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# Pioneering Engineered Macrophage Therapeutics

**January 2025**

# Cautionary Note Regarding Forward-Looking Statements

Statements in this slide deck about future expectations, plans and prospects, as well as any other statements regarding matters that are not historical facts, may constitute “forward-looking statements” within the meaning of The Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, statements relating to Carisma’s business, strategy, future operations, cash runway, the advancement of Carisma’s product candidates and product pipeline, and clinical development of Carisma’s product candidates, including expectations regarding timing of initiation and results of clinical trials. The words “anticipate,” “believe,” “contemplate,” “continue,” “could,” “estimate,” “expect,” “goals,” “intend,” “may,” “might,” “outlook,” “plan,” “project,” “potential,” “predict,” “target,” “possible,” “will,” “would,” “could,” “should,” and similar expressions are intended to identify forward-looking statements, although not all forward- looking statements contain these identifying words.

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# Directing Macrophage Function Through Genetic Engineering

## Targeting meaningful therapeutic outcomes across a wide spectrum of disease

| Macrophage Function | Therapeutic Objective | Carisma Platform | Indication |
|---|---|---|---|
| **Targeted Phagocytosis and Immune Activation** | Cancer cell depletion<br>Long-lasting immunity | CAR-M | Oncology |
| **Efferocytosis** | Anti-Fibrotic<br>Tissue Repair | TIM4 | Liver Fibrosis |
| **Immunosuppression** | Reduce inflammation | CAR-M | Autoimmune Disease |

**Harnessing the power of macrophages**

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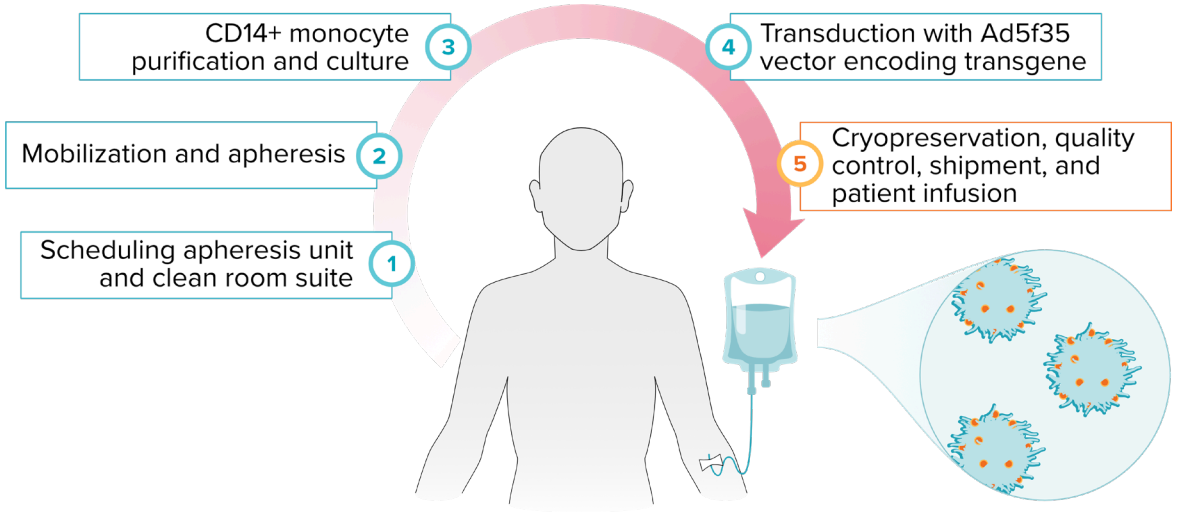
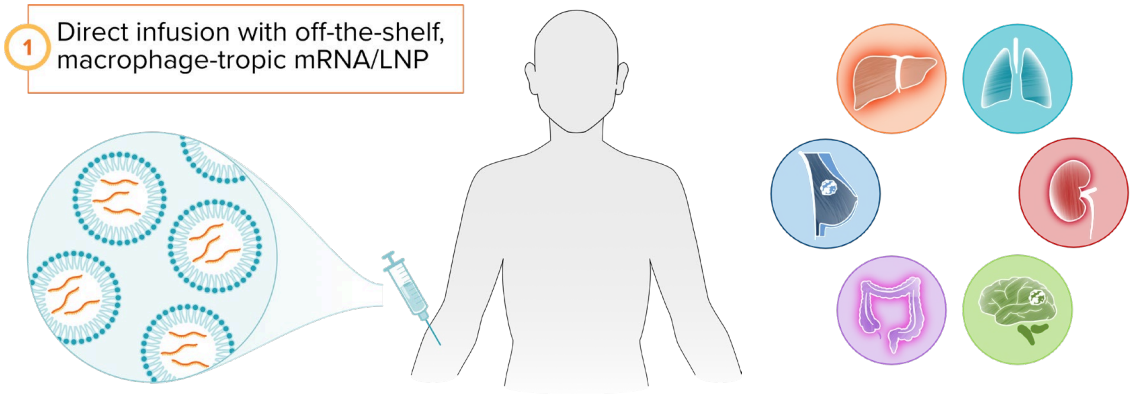
CAR-M: chimeric antigen receptor monocytes and macrophages; TIM4: T-cell immunoglobulin domain and mucin domain-4

# Two Distinct Approaches to Macrophage Based Therapeutics

## *ex vivo* Engineered Macrophages




## *in vivo* Macrophage Reprogramming




**Redefining the future of macrophage-based therapies**

*Decreased complexity, decreased cost, increased convenience*

# First-in-Class Pipeline

## Multiple value inflection points across therapeutic areas and modalities

| PRODUCT CANDIDATE | INDICATION | PLATFORM | DISCOVERY | PRE-CLINICAL | PHASE 1 | PHASE 2 | PHASE 3 | PARTNER |
|---|---|---|---|---|---|---|---|---|
| **Oncology** | | | | | | | | |
| CT-1119[1] | Mesothelin+ solid tumors | CAR-Monocyte (Autologous) | | | Next milestone: Phase 1 Trial initiation 1H 2025. Initial data 4Q 2025[2] | | | |
| Target #1 | GPC3+ solid tumors[3] | *In Vivo* CAR-M | | | Next milestone: IND filing[2] (Undisclosed) | | | moderna |
| 4 Nominated Targets | Undisclosed[3] | *In Vivo* CAR-M | | | Next milestone: Lead nomination / Development Candidate[2] (Undisclosed) | | | moderna |
| **Fibrosis** | | | | | | | | |
| CT-2401 | Liver Fibrosis | *In Vivo* TIM4 | | | Next milestone: Development candidate nomination[2] (1Q 2025, Regulatory submission in 2026) | | | |
| **Autoimmunity** | | | | | | | | |
| 2 Nominated[4] Targets | Autoimmune Disease | *In Vivo* CAR-M | | | Next milestone: Lead nomination[2] (Undisclosed) | | | moderna |

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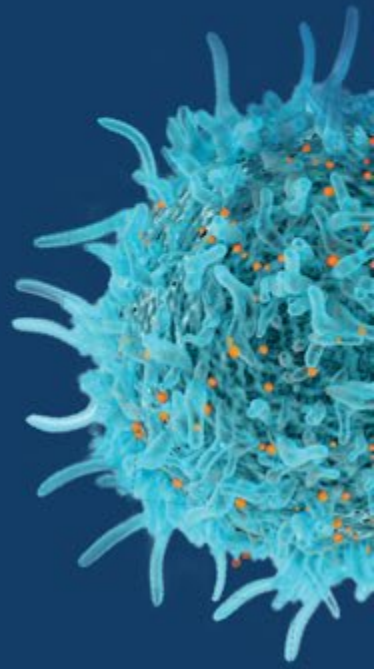
1. Includes next generation CAR and SIRPα knockdown technology; 2. Anticipated milestones 3. Moderna collaboration has nominated 5 total oncology targets, with the option to nominate an additional 5 oncology targets. First Development Candidate was nominated in 2Q 2024; 4. Carisma retains all rights in autoimmune disease beyond the two nominated targets exclusively partnered with Moderna. GPC3:Glypican-3

# CT-1119:
# Next-Gen CAR-M Phase 1 Trial

Anti-mesothelin CAR monocyte w/ next-gen CAR and anti-SIRPα shRNA for patients with mesothelin positive solid tumors



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# CT-1119: Building on the HER2 CAR-M Experience

## HER2 Program: Key Findings[1]

- Well tolerated, no severe CRS
- Deep reduction in ctDNA in HER2 3+ patients indicating clinical activity
- TME remodeling & anti-tumor T cell induction observed
- Monocyte approach improved yield, manufacturing, & potentially trafficking, & persistence[2]
- Pharmacokinetics suggest redosing every 3 weeks is the optimal regimen
- Baseline T cell exhaustion reduced efficacy suggesting combination with anti-PD1
- Future commercial and development challenges due to HER2 loss in >60% of patients post Enhertu led to discontinuation of HER2 program

## CT-1119 Opportunity

- **Enhanced CAR potency:** next gen CAR plus anti-SIRPα shRNA to overcome CD47 checkpoint
- **Improved** trafficking, persistence & repeat dosing[3] (every 3 weeks)
- **Combination** with anti-PD1 (tislelizumab)
- **Mesothelin** is highly expressed in solid tumors and is not lost in heavily pre-treated patients
- **Cost-effective and rapid** Phase 1 program planned in China

CRS: Cytokine Release Syndrome; TME: Tumor Microenvironment; 1. Based on results from CT-0508 study; 2: Based on pre-clinical CT-0525 data; 3. Based on preclinical studies

# CT-1119: Efficient Pathway to Clinical POC with Next-Generation CAR-M

Program wholly owned by Carisma

## Key Highlights

**Significant** unmet need, no approved anti-mesothelin therapies

**Highly expressed in** ovarian, pancreatic, lung, and other solid tumors

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**Research collaboration with CellOrigin** to conduct a Phase I Trial in China

Cost effective clinical program with rapid development plan to generate PoC data

Program **wholly owned** by Carisma

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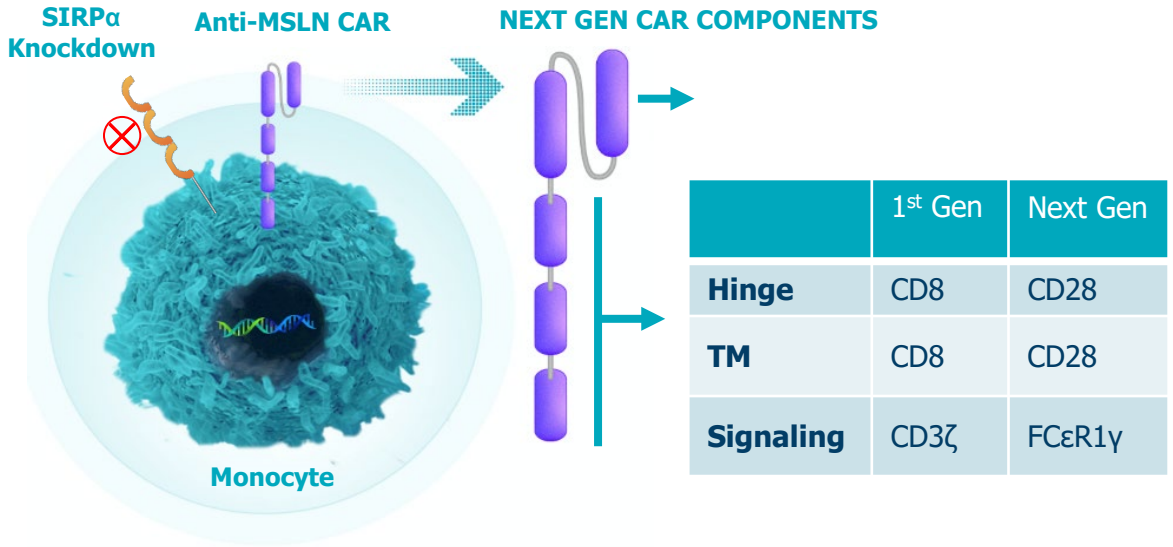
Phase 1 trial expected to be initiated in **1H 2025**

Initial **clinical data** expected **Q4 2025**




| | 1st Gen | Next Gen |
|---|---|---|
| **Hinge** | CD8 | CD28 |
| **TM** | CD8 | CD28 |
| **Signaling** | CD3ζ | FCεR1γ |

| CT-1119: Key Parameters | |
|---|---|
| **Cells** | Autologous monocytes |
| **Vector** | Ad5f35 |
| **Phenotype** | M1 (pro-inflammatory) |
| **CAR** | Next Generation Myeloid CAR |
| **Targeting Domain** | M15 humanized scFv |
| **Other Enhancements** | SIRPα knockdown to overcome the inhibitory CD47/SIRPα axis that limits CAR-M activity |
| **Manufacturing Time** | 1 day |

# CT-1119: Anticipated Phase 1 Study Design

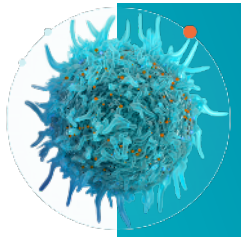
## Repeat CAR-Monocyte dosing in combination with anti-PD1

Mesothelin positive solid tumors (n=12)

→ G-CSF mobilization and apheresis, CT-1119 manufacturing, bridging therapy, baseline staging

→ **CT-1119:** Q3W for up to 5 cycles (up to 2 x $10^9$ CAR+ cells per infusion) with concurrent tislelizumab (anti-PD1)

→ Evaluate safety, tolerability, pharmacokinetics, clinical response (imaging, ctDNA, biomarkers), correlative studies



**PRIMARY OUTCOMES**

- Safety and tolerability

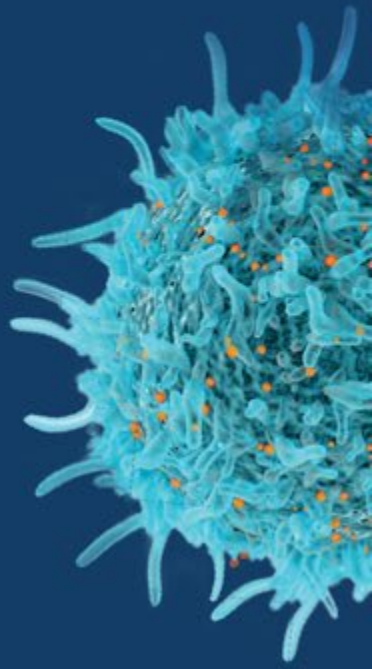
**SECONDARY OUTCOMES & ADDITIONAL ANALYSES**

- ORR (RECIST 1.1)
- PFS
- Trafficking
- TME activation
- T cell recruitment/activation
- T cell expansion/clonality

**Phase 1 trial expected to be initiated in 1H 2025; Initial data anticipated 4Q 2025**

Trial will be conducted in Zhejiang University in Hangzhou, China under a Research Collaboration Agreement with CellOrigin; ORR: Objective Response Rate; PFS: Progression-Free Survival; Q3W: Every-Three-Week.

# *In Vivo* CAR-M: Oncology & Autoimmune Disease



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# Driving Innovation through Strategic Collaboration

Collaboration with Moderna to discover, develop & commercialize *in vivo* CAR-M in oncology & autoimmune disease

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- ✓ Combines Carisma's **CAR macrophage** technology with Moderna's **mRNA/LNP** platform
- ✓ Robust platform with applications in **diverse oncology and autoimmune indications**
- ✓ **Off-the-shelf** product with ability to **redose**
- ✓ **Robust** anti-tumor activity observed in preclinical studies

**Research fully funded by Moderna**

**$3B in potential milestones + royalties**



Moderna has nominated four undisclosed oncology research targets under the collaboration and has the right to designate up to ten oncology targets as development targets and two autoimmune disease targets

# Glypican-3 (GPC3): A validated target in HCC

## HCC remains an area of significant unmet medical need

**HCC overview**:

- **>40,000 new cases** in the US in 2024**, and the 2nd leading** cause of cancer-deaths worldwide[1,2]
- **22% 5-year** survival for all HCC cases; **3.5% 5-year** survival for advanced HCC[1]

### GPC3

- GPC3 is a cell surface tumor-associated antigen
- Overexpressed in 70-80% of HCC cases, linked to poor prognosis[2]
- Silenced postnatally, minimally expressed in healthy tissues[2]
- Safety demonstrated with antibodies, ADCs, and CAR-T cells[2]
- No approved GPC3-targeted therapies

### Development Candidate

- Direct *in vivo* CAR-M utilizing mRNA/LNP encoding a novel, next-gen CAR targeting GPC3
- Preclinical data demonstrated that anti-GPC3 CAR mRNA/LNP induced robust anti-tumor activity in humanized metastatic solid tumor model[3]

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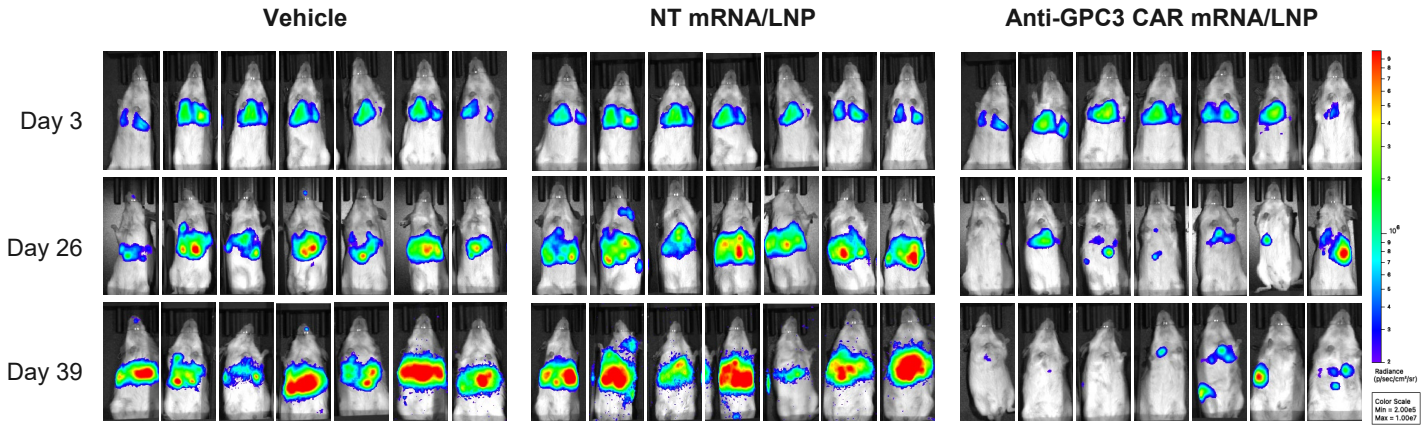
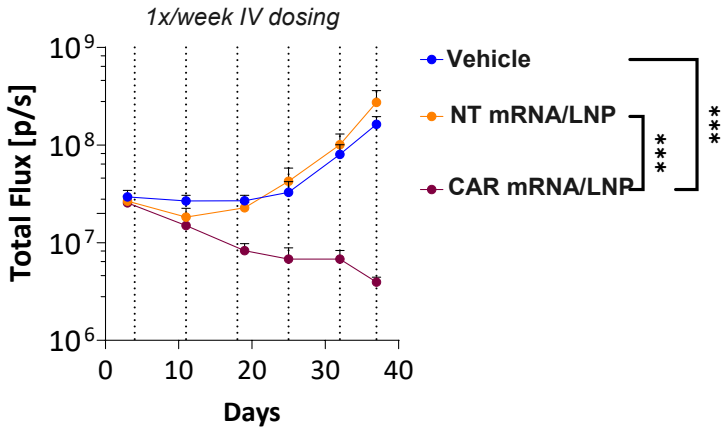
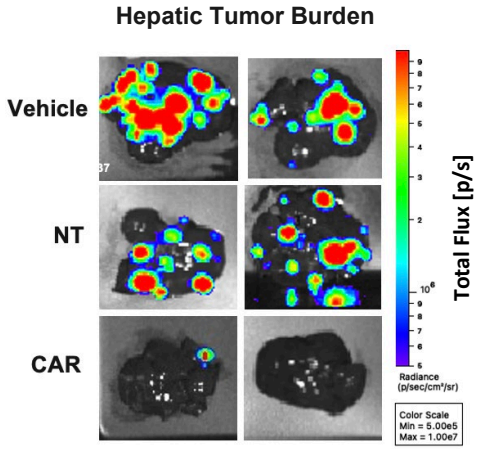
HCC: Hepatocellular carcinoma; SITC: Society for Immunotherapy of Cancer; 1. SEER Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. National Cancer Institute; 2. Guo M, Zhang H, Zheng J, Liu Y. Glypican-3: a new target for diagnosis and treatment of hepatocellular carcinoma. J Cancer. 2020;11(8):2008-2021; 3: Bagashev A, et al. SITC 2024.

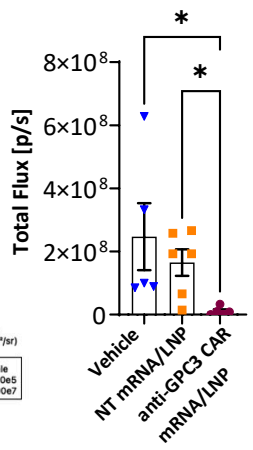
# Anti-GPC3 *In Vivo* CAR-M Induced Robust Anti-Tumor Activity*

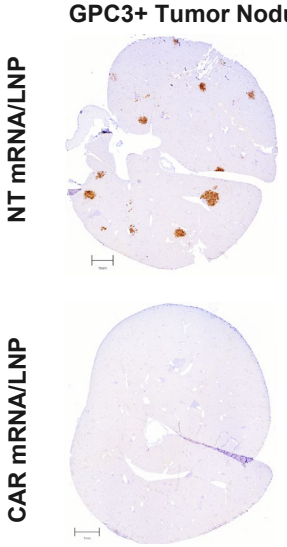
## Advanced/metastatic HCC remains an area of significant unmet medical need

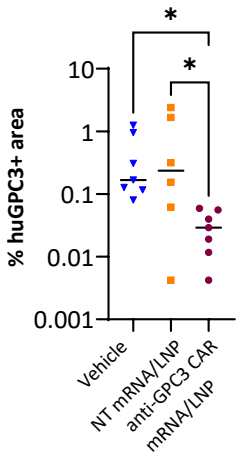



**1**. Systemic administration of anti-GPC3 CAR mRNA/LNP once per week **induced robust anti-tumor** activity in a humanized metastatic solid tumor model (top panel)

**2**. Hepatic tumor burden was significantly reduced by anti-GPC3 CAR mRNA/LNP treatment based on bioluminescence (bottom left) and GPC3 liver IHC at study termination (bottom right)

1: Bagashev A, et al. SITC 2024.; HCC: Hepatocellular carcinoma;; NT: Non-translating control; CAR: Chimeric antigen receptor; GPC3: glypican-3; *Pre-clinical data; IHC: immunohistochemistry

# Carisma/Moderna Collaboration: Key Next Steps

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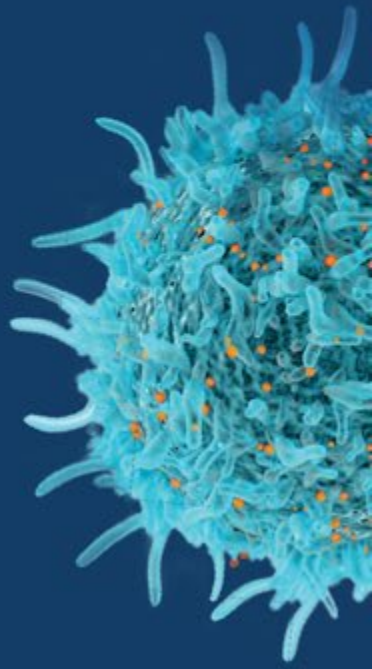
| | | |
|---|---|---|
| **Advance lead program,** anti-GPC3 *in vivo* CAR-M, into the clinic | **Advance 4 additional nominated** *in vivo* CAR-M oncology targets | **Advance 2 nominated** *in vivo* CAR-M autoimmune disease programs |

# CT-2401: Direct *In Vivo* Macrophage Engineering for Liver Fibrosis



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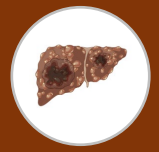
# Anti-Fibrotic Therapy in Advanced Fibrosis and Cirrhosis Represents A Major Unmet Need

| Fibrosis Stage | | | MASH Patients (US, 2030)[1] |
|---|---|---|---|
| F0 | No Fibrosis |  | 3.9M |
| F1 | Mild Fibrosis |  | 9.0M |
| F2 | Moderate Fibrosis |  | 6.1M |
| F3 | Advanced Fibrosis |  | 4.5M |
| F4 | Cirrhosis |  | 3.5M |

## Poor Survival

- Fibrosis stages F3 and F4 are associated with increased risks of liver-related complications, decompensation events, HCC, and death[2]

## Limited Therapeutic Options

- Only currently available therapy for F4 is liver transplant
- Resmetirom placebo-adjusted anti-fibrotic activity only seen in 10-12% of patients w/ F2-F3 fibrosis
- No added anti-fibrotic benefit from resmetirom/GLP-1 combination[3]
- FGF21 agonists (pegozafermin, efruxifermin) have shown placebo-adjusted anti-fibrotic activity in 20% of patients

## Growing Prevalence

- Patients staged as F4 are expected to represent ~20% of all MASH patients by 2030[1]
- Costs attributable to treatment of MASH are expected to reach $81.3B by 2030[4]

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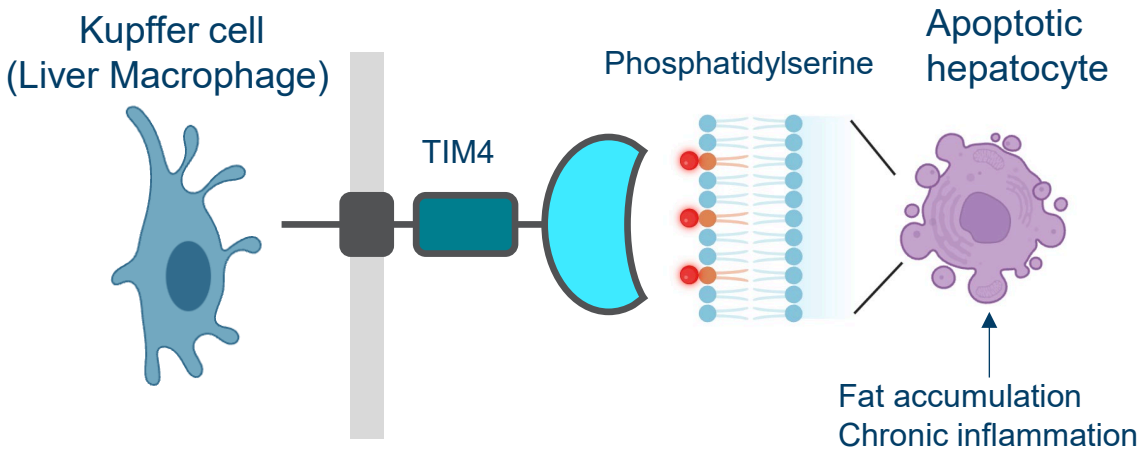
1: Estes C, et al. Hepatology. 2018. 2: Sanyal A, et al. N Engl J Med 2021. 3: Noureddin M, et al. AASLD 2024. 4: Younossi Z, et al. Clin & Exp Hepatology 2023.; MASH: Metabolic dysfunction-associated steatohepatitis

# TIM4, a key macrophage efferocytosis receptor, is lost in MASH

Efferocytosis is the normal clearance process for dead and dying (apoptotic) cells

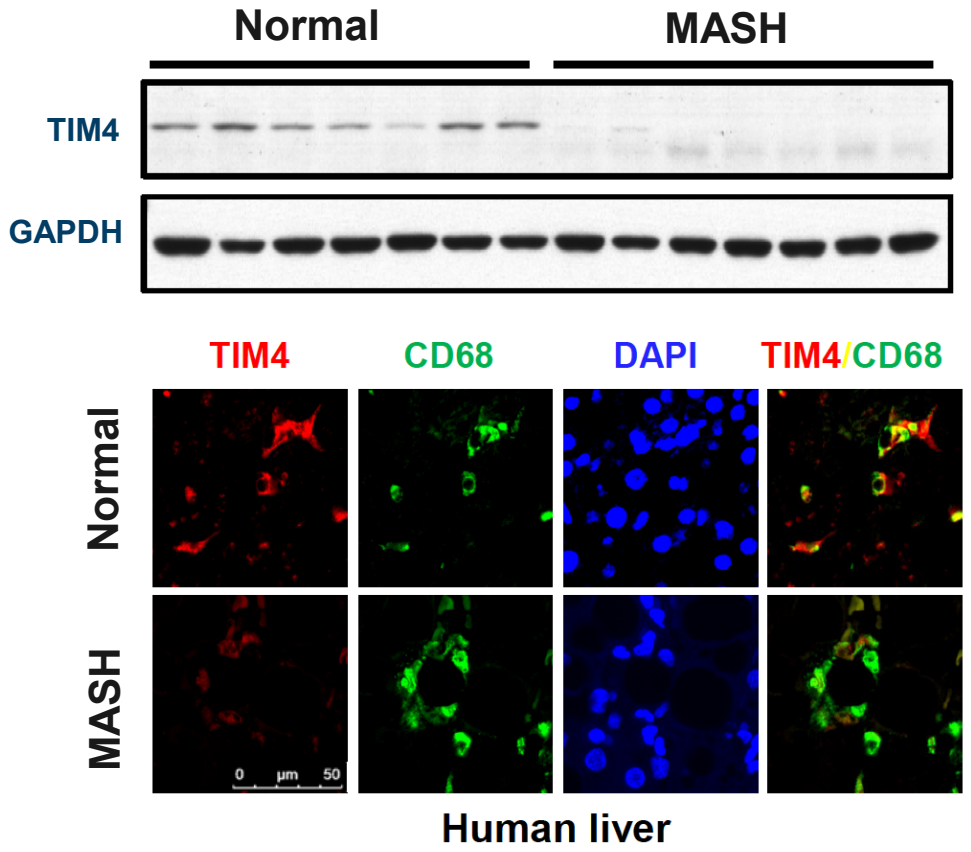
## TIM4 binds phosphatidylserine on apoptotic cell surface to drive efferocytosis




## Loss of TIM4 induces:

- Impaired clearance of apoptotic hepatocytes
- Hepatic stellate cell activation
- Increased fibrosis and inflammation
- Impaired tissue repair

## Loss of TIM4 in MASH patient liver

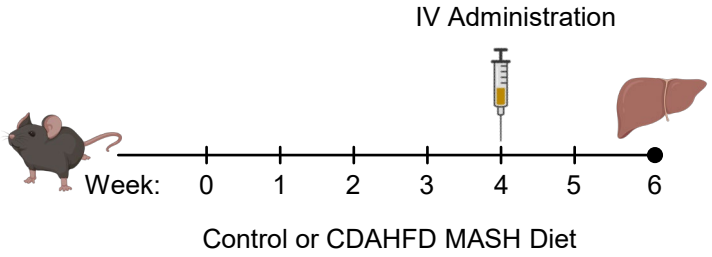




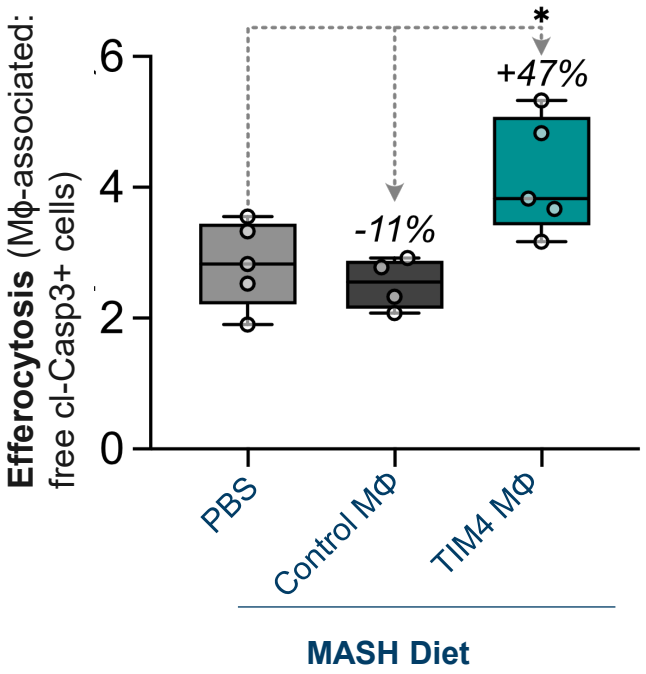

Shi H, et al. Loss of TIM4-Dependent Efferocytosis in Kupffer Cells Promotes Liver Fibrosis in Nonalcoholic Steatohepatitis. *Biorxiv.* 2024.

# A Single Dose of Engineered Macrophages Significantly Reduced Liver Fibrosis[1]

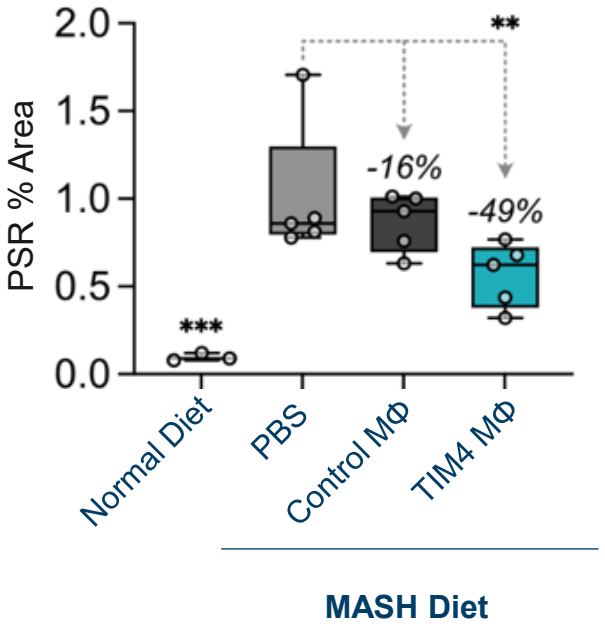
## Experiment Design




## Hepatic Efferocytosis: ↑47%




## Fibrosis: ↓49%




## Key Takeaways:

**Fibrosis:**
- **49%** reduction in collagen

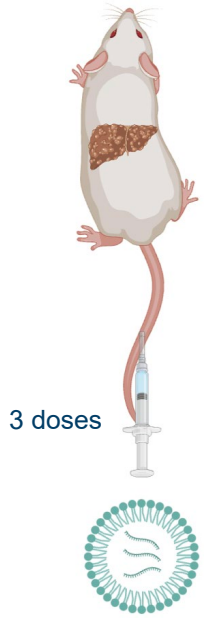
**Efferocytosis:**
- **47%** increases in efferocytosis

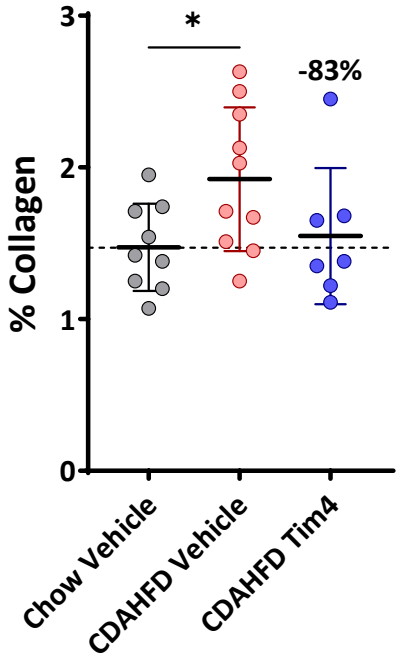
**TIM4 Mϕ significantly reduced hepatic collagen & repaired efferocytosis**

Mϕ: Macrophage; CCl4: Carbon tetrachloride; CDAHFD: Choline-deficient, L-amino acid-defined, high-fat diet; PSR: Picrosirius red; PBS: Phosphate-buffered saline
* p<0.05; **p<0.01; 1: Sloas C, et al. AALSD 2024.; Data on this slide is from preclinical mouse model

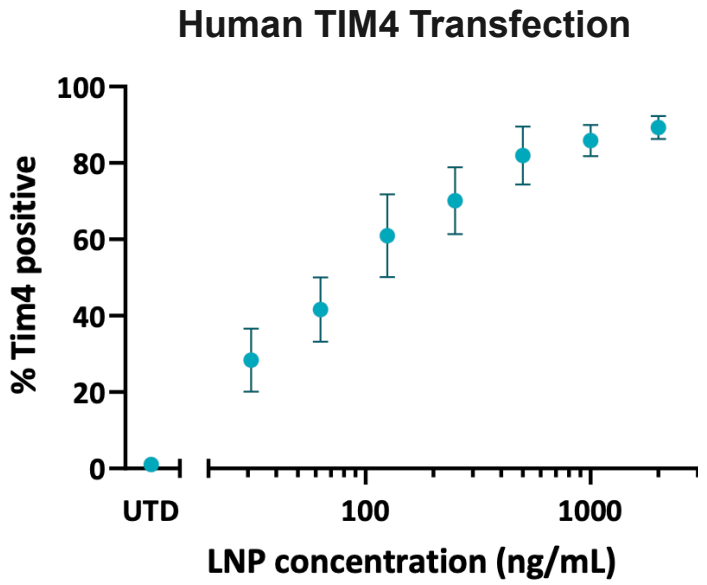
# TIM4 mRNA/LNP was well tolerated with no weight loss, no increase in liver enzymes

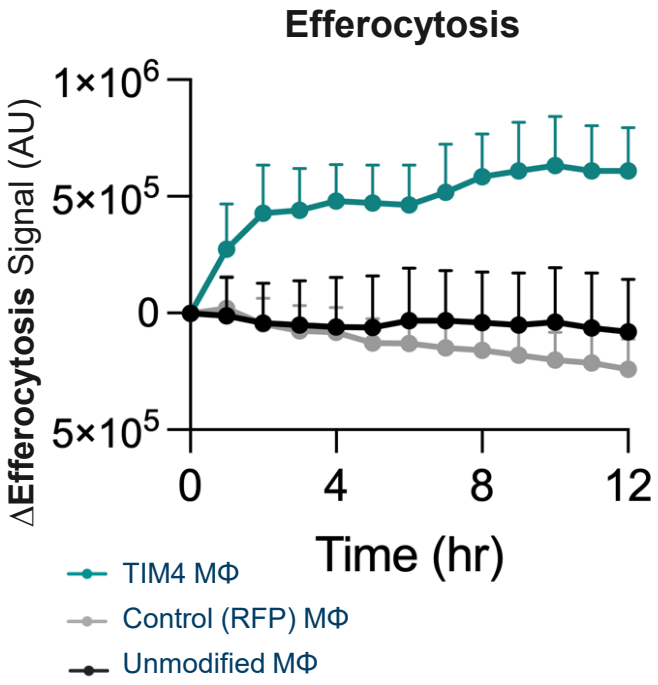
**Systemic TIM4 mRNA/LNP (MC-3) led to a median 83% fibrosis decrease in the CDAHFD (MASH) model**




**Successful translation from murine system to primary human macrophages *ex vivo***

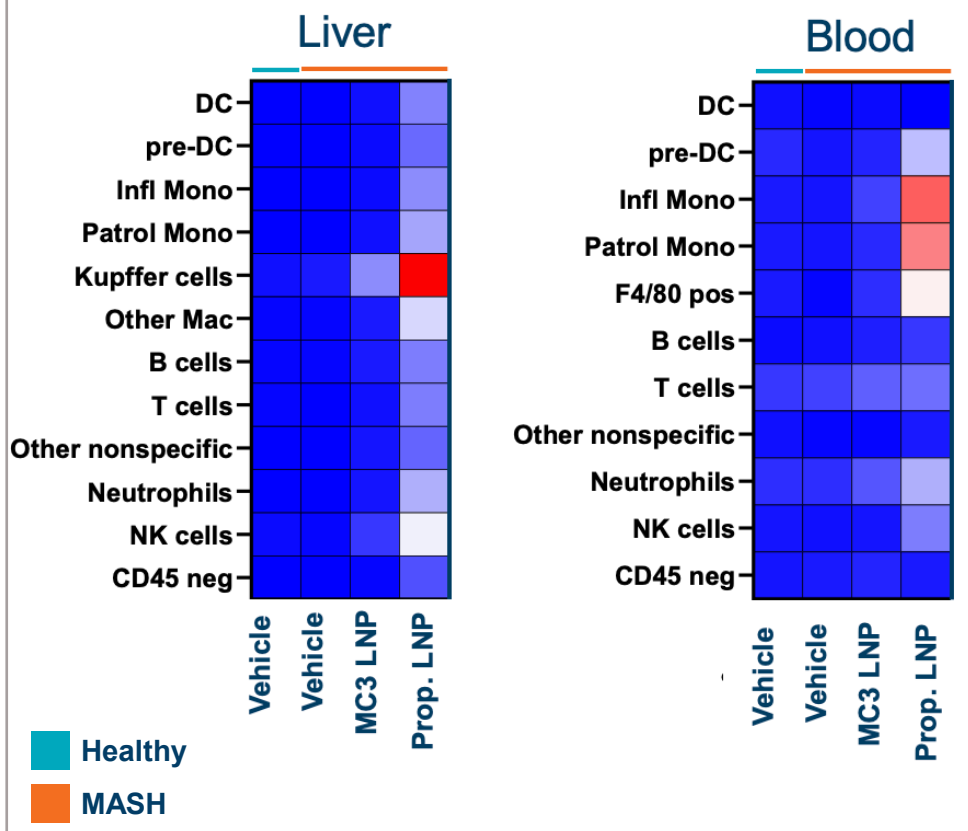


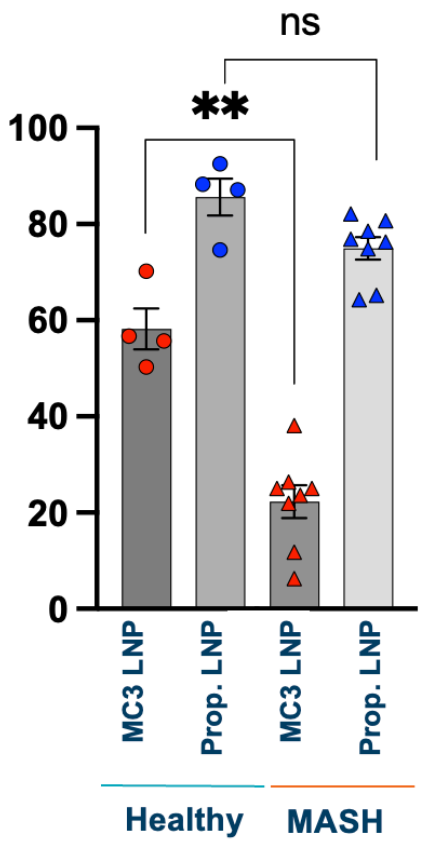
# CT-2401 utilizes proprietary LNP optimized for liver fibrosis

## Increased specificity for Kupffer cells and maintains high transfection efficiency in MASH

### Proprietary LNP is myeloid tropic




### High transfection efficiency in fibrotic liver




- ✓ MC-3 is a **clinically used LNP** (Onpattro®, Alnylam)
- ✓ **MC-3 lost 50%** of transfection efficiency in fibrotic animals
- ✓ **Proprietary LNP** maintained transfection efficiency in fibrotic animals
- ✓ **>75% Kupffer cells** transfected with 1 dose

MC3: control liver tropic LNP, common liver tropic LNP; Prop. LNP: Proprietary LNP; A single dose of mRNA/LNP was administered to healthy or CDAHFD MASH mice and biodistribution was evaluated after 24 hours.

# *In Vivo* mRNA/LNP Anti-Fibrotic Macrophage Program Timeline

Targeting IND Submission and Phase 1 Initiation in 2026

## POC & Lead Nomination

**2024[1]**

- Preclinical Proof-of-Concept Achieved (ASGCT, AASLD)
- Lead Nomination and Candidate Selection

## Development Candidate

**2025[1]**

- License Agreement to formalize mRNA/LNP and manufacturing
- IND-Enabling Studies
- Begin GMP Manufacturing and Batch Production/Release
- Preclinical proof of concept in pulmonary fibrosis

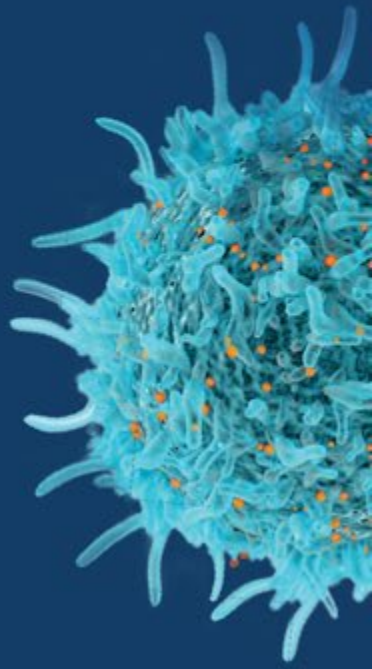
## Phase 1 Trial

**2026[1]**

- Regulatory submission
- Phase 1 Clinical Trial Initiation

1. Anticipated milestones

# Corporate & Financial



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# Operating Plan and Corporate Milestones

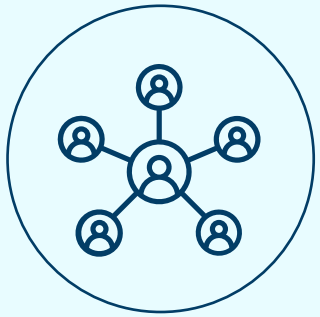
## Capital efficient R&D program designed to reach significant value inflection points

| INDICATION | PRODUCT CANDIDATE | PLATFORM | ANTICIPATED MILESTONES | |
|---|---|---|---|---|
| **Oncology** | | | | |
| Mesothelin+ solid tumors | CT-1119 | CAR-Monocyte (Autologous) | **1H 25** | Initiate Phase 1 trial |
| | | | **4Q 25** | Initial Phase 1 data |
| GPC3+ solid tumors | Target #1 | *In Vivo* CAR-M | **2Q 24** | Development Candidate nominated |
| | | | **Pending** | IND application |
| Undisclosed | 4 Nominated Targets[1] | *In Vivo* CAR-M | **Pending** | Nominate next lead candidate |
| **Liver Fibrosis** | | | | |
| Liver Fibrosis | CT-2401 | *In Vivo* TIM4 | **4Q 24** | Reported preclinical proof of concept data (AASLD 2024) |
| | | | **1Q 25** | Nominate Development Candidate |
| | | | **4Q 25** | Complete IND enabling studies |
| | | | **2026** | Regulatory submission |
| **Autoimmune** | | | | |
| Autoimmune disease | 2 Nominated Targets | *In Vivo* CAR-M | **Pending** | Nominate lead candidate |

1. Moderna collaboration has identified 5 total oncology targets, with the option to identify an additional 5 oncology targets;

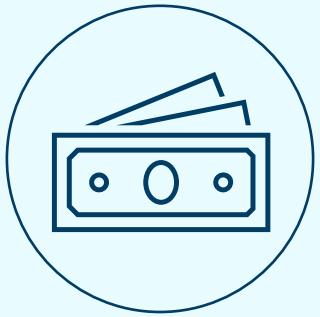
# Financial Snapshot

As of September 30, 2024



**41.75M**

Shares outstanding



**$26.9M**

Cash and cash equivalents

**Into 3Q 2025**

Expected cash runway