AsherBio

Engineering Cis-Targeted Immunomodulators to Enhance Their Selectivity and Effectiveness as Therapeutics

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PEGS- Europe
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Agenda

- Overview of Asher Biotherapeutics
- Cis-Targeting Technology
- Lead Program AB248: CD8 T cell Targeted IL-2
- Platform of Cis-Targeted Fusions

Introduction to Asher Bio

- A **preclinical-stage immunotherapy company** located in South San Francisco, CA
  - Founded in 2019 by Ivana Djuretic, Andy Yeung, Bob Schreiber (Wash U) and Ton Schumacher (NKI)
  - Experienced management team led by Craig Gibbs, CEO (formerly Forty Seven & Gilead)
  - Strong expertise in immunology, protein engineering, preclinical and clinical development
  - Advised by world renowned SAB members: Bob Schreiber, Ton Schumacher, Miriam Merad (Mount Sinai), George Georgiou (U. of Texas) & Mario Sznol (Yale)
- Advancing **cis-targeting platform** yields immunotherapies that specifically activate selected immune cell subsets
- Building a **broad pipeline of novel cis-targeted therapies** derived from diverse cytokines and cell-types
  - Applications span oncology, cell therapy, infectious disease, and autoimmune disease
- **Lead program AB248**, a CD8 T cell selective IL-2
  - Potential best-in-class based on direct comparison with a 2nd gen “not alpha” IL-2 molecule
  - Projected IND in 2022

Overview of Technology

Systemic Delivery of Immunomodulators Drives Pleiotropic Effects

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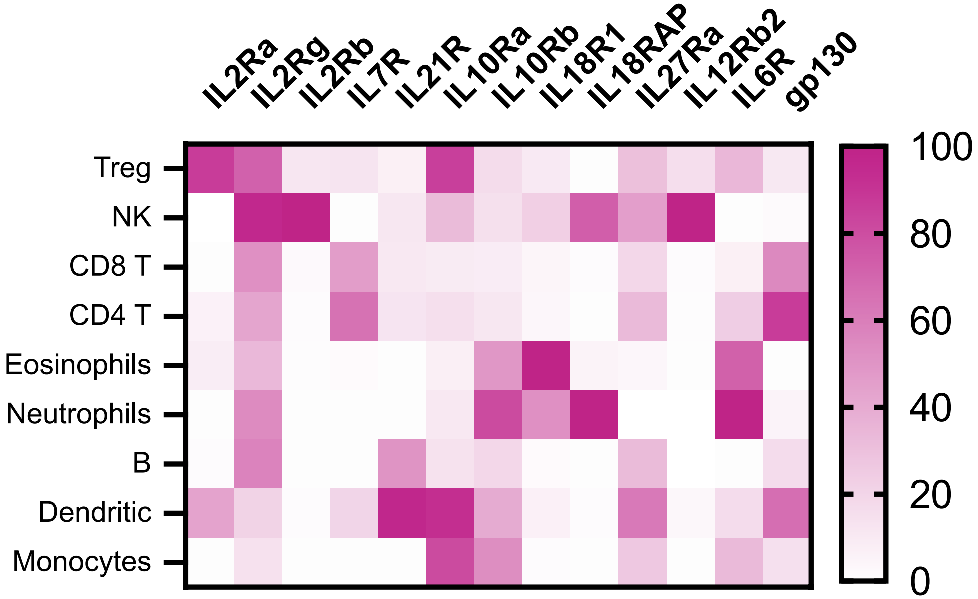
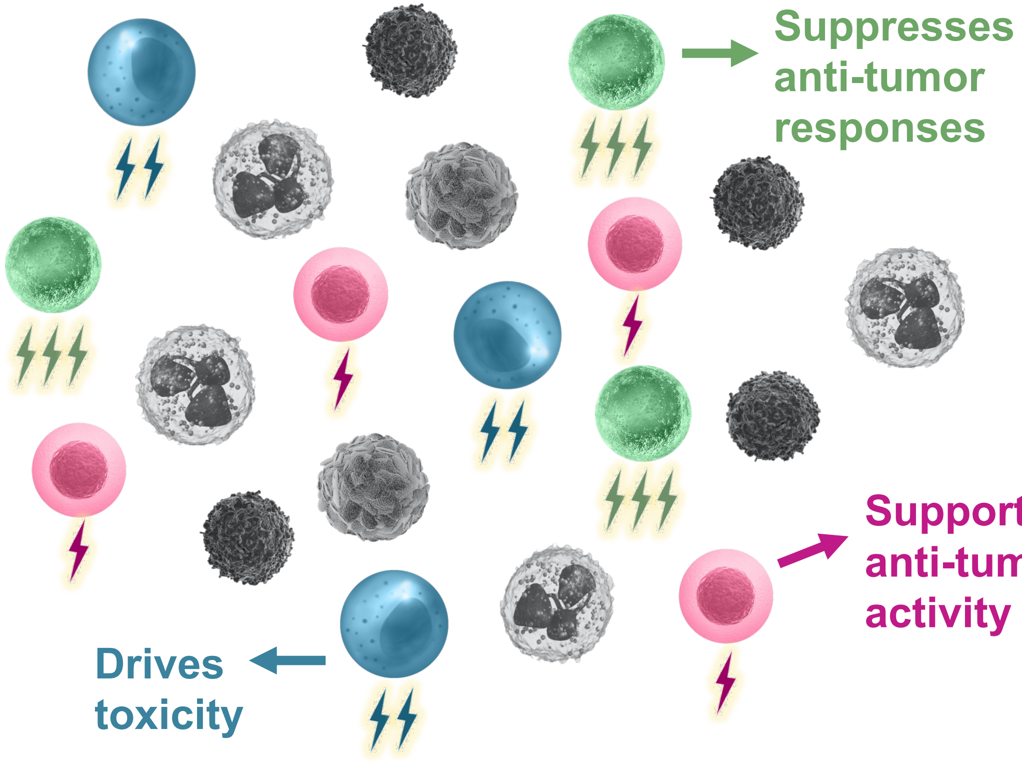
Cytokines and other immunotherapies exhibit functional pleiotropy, with heterogenous activity across different cell types.



RNA expression of cytokine receptors across immune cell types (Blueprint database)

When used as therapies, they often induce desired biology and undesired consequences simultaneously, limiting efficacy and driving toxicity



Suppresses anti-tumor responses

Supports anti-tumor activity

Drives toxicity

Precision Targeting of Pleiotropic Immunotherapies to Maximize Benefit

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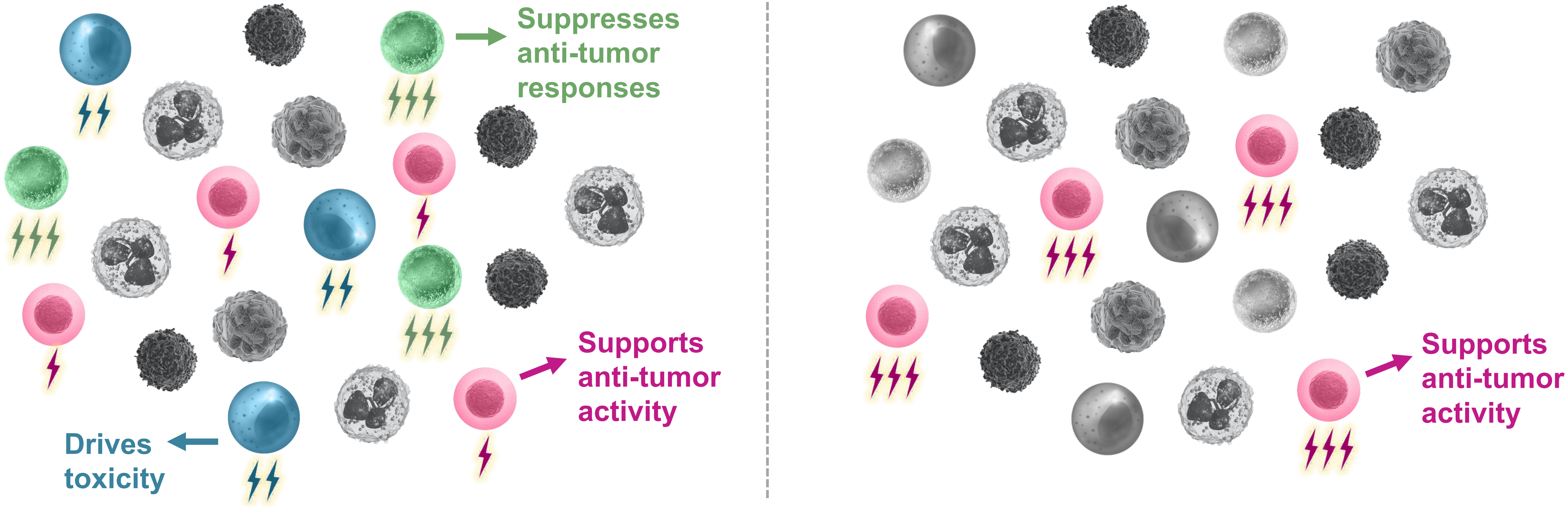
Current Therapies

Asher Bio: Targeted Immunomodulation


Suppresses anti-tumor responses
Supports anti-tumor activity
Drives toxicity
Supports anti-tumor activity

Asher Bio is solving this problem by creating targeted biotherapeutics precisely directed to desired effector cells. This may mitigate toxicity, pharmacologic sinks, and opposing signaling for **improved efficacy and therapeutic outcomes**.

Asher Bio's Process to Solve the Pleiotropy Problem

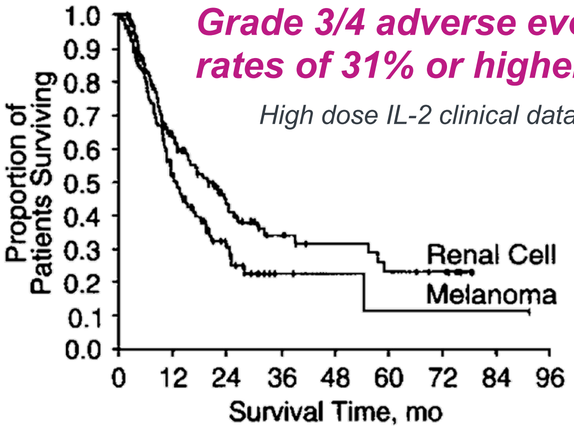
Cytokine of interest
Focus on candidates with clinical efficacy and a problem to solve

→

Deconvolute biology responsible for efficacy vs. undesired consequences

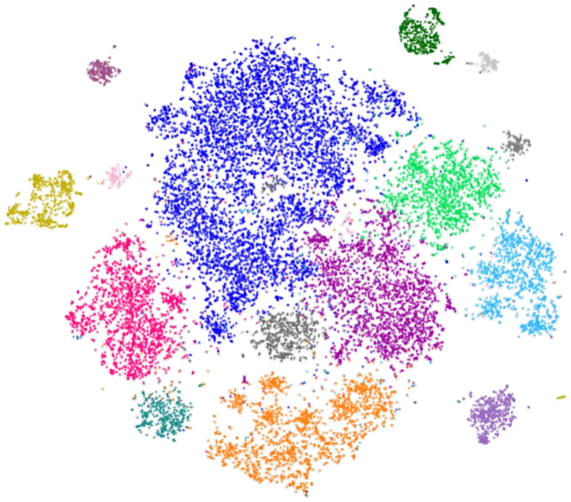
⟳

Engineer *cis*-targeted therapies for stronger efficacy and lowered toxicity

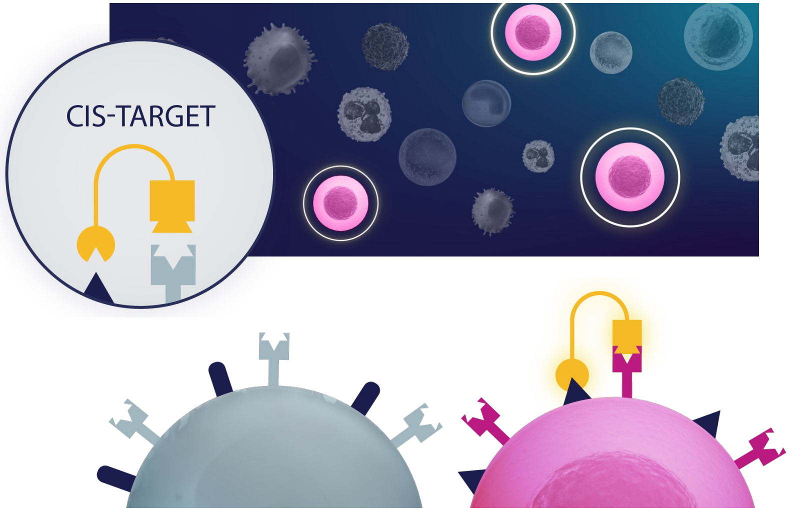


Grade 3/4 adverse event rates of 31% or higher[1]

High dose IL-2 clinical data



Examples - scRNAseq analysis



Asher Bio aims to maximize the impact of cytokine therapies
by selectively activating desired effector cells and avoiding counterproductive signaling that limits efficacy and reduces therapeutic index

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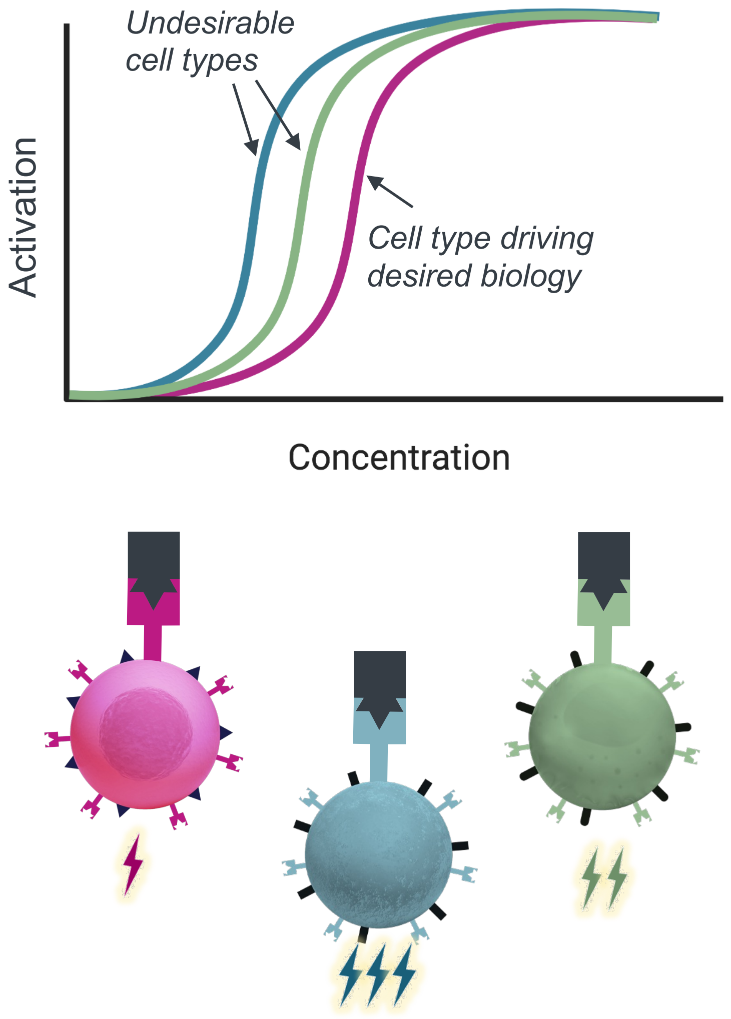
[1] Rosenberg et al., *JAMA*, 1994

How Does cis-Targeting Work?

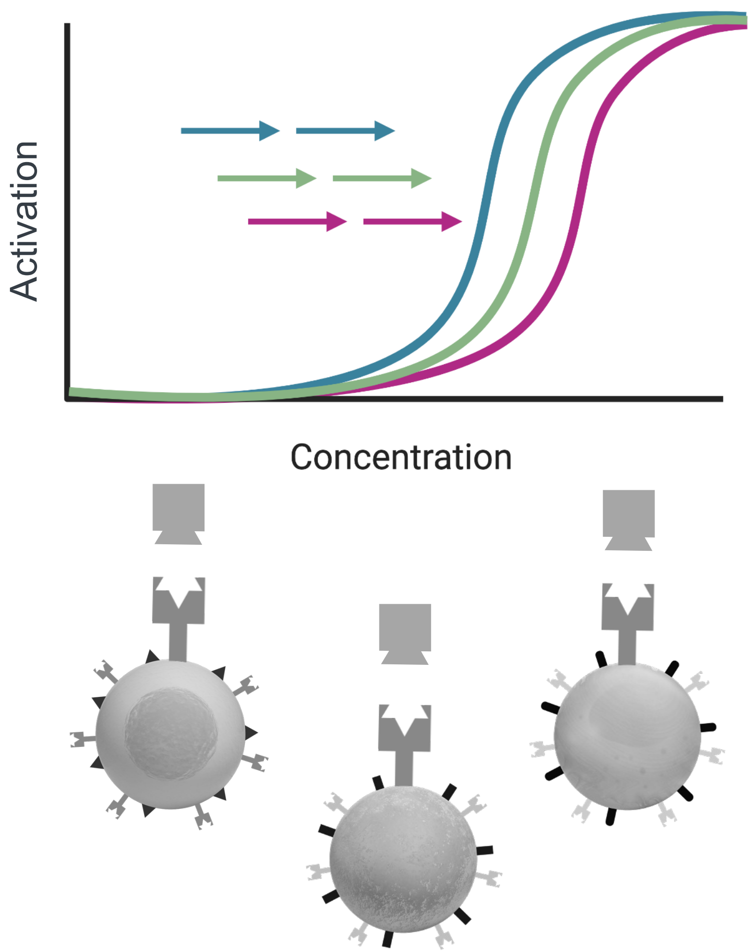
Native cytokine

activates all cell types


Undesirable
cell types
Cell type driving
desired biology
Activation
Concentration

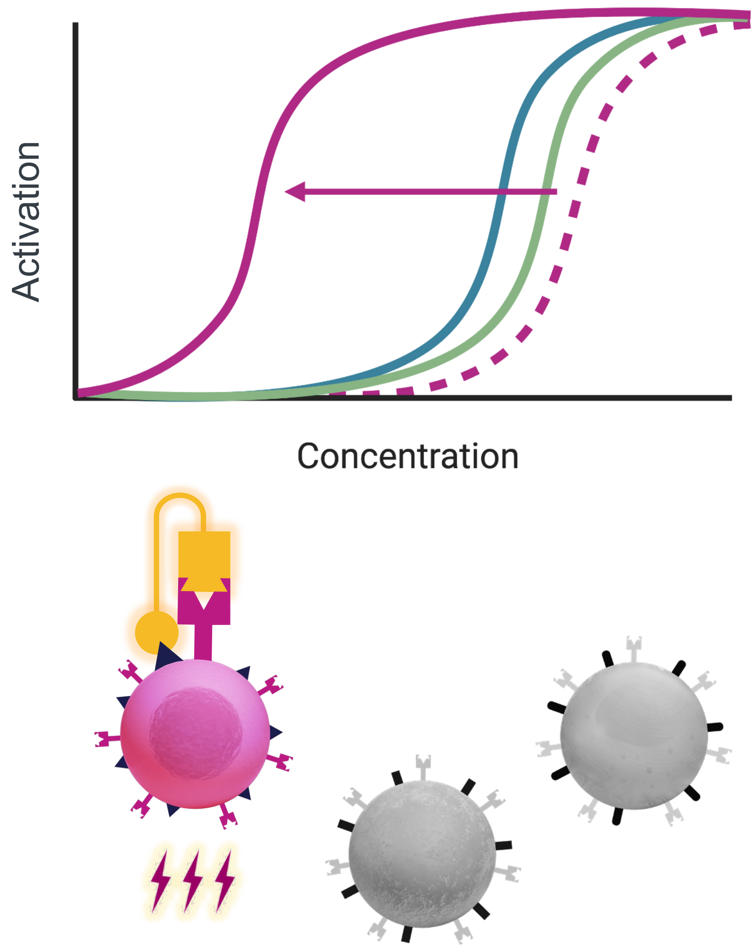
Attenuated cytokine mutein

has weak to no activities on all cell types

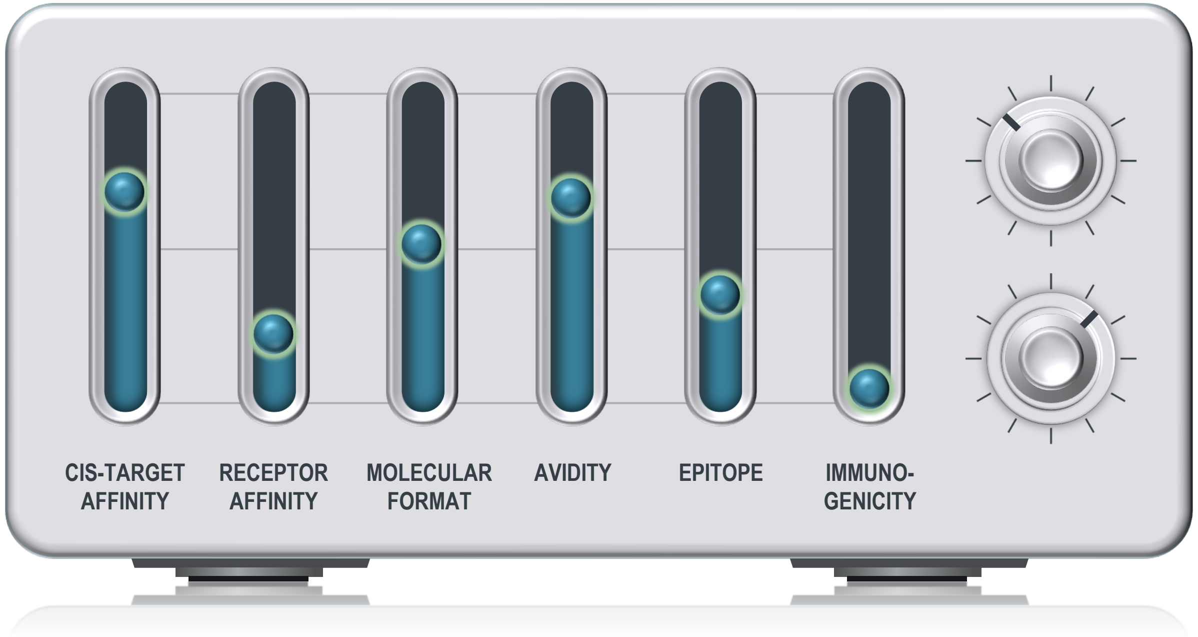

Activation
Concentration

cis-targeted cytokine

only activates the desired cell type

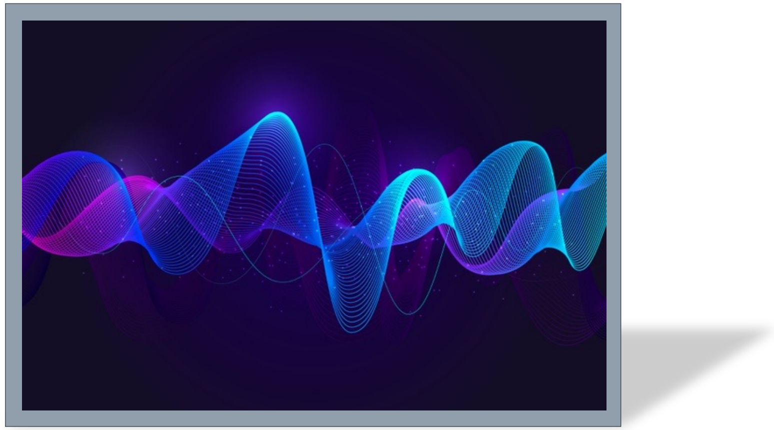

Activation
Concentration

Complexities in Developing a cis-Targeted Candidate


CIS-TARGET AFFINITY
RECEPTOR AFFINITY
MOLECULAR FORMAT
AVIDITY
EPITOPE
IMMUNO-GENICITY

Optimization of interconnected properties

Molecule with ideal PK/PD, Selectivity, Safety, and Efficacy Profile



Building an optimal *cis*-targeted molecule is complex, requiring optimization of many properties in parallel to generate a molecule with optimal *in vivo* profile and improved efficacy

Lead Program AB248: CD8 T cell targeted-IL2

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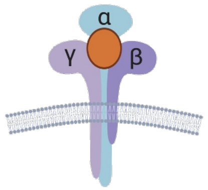
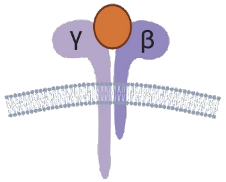
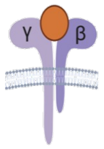
Overview of IL-2 and “not alpha” IL-2 molecules

Molecule Class	**IL-2** *and molecules retaining IL2Rα binding*	**“Not-alpha” IL-2 variants** *including IL-15 superagonists*
Receptors	 ***IL2Rαβγ*** ***IL2Rα Expression*** T cell inducible Treg +++ NK +/- ILCs +++	 ***IL2Rβγ*** ***IL2Rβγ Expression*** T cell + Treg + NK +++ ILCs +
Examples	aldesleukin, bempegaldesleukin (NKTR-214), BAY 50-4798	THOR-707, simlukafusp alfa (FAP-IL2v), nemvaleukin alfa (ALKS 4230), N-803 (ALT-803), SOT101
Monotherapy Clinical Efficacy	**ORR of ~20% with CR rate of 5-10%** in RCC and melanoma (high dose aldesleukin)	Sporadic reports of PRs **No reported CRs to-date**
Clinical Toxicities	**IL2Rα-dependent toxicity dominates** – numerous, but vascular leak syndrome (VLS) most problematic ***VLS is driven by IL2Rα+ cells***	**IL2Rβγ-dependent tox unmasked,** including liver tox and cytokine release syndrome (CRS) ***Likely driven by IL2Rβ^{high} cells like NK cells***

Not alpha IL-2s were designed to avoid vascular leak syndrome and Treg activation observed with high dose IL-2 but additional liabilities remain: toxicity and suboptimal efficacy

2nd Gen. IL-2 “Not α” Agonists (incl. IL-15) Have Suboptimal Profiles

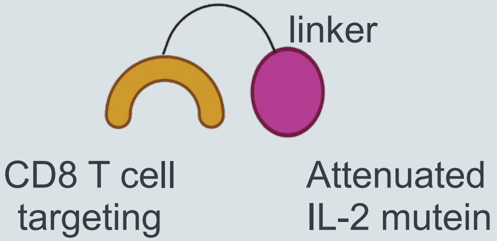
IL-2/15



	Company and Drug		Description	*In vitro* EC50 (pSTAT5, nM)			Clinical Peripheral Cell Expansion (fold change)			Current Phase	Monotherapy activity in solid tumors?
				CD8	Treg	NK	CD8	Treg	NK		
	NEKTAR	***NKTR-214*** ***Bempeg***	PEG IL-2	**0.5**	**0.001**	**0.3**	**1.7 - 2.1X**	**5 - 10X**	**3.2 - 5X**	3	**No. 60% ORR in 1L Mel with αPD1.**
2nd gen “not α” IL2Rβγ agonists	synthorx SANOFI	***THOR-707***	PEG IL-2 (site specific)	**5.7**	**2.0**	**0.6 - 1**	**3.7-4.5X**	**1.7-3.5X**	**7.7-13X**	1/2	**Yes, one PR**
	Roche	***FAP-IL2v***	anti-FAP antibody IL-2 ”not α” fusion	**1.6**	**0.7**	**0.4**	**2.7-3.4X**	**2X**	**13X**	N/A	**Yes, 9% ORR**
	Alkermes	***ALKS 4230***	IL-2 mutein fused to CD25 ECD	**1-2**	**0.59**	**0.45**	**2.2X**	**2.6X**	**8.4X**	2	**Yes, 4 melanoma PRs**
	ImmunityBio	***N-803*** ***ALT-803***	IL-15 super-agonist Fc fusion	**0.03†**	**Not reported**	**0.005†**	**1 - 2X**	**1-1.3X**	**8X**	2	**No**
	sotio	***SO-C101***	IL-15Ra/IL-15 complex	**0.02†**	**Not reported**	**0.005†**	**1.5X**	**Not reported**	**12X**	1	**Yes, 1 squamous cell carcinoma PR**

- ”Not α” IL-2 and IL-15s avoid vascular leak, but clinical activity is suboptimal compared to WT IL-2
- ”Not α” IL-2 and IL-15s still activate Tregs, although not as extensively as WT IL-2 and NKTR-214; they also preferentially activate toxicity-inducing NK cells due to their high expression of IL2Rβγ
- **An ideal agent would selectively activate CD8+ T cells *without* activating Treg or NK cells,** which may allow for an improved efficacy and safety profile

Our solution: AB248*



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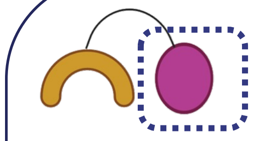
†Representative molecules; data from third party (Miyazaki et al., SITC, 2019). References: AACR 2021, Sanofi R&D Day June 2020; ENA 2020; SITC 2020; SVB Leerink Research 2020; Romee et al., Blood, 2018; ALKS investor day 2021, Spisek et al., CBCI, 2021, and Miyazaki et al., SITC 2019. Note: i.v. ALKS data used here. Colors for in vitro EC50s normalized per molecule. IL-2 data used for NKTR-214, representing fully de-PEGylated molecule

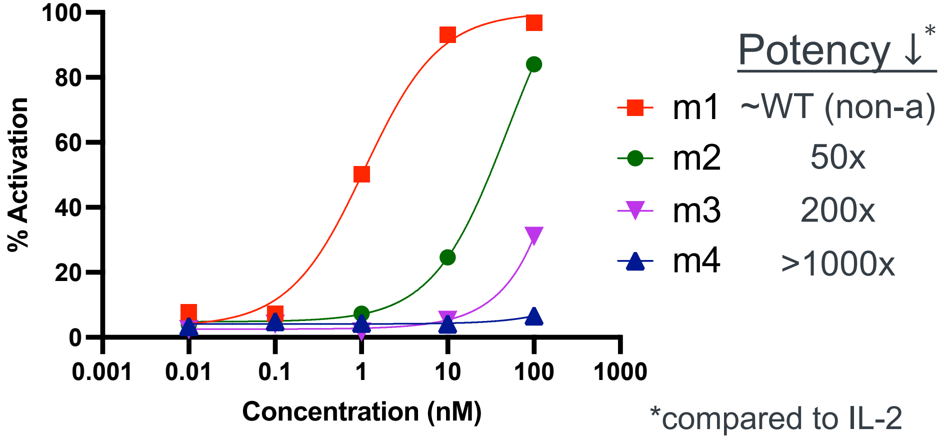
*Not actual structure

Screening of Targeting Antibody and IL-2 Muteins



Tuning of IL-2 Mutein Potency

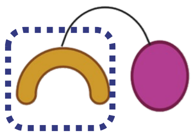
Untargeted IL-2 muteins on IL-2Rβγ+ CD4 T cells

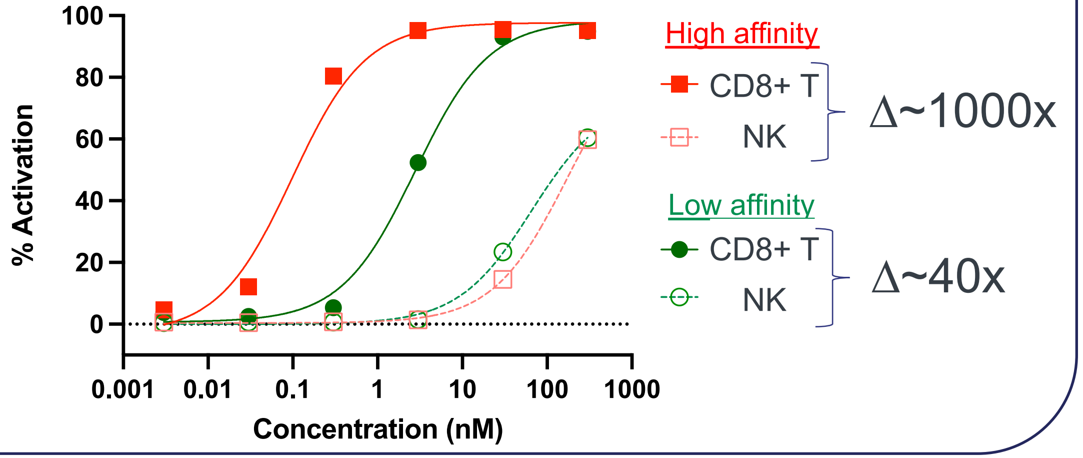


*compared to IL-2

Tunning of Targeting Arm Affinity

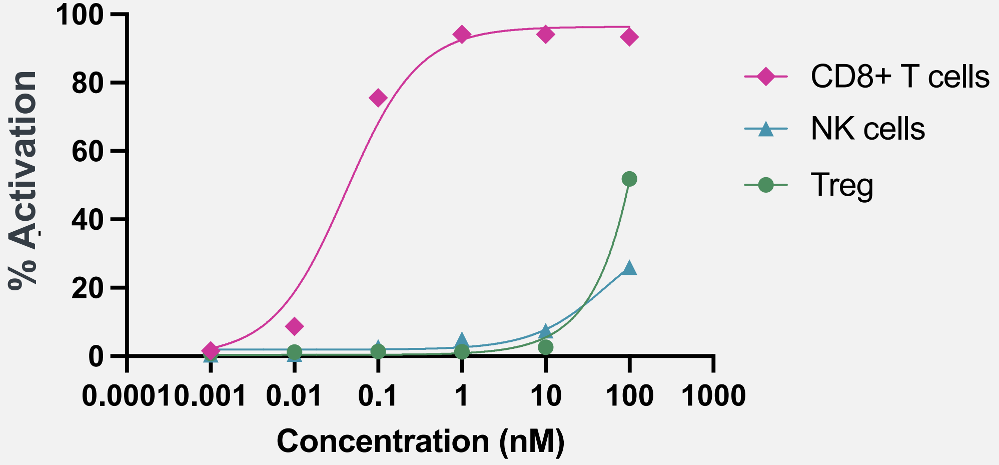
Activity comparison on CD8 vs NK cell





Activation Profile of AB248 (CD8-IL2)

>3 log of preferential activation on CD8 T cells



In Vitro Activation Profiles of IL-2 Based Molecules

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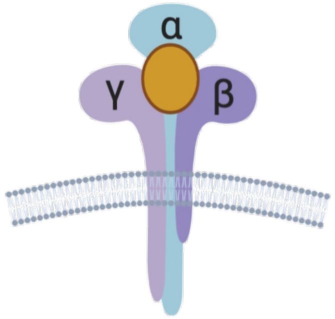
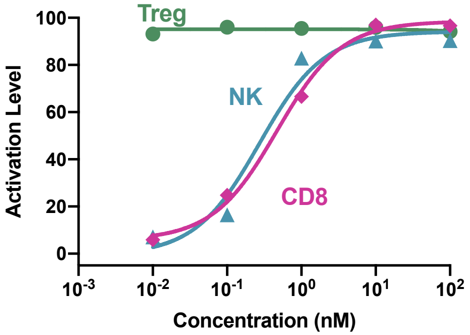
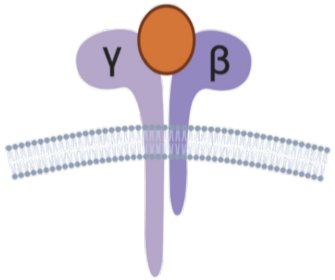
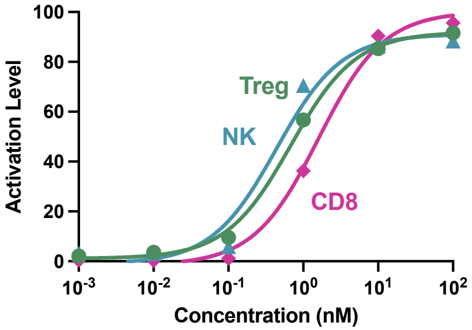
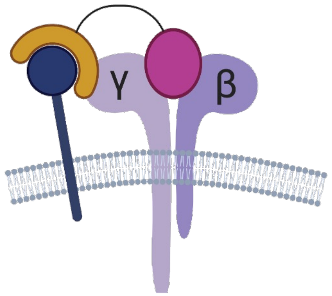
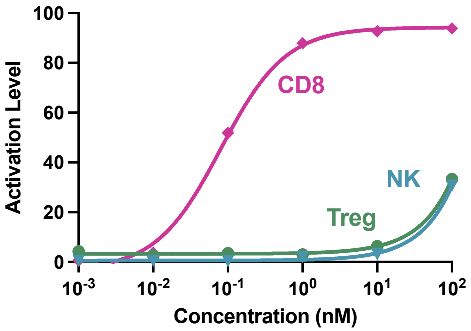
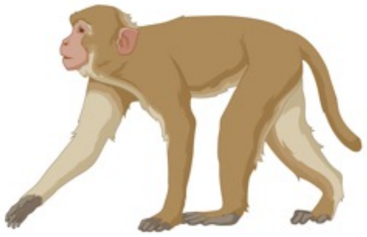
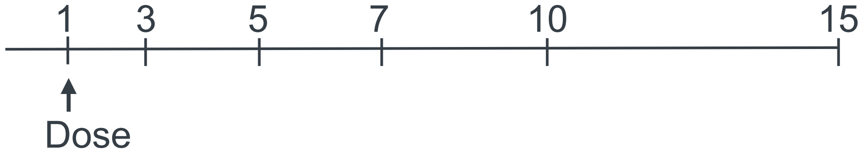
Molecule Class	Receptors	*In vitro* Activation	Vascular leak	Half life	Avoids Tregs	Avoids NK	CD8 potency
NATIVE CYTOKINE *Aldesleukin*			X	X	X	X	-
"NOT-α" VARIANTS *e.g. FAP-IL2v (Roche), THOR-707 (SynthorX), ALKS 4230 (Alkermes)*			✓	✓	-	X	-
AB248: CD8-targeted IL-2 *AB248 (Asher Bio)*			✓	✓	✓	✓	✓

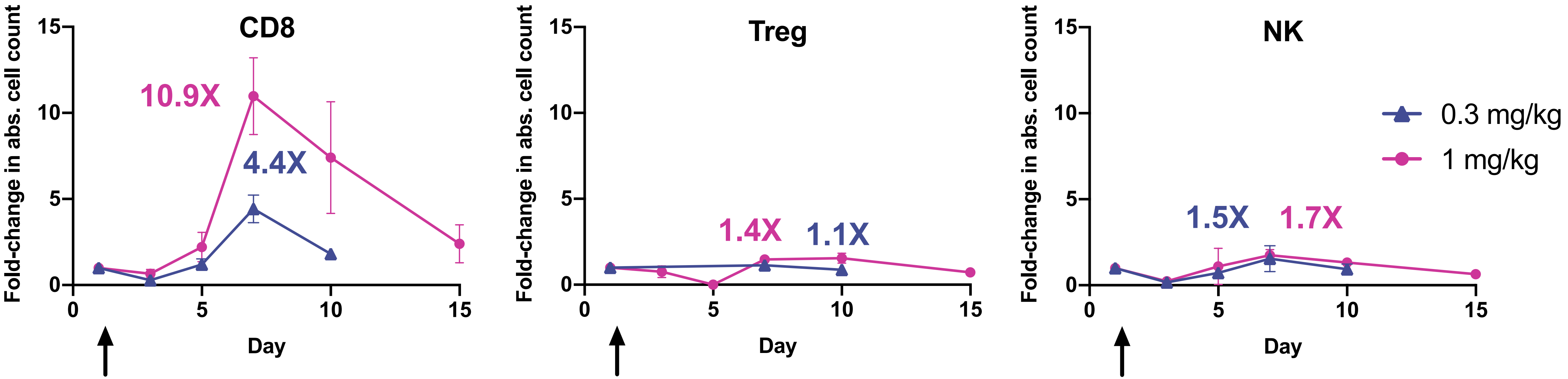
Pharmacodynamic Profile of CD8-IL2 in Cynomolgus Monkeys



Cynomolgus monkey
n = 2 per dosing level

Bleed Dates





- The desired PD profile is seen in cynomolgus monkeys

Monotherapy in Established MC-38 Colorectal Tumors

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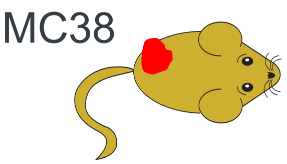
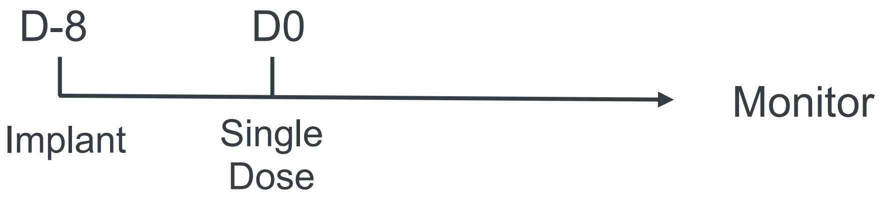
MC38





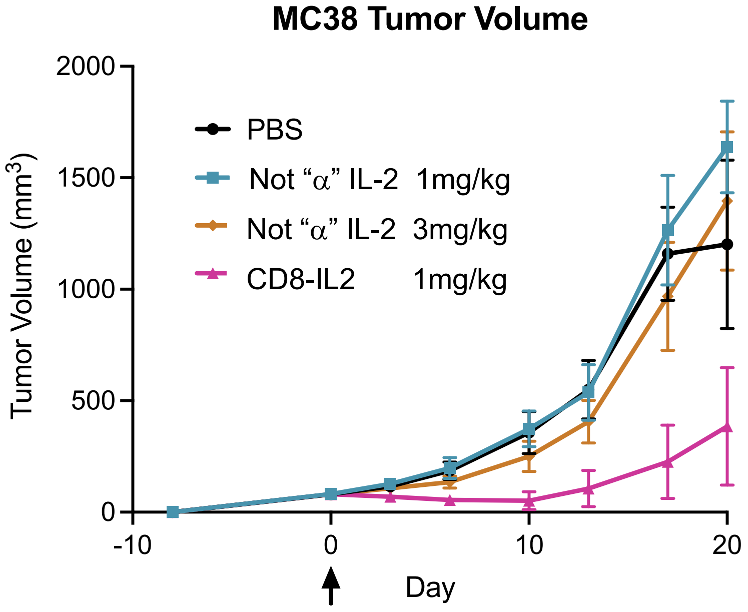
D-8

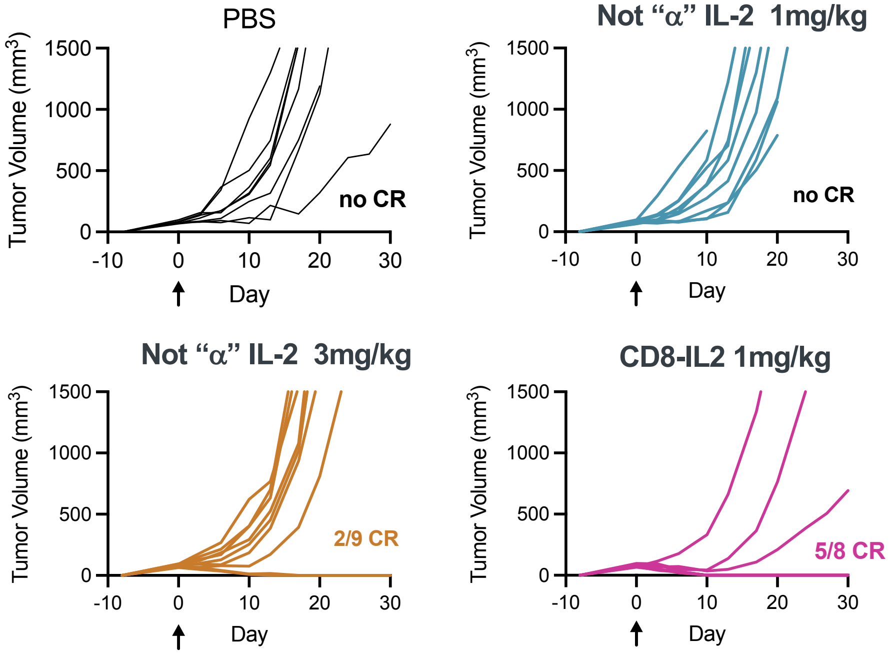
Implant

D0

Single Dose

Monitor

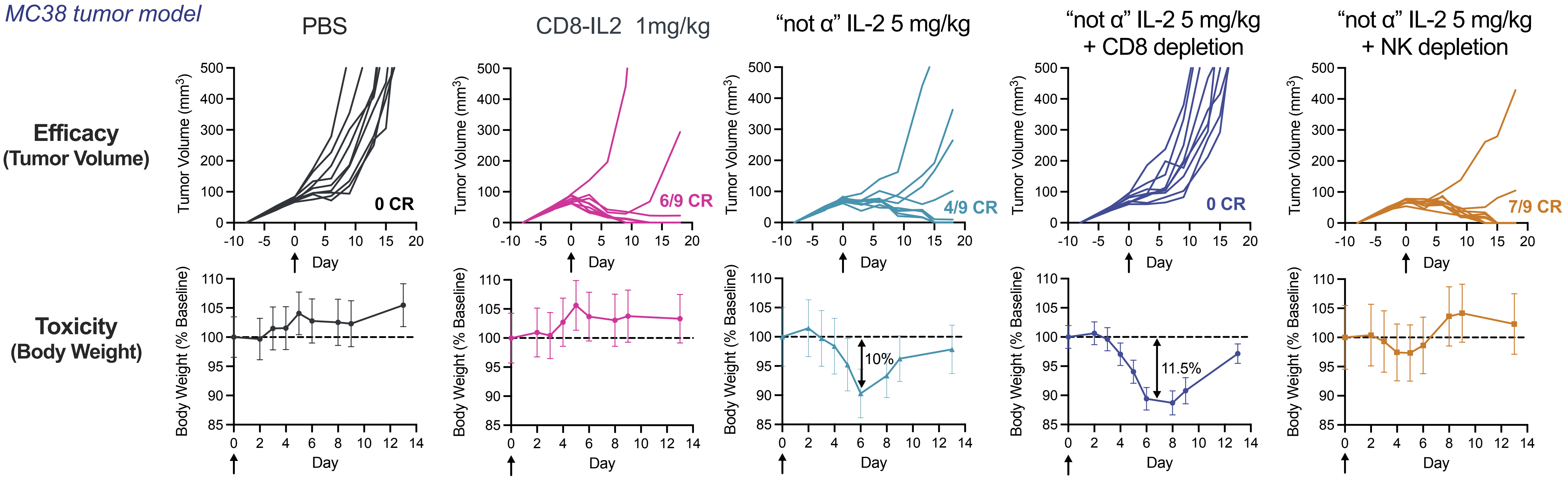




- **Strong monotherapy efficacy** is observed with single dose of CD8-IL2 with **no observed toxicity**
- CD8-IL2 demonstrated superiority over a representative "not α" IL-2

*CD8-IL2 molar equivalent to "not-α" IL-2

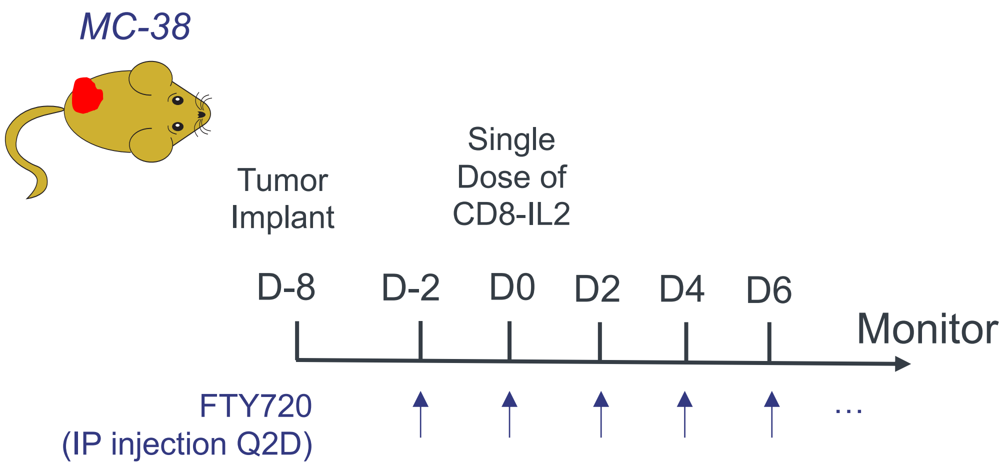
Efficacy of Untargeted “Not α” IL-2 is Only Achieved at Toxic Doses; Toxicity is NK Dependent, but Efficacy is CD8 Dependent



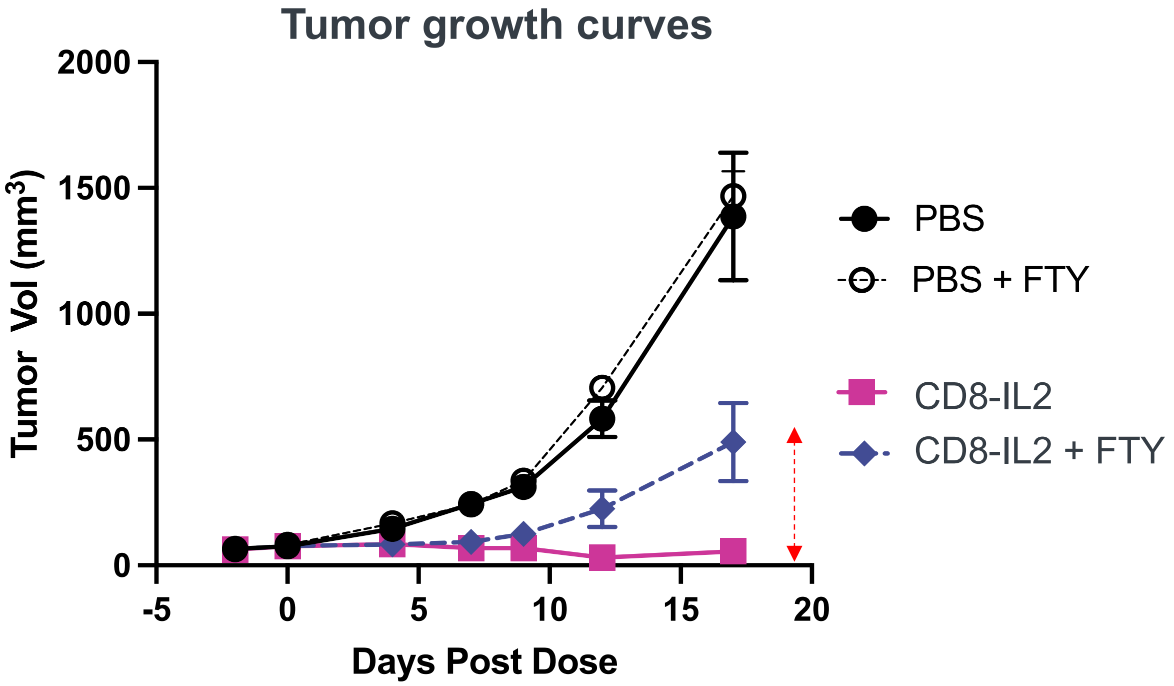
- Anti-tumor efficacy is completely abrogated with CD8 T cell depletion, but body weight loss remains: **CD8 T cells are essential for efficacy but do not contribute directly to toxicity** with “not α” IL-2 therapy
- Anti-tumor efficacy is fully retained with NK cell depletion, but body weight loss is abrogated: **NK cells drive toxicity but are dispensable for efficacy** with “not α” IL-2 therapy

Understanding the Mechanism of Action for CD8-IL2

Contribution by Peripheral vs Intratumoral CD8+ T cells to anti-tumor response


MC-38
Tumor Implant
Single Dose of CD8-IL2
D-8
D-2
D0
D2
D4
D6
Monitor
FTY720
(IP injection Q2D)
…

- FTY720, an S1P1R agonist which traps lymphocytes in lymph nodes



- Treatment with FTY720 shows partial loss of efficacy
- **Both intratumoral and peripheral T cells contribute to efficacy with CD8-IL2**.

Cis-Targeting Platform

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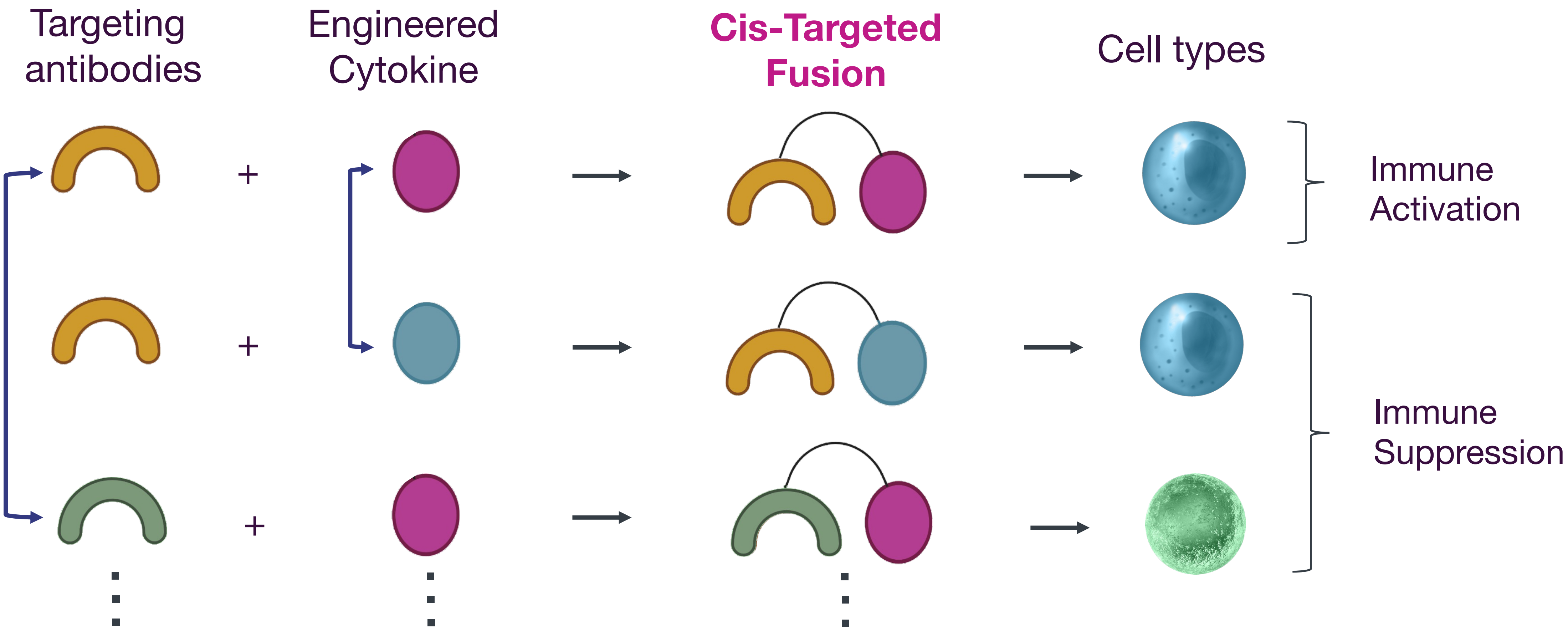
Modularity of the Platform Enables Rapid Build of a Broad Pipeline of Assets


Targeting antibodies
Engineered Cytokine
Cis-Targeted Fusion
Cell types
+
+
+
Immune Activation
Immune Suppression

- Library of targeting arms and engineered cytokines can be readily recombined to generate new molecules for treatments in multiple disease areas

Additional Examples of Cis-Targeted Fusions

Fusion A

(Target 1-Cytokine X)

Fusion B

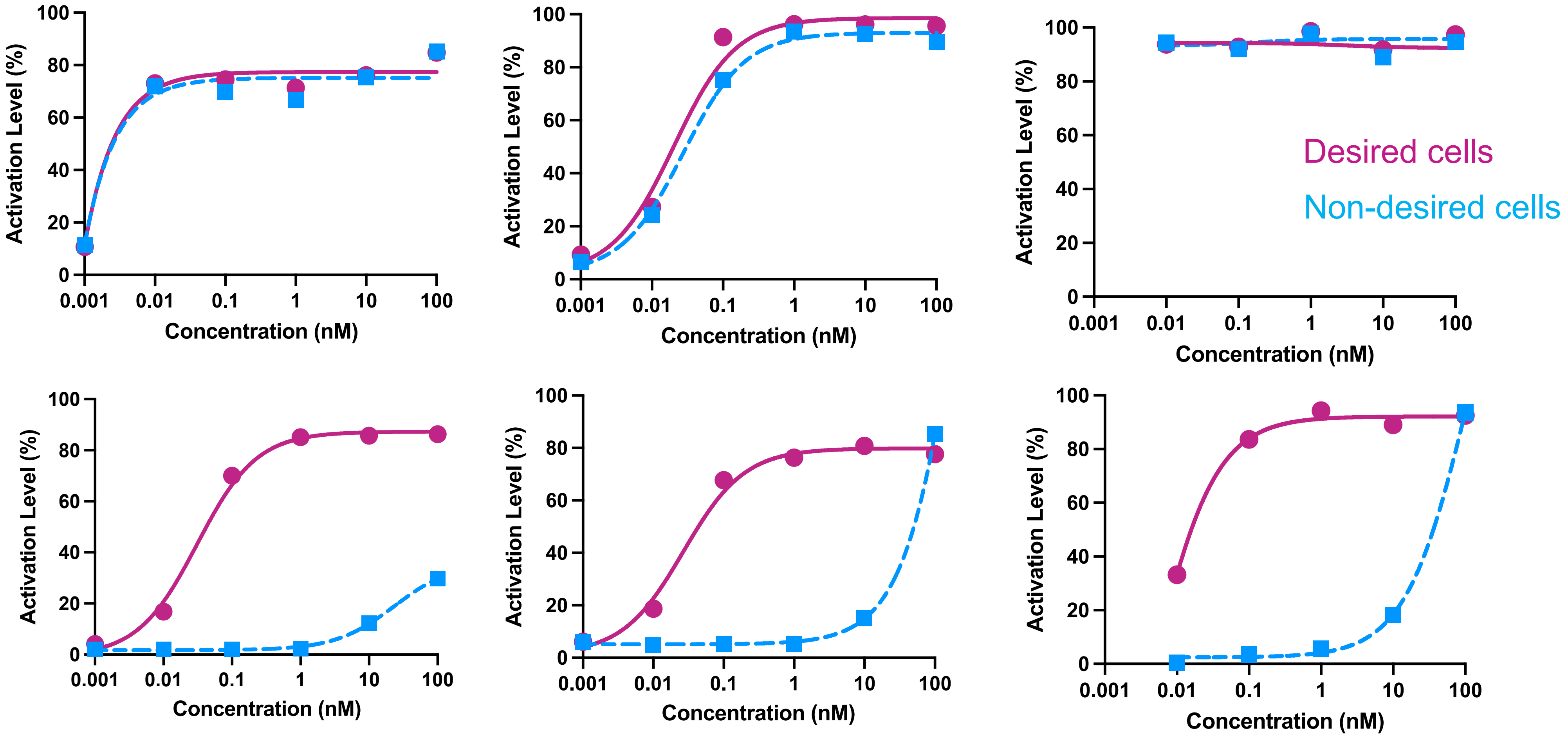
(Target 1-Cytokine Y)

Fusion C

(Target 2-Cytokine Z)

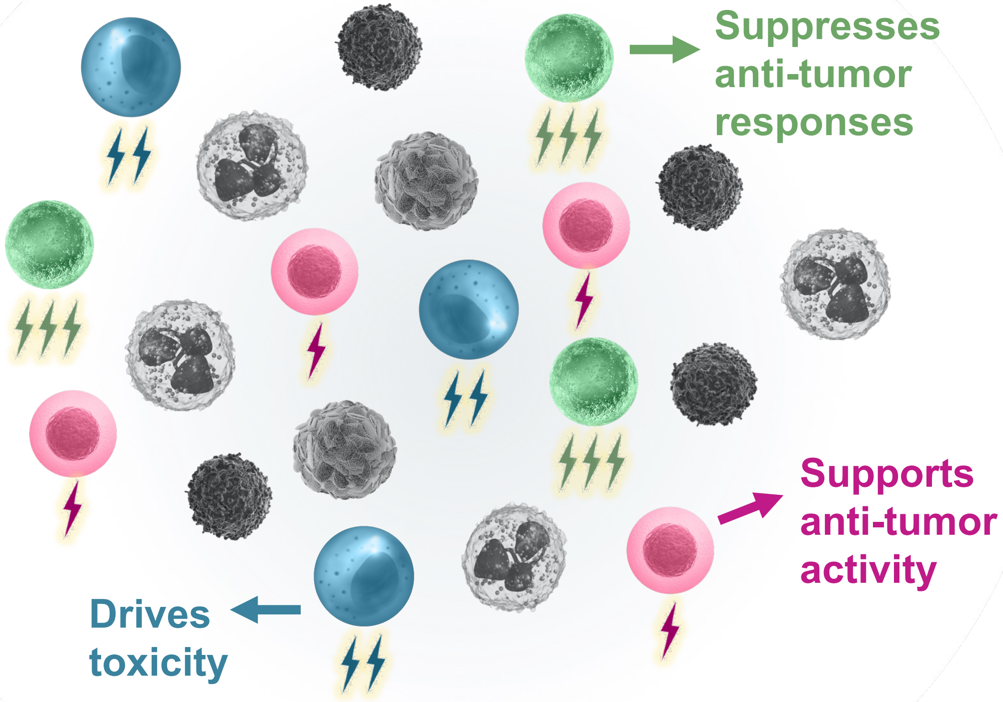
WT

CIS-TARGETED FUSION



Solving the Pleiotropy Problem to Harness Immunotherapies

Standard approaches



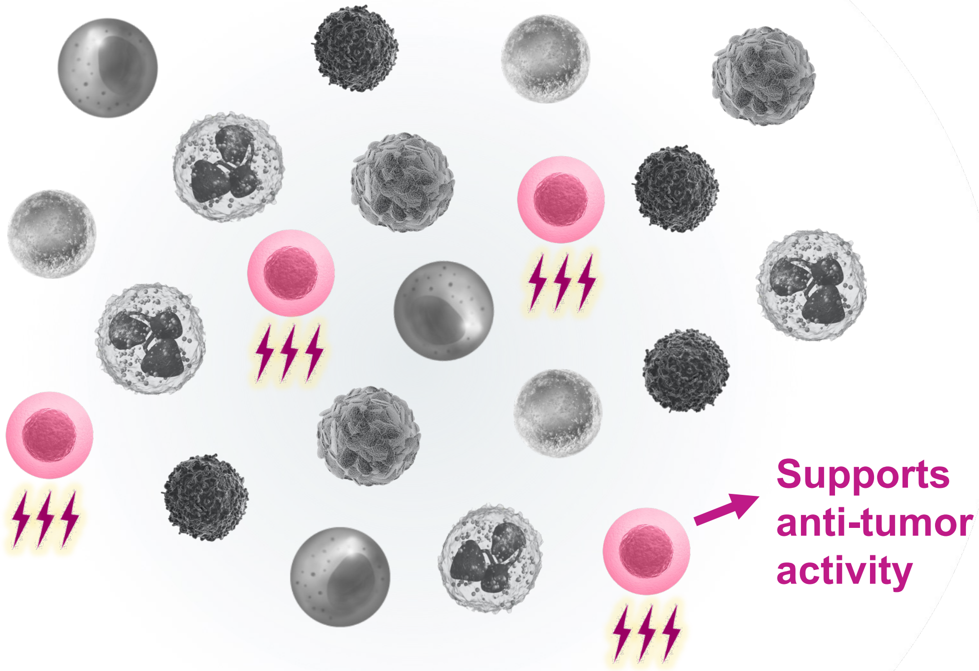
Suppresses anti-tumor responses

Supports anti-tumor activity

Drives toxicity

Undesirable cell types activated, compromising efficacy and driving toxicity

cis-targeted therapies



Supports anti-tumor activity

*Steer activity **specifically** to cell types of interest, avoiding counterproductive responses*

Breakthrough immunotherapies will be enabled by cell-type selectivity

Acknowledgement

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Lioudmila Tchistiakova (Third Rock)

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Back up

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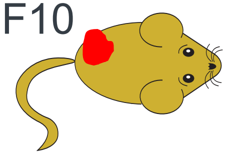
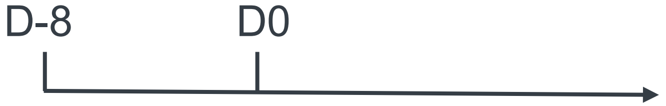
PD-1 Combination Therapy in Immunologically Cold B16F10 Melanoma



B16F10



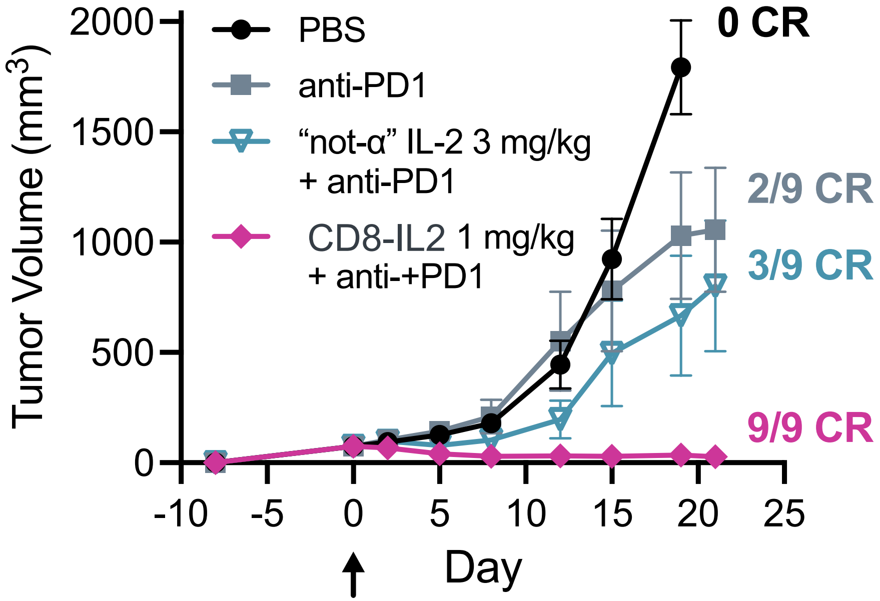
D-8

D0

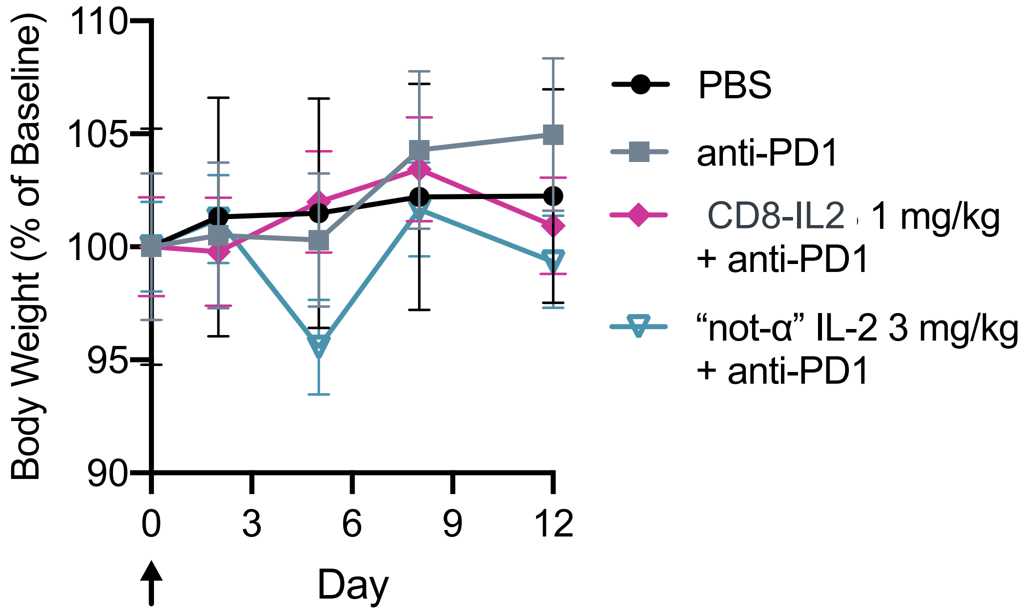
Implant

Single
Dose

Monitor



B16F10 Combination Efficacy



Body Weight (B16F10)

Clear efficacy of a single dose in combo with anti-PD1 in challenging B16F10 melanoma model; superiority again demonstrated over a representative 2nd generation “not α” IL-2