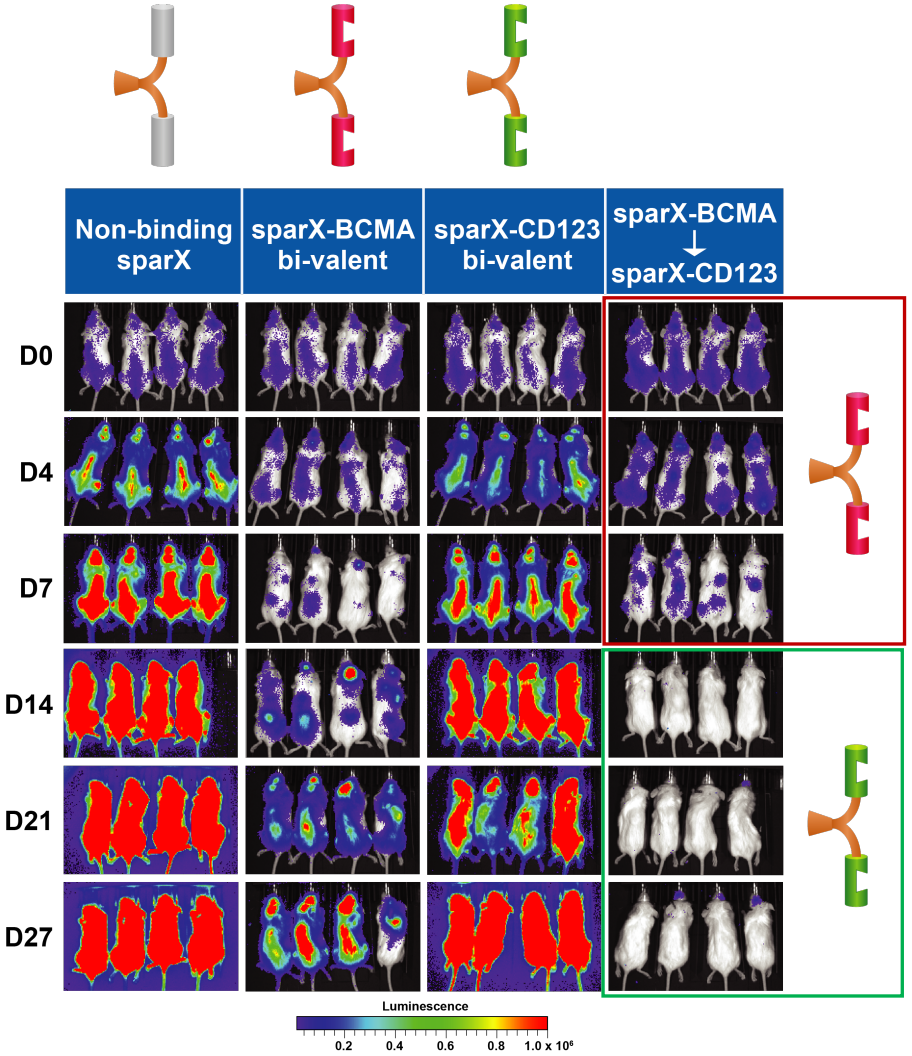
Control of ARC-T potency through SparX dosing



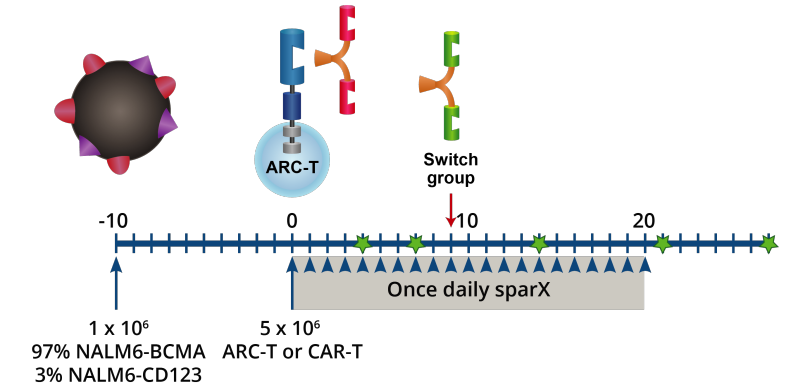
Control of ARC-T potency through SparX affinity and valency

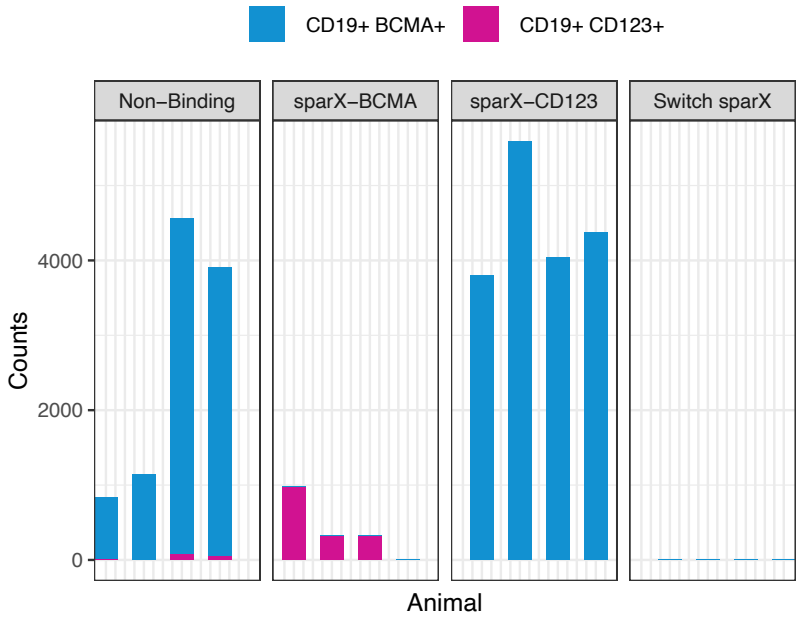


ARC-SparX Advantage: Adaptable Targeting



Day 24
Flow analysis





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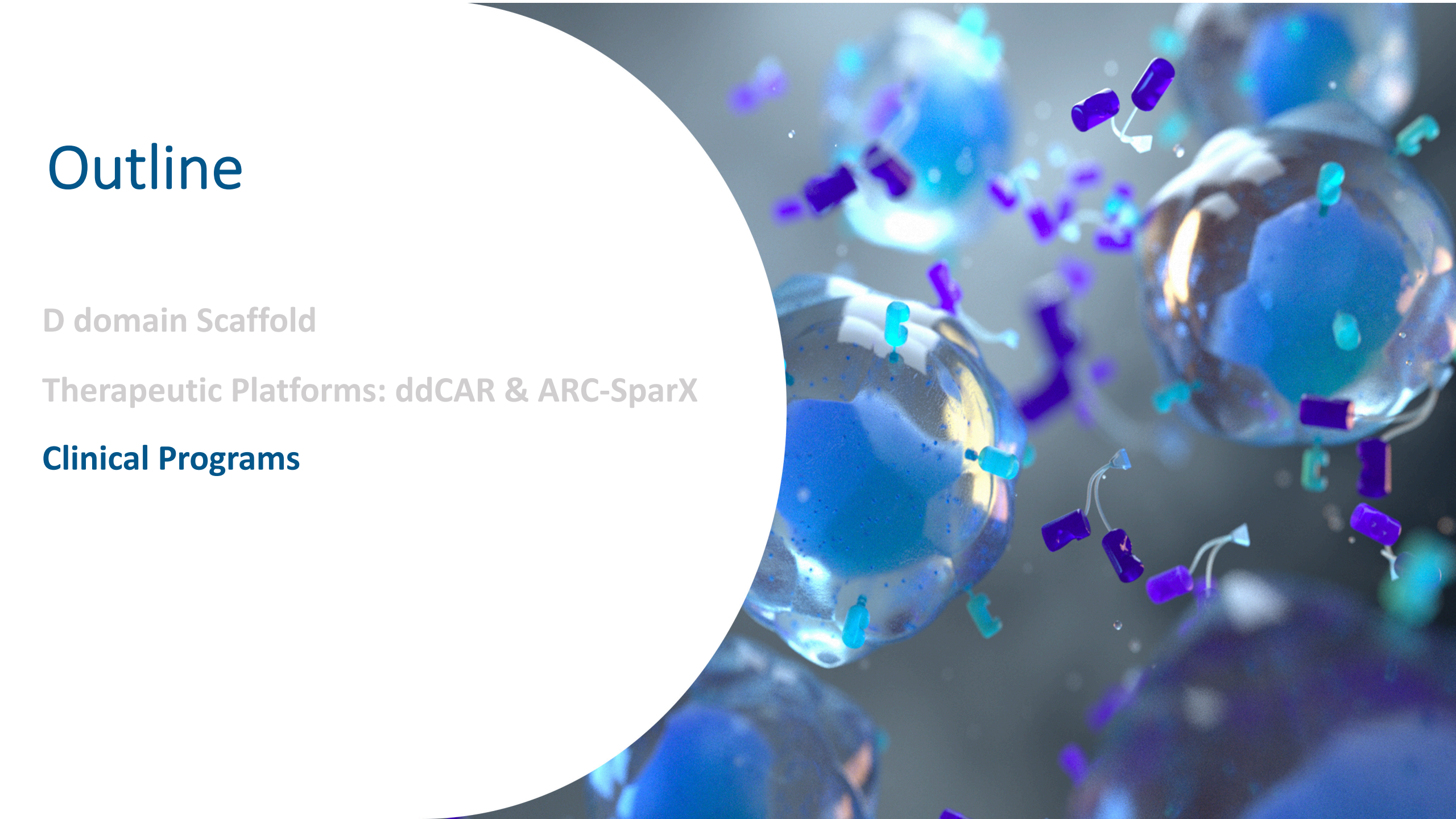
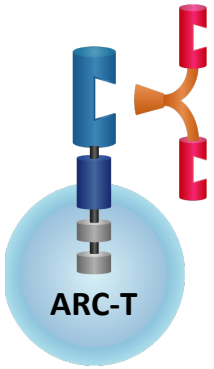
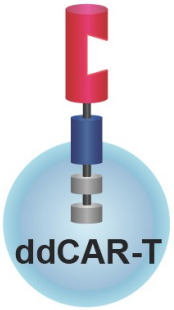


Clinical Programs



ACLX-001

- First ARC-SparX clinical program
- 2-component therapy: ARC-T Cell + bivalent SparX, targeting BCMA
- For treatment of relapsed and refractory multiple myeloma
- FDA clearance of IND application for ACLX-001 (March 2021)
- Phase 1 clinical trial expected to begin in the second half of 2021



CART-ddBCMA

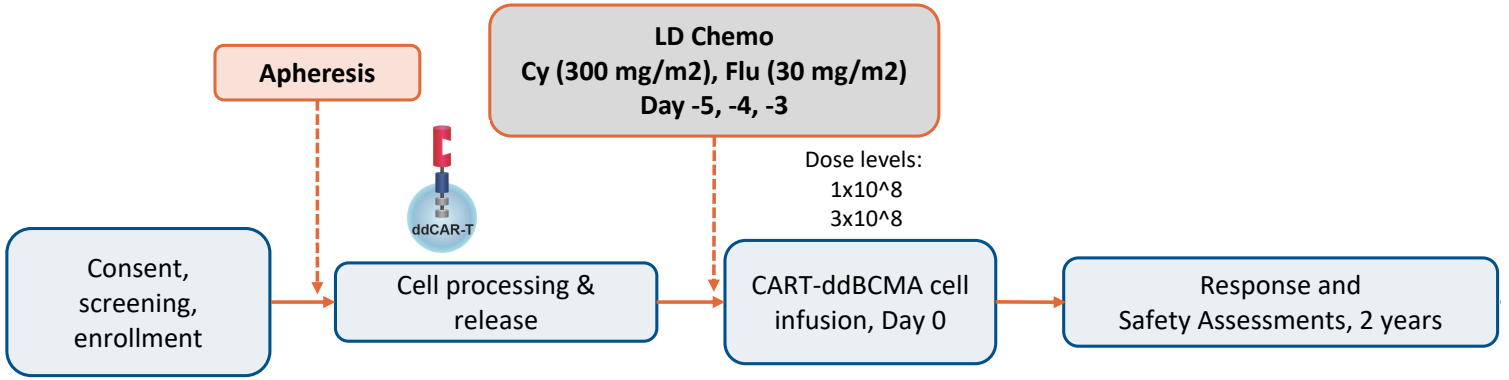
- First ddCAR clinical program
- Targeting BCMA
- For treatment of relapsed and refractory multiple myeloma
- Phase 1 clinical trial is in progress

Clinical Programs: CART-ddBCMA

Adapted from Frigault et al, ASH 2020 Abstract #3199; please refer to full ASH presentation for safety and efficacy data.

Eligibility

- Prior IMiD, PI, and CD38-targeted therapy
- Received ≥3 prior therapies or triple refractory



Subject #	Age/Sex	Myeloma	Prior Lines / Prior ASCT	Prior Therapy Status	High Risk Cytogenetics	Bone Marrow Plasma Cells	Extra-Medullary	Dose (+/- 20%) CAR+ T Cells	CART-ddBCMA Release	
									VCN*	% CAR+
1	73/M	IgA	5 / No	penta-refractory	t(4;14), 1q+	95%	Yes	100 million	2.34	78
2	73/F	Light Chain	5 / No	penta-refractory + BRAFi	sample not evaluable	0%	Yes	100 million	2.12	76
3	75/M	IgA	7 / No	penta-refractory + anti-CS1 mAb	1q+	95%	Yes	100 million	2.61	72
4	74/F	IgG	5 / Yes	penta-refractory	del17p, 1q+	70%	No	100 million	2.33	76
5	66/F	Light Chain	5/ Yes	penta-refractory +BRAFi	1q+	10%	No	100 million	2.33	73
6	66/F	IgA	7 / Yes	penta-refractory + anti-CS1 mAb	1q+	< 5%	Yes	100 million	3.07	87

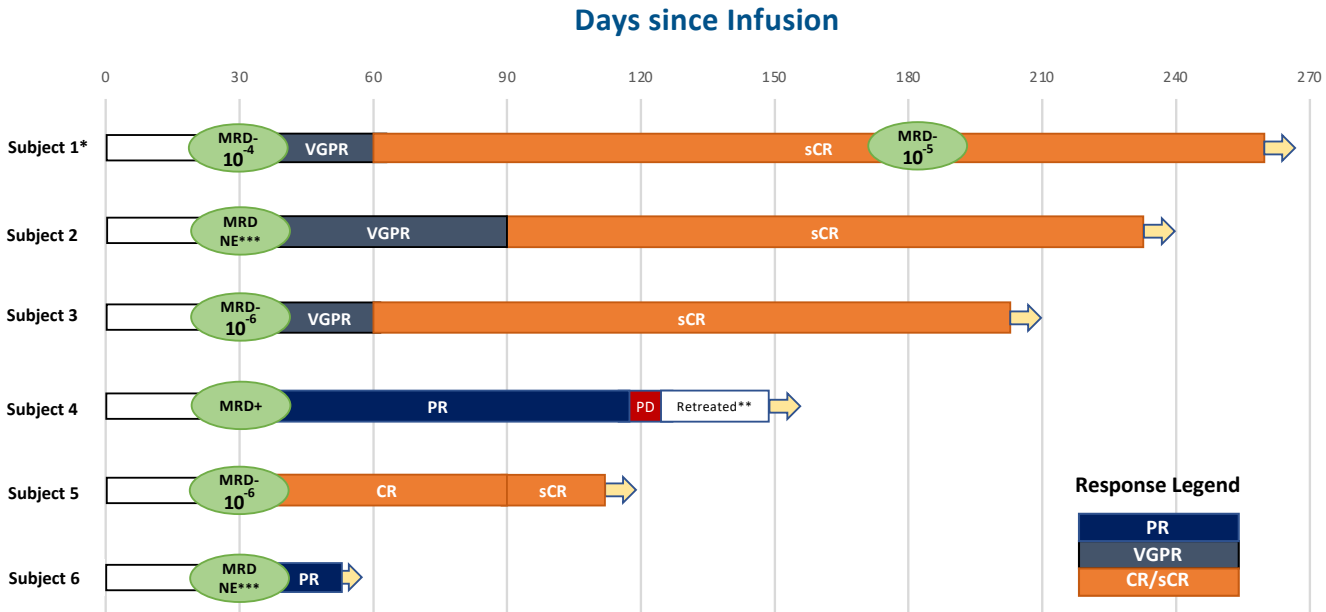
Penta-refractory: refractory to ≥2 PIs, ≥2 IMiDs, and anti-CD38

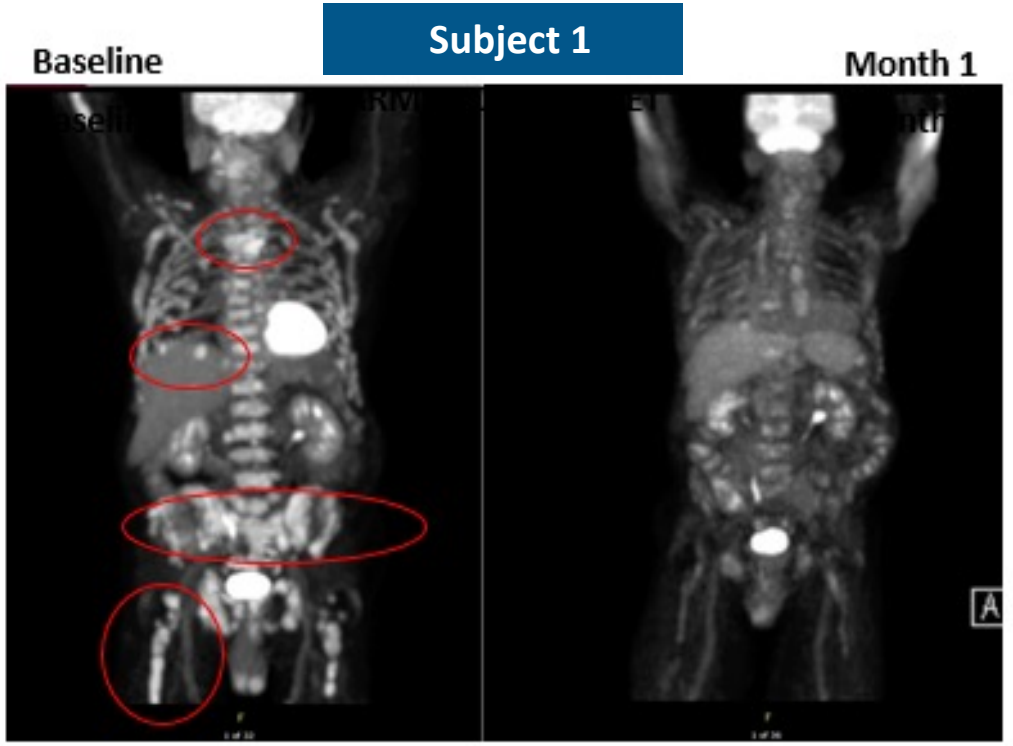
**Vector Copy Number*

Time on Study from CART-ddBCMA Infusion (as of 29 Oct 2020)

Adapted from Frigault et al, ASH 2020 Abstract #3199; please refer to full ASH presentation for safety and efficacy data.

- First 6 patients received 100 million CART-ddBCMA+ cells and showed robust cell expansion
- 100% response rate among first six patients per IMWG criteria
- 4 stringent complete responses (sCR), 2 partial responses (PR)
- 5/6 subjects experienced rapid clearance of sFLC and SPEP within 2 months





- **Baseline:** High disease burden (95% BMPC) with IgA myeloma, extra-medullary disease, penta-refractory, and high-risk cytogenetics.
- **Month 1:** Bone marrow negative, Minimal Residual Disease (MRD)-negative, and PET-CT negative

Summary

- **D domains** are a robust scaffold for the generation of binders to a variety of targets and exhibit properties required in a targeting domain
- The **ddCAR** and **ARC-SparX** platforms offer high performance and novel solutions to difficult therapeutic situations
- **CART-ddBCMA** facilitates deep and durable responses in patients with poor prognoses

Thank You

Arcellx Team

Clinical Teams

- University of Chicago Comprehensive Cancer Center
- Massachusetts General Hospital Cancer Center
- Beth Israel Deaconess Medical Center
- Dana-Farber Cancer Institute

Patients and their families

David LaFleur
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