



# HARNESSING THE POWER OF ENGINEERED MACROPHAGES

CARISMA Therapeutics  
October 2021



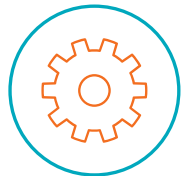
# Harnessing the Power of Engineered Macrophages

CARISMA is a private, clinical stage, vertically integrated biotech company developing our first-in-class CAR-M technology for advanced cancers and other diseases

## Proprietary Platform and Capabilities



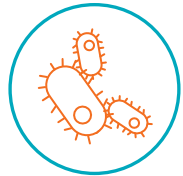
**Myeloid Specific Cell Engineering**



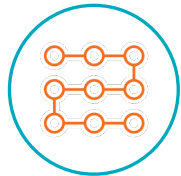
**Proprietary Vectors**



**Gene Editing Capabilities**



**Auto/Allo Cell Source**



**Cell & Vector Manufacturing**



**Significant IP**

**~\$120M Raised To Date**

## First-in-Class CAR-M Pipeline

- Solid tumor targets (HER2, Meso, PSMA) in development
- Lead program CT-0508 (HER2) currently enrolling patients in Phase I clinical study (NCT04660929)
- Rationally selected heme malignancy targets (CD7)
- Non-oncology applications (liver fibrosis, neurodegeneration, and auto-immunity)

## Experienced Leadership and Focused Strategy

- Deep research, clinical and operational expertise in cell and gene therapy and oncology
- Capital efficient discovery, manufacturing and development program to rapidly establish human safety and proof of concept
- Broad scope of research and process development initiatives allowing optionality and scalability as we advance pipeline

# Strong Leadership Team and Advisors

## Management



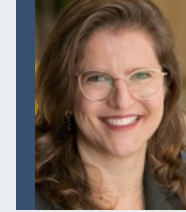
**Steven Kelly**  
President & CEO



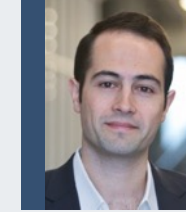
**Dan Cushing, PhD**  
CDTO



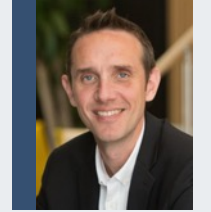
**Rich Morris**  
CFO



**Debora Barton, MD**  
CMO



**Michael Klichinsky,  
PharmD PhD**  
Co-Founder & SVP, Research

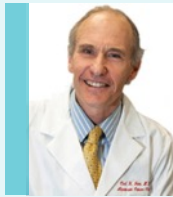


**Tom Wilton**  
CBO

## Advisors



**Saar Gill, MD PhD**  
Co-Founder  
U Penn



**Carl June, MD**  
University of  
Pennsylvania



**Hy Levitsky, MD**  
Former CSO of Juno  
Therapeutics



**Lisa Coussens, PhD**  
Oregon Health &  
Science University



**Prasad  
Adusumilli, MD**  
MSKCC



**Nina Bhardwaj,  
MD, PhD**  
Mt. Sinai



**Nabil Ahmed, MD**  
Baylor College  
of Medicine

## Board of Directors



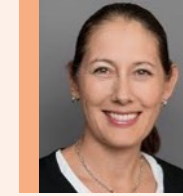
**Briggs Morrison**  
Independent



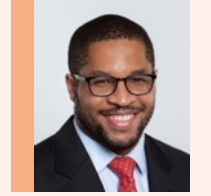
**Margarita Chavez**  
AbbVie Ventures



**Jacob  
Gunterberg**  
HealthCap



**Regina Hodits**  
Wellington



**Chidozie  
Ugwumba**  
Symbiosis

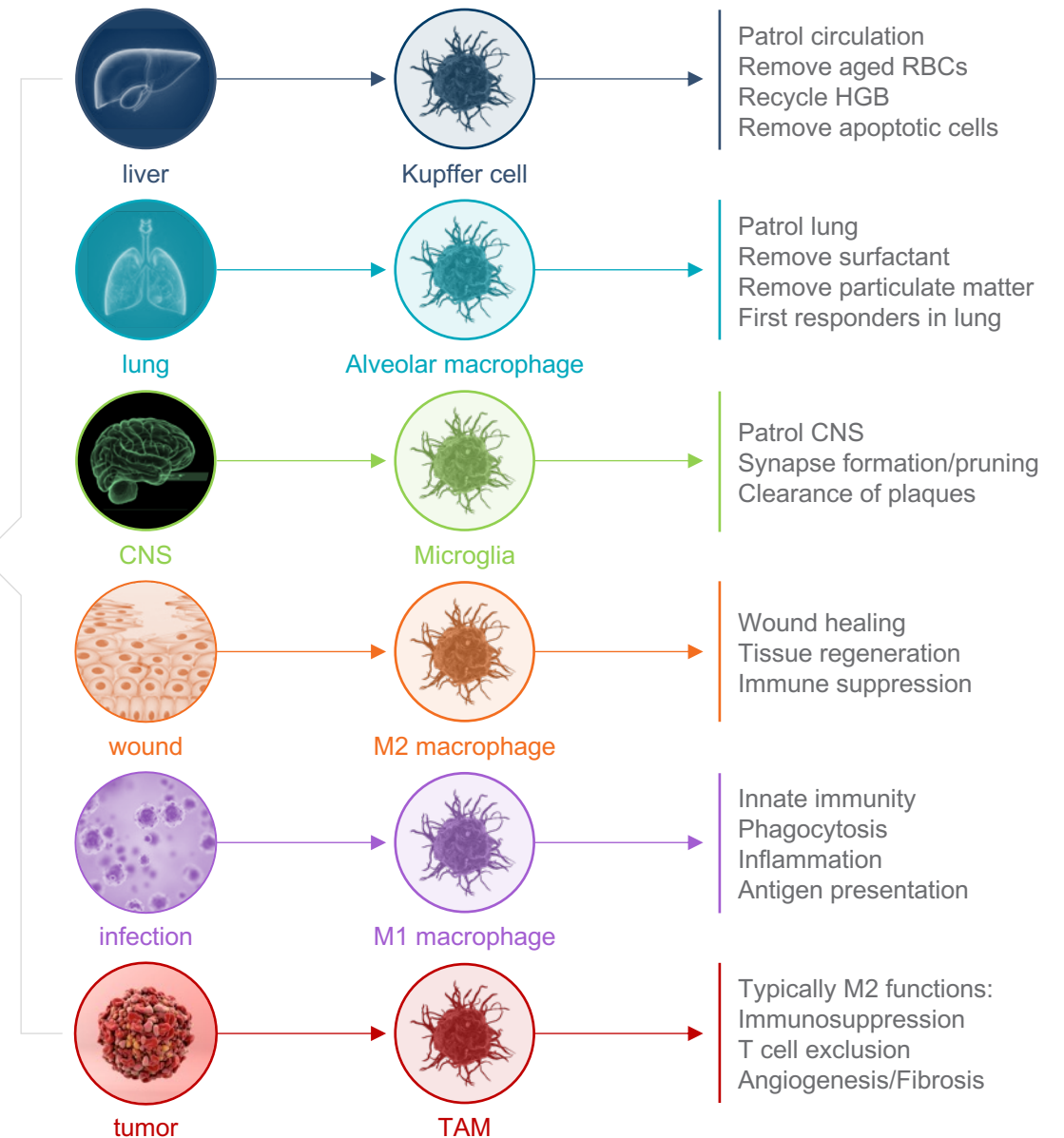
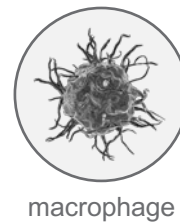


# Macrophages: The Ultimate Multitasker

Macrophages are powerful immune cells that drive both innate and adaptive immunity

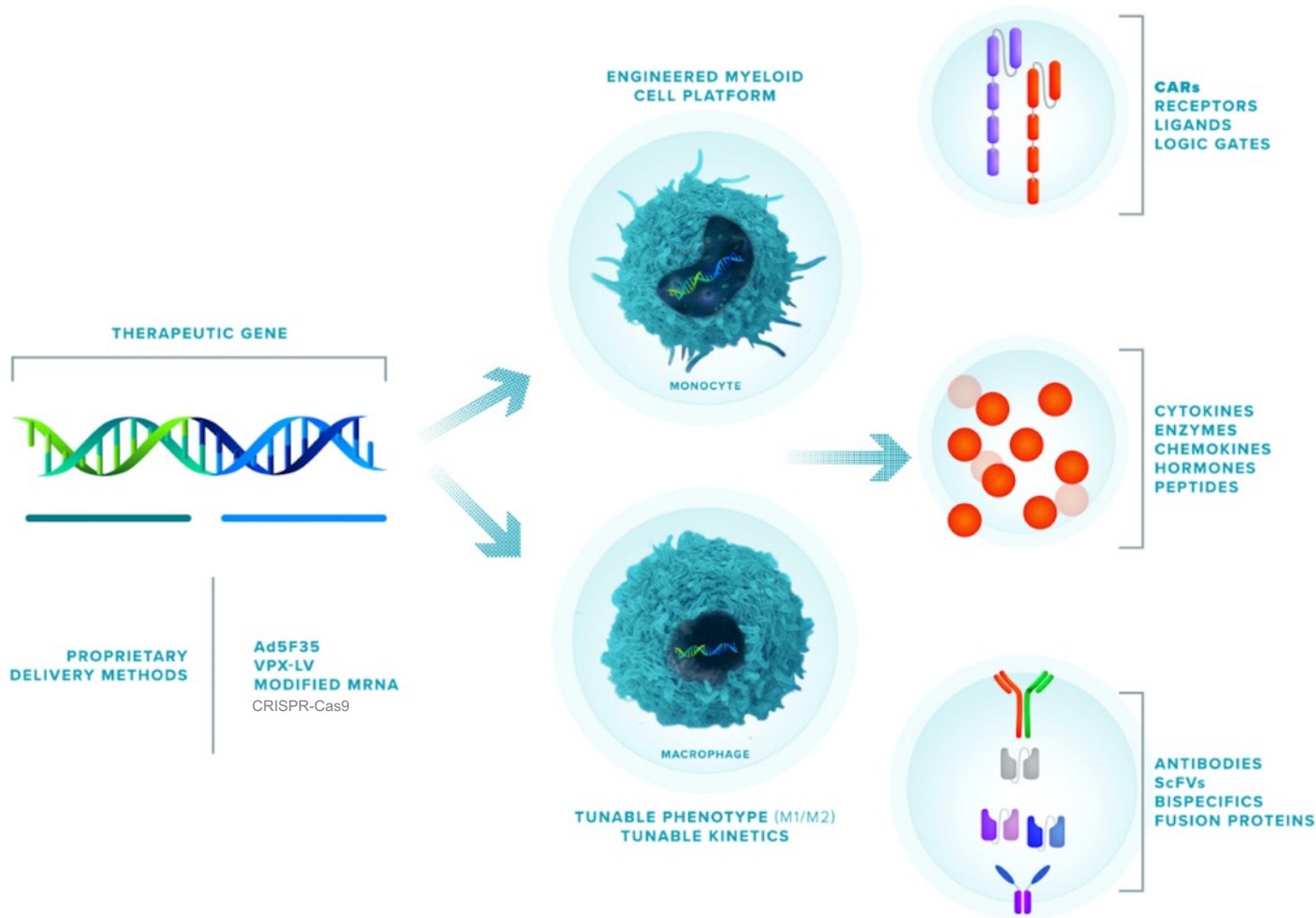
Macrophages can:

- Traffic to tumors/inflammation
- Phagocytose
- Initiate immune response
- Present antigen to T-cells
- Resolve fibrosis
- Tissue regeneration
- Resolve immune response



# CARISMA's Broad Myeloid Cell Engineering Platform

Proprietary technology, world-leading macrophage engineering know-how, and strong IP estate ensure leadership position



## Monocyte & Macrophage Engineering Capabilities:

- Proprietary platforms for durable macrophage engineering with Ad5f35<sup>1</sup> and Vpx-LV<sup>2</sup>
- Proprietary platform for transient macrophage engineering: Modified mRNA<sup>3</sup>
- Methods to control macrophage phenotype toward M1 & M2<sup>3</sup>
- Ability to deliver large/multiplexed payloads
- Efficient gene editing methods using CRISPR/Cas9<sup>3</sup>

# Key Challenges for Cell Therapy Treatment of Solid Tumors

## Incredible Progress in Cell Therapy...

- CAR-T is revolutionizing treatment of hematological malignancies
- Three products now approved – Kymriah, Yescarta and Abecma

## ... But Challenges Remain in Solid Tumors

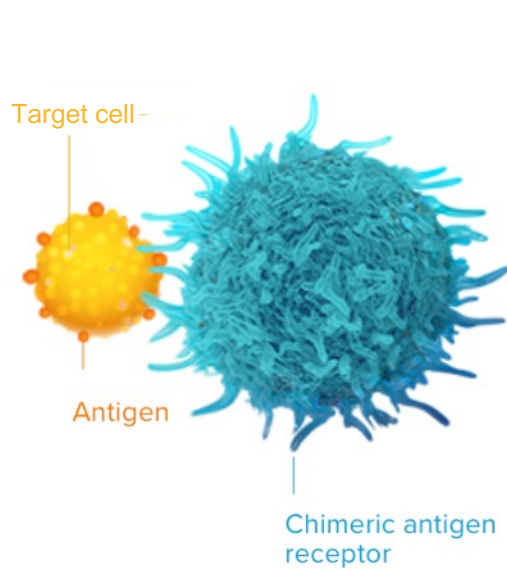
1	Lack of Trafficking to Tumors	Need natural recruitment to tumors and metastatic sites	
2	Suppressive TME	Need ability to induce a pro-inflammatory TME	
3	Antigen Heterogeneity	Need ability to activate the immune system via antigen presentation	

# CAR-M's Multi-Factorial Attack on Cancer

Carisma's technology addresses the key challenges involved in treating solid tumors

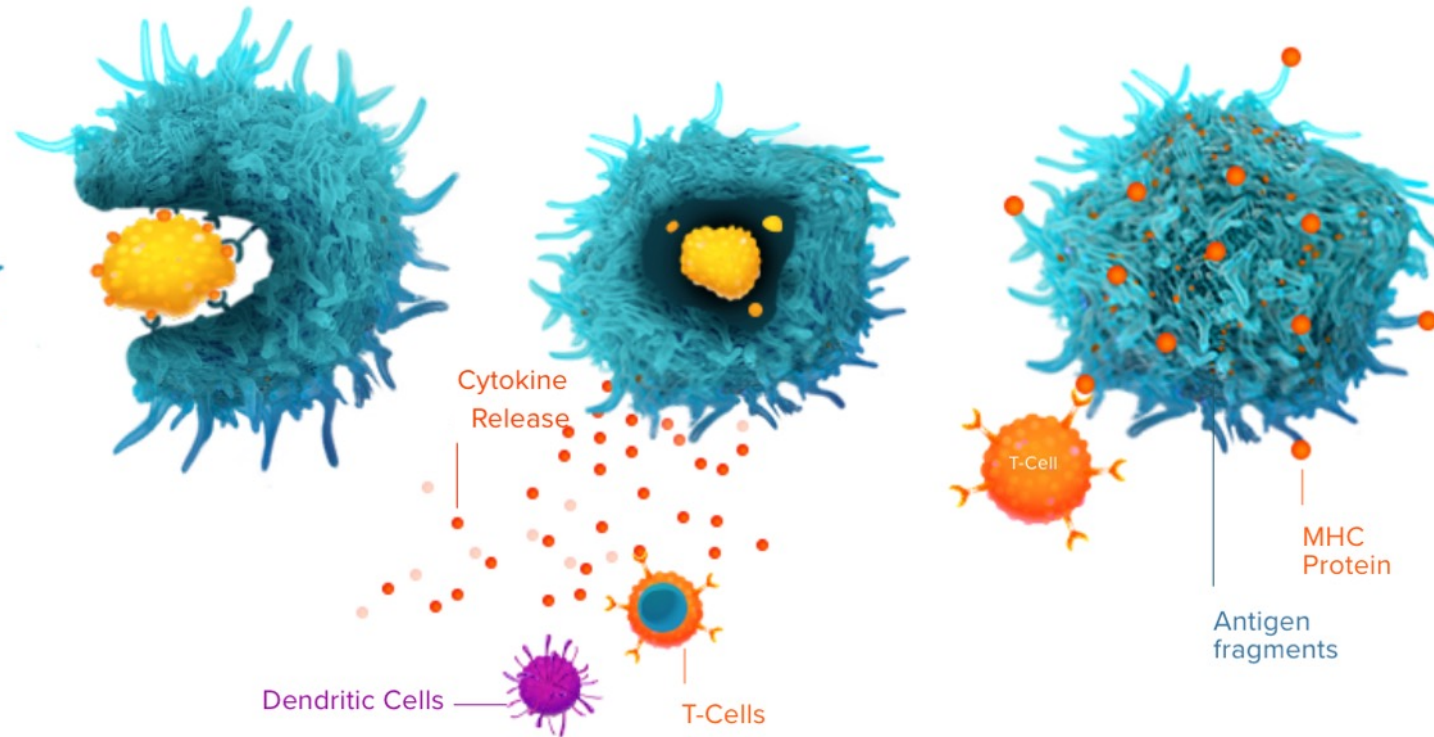
1

TRAFFICKING AND PHAGOCYTOSIS



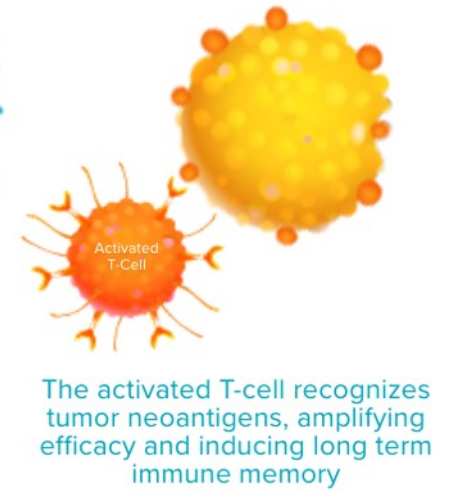
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IMMUNE ACTIVATION



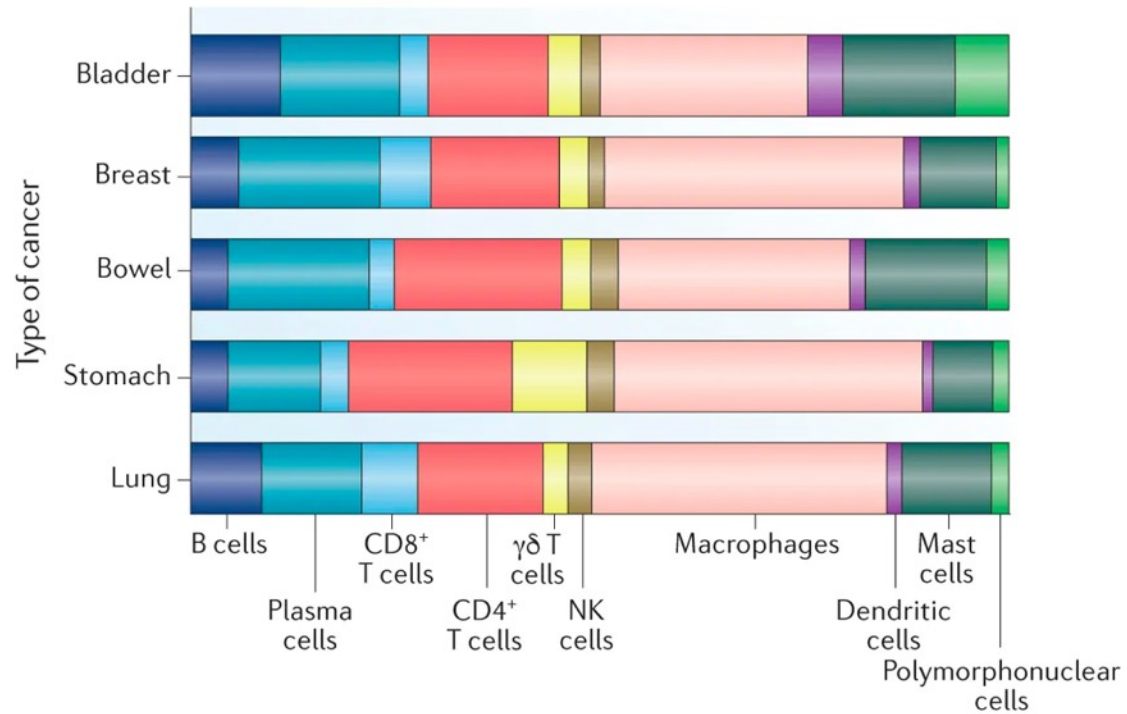
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ANTIGEN PRESENTATION



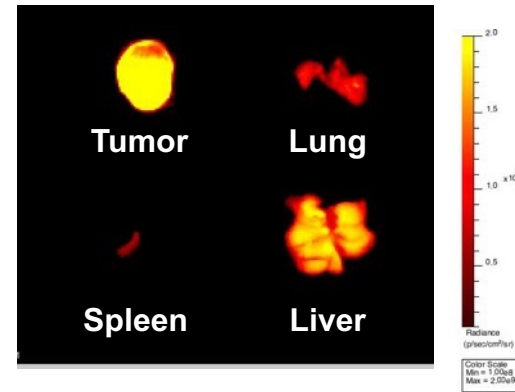
# Monocytes & macrophages home to tumors

## Myeloid cells are abundant in solid tumors



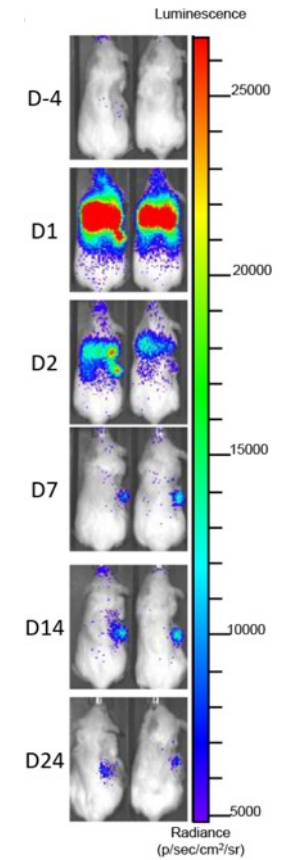
Pollard JW, et al. Nat Rev Drug Discov. 2019.

## Adoptively transferred macrophages home to tumors



Biodistribution of IR-labeled human CAR-M (Gastric carcinoma xenograft model)

Klichinsky M, et al. 2020.

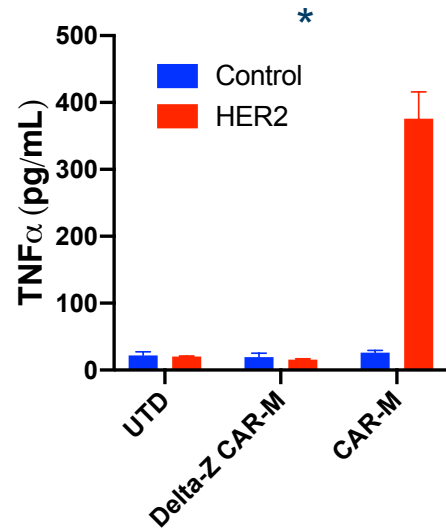


Brempeles K, et al. 2020.

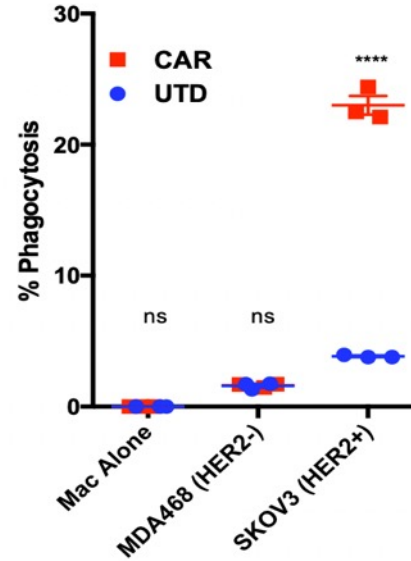


# Primary human CAR-M demonstrate broad anti-tumor activity

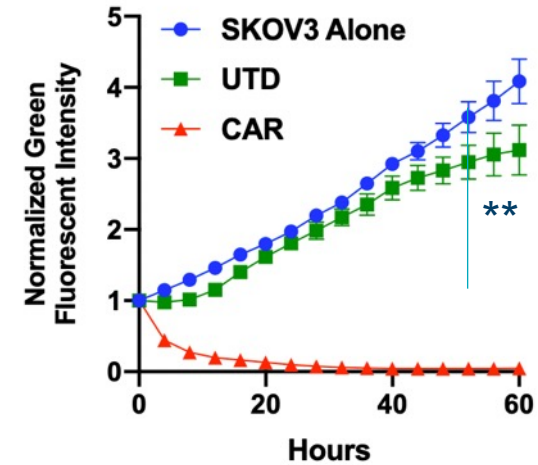
### CAR-M Cytokine Production



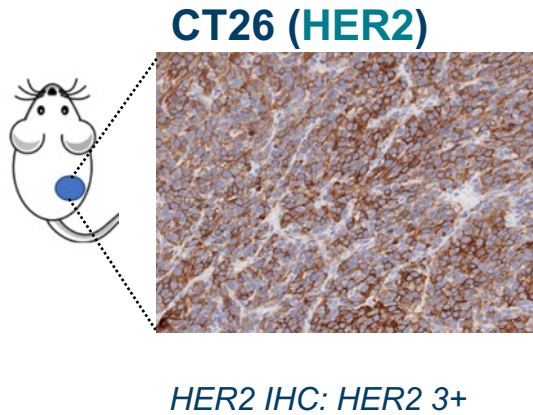
### CAR-M Phagocytosis



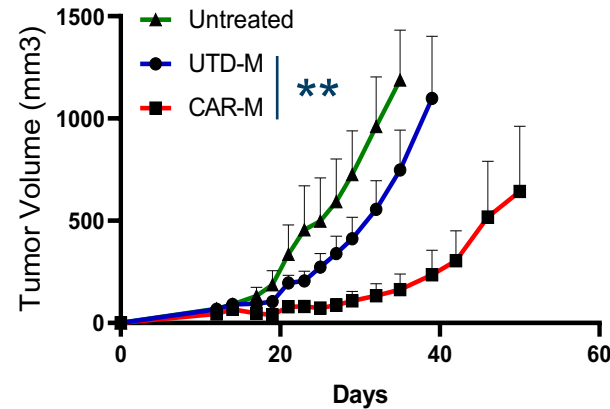
### CAR-M Killing



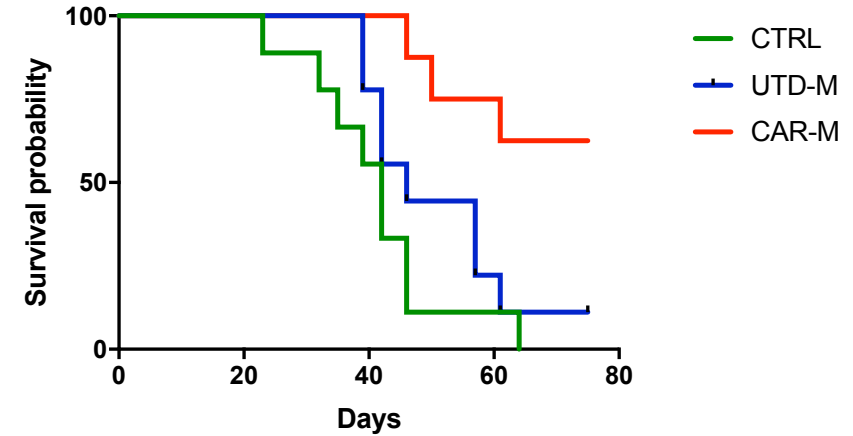
# CAR-M shrink tumors, modulate the TME, and induce systemic T cell responses in immunocompetent models



Average tumor growth curves:

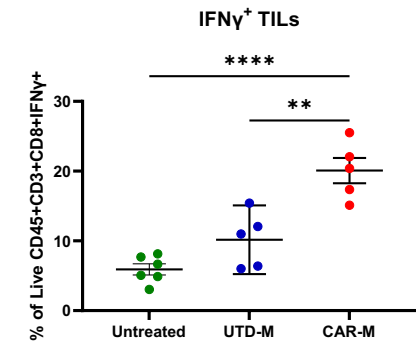
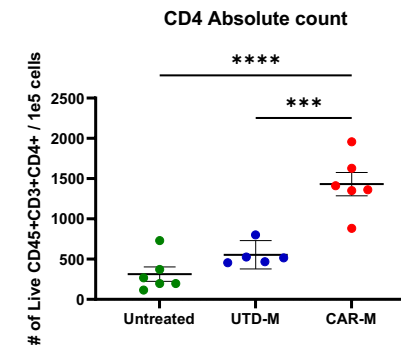
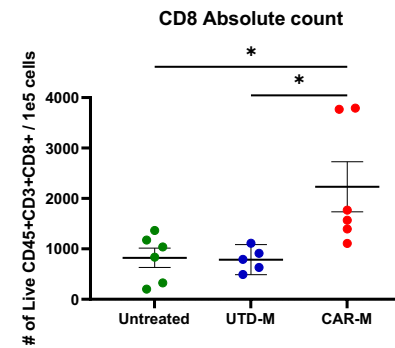
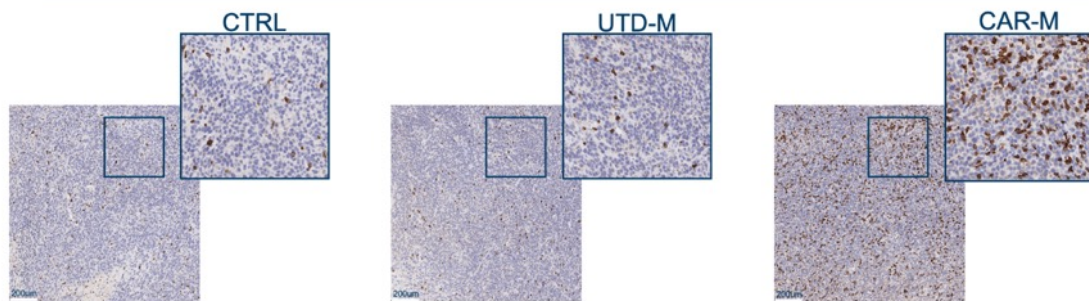


Kaplan Meier Survival Curve:



## CAR-M modulate the TME – CD8+ T cell infiltration

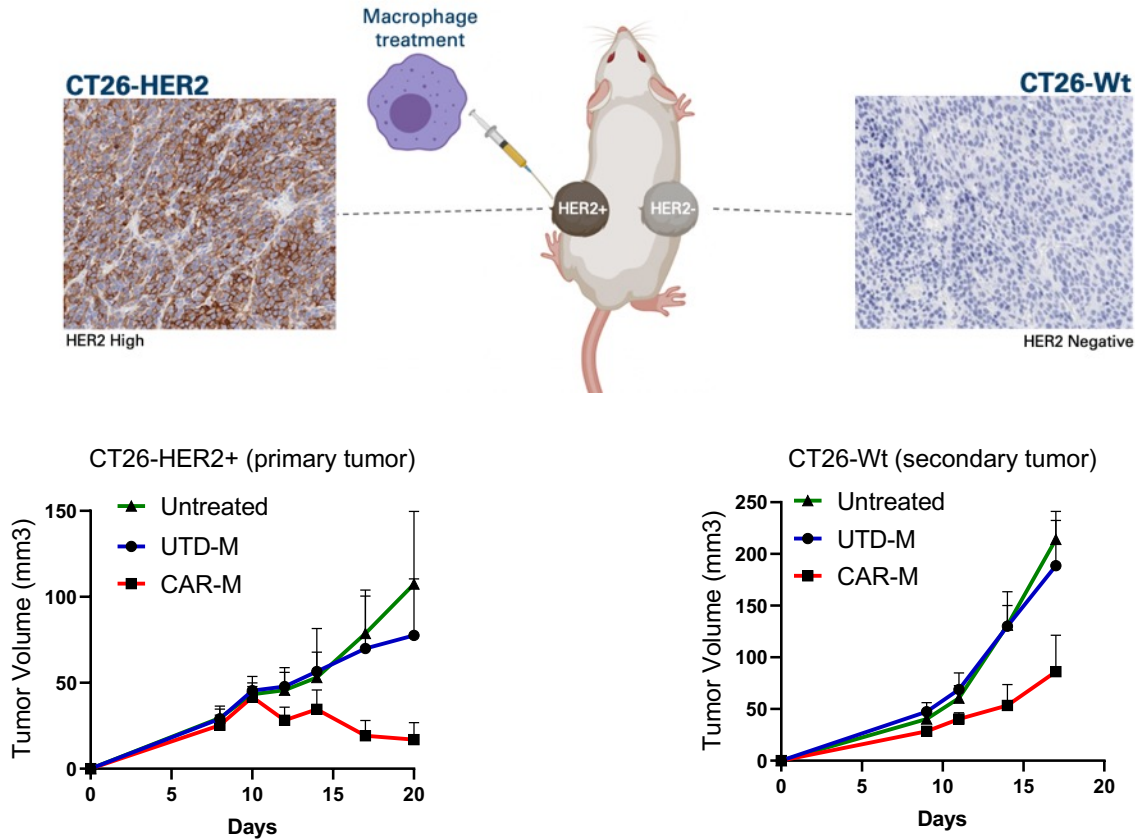
Representative CD8 IHC on CT26-HER2 tumor samples



# CAR-M Lead to Epitope Spreading In Vivo

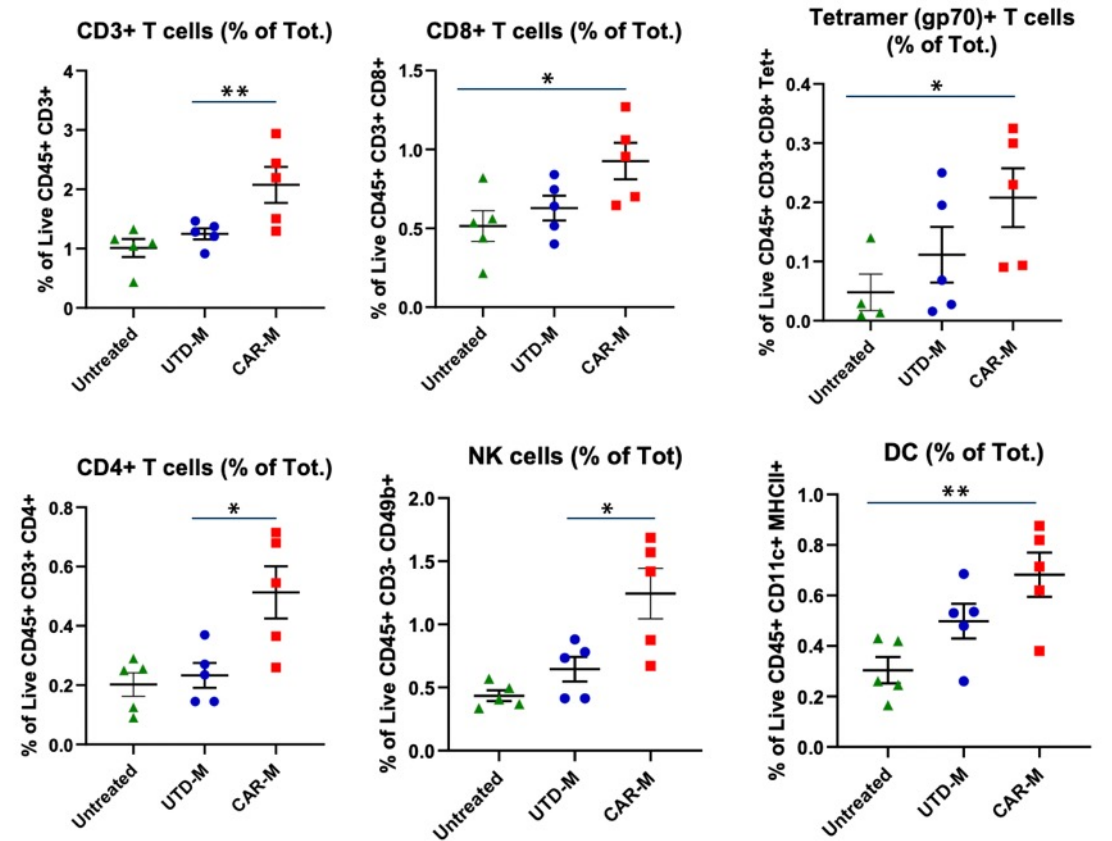
Anti-HER2 CAR-M shrink HER2+ tumors and reduce growth of HER2- tumors

## CAR-M lead to an abscopal effect against HER2- tumors



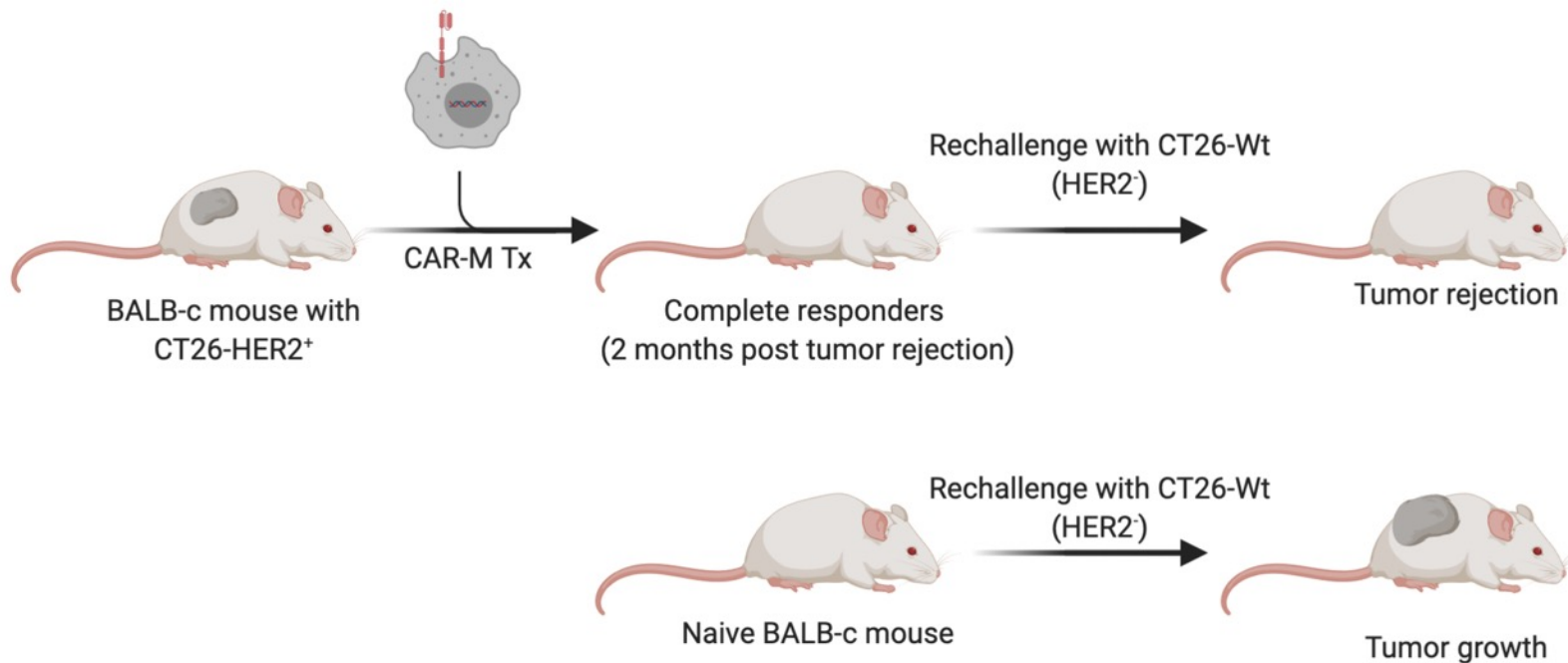
n=7-8 mice per group

## Evaluation of the HER2- tumor TME (2 weeks post Tx)

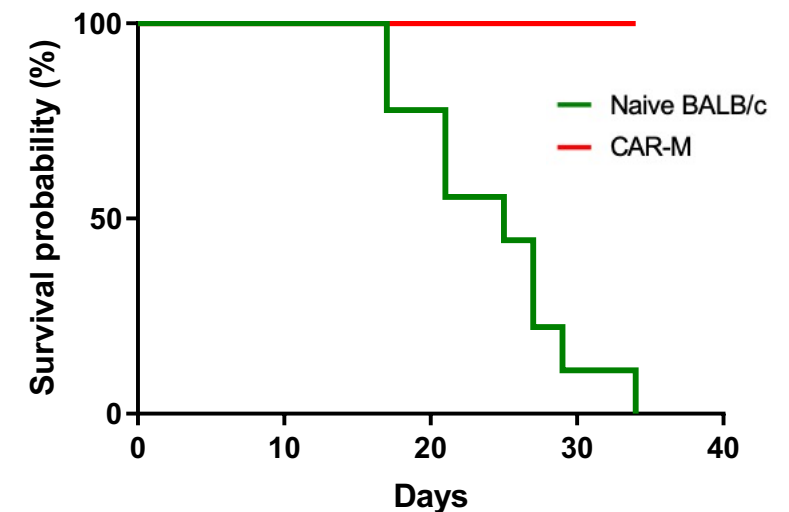


# CAR-M Therapy Vaccinates Mice Against Tumor Recurrence and Prevents Antigen Negative Relapse

Mice that achieved CRs post anti-HER2 CAR-M therapy rejected HER2- tumors upon rechallenge 2 months later, demonstrating long term immune memory

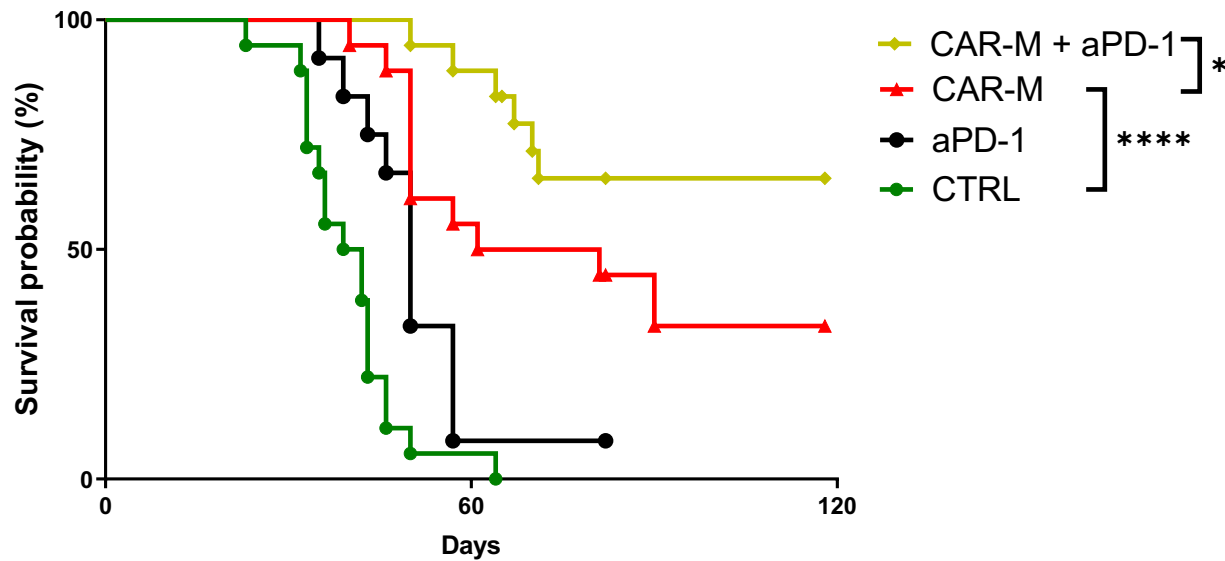


CT26 Wt (HER2-) rechallenge: Kaplan Meier Survival Curve



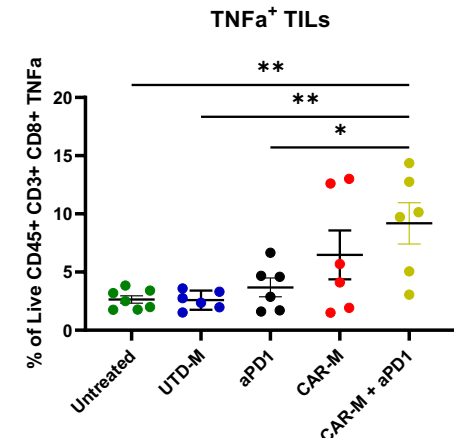
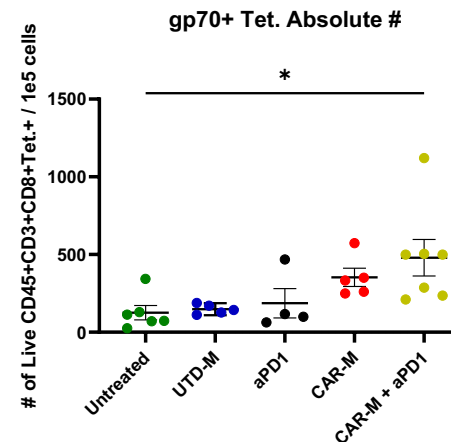
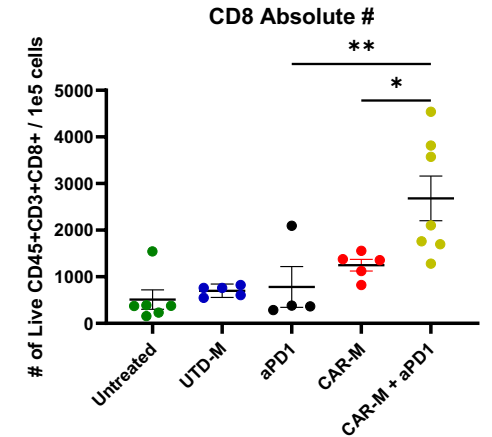
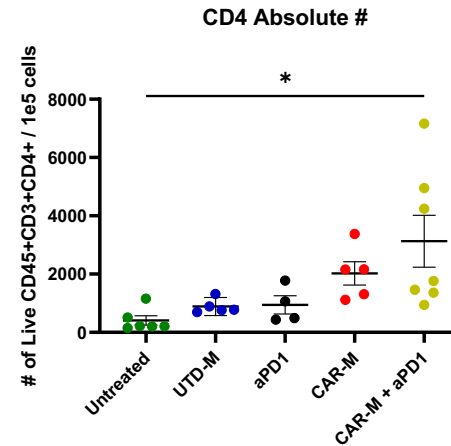
# CAR-M + PD1 Blockade Leads to Improved Tumor Control and Survival in Immunocompetent Animals

Synergistic anti-tumor activity:



Groups	n	Subject Alive	Median Survival
CTRL	18	0/18	40.5 days
CAR-M	18	7/18	71 days
aPD-1	12	1/12	50 days
CAR-M + aPD-1	18	12/18	Undefined

Synergistic TME modulation:



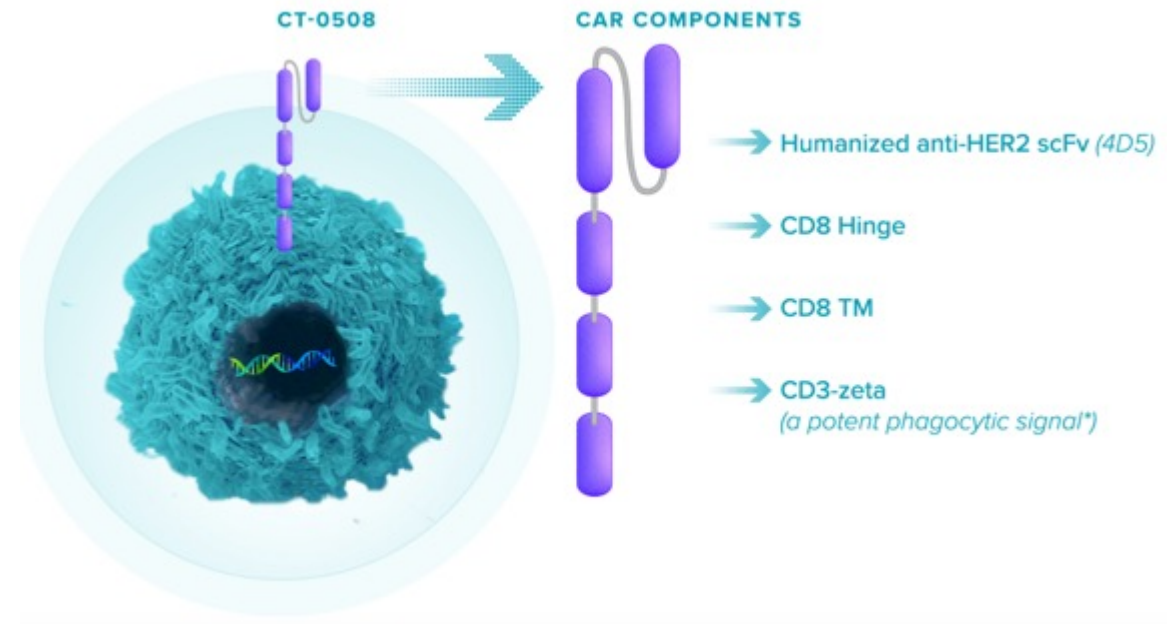
# Lead Program CT-0508: HER2 Targeted CAR-Macrophage

## Program Status

- Phase I study ongoing
- 2 patients treated to date
- Early data read supports platform's Safety and MOA
- Three clinical sites open for screening & enrollment and 3 additional sites undergoing activation

## Future Milestones

- Goal of enrolling up to two patients/month for a total of 18 patients
- Preliminary data presentation at SITC '21 / Expanded data presentation at ASCO '22
- Expanded clinical program including regional administration and T cell checkpoint combination in planning stages

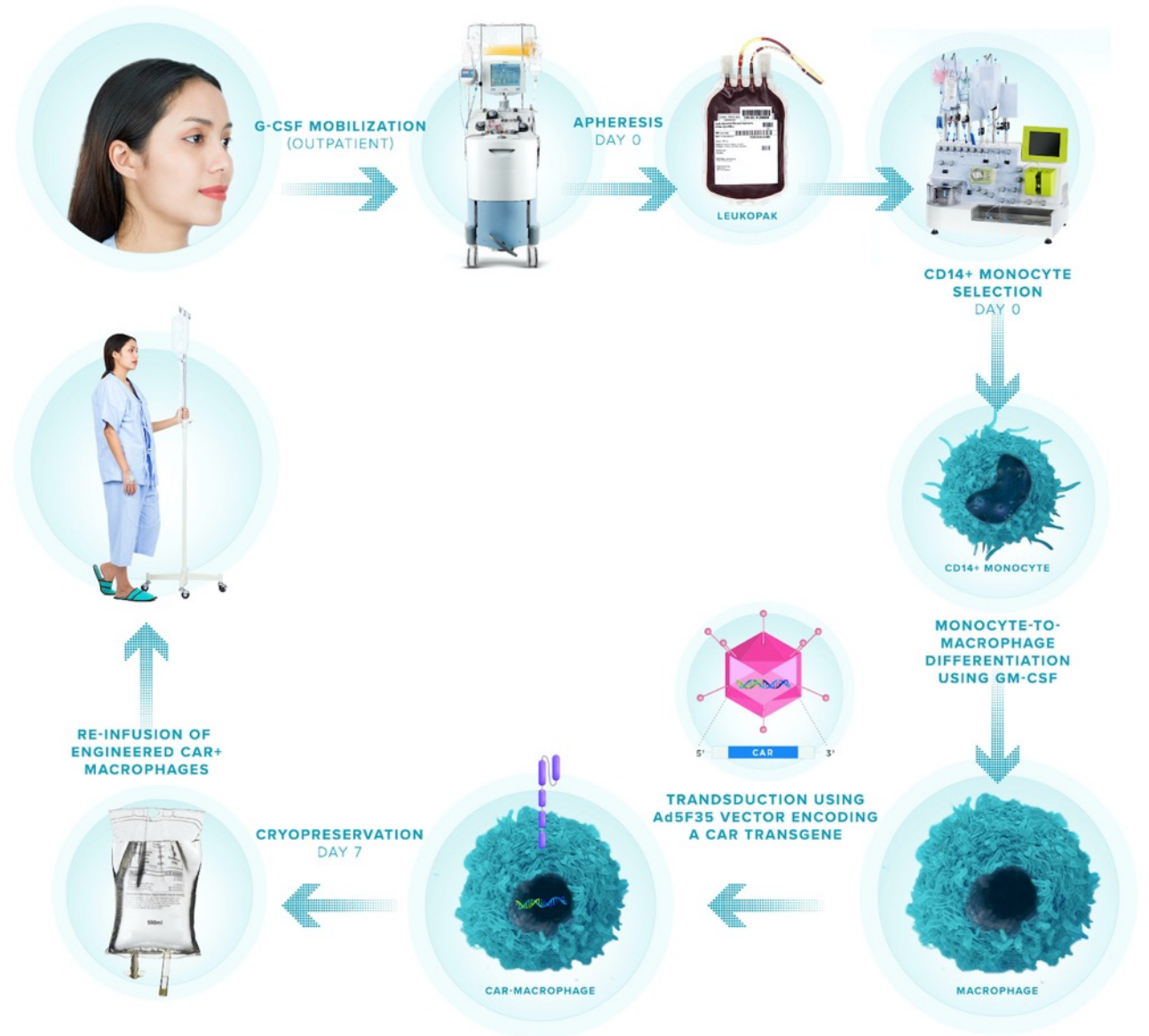


**Cells:** Autologous monocyte derived macrophages  
**Vector:** Ad5f35  
**Phenotype:** M1  
**Target:** HER2

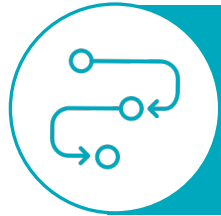
**FDA Fast Track Designation Granted Sept 2021**

# CAR-M Manufacturing Process and Partners

- **Source:** Autologous mobilized peripheral blood
- **Manufacturing time:** 7-days
- **Vein to vein:** 3 weeks
- **Vector:** Ad5f35
- **Process:** Partially automated
- **Fill format:** Cryopreserved 20mL bags



# CT-0508 Phase I Clinical Design



Study Design and Planning: A multi center, open-label single arm Phase I study to establish safety and feasibility of intravenously administered adenoviral transduced HER-2 specific CAR modified autologous macrophage cells in patients with recurrent/metastatic solid tumors

N=18 HER-2 overexpressing solid tumors

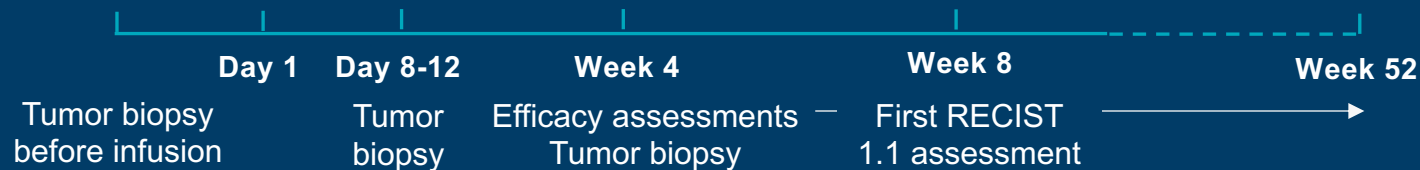
G-CSF mobilization and apheresis, CAR-M manufacture, bridging therapy, baseline staging



CT-0508 infusion

Group 1, N=9, D1-3-5  
No preparative chemotherapy

Group 2, N=9, D1  
1st bag Zr-89 labeled  
No preparative chemotherapy



## Study Objectives

### Primary

- Safety
- Manufacture feasibility

### Secondary

- Pharmacokinetics
- OR (RECIST 1.1)
- OS and PFS
- Persistence

### Correlates

- Phenotype
- Bioactivity
- Immune cell interaction



# Initial CT-0508 Phase I Data

Data to be presented at upcoming scientific conferences

## Objectives

Manufacturing

Safety

PK

Biomarkers

TME Activation

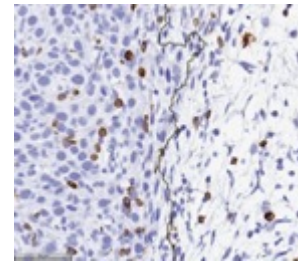
Adaptive Immune Response



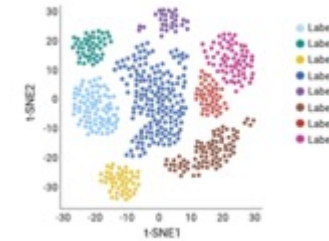
Serum cytokines



Imaging – efficacy & trafficking



TME evaluation



Single cell analysis



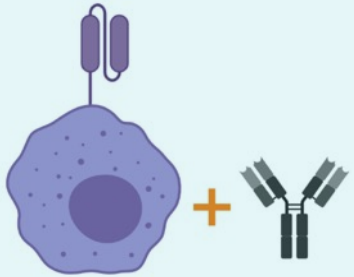
TCR clonality

# Powering the Engine of Next-Generation Cell Therapies

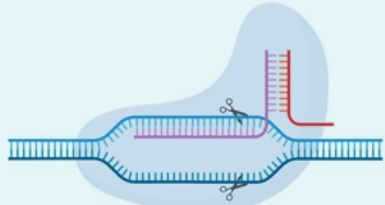
Current Pipeline	Target	Indication	Route	Discovery	Preclinical	Phase I
CT-0508	HER2	Solid tumors	IV			
CT-0508	HER2	Intraperitoneal ovarian cancer	IP			
CT-0508	HER2	BC brain mets/primary gliomas	ICV			
CT-0508 + anti-PD1	HER2	Solid tumors	multiple			
CT-0508 + anti-CD47	HER2	Solid tumors	multiple			
CT – 1119	Mesothelin	Solid tumors	multiple			
CT – 0729	PSMA	mCRPC	IV			
<b>R&amp;D ENGINE</b>						
Heme malignancy	Undisclosed					
Liver Fibrosis	Undisclosed					
Neurodegeneration	Undisclosed					

# Robust Internal & External R&D Program Driving Platform Enhancements

## Platform Enhancements



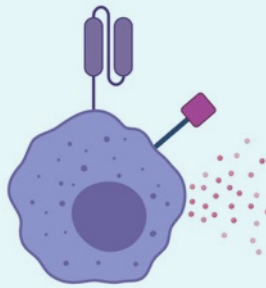
Combination therapies



Gene edited CAR-M



Novel CAR designs

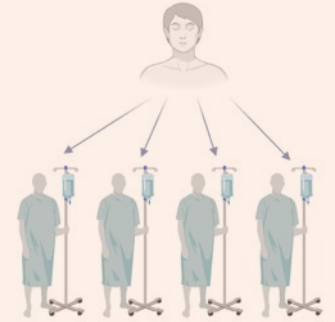


Multiplexed engineering

## Product Enhancements



CAR Monocytes

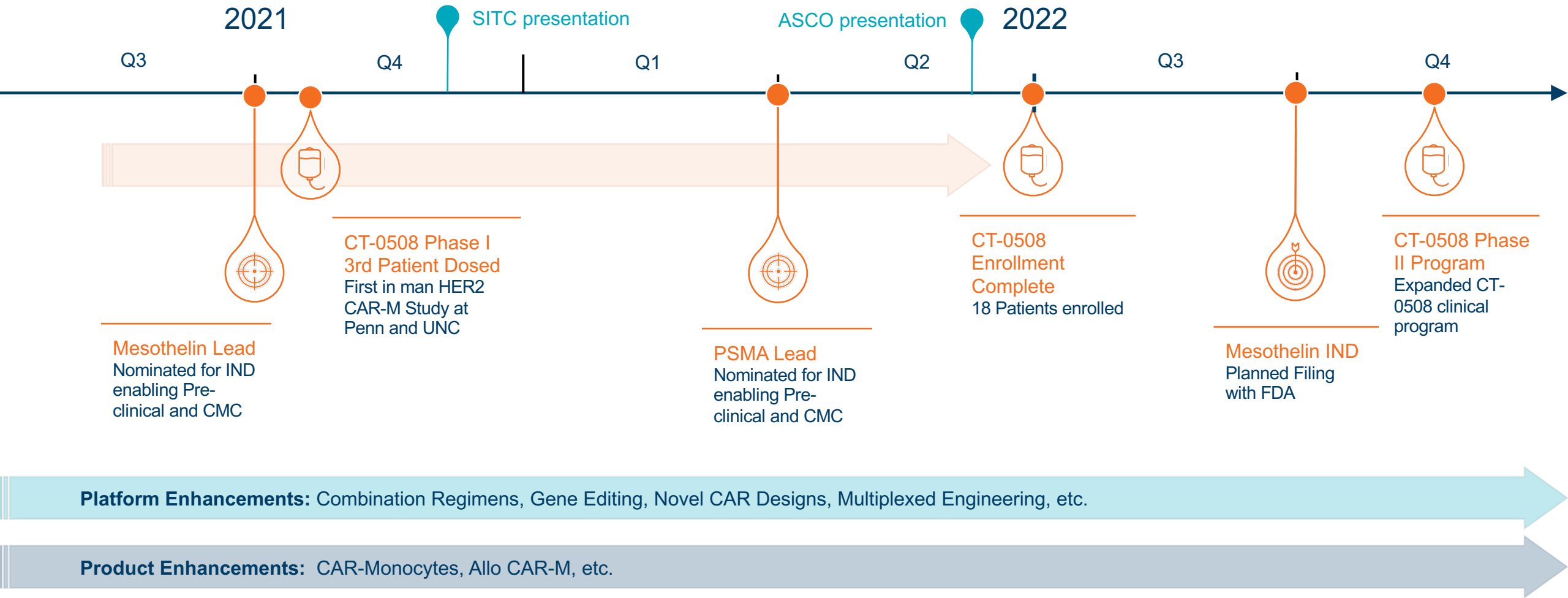


Allogeneic CAR-M

Academic Collaborators:



# Upcoming Milestones



# Corporate Summary

**CARISMA is The Leader in Engineered Macrophage Technology with Broad Therapeutic Applications Including the Treatment of Solid Tumors**



Proprietary Engineered Macrophage Platform



Emerging Pipeline of Oncology CAR-Ms



Established GMP Vein-to-vein Supply Chain



Experienced Leadership Team and Advisors



Multiple Value Catalysts over Next 12 Months

THANK YOU



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