

FT536: A First-of-Kind, Off-the-Shelf CAR-iNK Cell Product Candidate for Solid Tumors Designed to Specifically Target MICA/B Stress Proteins and Overcome Mechanisms of Tumor Evasion

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Forward-Looking Statements



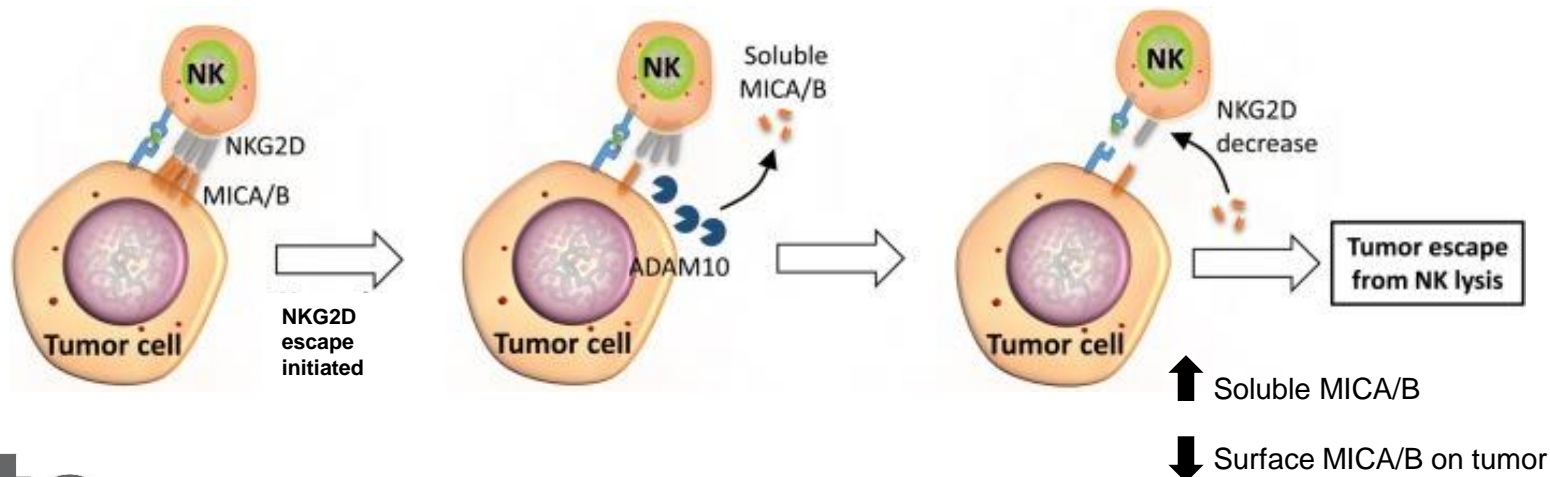
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Harnessing the NKG2D:MICA/B axis as a pan-tumor targeting strategy

- NKG2D = activating receptor responsible for tumor surveillance by NK and T cells (Guerra et al. Immunity, 2008).
- In advanced human cancers, tumor cells shed NKG2D ligands, namely MICA and MICB, to evade immune recognition.
- Soluble MICA/B = associated with poor clinical prognosis in patients.
- Overcoming MICA/B shedding & re-engaging NKG2D:MICA/B mediated tumor recognition is emerging as a novel tumor targeting approach.

NKG2D ligands expression in human cancers

Tumor type	Ligands identified	Known regulation
Carcinoma		
• Ovarian	MICA/B, ULBP2	Shedding
• Cervical cancer	MICA	Shedding
• Breast	MICA/B HER2/3,	Shedding
• Lung	MICA/B	Shedding
• Hepatocellular	MICA/B	Viral, retinoic acid
• Colon	MICA	Shedding
• Renel	MICA, MICB	?
• Prostate	MICA (Hi), ULBP (lo)	Shedding
• Pancreatic	MICA/B	?
• Head and neck cancer	MICA/B	Shedding
Leukemia	MICA/B	Methylation
Lymphoma	MICA, ULBP _s	Shedding
Multiple myeloma	MICA	Shedding
Melanoma	MICA, ULBP-2	Shedding
Giloma	MICA/B,ULBP1-3	TGF-b
OsteoSarcoma	MICA	?
Neuroblastoma	MICA, ULBP-2	Releasing soluble form

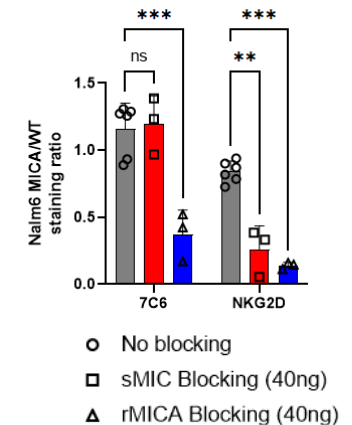
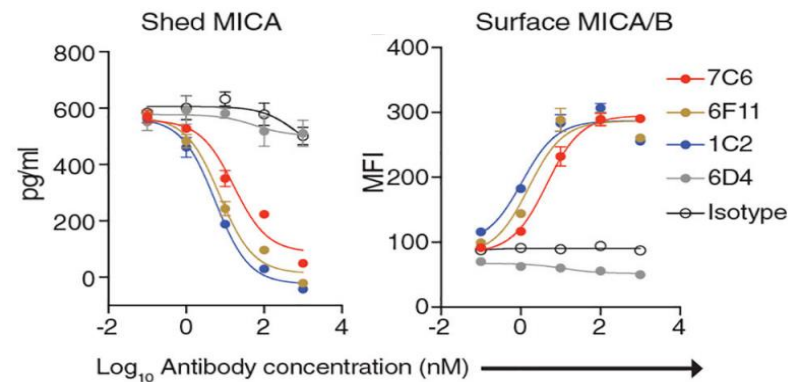
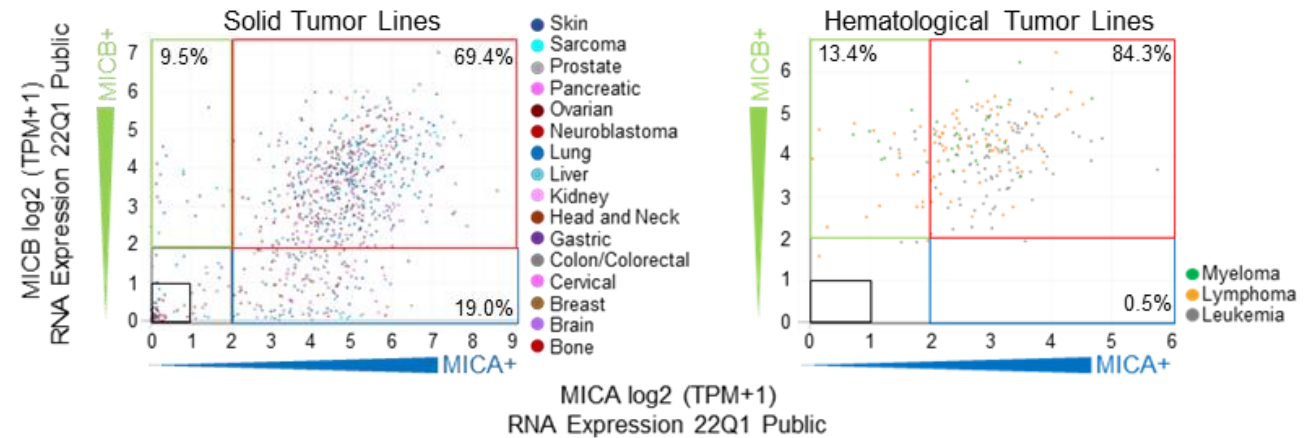
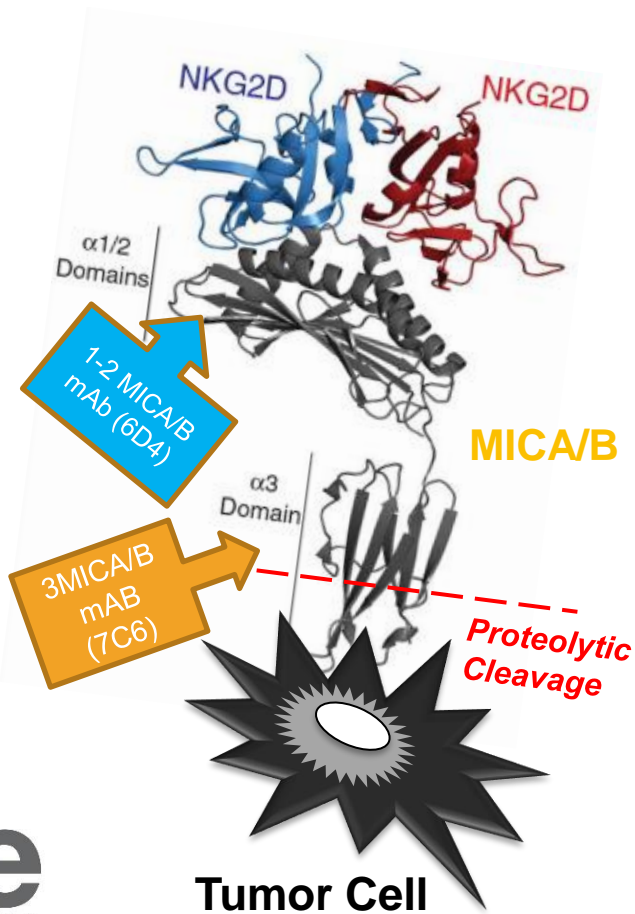


Dhar P, Wu JD. *Curr Opin Immunol.* 2018 Apr;51:55-61.

MICA/B $\alpha 3$ domain targeting provides a novel strategy to mitigate multiple tumor evasion strategies



- MICA/B proteins contain highly polymorphic $\alpha 1$ -2 domains and more conserved $\alpha 3$ domains
- MICA/B proteins are ubiquitously expressed on many solid & hematological tumors
- $\alpha 3$ domain targeting prevents MICA/B shedding, augments surface density & resists sMICA/B inhibition

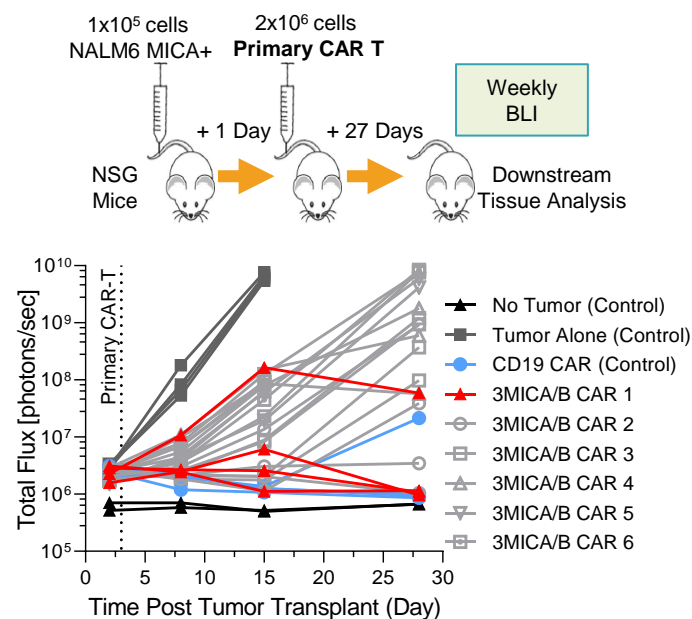
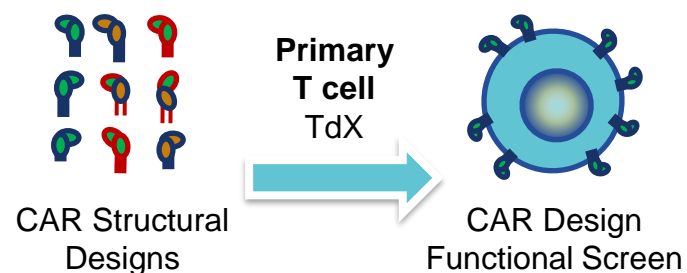


*Ferrari de Andrade et al, Science 2018

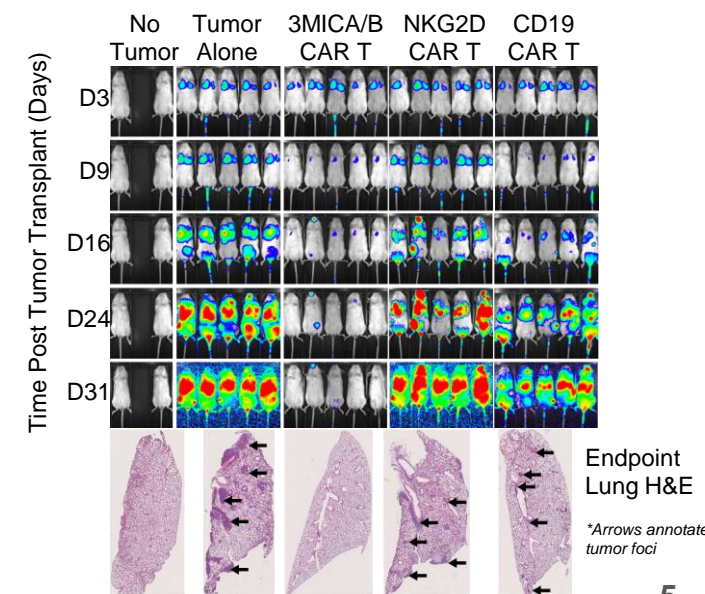
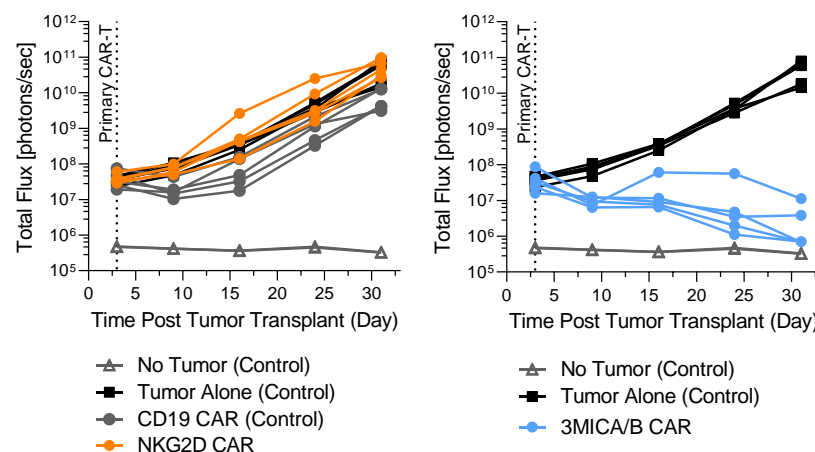
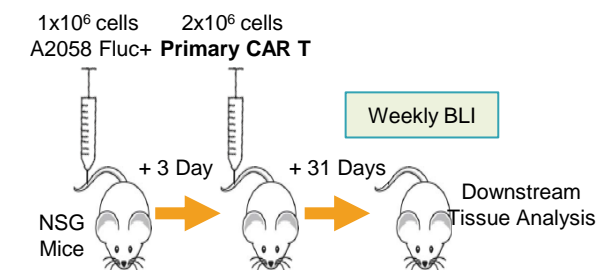
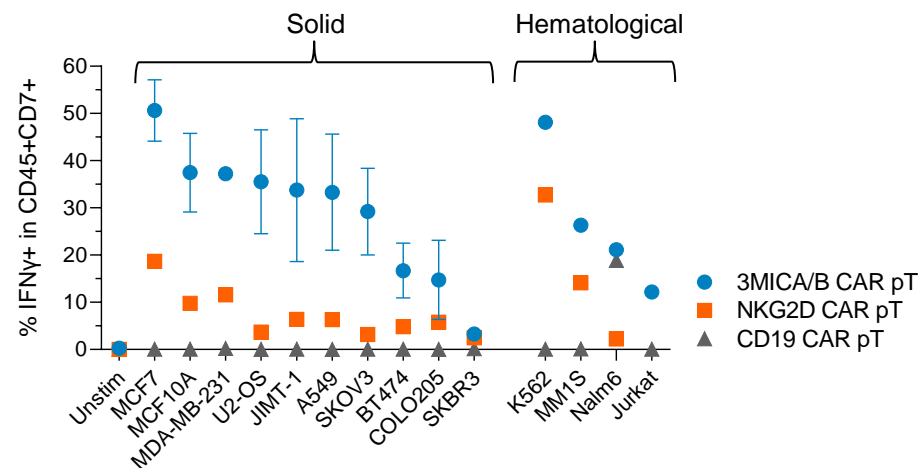
Development of 3MICA/B CAR - a novel synthetic receptor targeting the $\alpha 3$ domain of MICA/B stress induced ligands



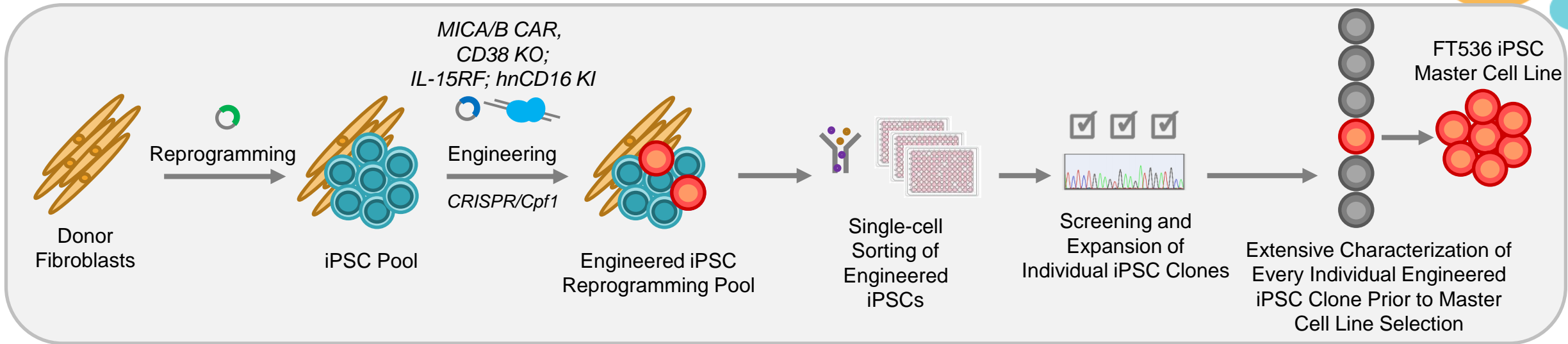
3MICA/B CAR Screen



3MICA/B CAR Lead Design Proof-of-Concept

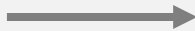


Single-cell isolation of a multiplexed-engineered iPSC and creation of a clonal master iPSC bank



FT536 iPSC Master Cell Line Expanded to generate FT536

Consistent and homogeneous NK cell manufacturing from renewable iPSC MCB



Uniform off-the-shelf NK Cell Products

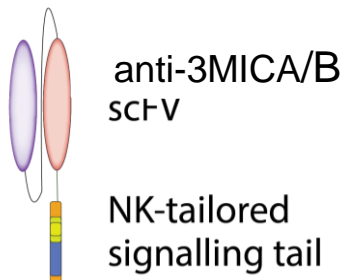
- *Does not require patient or donor sourced cells*
- *Eliminates stochastic editing variability associated with pool editing*
- *Consistent, cost effective and highly scalable manufacture process*
- *Analogous to pharmaceutical drug product development*
- *Administered off-the-shelf in outpatient setting*

Extensive clonal master iPSC bank characterization

Novel Multi-antigen Targeting Strategy to Overcome Tumor Heterogeneity and Antigen Escape for a Durable Response in Solid and Liquid Tumors

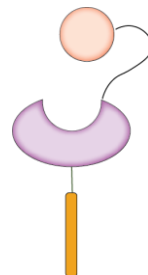
3MICA/B-CAR

Pan-Tumor
Associated Antigen
anti-3MICA/B scFv



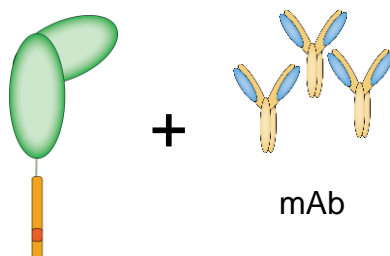
IL-15RF

Designed to Promote
Survival, Proliferation
and anti-Tumor Activity



hnCD16

High-affinity (158VV),
Non-cleavable CD16
to Maximize ADCC



CD38 knockout

CD38 KO for Enhanced
Metabolic Fitness and Innate
Function



Extensive characterization process leading to clonal master iPSC bank

- Multiplexed Engineered iPSC clones selected
- Clones with copy number and locus-target verified
- Clones maintaining pluripotency
- Clones free of reprogramming vectors
- Clones demonstrating genomic stability
- Clones without off-target edits
- Clones with ideal propensity to become NK cells
- Clones with desired functional activity & specificity
- Selected FT536 MCB passing all test criteria

>500 clones

1

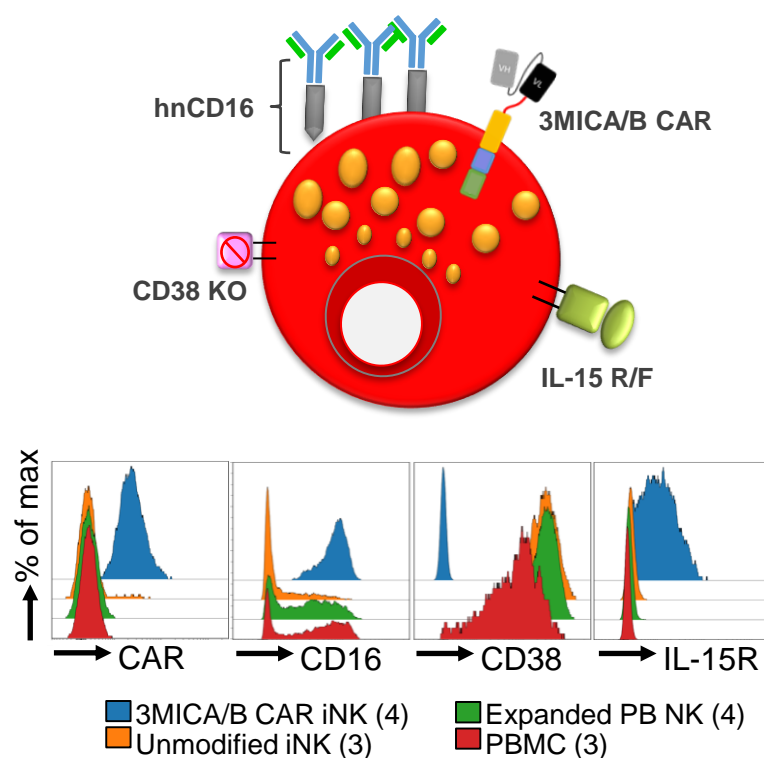
Top Candidate Clone

Clones with Desired Attributes

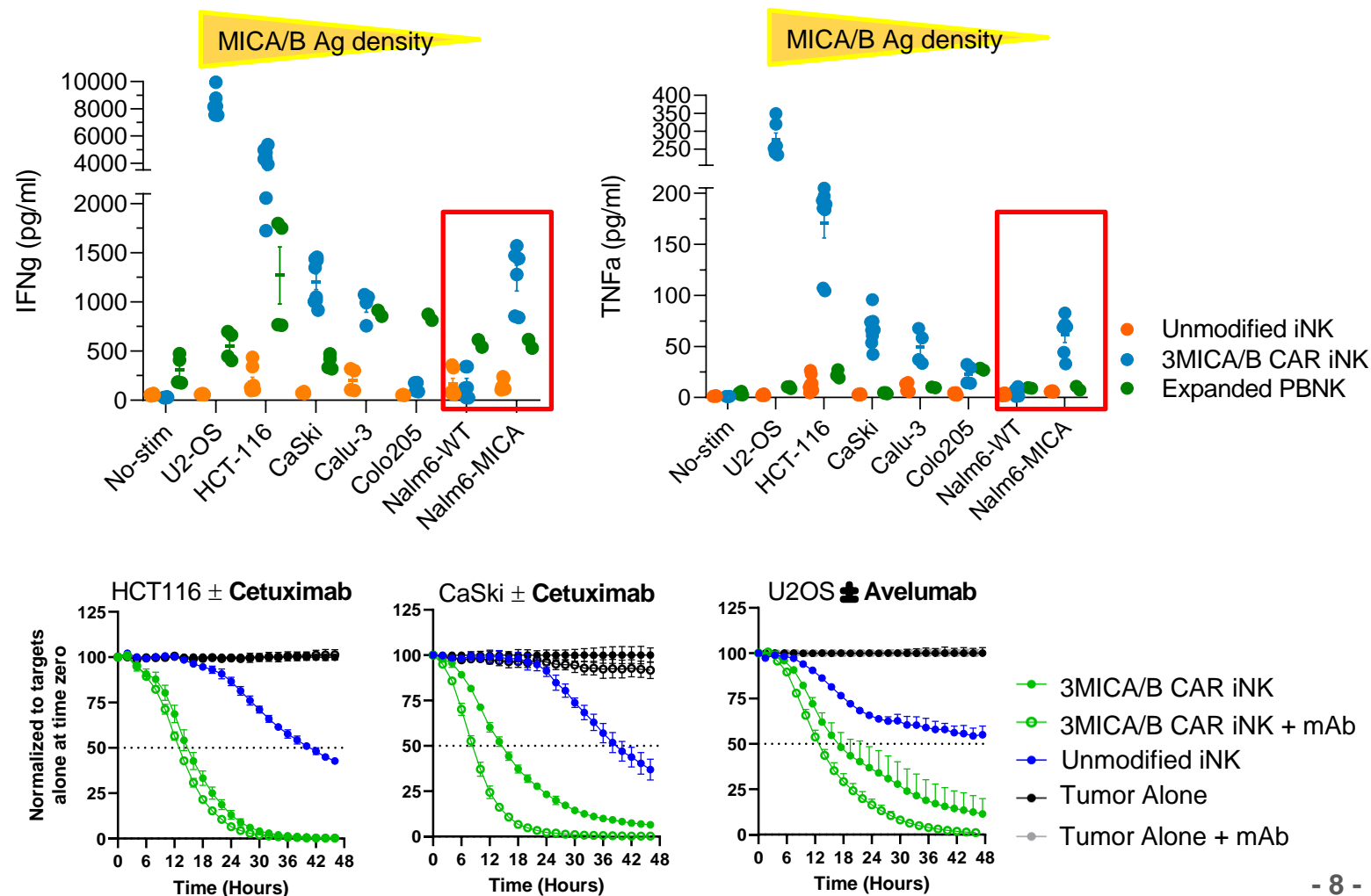
FT536: 3MICA/B CAR + IL-15RF + hnCD16 + CD38KO iPSC-derived NK Cell Product Candidate

Four functional elements uniformly engineered into master iPSC bank; Renewable source for mass production of FT536

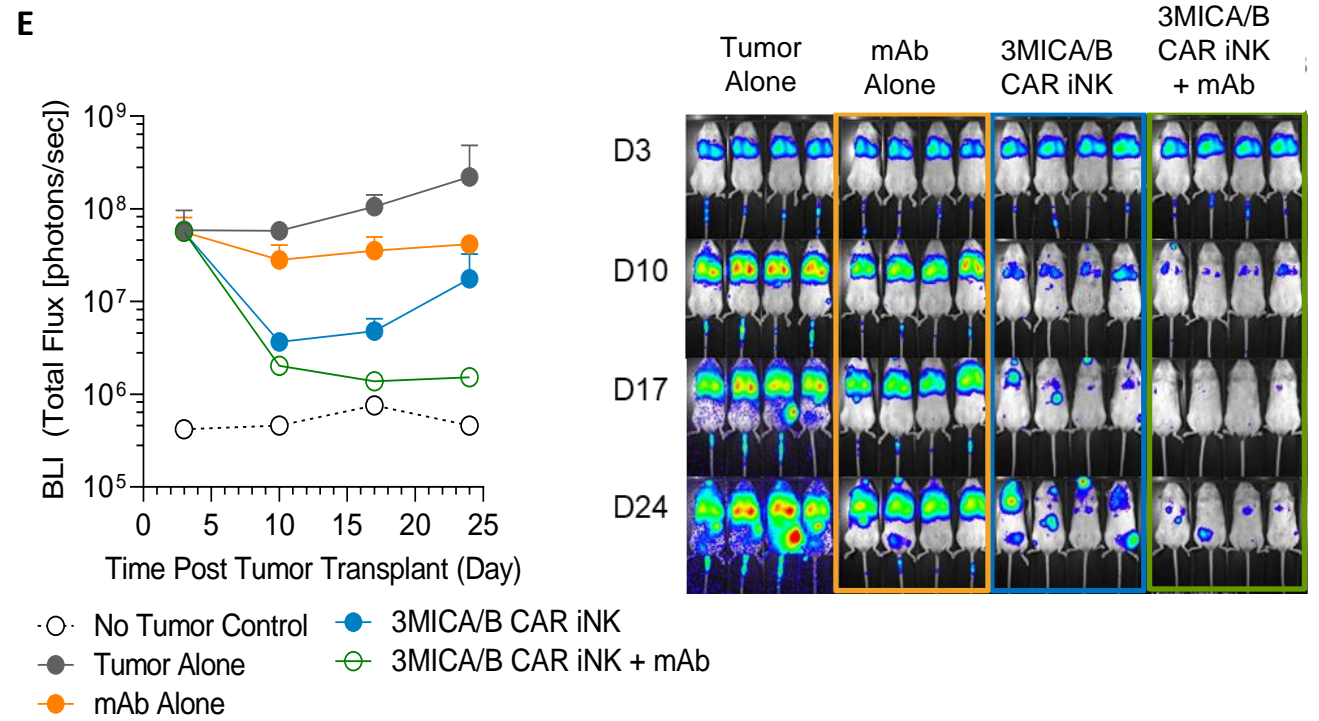
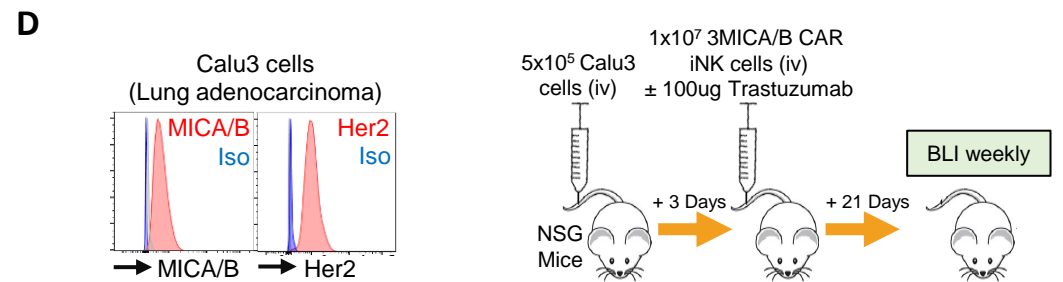
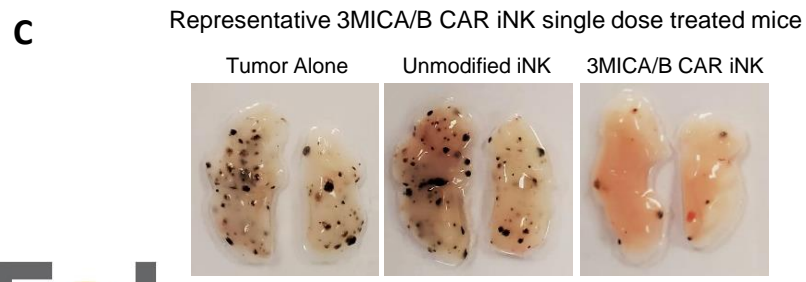
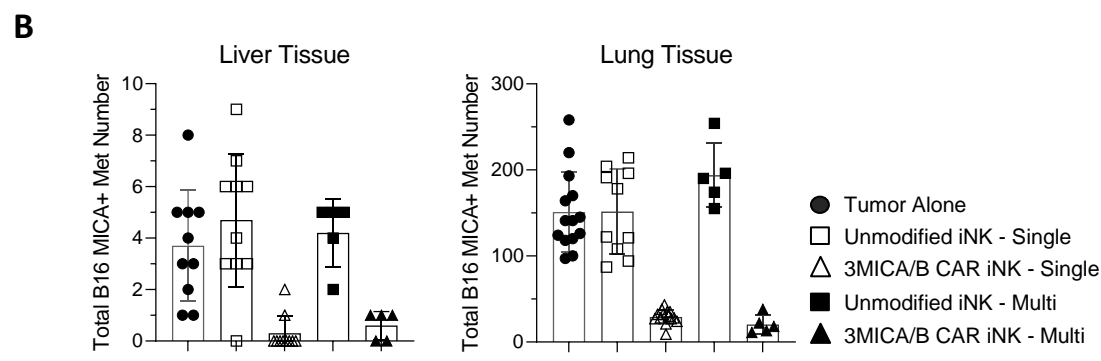
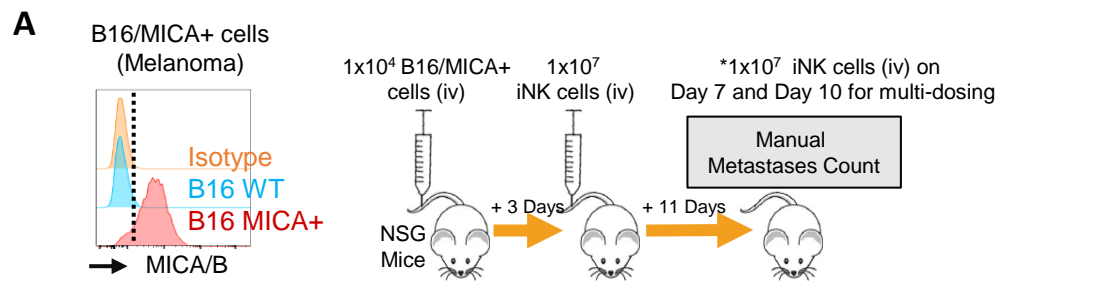
3MICA/B CAR iNK (FT536)



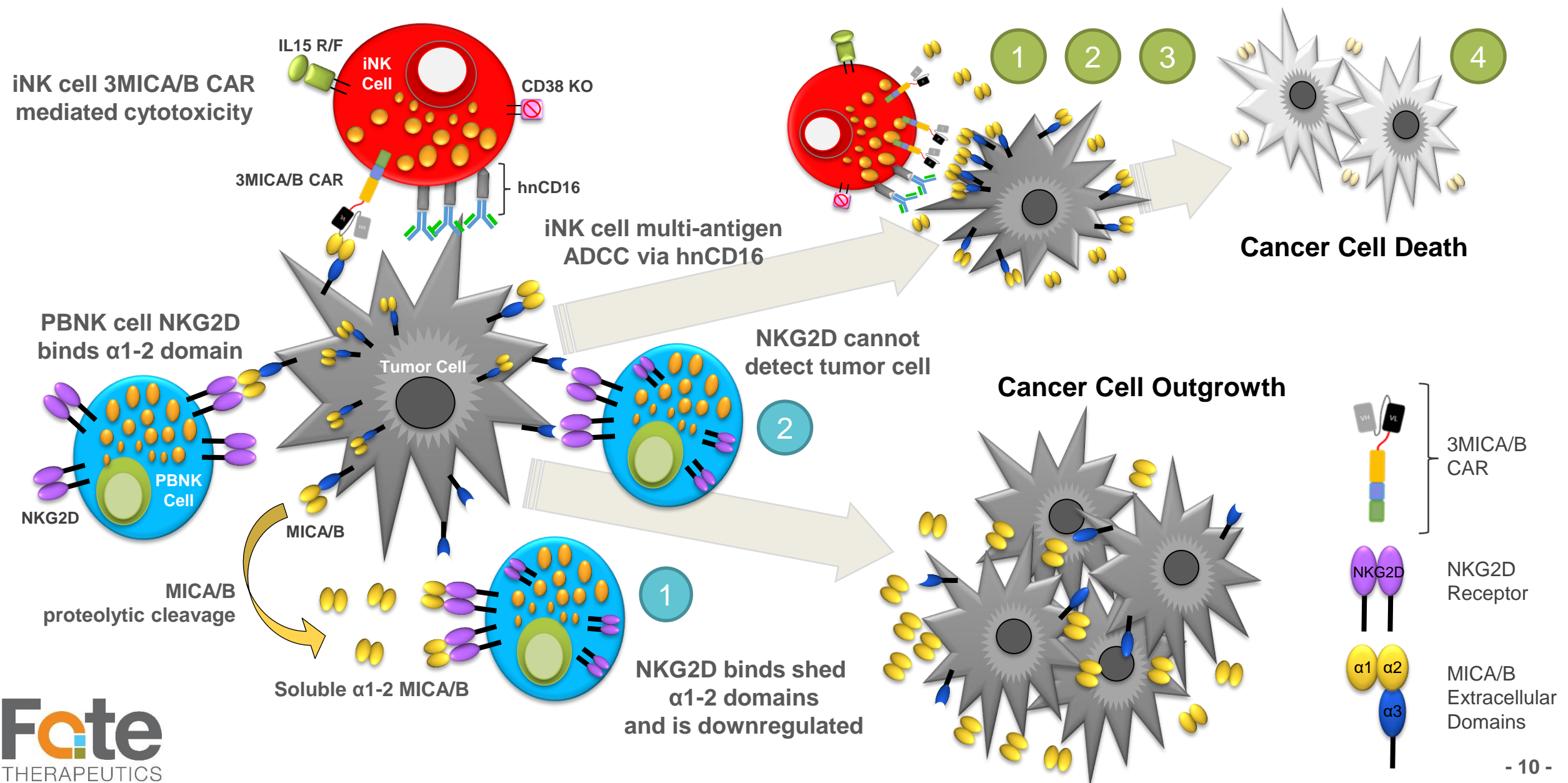
In vitro functionality – Antigen Sensitivity, Specificity & Cytotoxic Potency



FT536 demonstrates durable TGI when administered as monotherapy or in combination with a therapeutic antibody



FT536: Multi-edited iPSC derived iNK cells expressing 3MICA/B CAR demonstrate potent pan-tumor multi-antigen activity and are equipped with multiple tumor evasion mitigation competency





Lessons/Take Home Message

- Proprietary iPSC product platform was used to create a clonal master iPSC bank from a multiplexed-engineered, single iPSC
 - Serves as a renewable source of starting material for mass production of FT536
 - Cost effective and available on-demand for broad patient access
- FT536 incorporates *four* novel anti-tumor MOAs:
 - 3MICA/B-CAR
 - $\alpha 3$ domain targeting mitigates against antigen loss/tumor evasion
 - Resists sMICA/B competitive inhibition
 - Enables pan-tumor targeting of stress-induced antigens
 - hnCD16 for enhanced ADCC & heterogenous tumor/antigen targeting
 - CD38 KO for enhanced metabolic fitness
 - IL-15RF for cytokine independent persistence
- FT536 has potent activity against multiple solid/liquid tumors *in vitro* and solid tumor xenografts *in vivo*
- FT536 IND has cleared, and Phase 1 Safety/Dose Escalation Trial to commence soon

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