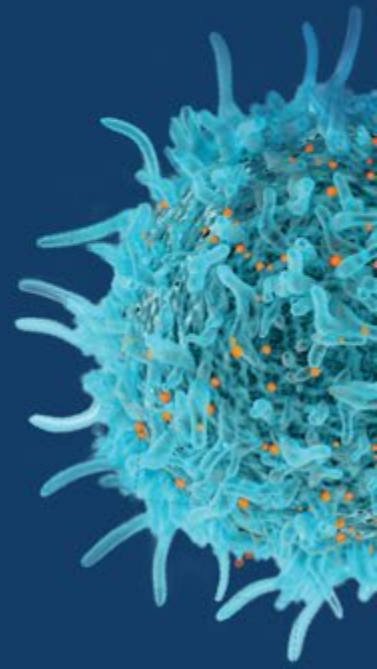
In vivo CAR-M:
Redirecting endogenous myeloid cells with mRNA for cancer immunotherapy



Bindu Varghese, PhD

Carisma Therapeutics Inc.

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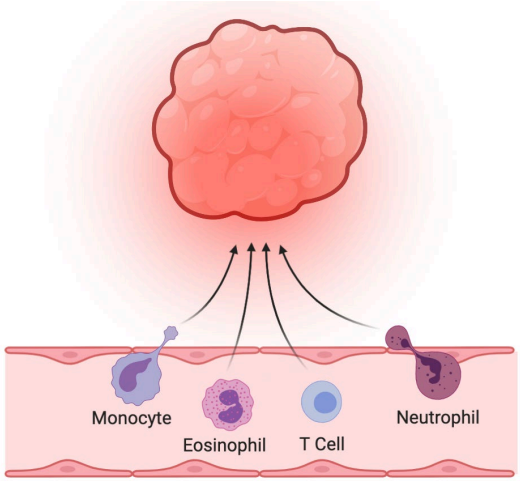
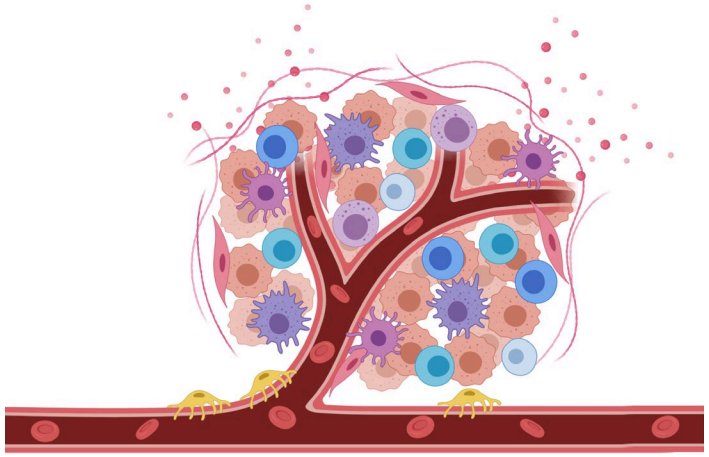
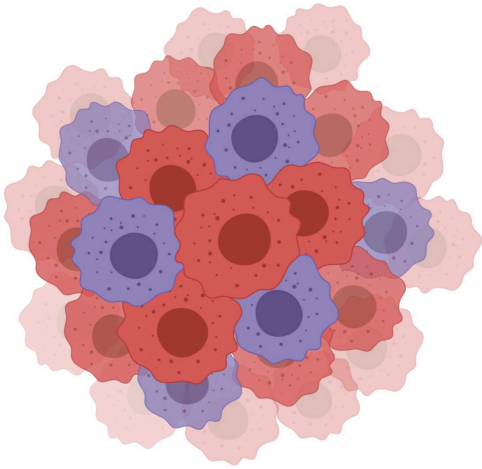
Key challenges for cell therapy in cancer







1. Trafficking & penetration

- Homing
- Extravasation
- Sufficient local concentration

2. Tumor microenvironment

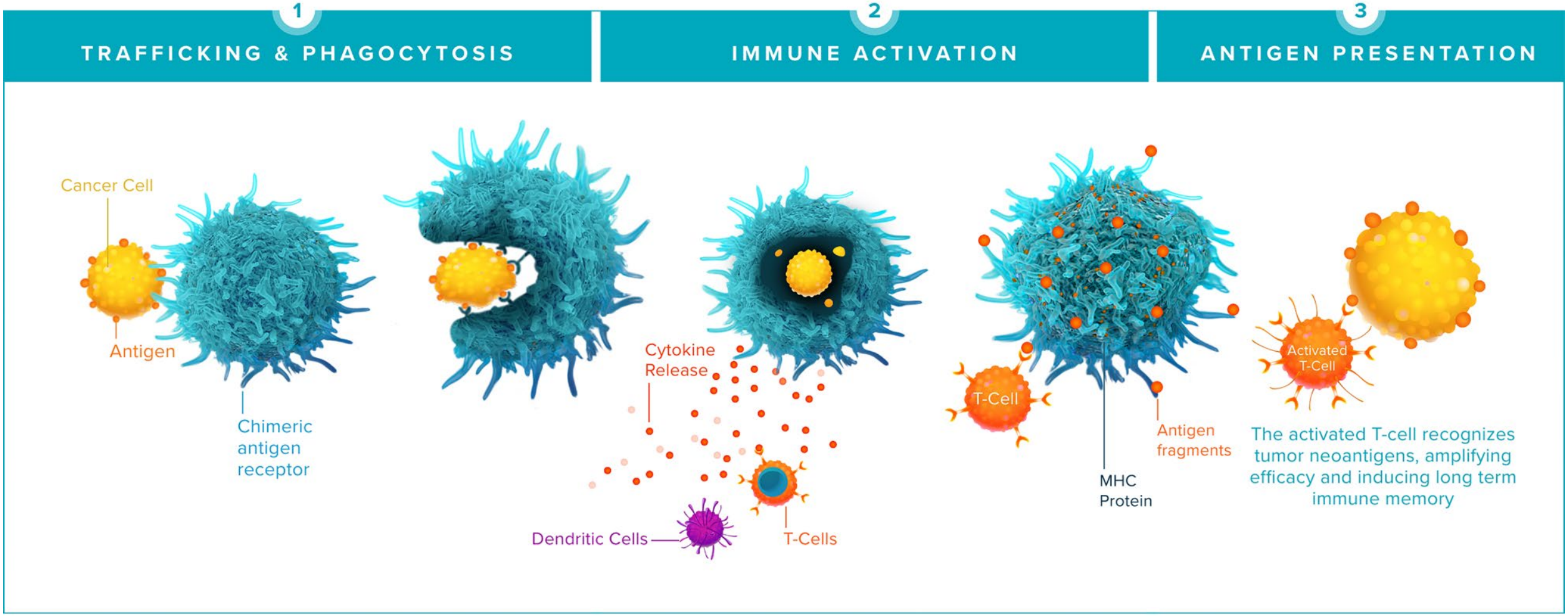
- Immunosuppression
- Exhaustion/Anergy
- Low APC function
- Low Tumor Inflammatory Score

3. Target antigen heterogeneity

- Inherent resistance of Ag(-)
- Downregulation
- Antigen negative relapse

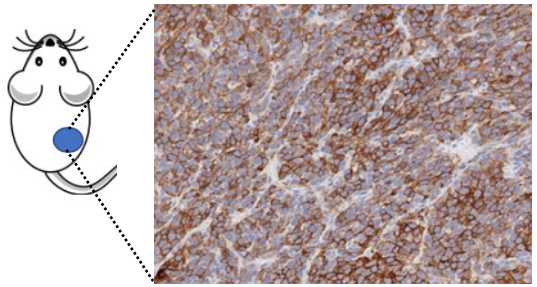
Chimeric Antigen Receptor Macrophages (CAR-M)

Redirecting myeloid cells to overcome barriers to successful cancer immunotherapy



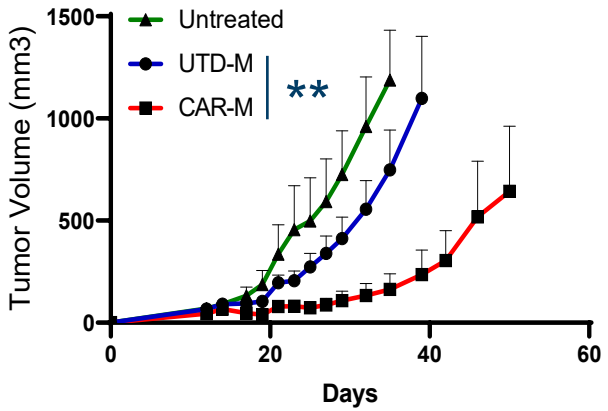
Ex vivo CAR-M shrinks tumors, modulates the TME, and induces systemic T cell responses in immunocompetent models

CT26 (HER2)

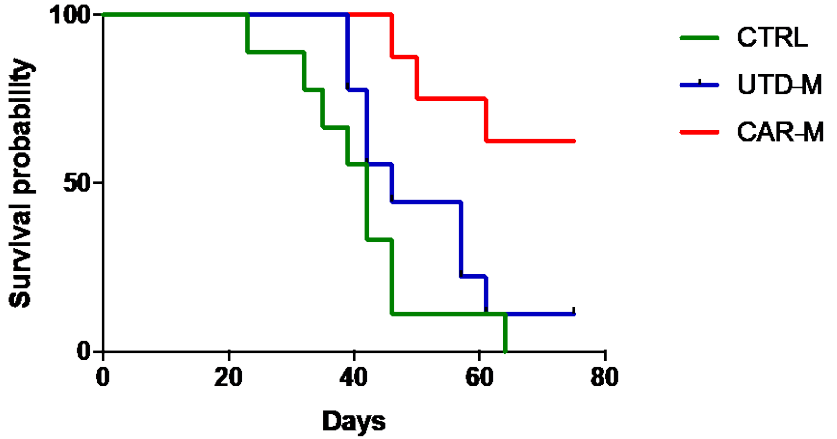


HER2 IHC: HER2 3+

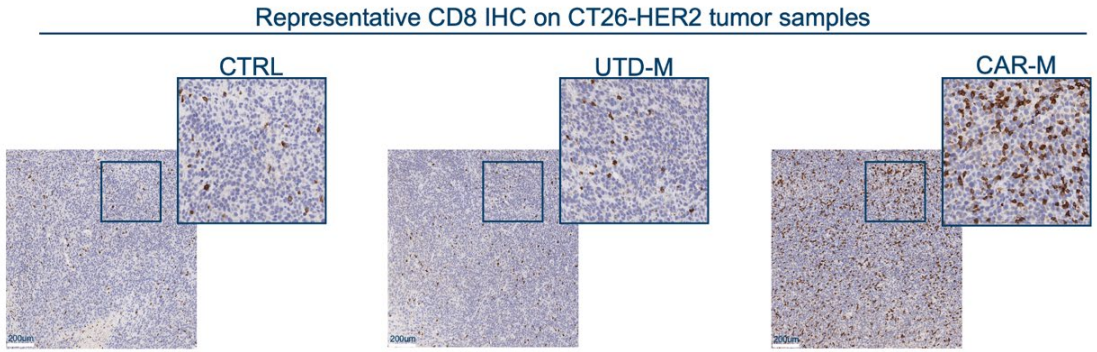
Tumor Growth

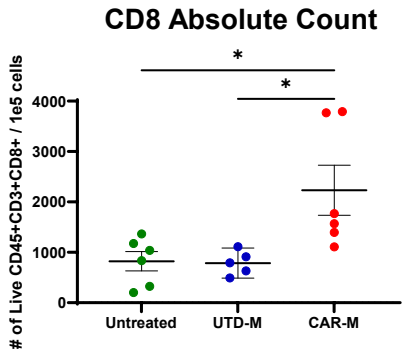


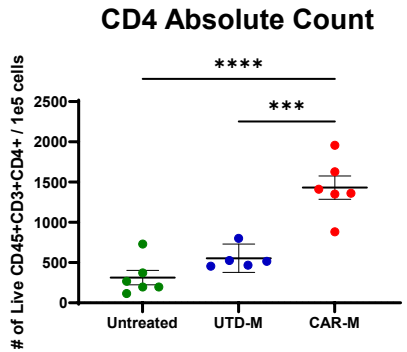
Kaplan Meier Survival Curve

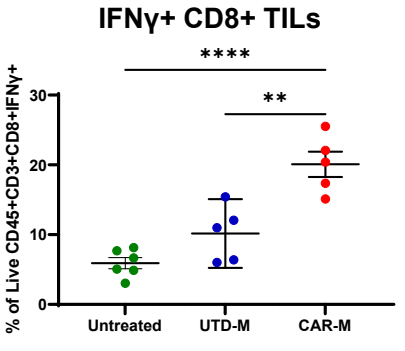


CAR-M modulate the TME – CD8 & CD4 T cell infiltration









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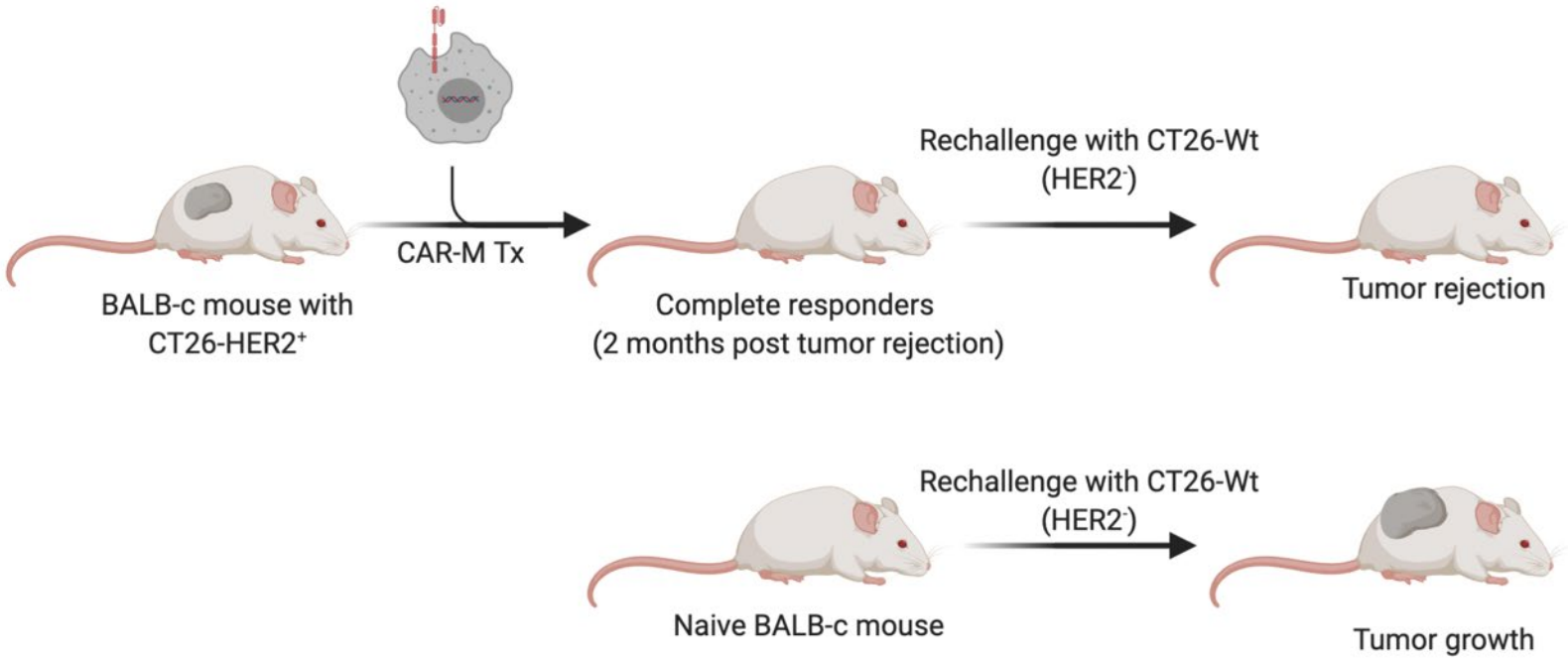
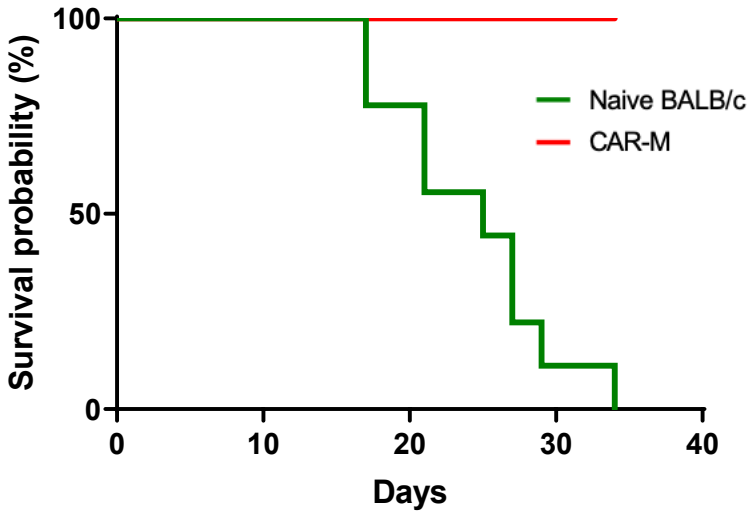
Ex vivo CAR-M Therapy Protects Mice Against Tumor Recurrence and Prevents Antigen Negative Relapse



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



CT-0508 Phase I Study: Safety, Feasibility, and Evidence of CAR-M Mechanism of Action in Pts w/ HER2+ Solid Tumors

FEASIBILITY

- Successful manufacturing from autologous monocytes
- High CAR expression
- High purity/viability
- Robust M1 phenotype

PRELIMINARY CLINICAL PROFILE

- No dose limiting toxicities
- No severe CRS/ICANS
- No on target/off tumor tox
- Best overall response of SD
- SD in HER2 3+ population 44.4% (n=4/9); SD in HER2 2+ population 0% (n=0/5)

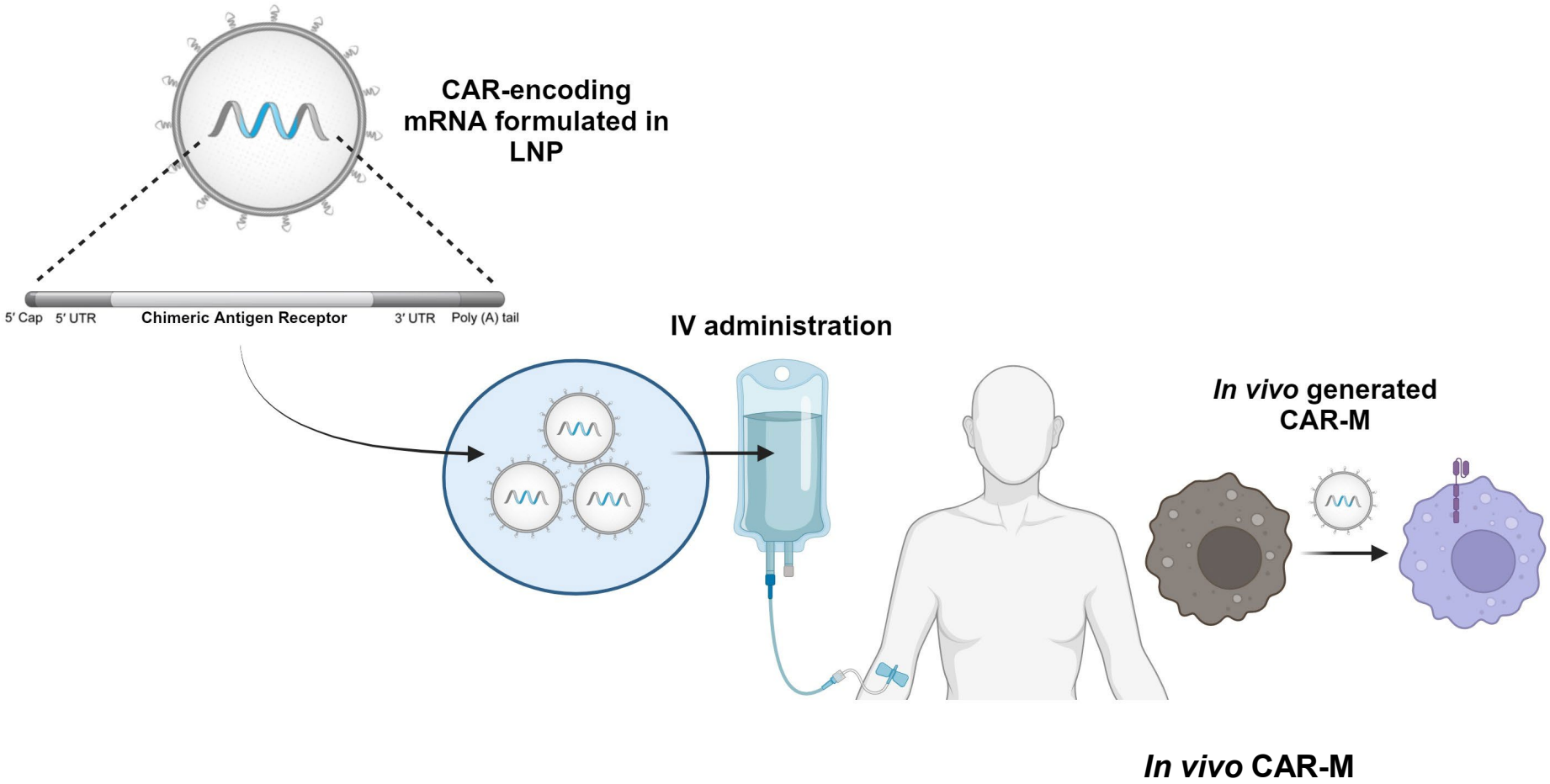
MECHANISM OF ACTION

- CT-0508 tumor infiltration detected
- TME remodeling correlates with clinical outcome
- T cell expansion and fitness correlates with clinical outcome
- Exhausted T cells increase on treatment

CT-0508 + Keytruda® (pembrolizumab) Phase I safety study enrolling in US

Directly Reprogramming Myeloid Cells *In Vivo* with mRNA/LNP

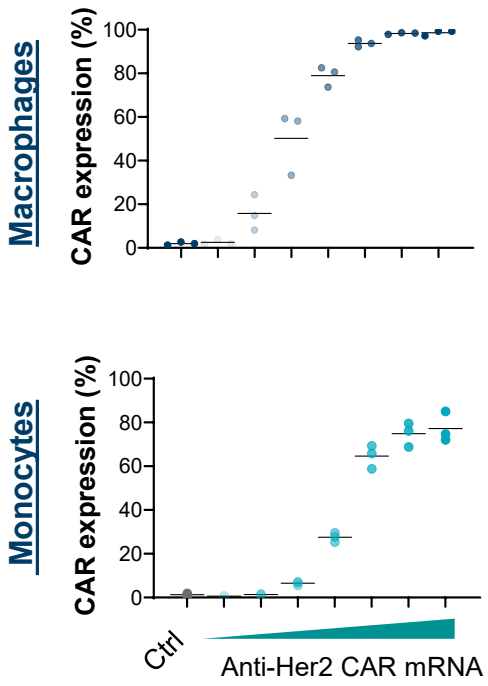
Redirecting endogenous myeloid cells with mRNA for cancer immunotherapy



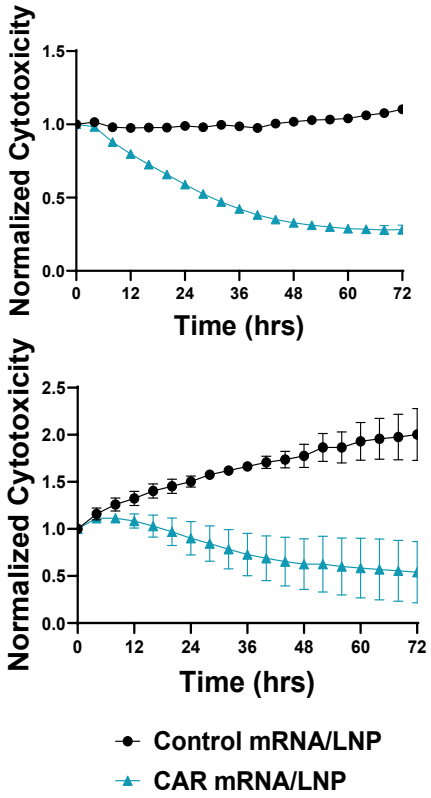
mRNA/LNP transfection generates highly functional CAR-M

Human macrophages and monocytes engineered with CAR-encoding mRNA/LNP *in vitro* demonstrated high CAR expression and antigen specific killing of tumor cells in 2D and 3D.

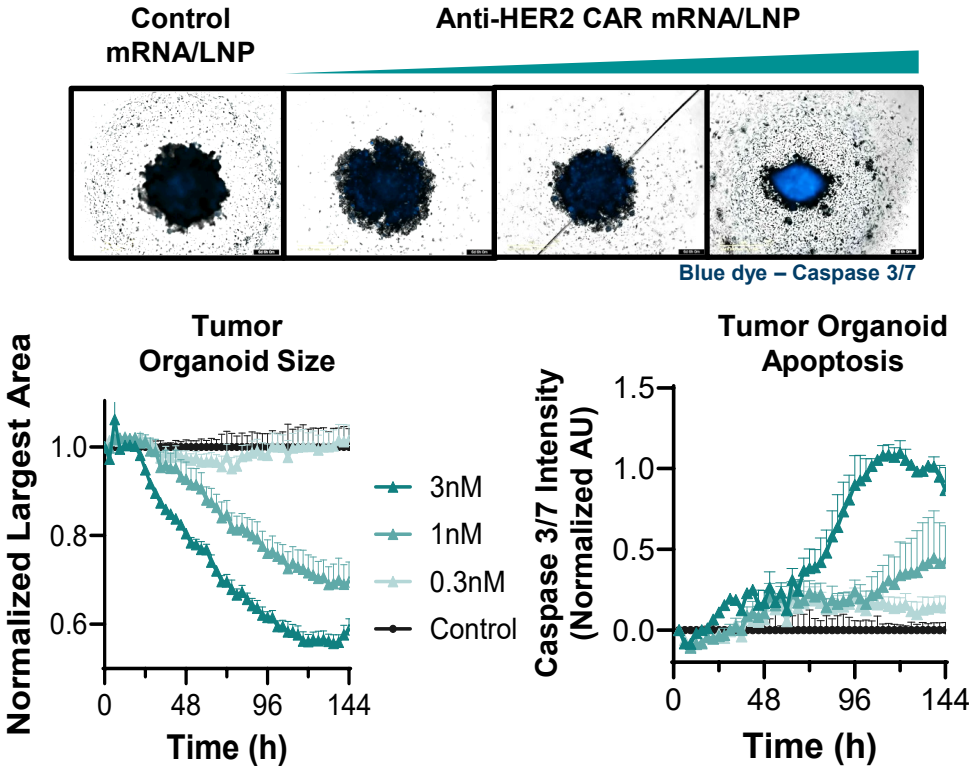
CAR Expression



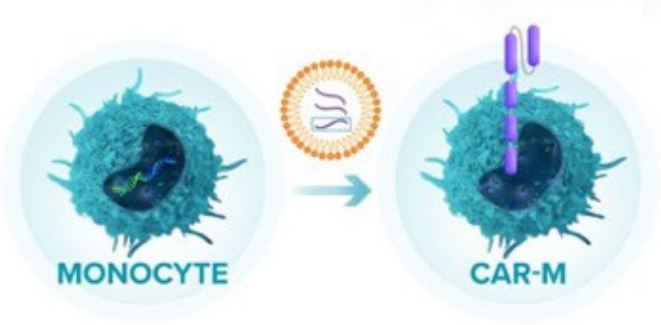
Tumor Killing

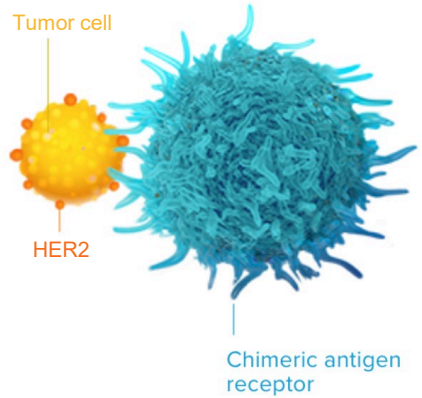


In Situ Reprogrammed TAMs Shrink Tumor Spheroids

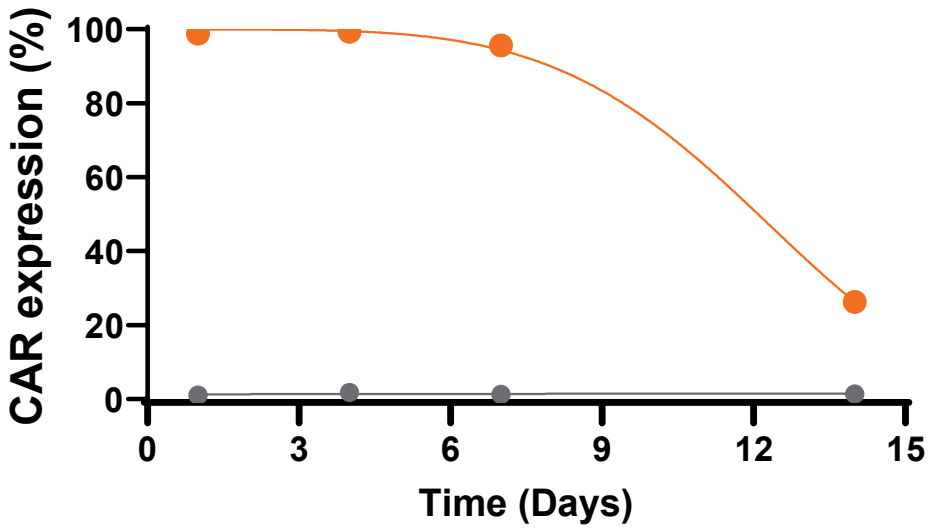


CAR expression and serial killing capacity following a single mRNA/LNP CAR transfection

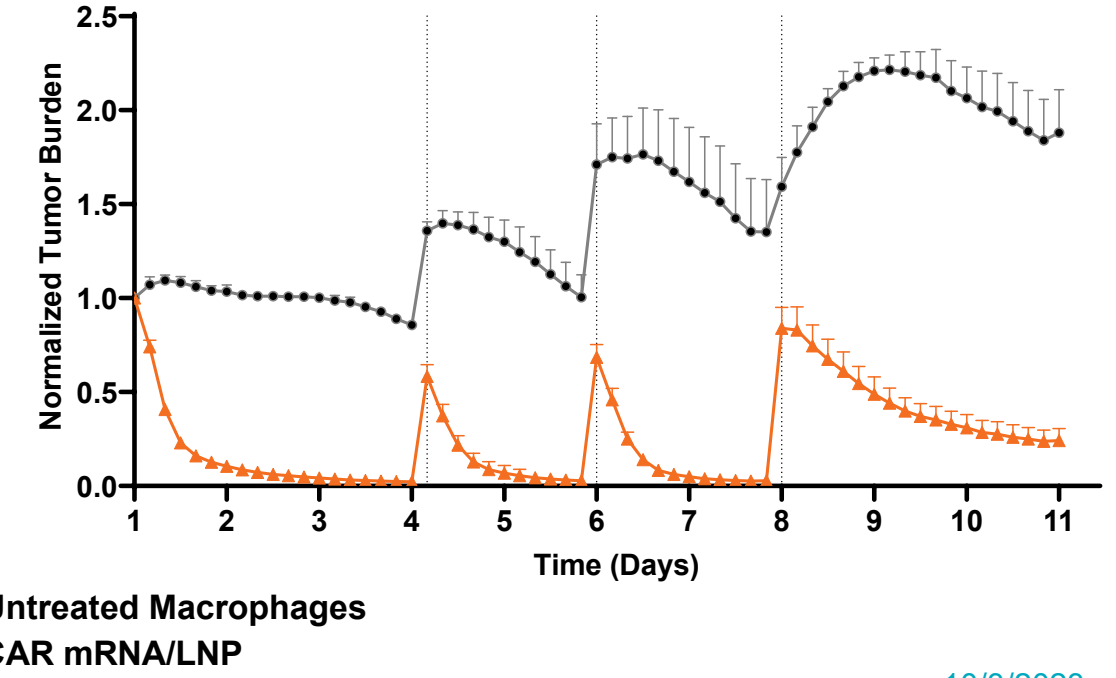




CAR Persistence Following Single Transfection



Serial Killing of HER2+ AU565 Breast Cancer Cells



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mRNA/LNP transfection generates highly functional CAR-M

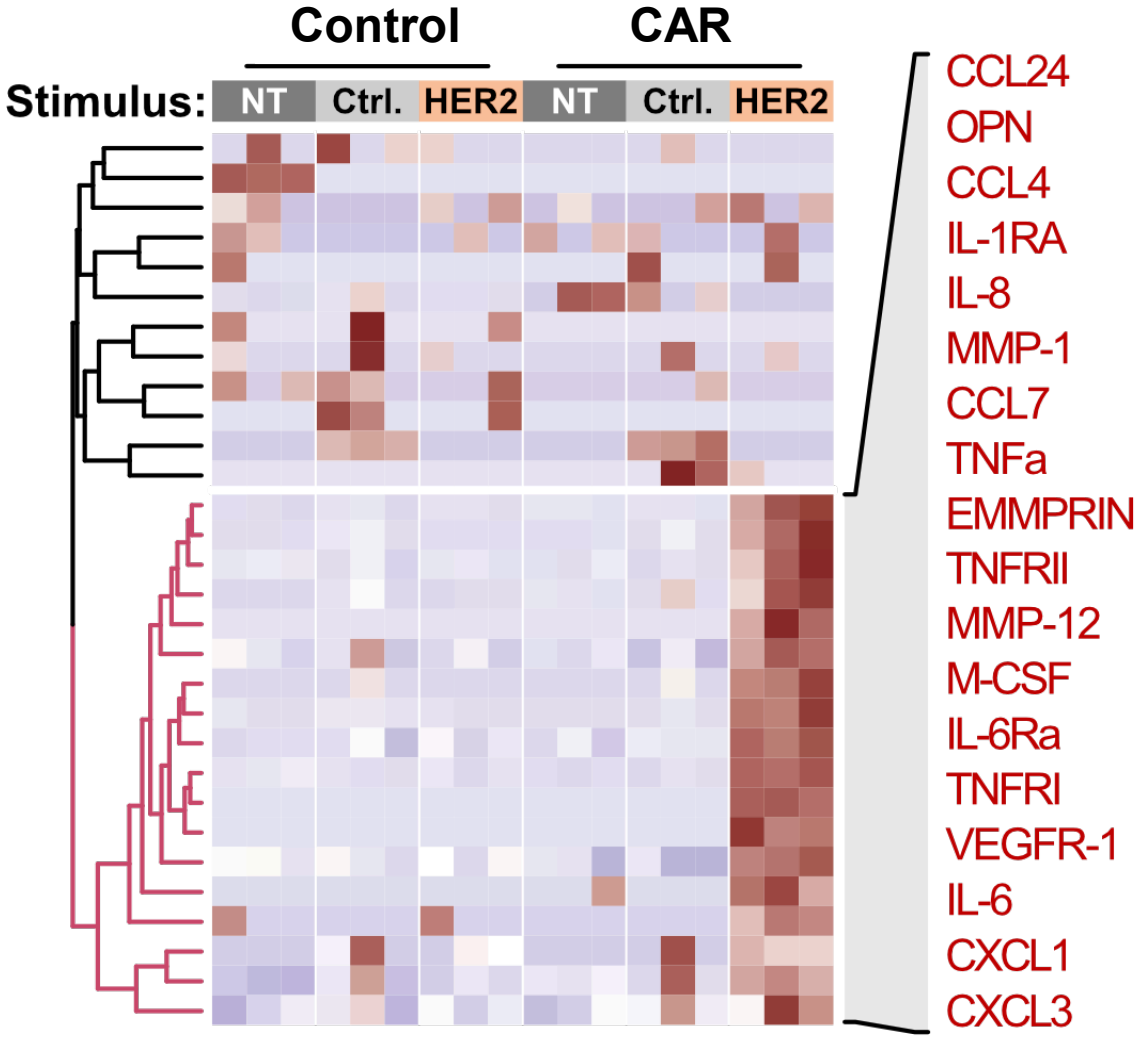
Antigen dependent CAR signaling leads to broad proinflammatory cytokine secretion

+

No Treatment (NT)

Control Ag MSLN (Ctrl)

Target Ag HER2 (HER2)



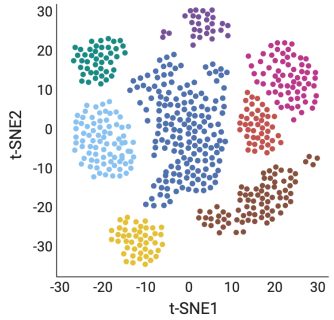
CAR engagement leads to CAR-M M1 polarization

+

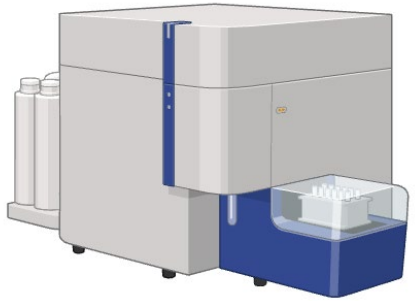
Control Ag MSLN (Ctrl)

Target Ag HER2 (HER2)

RNA Sequencing



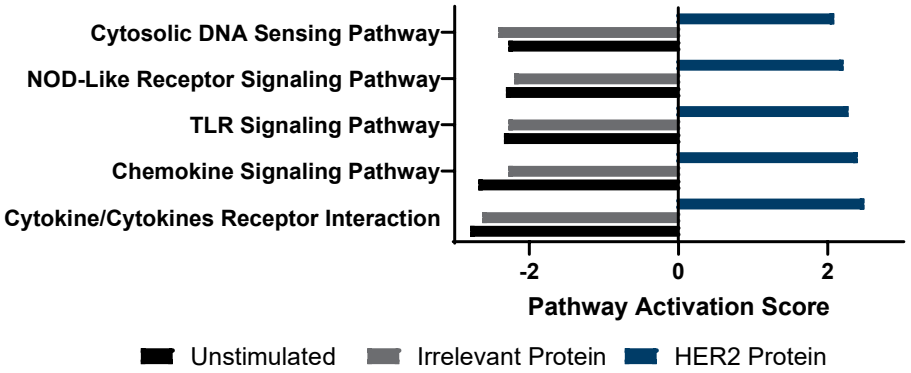
FACS



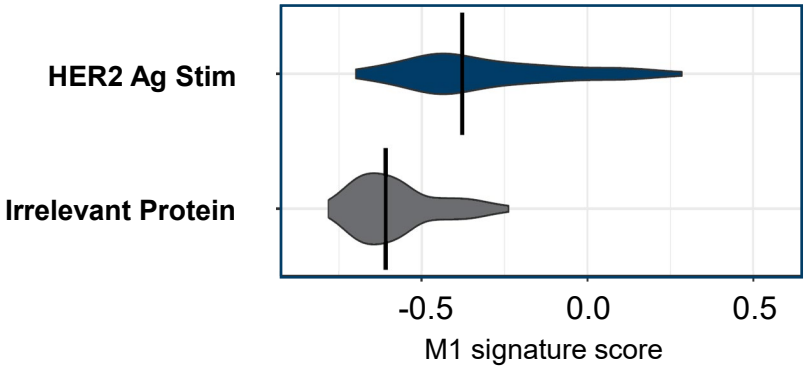
M1 / M2 Analysis

RNA-Sequencing Analysis of M1 Macrophage Gene Expression

CAR signaling activates pro-inflammatory pathways

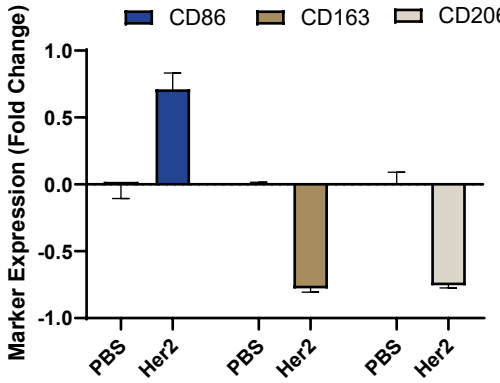


CAR signaling enhances M1 signature score



M1/M2 Surface Markers

Increased M1 & Decreased M2 Markers



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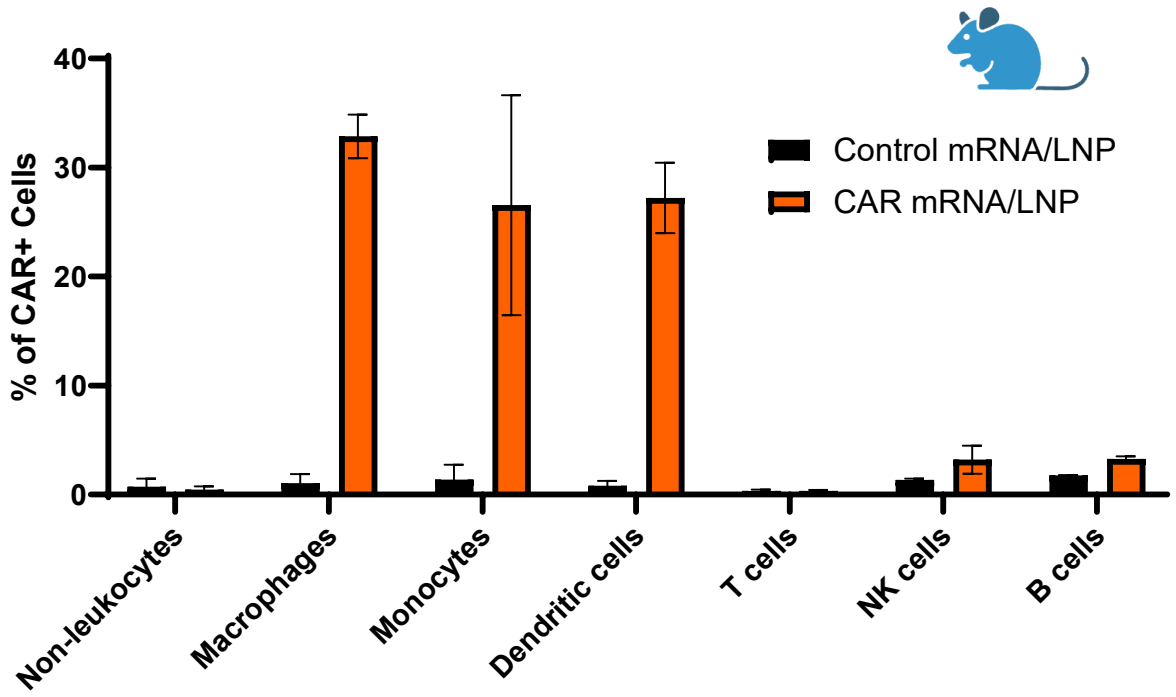
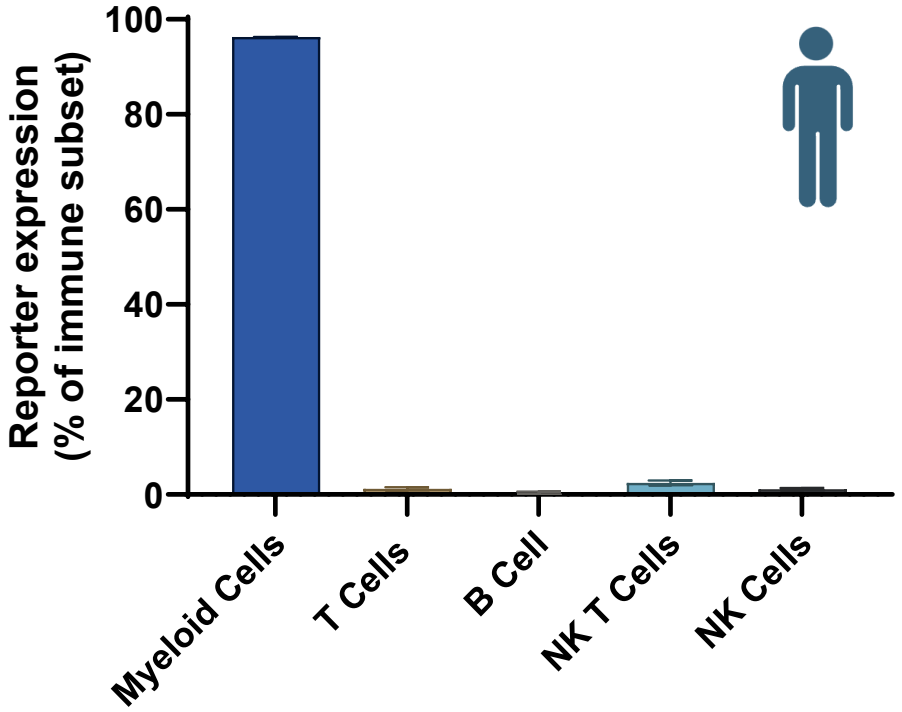
Systemic CAR mRNA/LNP administration leads to preferential expression in myeloid cells *in vivo*

Significant CAR expression observed in macrophages, monocytes, and dendritic cells

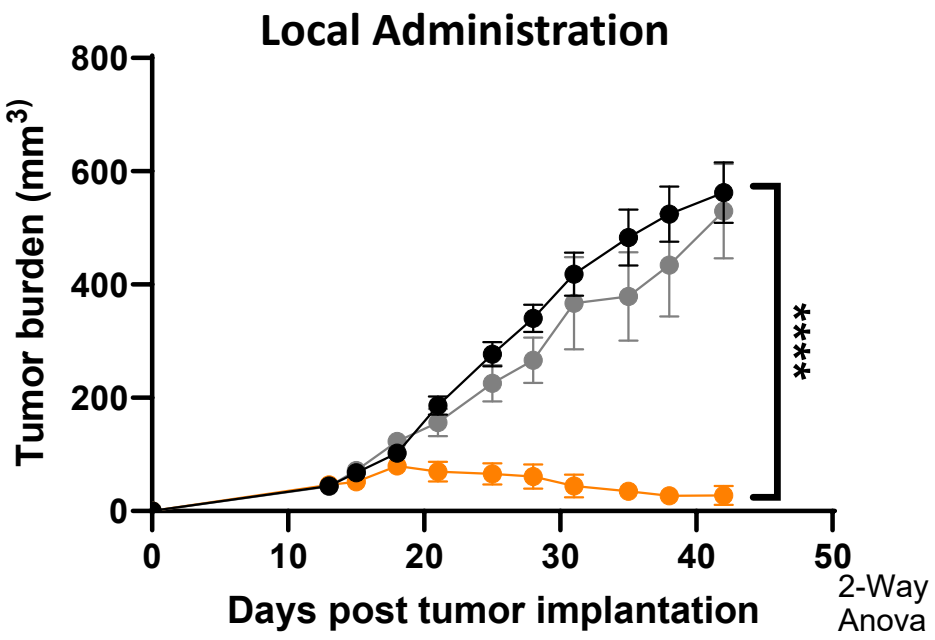
CAR Distribution *in vivo* (Mouse Blood)

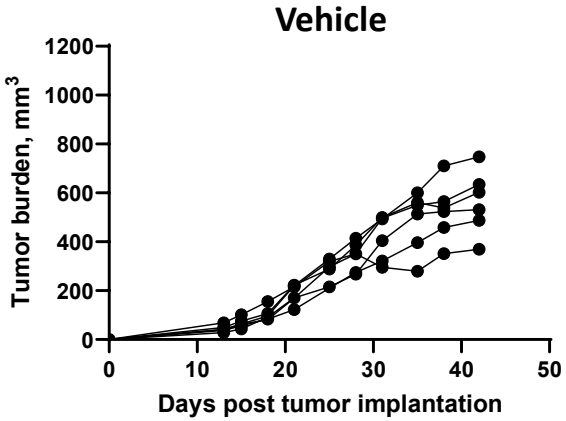


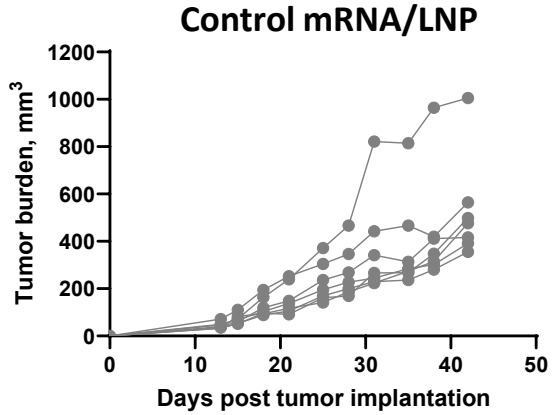
CAR Expression *in vitro* (Human PBMC)

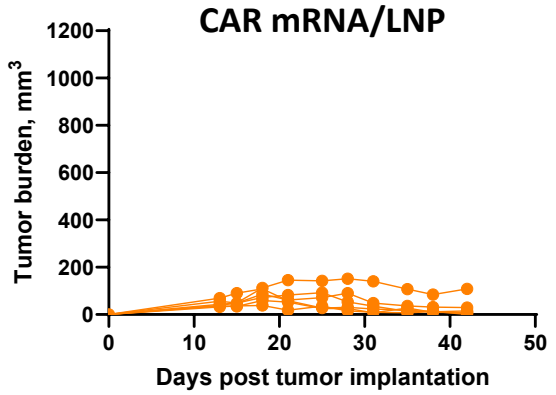


Local administration of CAR mRNA/LNP in humanized mice leads to significant solid tumor control









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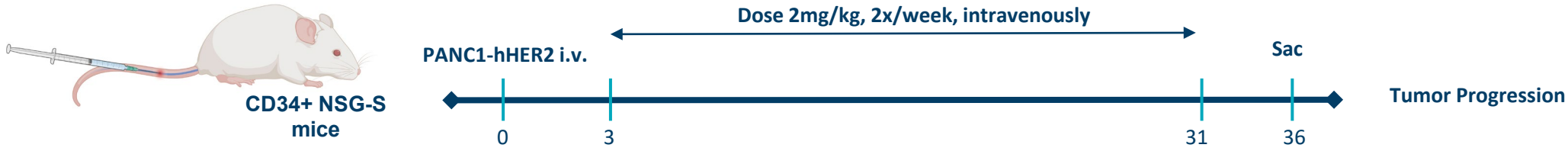
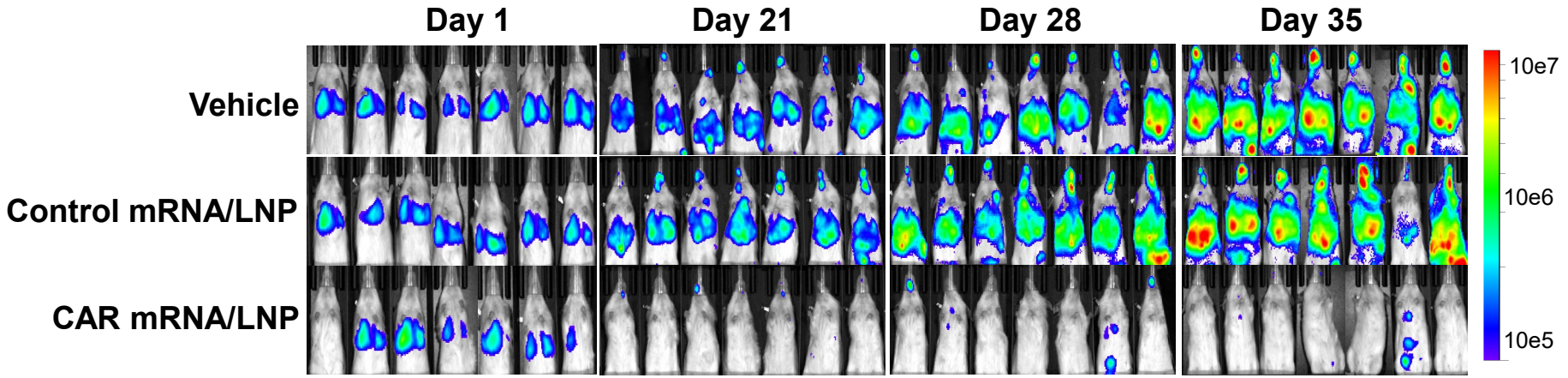
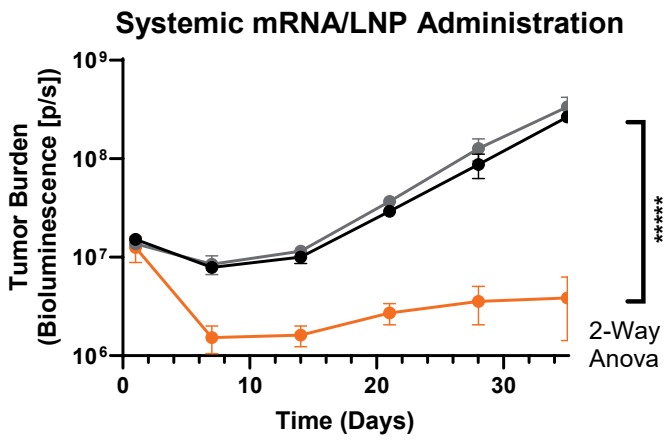
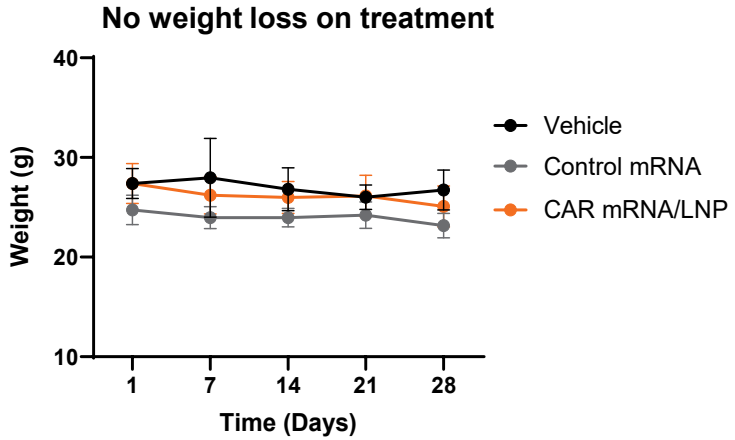
Intravenous administration of CAR mRNA/LNP leads to suppression of metastatic pancreatic tumor growth









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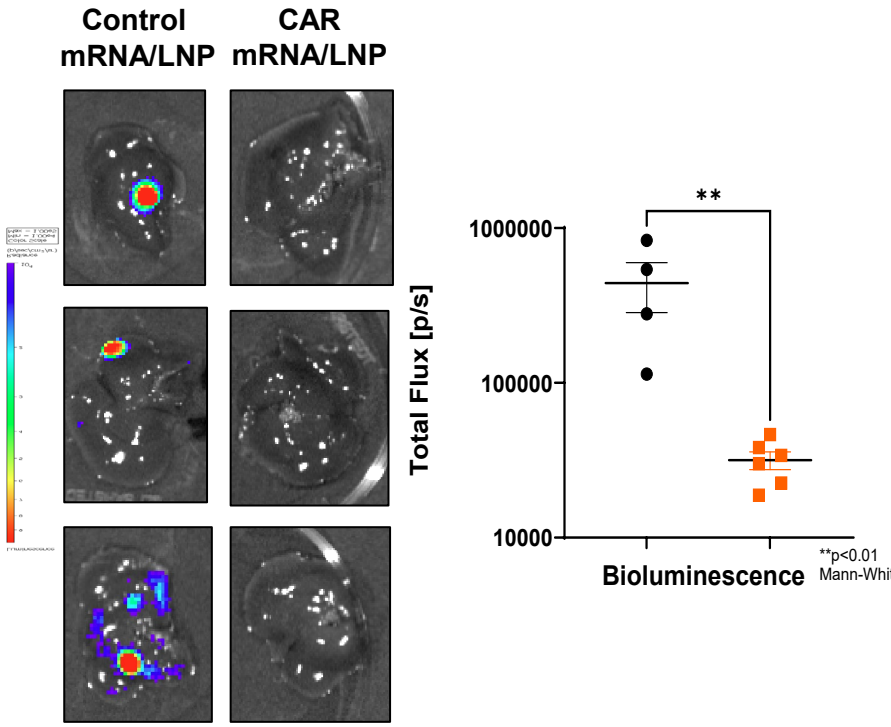
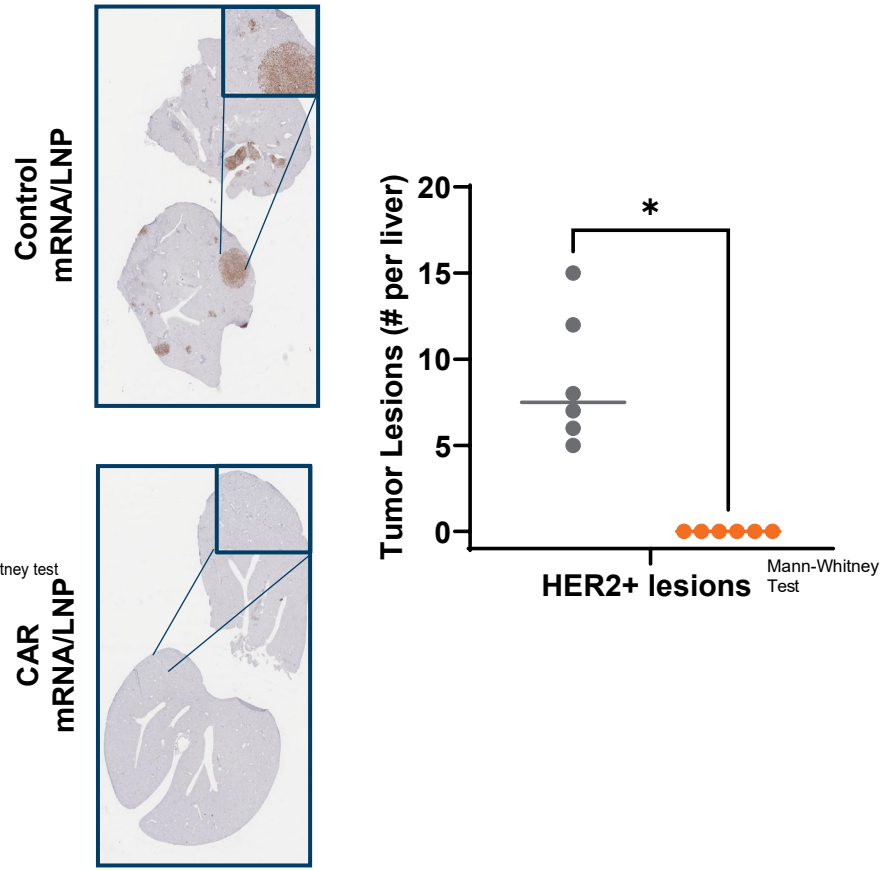
Intravenous delivery of CAR mRNA/LNP clears liver metastasis and reduces lung metastasis

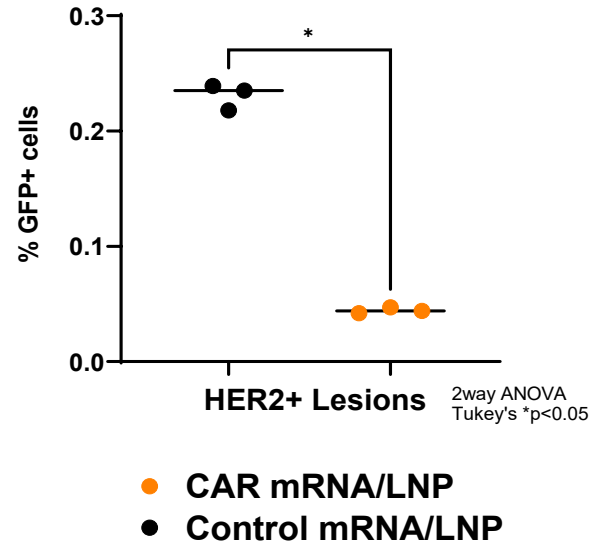
Tumor Lesions in Liver (BLI)



Tumor Lesions/Liver (IHC)

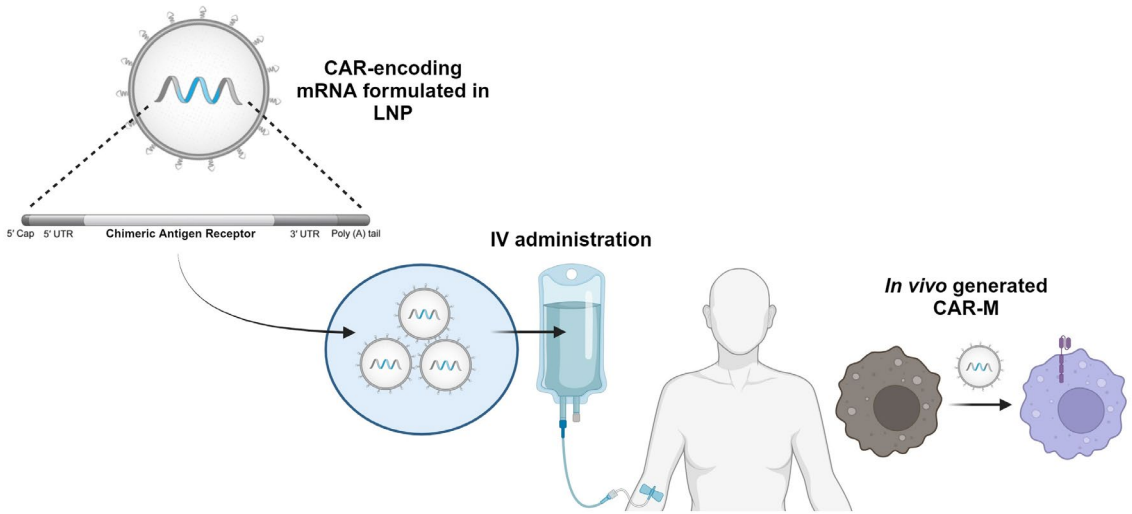


Tumor Lesions in Lung (IHC)



In Vivo CAR-M: A novel cancer immunotherapy platform

Redirecting endogenous myeloid cells with mRNA for cancer immunotherapy



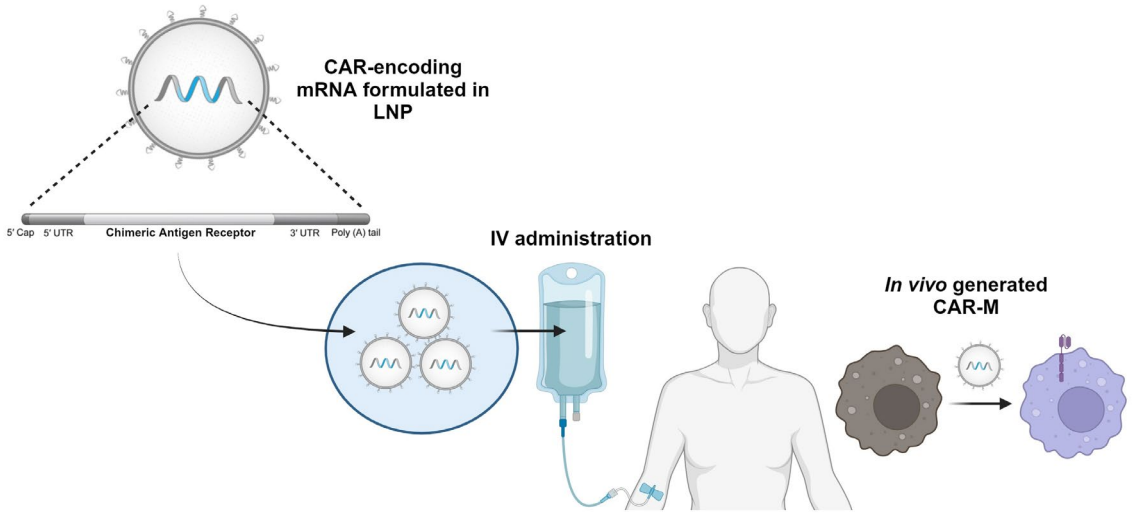
***In vivo* CAR-M**

Summary and Key Takeaways

- ✓ mRNA/LNP CAR-M are highly functional
- ✓ CAR-M demonstrate targeted killing and secrete a broad array of inflammatory mediators
- ✓ CAR engagement polarizes CAR-M toward M1 phenotype
- ✓ Robust transfection of CAR+ myeloid cells in vivo w/minimal transfection of non-myeloid cells
- ✓ In Vivo CAR-M controls tumors upon regional or systemic administration and clears metastasis
- ✓ In Vivo CAR-M well tolerated in pre-clinical models

In Vivo CAR-M: A novel cancer immunotherapy platform

Redirecting endogenous myeloid cells with mRNA for cancer immunotherapy



***In vivo* CAR-M**

Key Advantages

- ✓ Off-the-shelf
- ✓ Full MHC matching (redirecting patient's own cells)
- ✓ Non-viral, mRNA-based platform
- ✓ Ability to re-dose to maintain pharmacologic pressure
- ✓ Robust platform that can be developed against diverse tumor antigens/indications

- ✓ **Benefits of CAR-M therapy:**
  - Targeted anti-tumor activity
  - Tumor infiltration
  - TME activation
  - T cell recruitment
  - Epitope spreading

Acknowledgements

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Stefano Pierini, Asen Bagashev, Yumi Ohtani, Rashid Gabbasov, Kayleigh Ross, Shuo Huang, Amanda Bona, Sherly Mardiana, Kate Slovik, Alison Worth, Karan Nagar, Robert Saporito, Chris Sloas, Michael Ball, Rehman Qureshi, Nicholas Minutolo, Kevin Tosh, Claudia Lee, Louise Calabretta, Sascha Abramson, Michael Klichinsky, Thomas Condamine

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Simone Mori, Christine Lukacs, Kate Jeffrey, Tatiana Novobrantseva, Lin Guey

THANK YOU

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