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THERAPEUTICS

HARNESSING THE POWER OF ENGINEERED MACROPHAGES

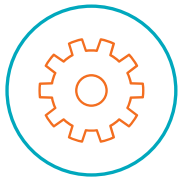
CARISMA Therapeutics
December 2021

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

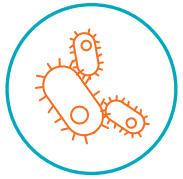
Proprietary Platform and Capabilities

Myeloid Specific Cell Engineering

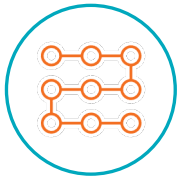


Proprietary Vectors

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)

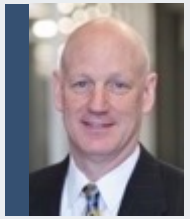
Experienced Leadership and Focused Strategy

- 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

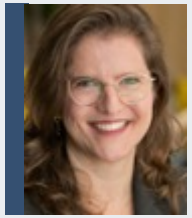
Management

Steven Kelly
President & CEO

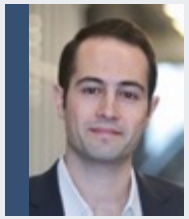


Dan Cushing, PhD
CDTO

Rich Morris
CFO



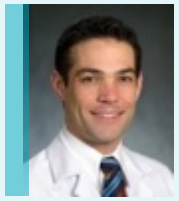
Debora Barton, MD
CMO



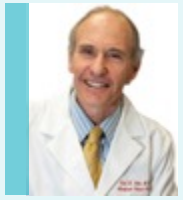
Michael Klichinsky, PharmD PhD
Co-Founder & SVP, Research

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

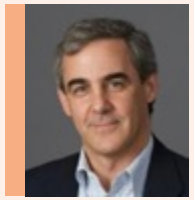
Prasad Adusumilli, MD
MSKCC

Nina Bhardwaj, MD, PhD
Mt. Sinai

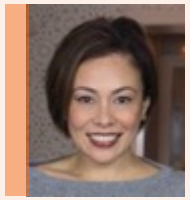
Nabil Ahmed, MD
Baylor College of Medicine

Board of Directors

Sanford Zweifach
Chairman

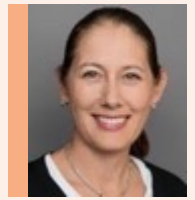


Briggs Morrison
Independent

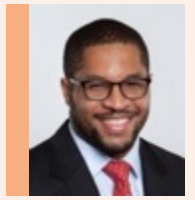


Margarita Chavez
AbbVie Ventures

Jacob Gunterberg
HealthCap



Regina Hodits
Wellington



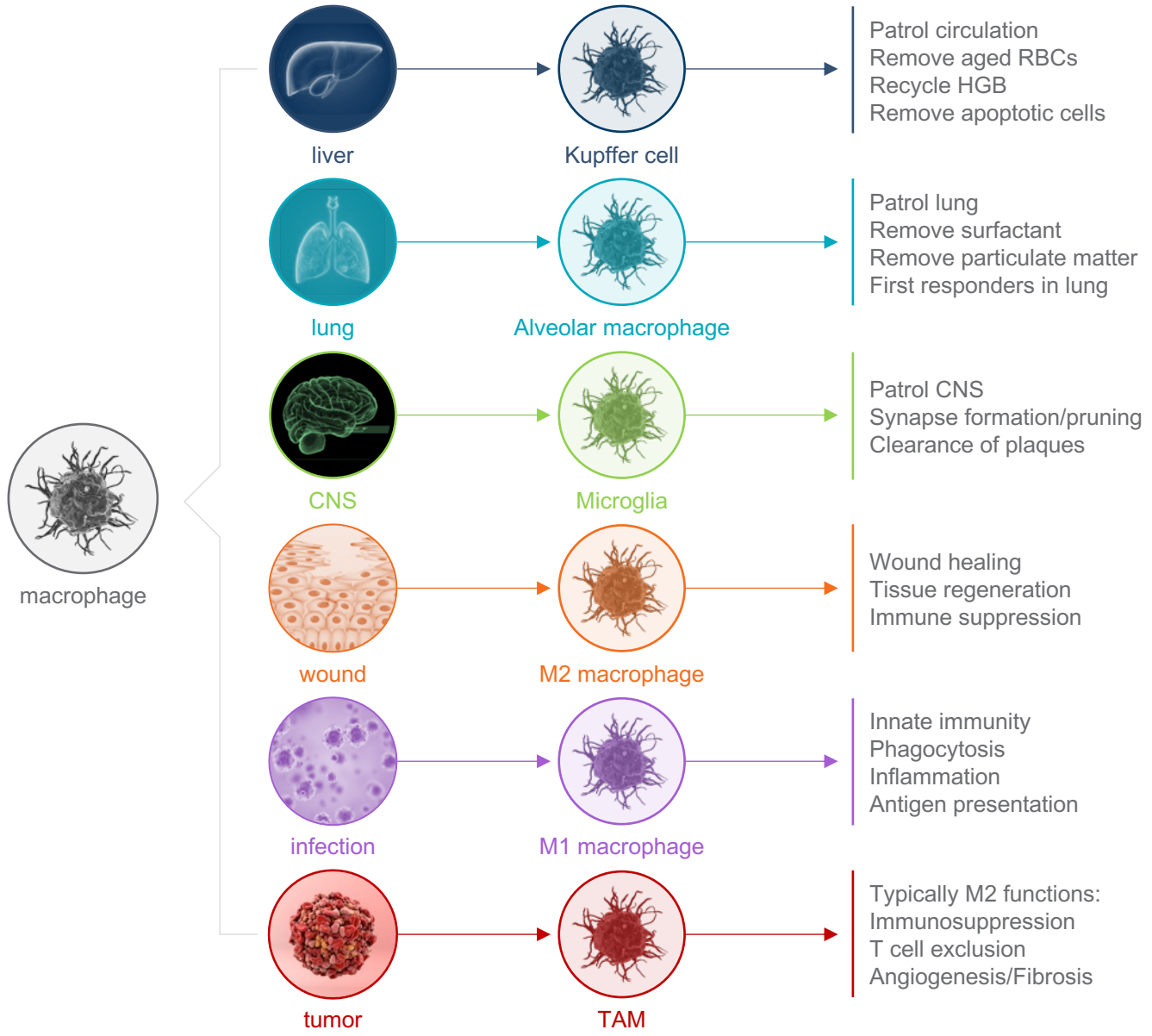
Chidozie Ugwumba
Symbiosis

Macrophages: The Ultimate Multitasker

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

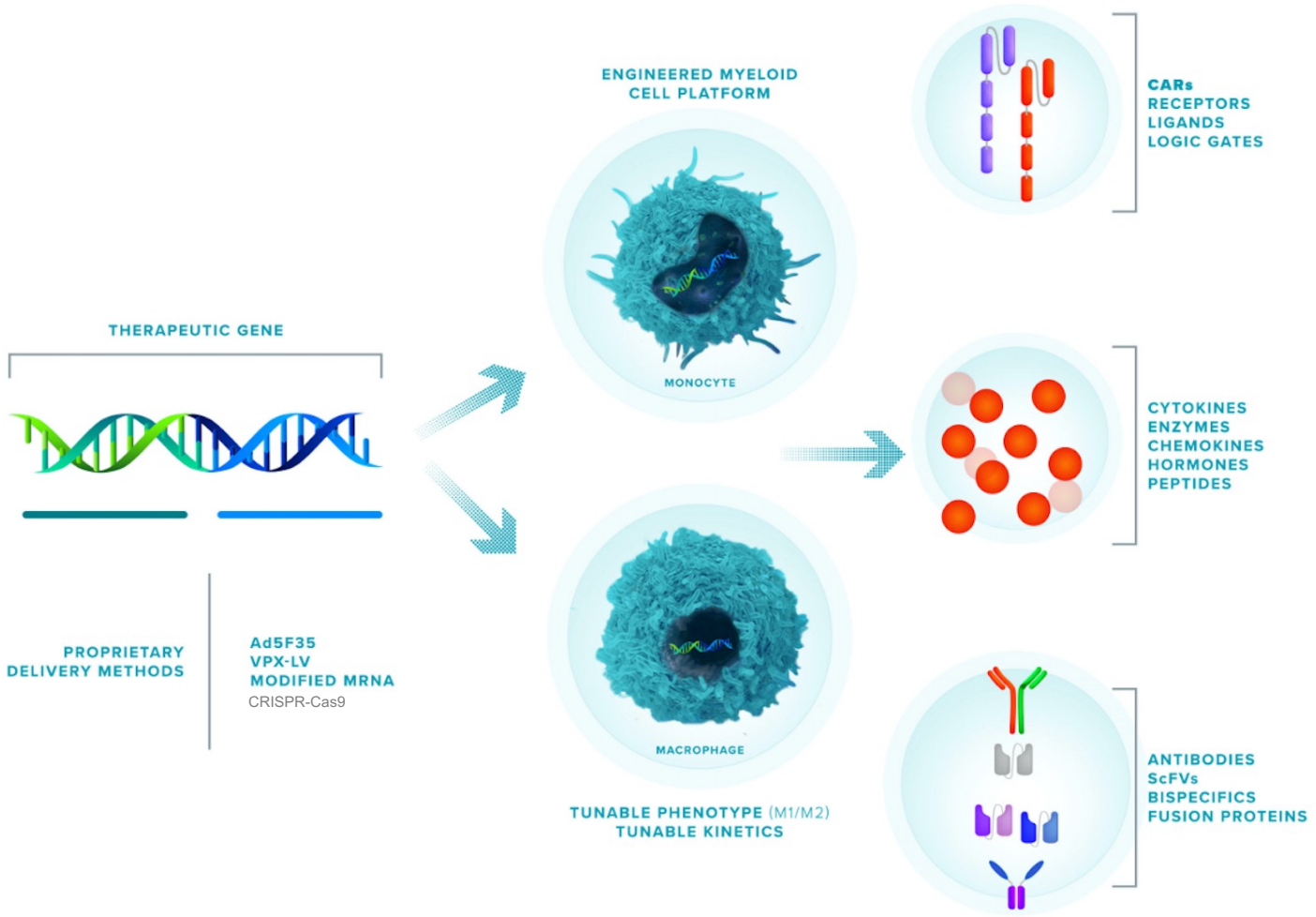
Macrophages can:

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

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[1] Licensed from UPenn
[2] Licensed from NYU
[3] Carisma developed

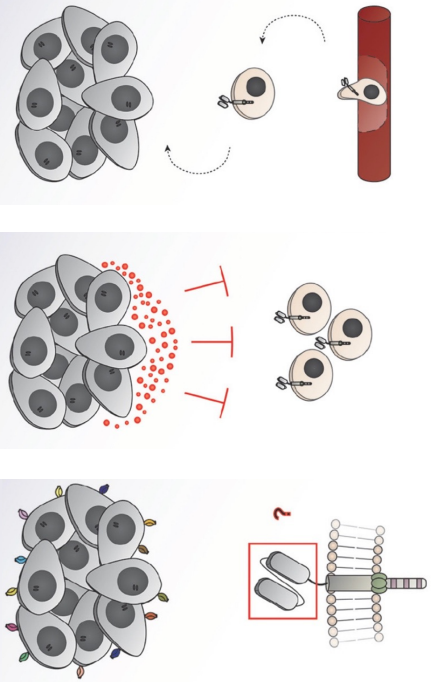
Key Challenges for Cell Therapy Treatment of Solid Tumors

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

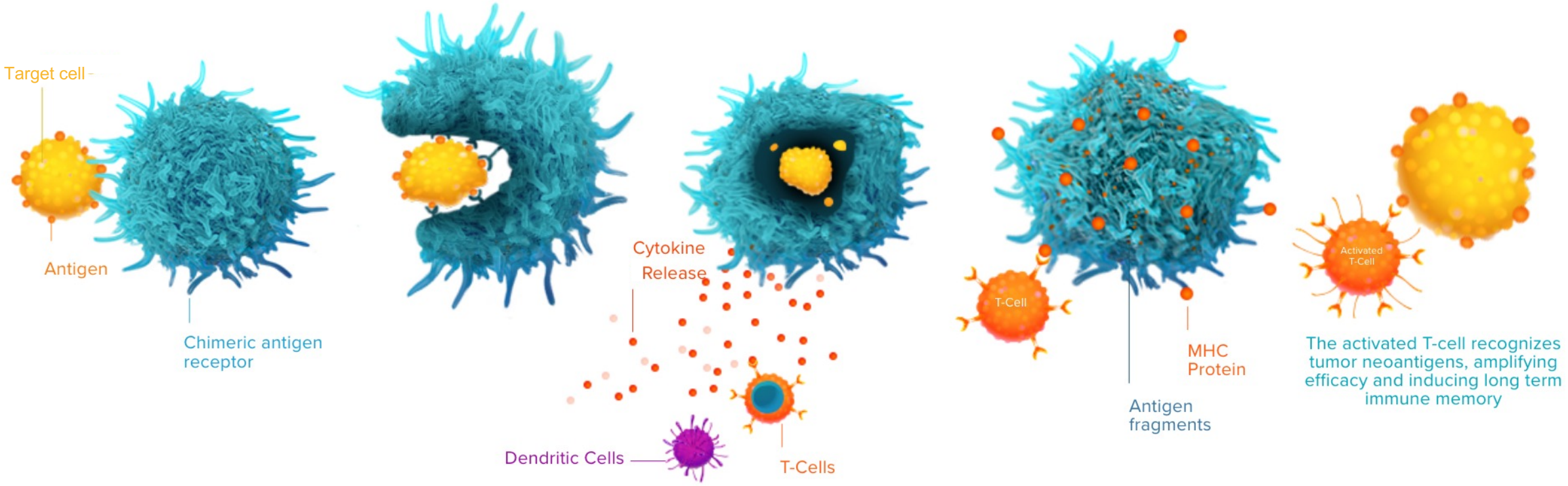
1	Lack of Trafficking to Tumors	Need natural recruitment to tumors and metastatic sites
2	Suppressive TME	Need ability to induce a pro-inflammatory TME
3	Antigen Heterogeneity	Need ability to activate the immune system via antigen presentation



CAR-M's Multi-Factorial Attack on Cancer

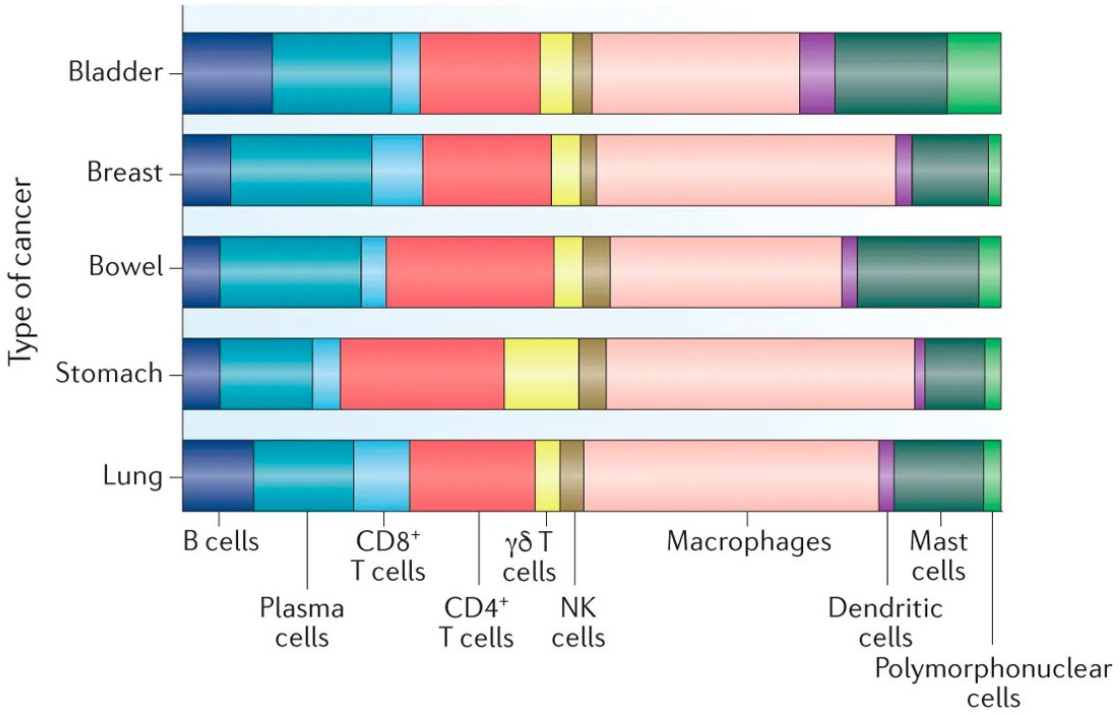
Carisma's technology addresses the key challenges involved in treating solid tumors

1	2	3
TRAFFICKING AND PHAGOCYTOSIS	IMMUNE ACTIVATION	ANTIGEN PRESENTATION



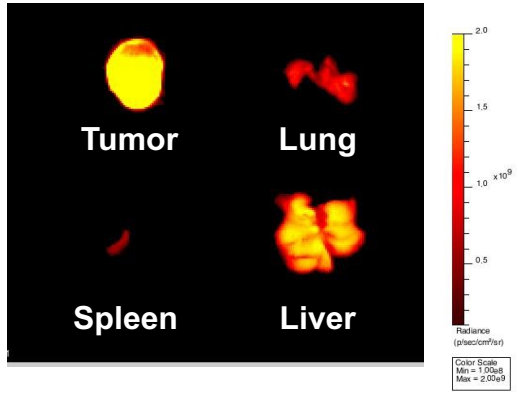
Monocytes & macrophages home to tumors

Myeloid cells are abundant in solid tumors



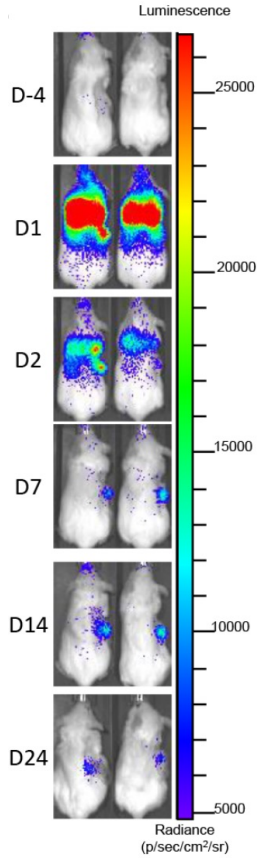
Pollard JW, et al. Nat Rev Drug Discov. 2019.

Adoptively transferred macrophages home to tumors



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

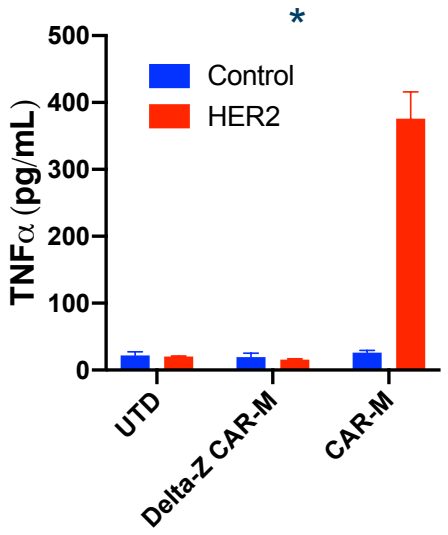
Klichinsky M, et al. 2020.



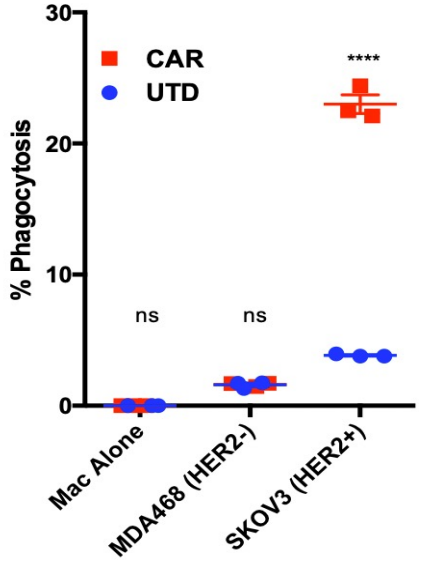
Brempelis K, et al. 2020.

Primary human CAR-M demonstrate broad anti-tumor activity

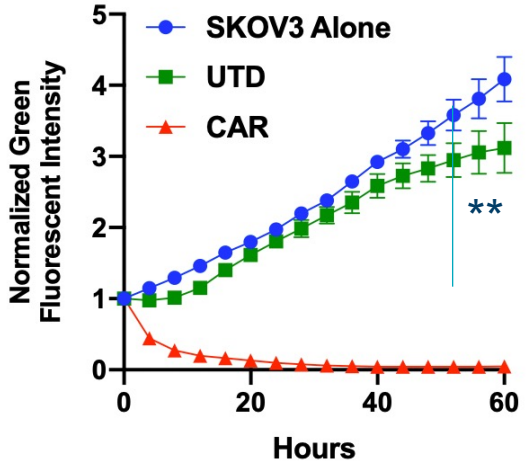
CAR-M Cytokine Production



CAR-M Phagocytosis



CAR-M Killing



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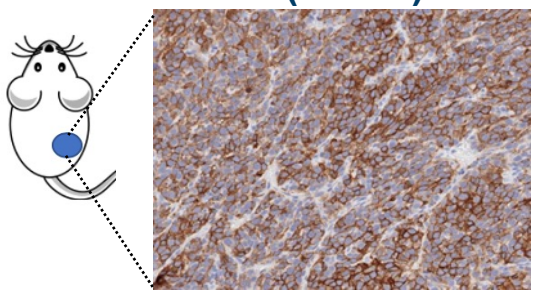
Klichinsky M, et al. Nature Biotechnology. 2020.

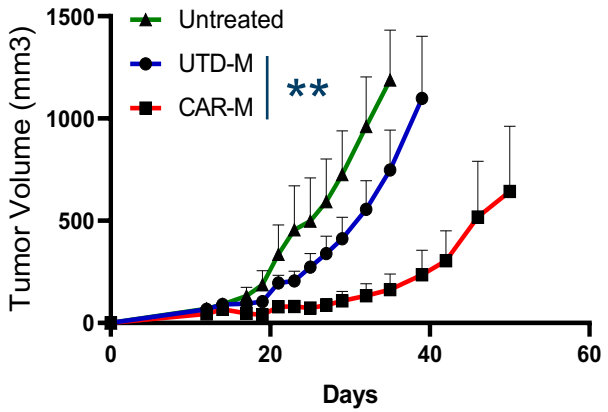
CAR-M shrink tumors, modulate the TME, and induce systemic T cell responses in immunocompetent models

CT26 (HER2)

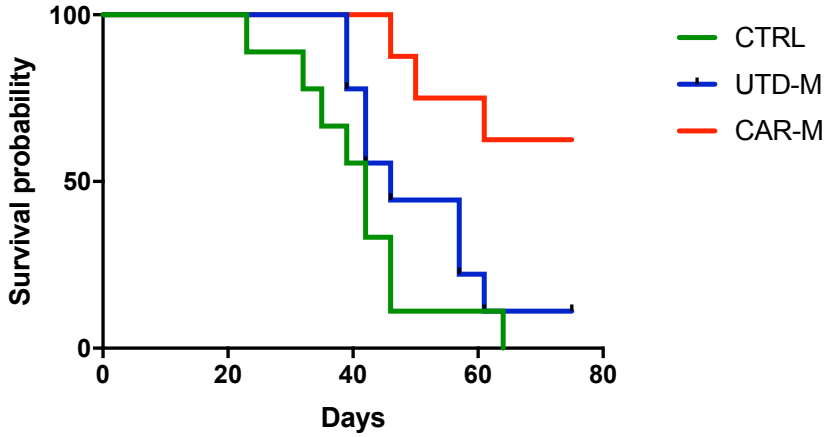


HER2 IHC: HER2 3+

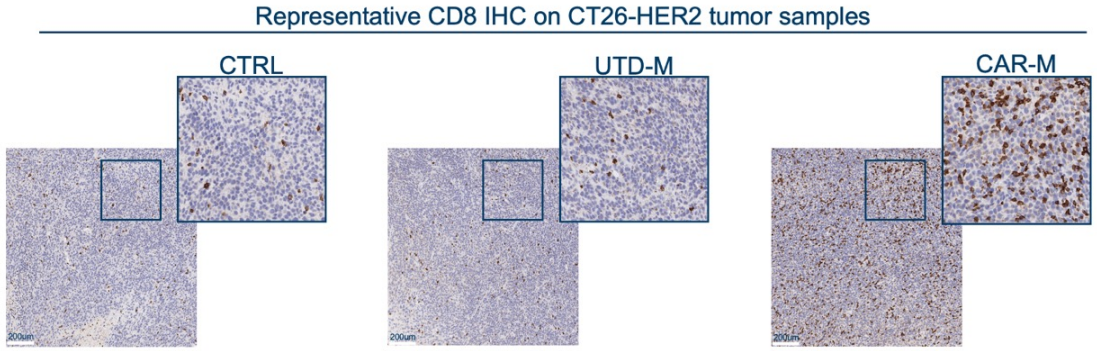
Average tumor growth curves:

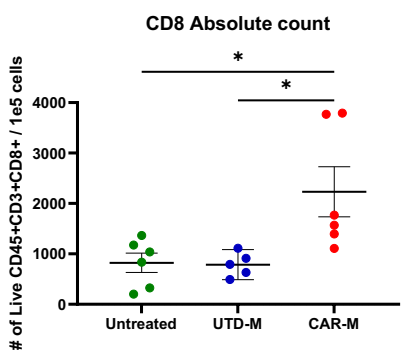


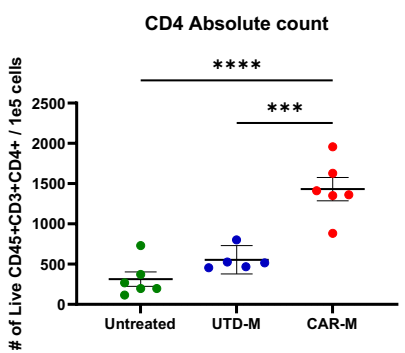
Kaplan Meier Survival Curve:

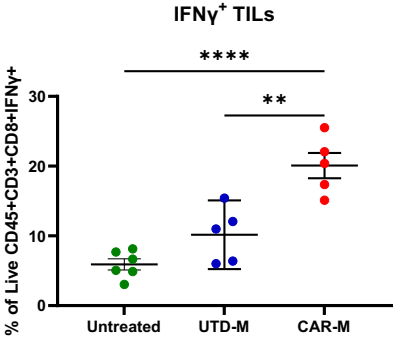


CAR-M modulate the TME – CD8+ T cell infiltration





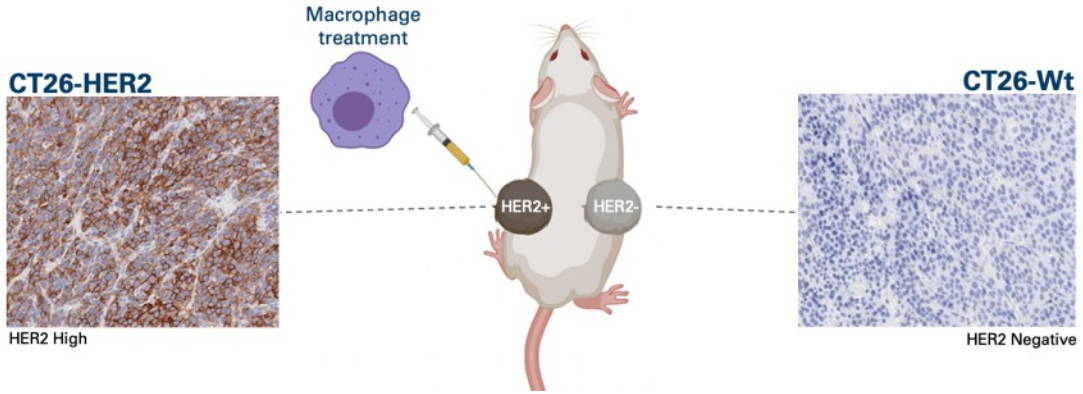


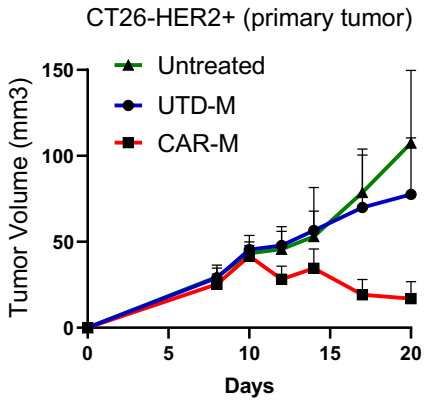


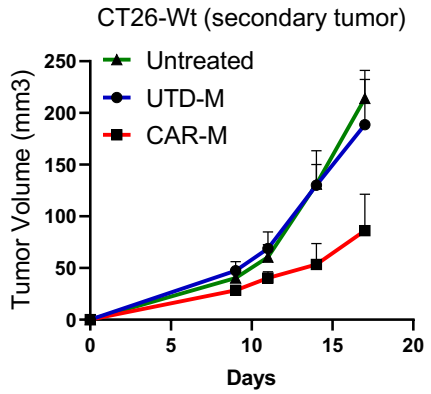
CAR-M Lead to Epitope Spreading In Vivo

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

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

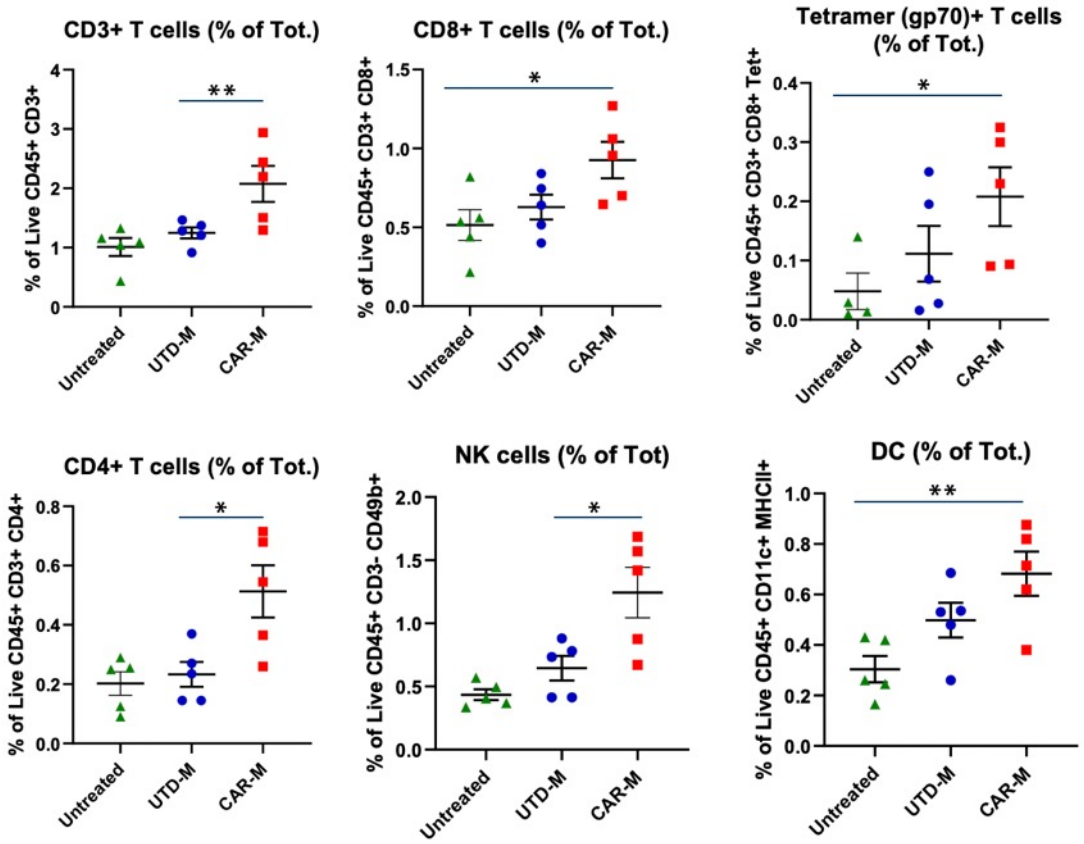






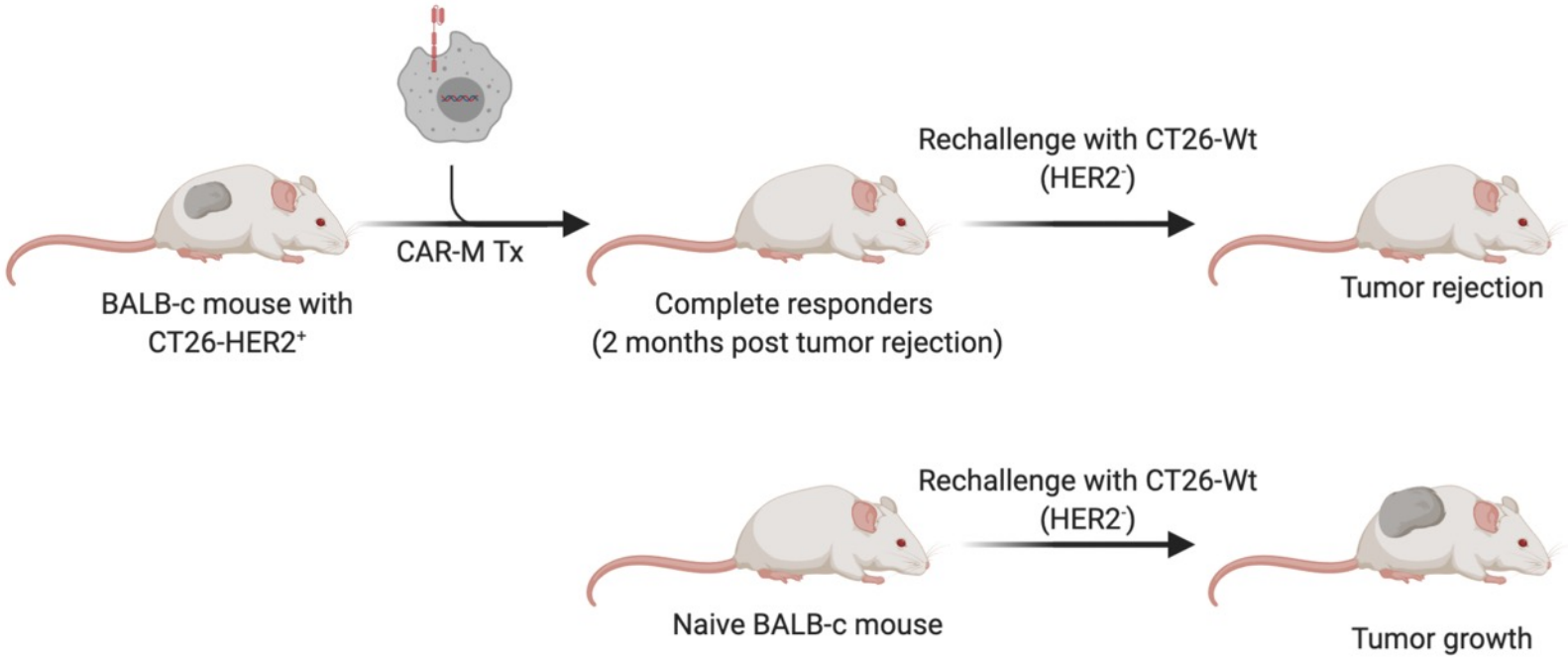
n=7-8 mice per group

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

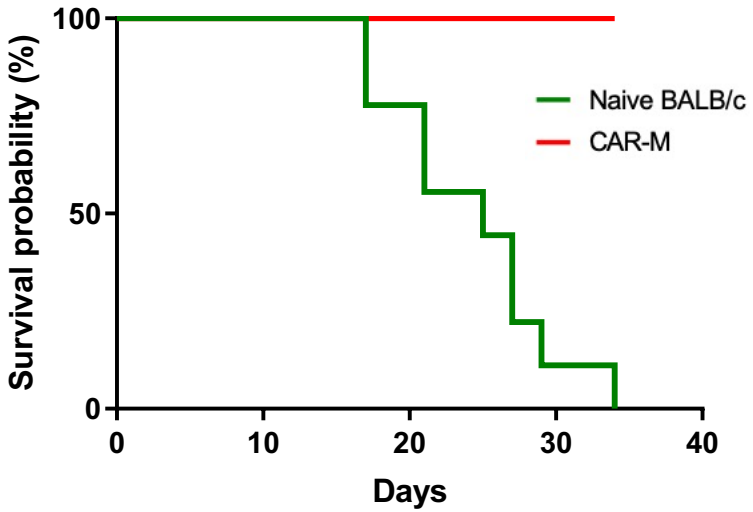


CAR-M Therapy Vaccinates Mice Against Tumor Recurrence and Prevents Antigen Negative Relapse

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

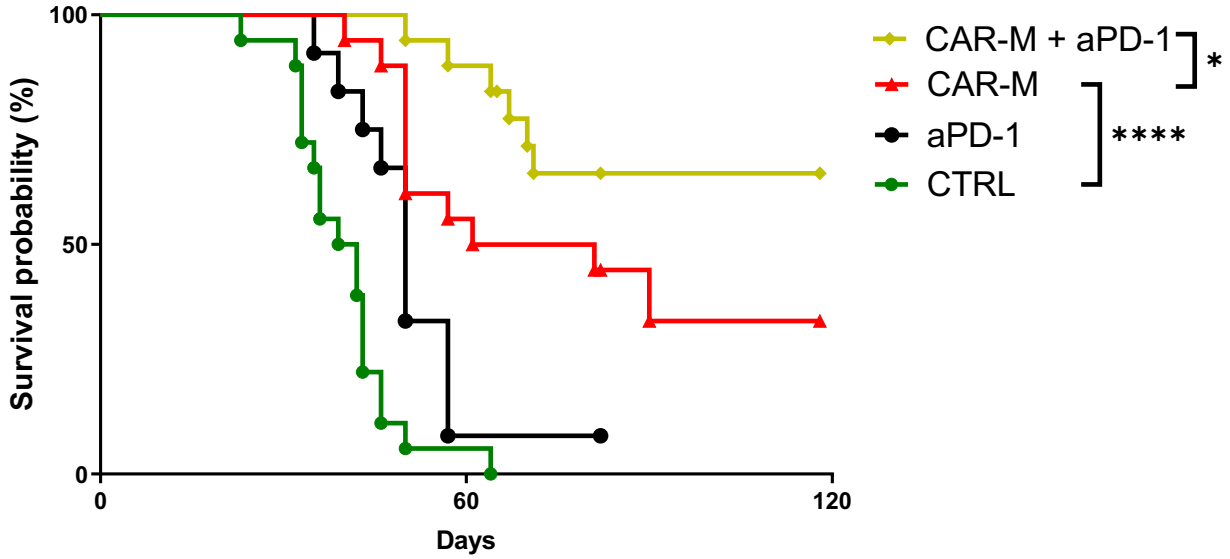


CT26 Wt (HER2-) rechallenge: Kaplan Meier Survival Curve



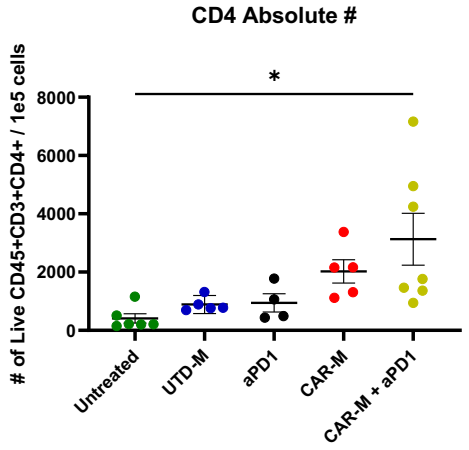
CAR-M + PD1 Blockade Leads to Improved Tumor Control and Survival in Immunocompetent Animals

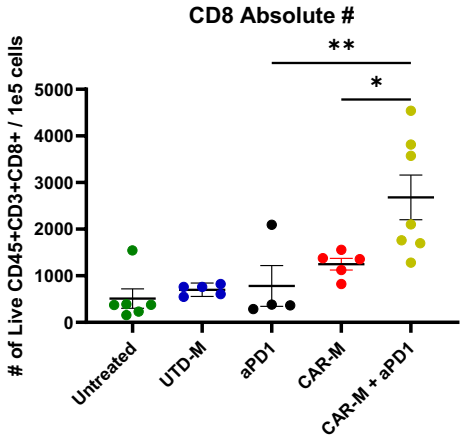
Synergistic anti-tumor activity:

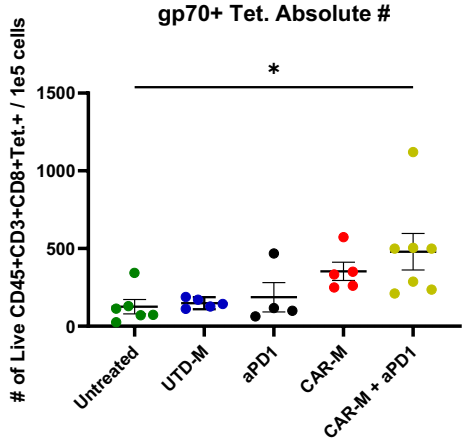


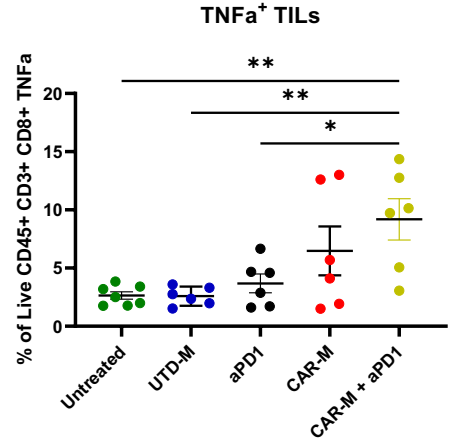
Groups	n	Subject Alive	Median Survival
CTRL	18	0/18	40.5 days
CAR-M	18	7/18	71 days
aPD-1	12	1/12	50 days
CAR-M + aPD-1	18	12/18	Undefined

Synergistic TME modulation:









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			
R&D ENGINE						
Heme malignancy	Undisclosed					
Liver Fibrosis	Undisclosed					
Neurodegeneration	Undisclosed					

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IV: Intravenous ; IP: intraperitoneal ; ICV: intracranial ventricle ; BC: breast cancer ; mCRPC: metastatic castrate resistant prostate cancer

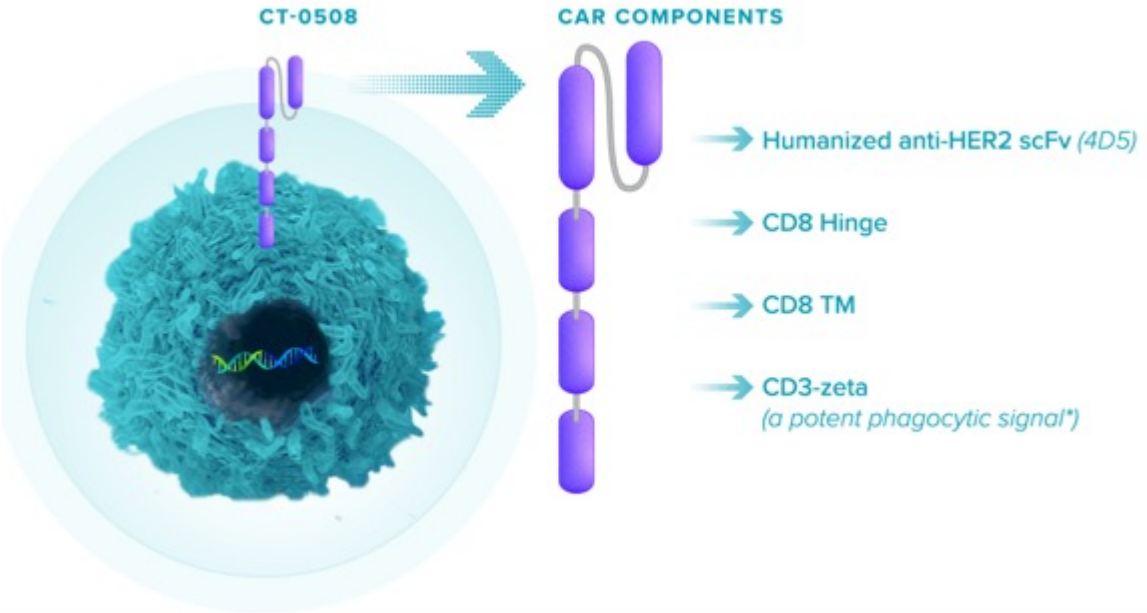
Lead Program CT-0508: HER2 Targeted CAR-Macrophage

Program Status

- Phase I study ongoing
- 4 patients treated to date
- Early data read supports platform's Safety and MOA
- Four clinical sites open for screening & enrollment and two 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 mid-'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

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

Day 1	Day 8-12	Week 4	Week 8	Week 52
Tumor biopsy before infusion	Tumor biopsy	Efficacy assessments Tumor biopsy	First RECIST 1.1 assessment	→

Study Objectives

Primary
- Safety
- Manufacture feasibility

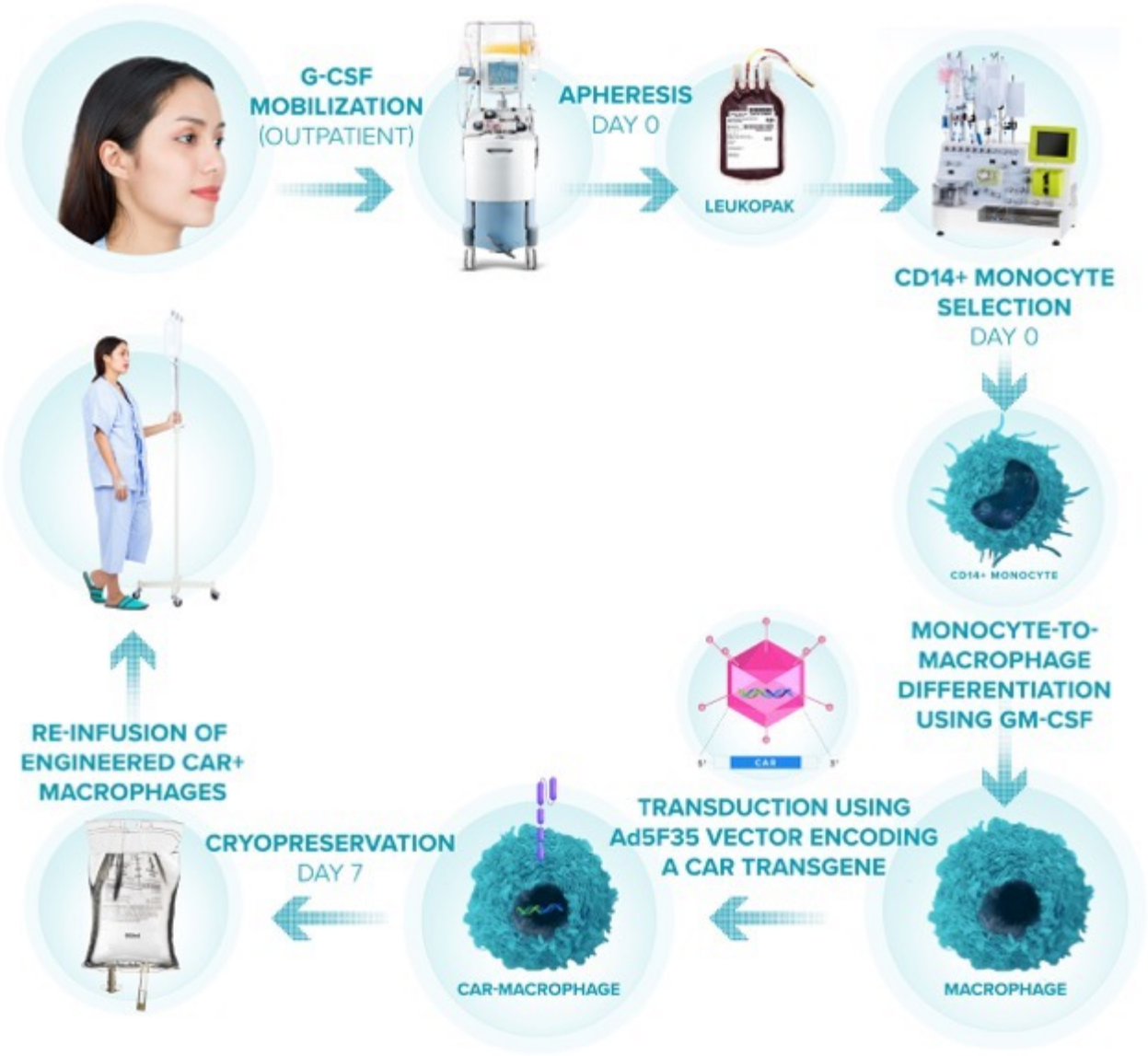
Secondary
- Pharmacokinetics
- OR (RECIST 1.1)
- OS and PFS
- Persistence

Correlates
- Phenotype
- Bioactivity
- Immune cell interaction

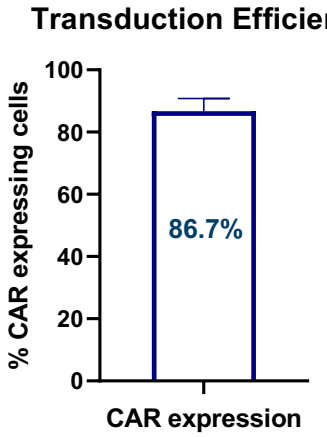
www.clinicaltrials.gov ref. NCT04660929

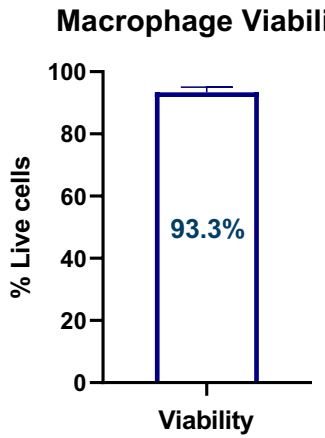
CT-0508 Manufacturing Process

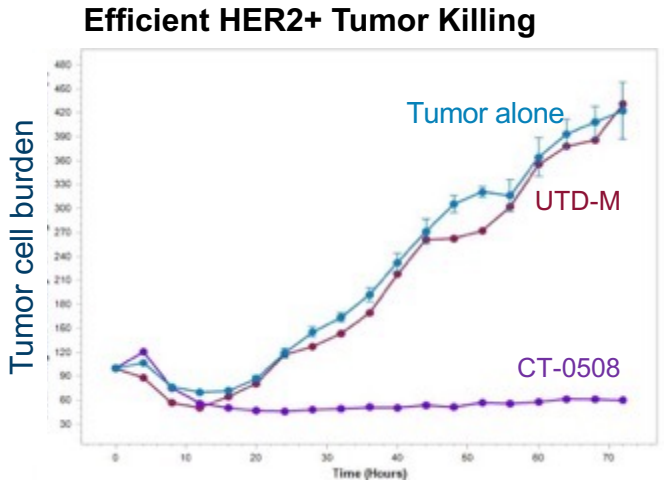
- **Source**: Autologous mobilized peripheral blood
- **Manufacturing time**: 1 week
- **Vein to vein**: 3 weeks
- **Vector**: Ad5f35
- **Process**: Automated
- **Fill**: Cryopreserved

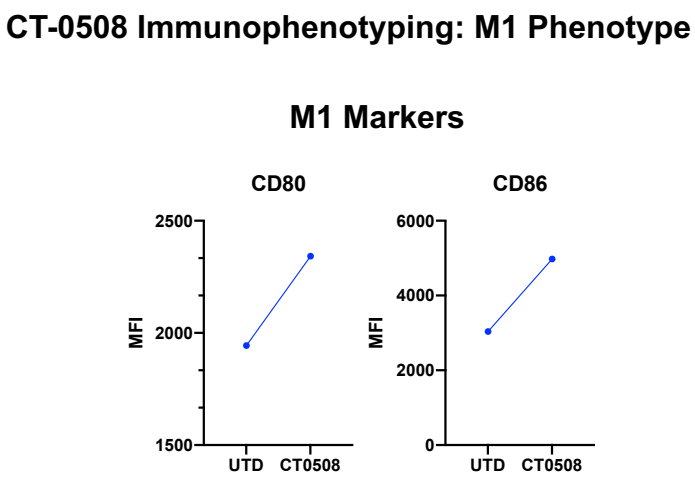


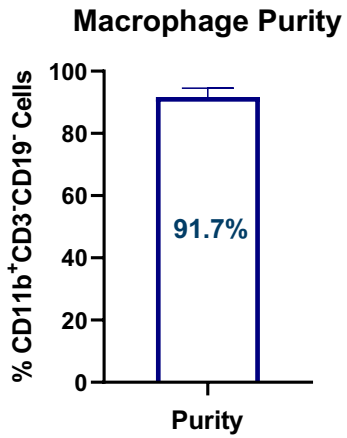
CT-0508 CAR-M Manufacturing: Functional M1 Polarized CAR Macrophages Generated from Patients

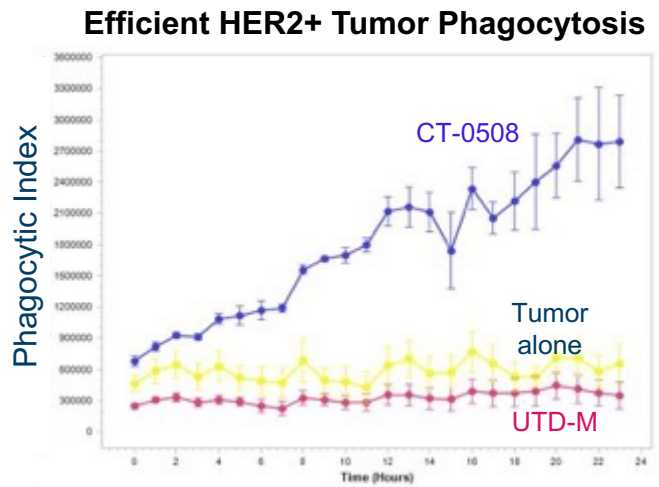


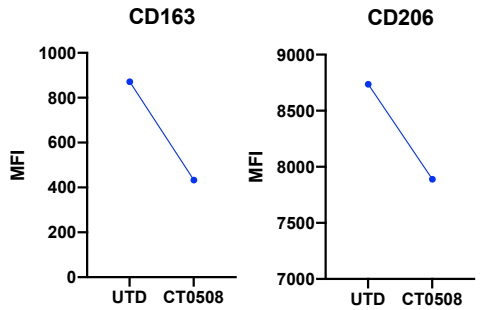












Note: Killing / phagocytosis / Immunophenotyping assays from 1 representative run.

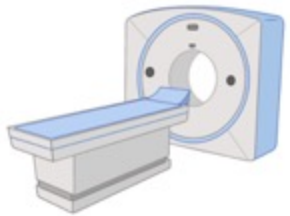
Initial CT-0508 Phase I Data

Extensive correlative studies focused on full mechanism of action

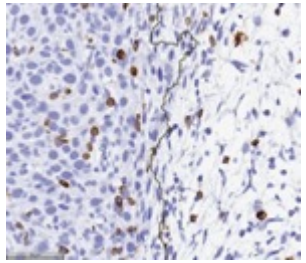
Objectives

Manufacturing → Safety → PK → Biomarkers → TME Activation → Adaptive Immune Response

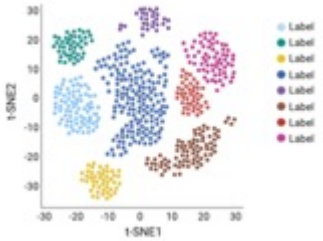
Serum cytokines



Imaging – efficacy & trafficking



TME evaluation



Single cell analysis

TCR clonality

Initial CT-0508 Phase I Data

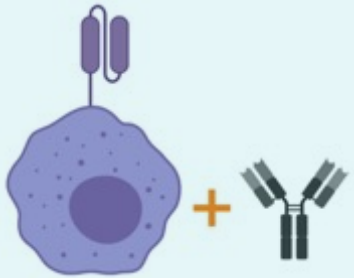
Preliminary dataset demonstrates strong safety profile and supports mechanism of action

Objectives

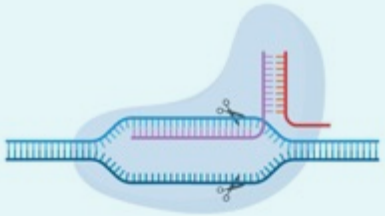
Manufacturing	Safety	PK	Biomarkers	TME Activation	Adaptive Immune Response
CT-0508 cell product was generated successfully, showing high CAR expression, high viability, high purity, M1 phenotype, and good *in vitro* anti-tumor function	No significant treatment related adverse events No dose-limiting toxicities CT-0508 infusion was well tolerated	Short persistence of CT-0508 in the blood (~4-6 hours) consistent with rapid migration to tissue	Serum cytokines and chemokines were only transiently increased following infusion and rapidly normalized to baseline levels	Single cell transcriptomic analysis of tumor infiltrating leukocytes demonstrated pro-inflammatory remodeling of the myeloid compartment and a significant enrichment/ activation of tumor reactive $CD8^+$ T cells	T cell repertoire analysis in the blood demonstrated initiation of an adaptive immune response

Robust Internal & External R&D Program Driving Platform and Product Enhancements

Platform Enhancements

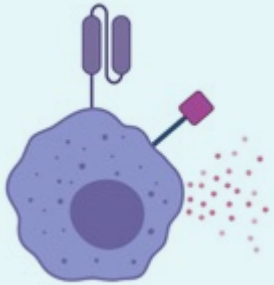


Combination therapies



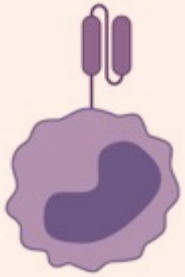
Gene edited CAR-M

Novel CAR designs

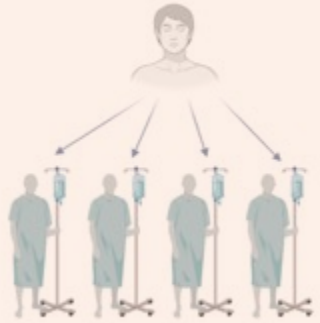


Multiplexed engineering

Product Enhancements



CAR Monocytes



Allogeneic CAR-M

Academic Collaborators:

Penn — University of Pennsylvania

UNC School of Medicine

NYU Langone Medical Center

University of Minnesota Medical School

City of Hope

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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