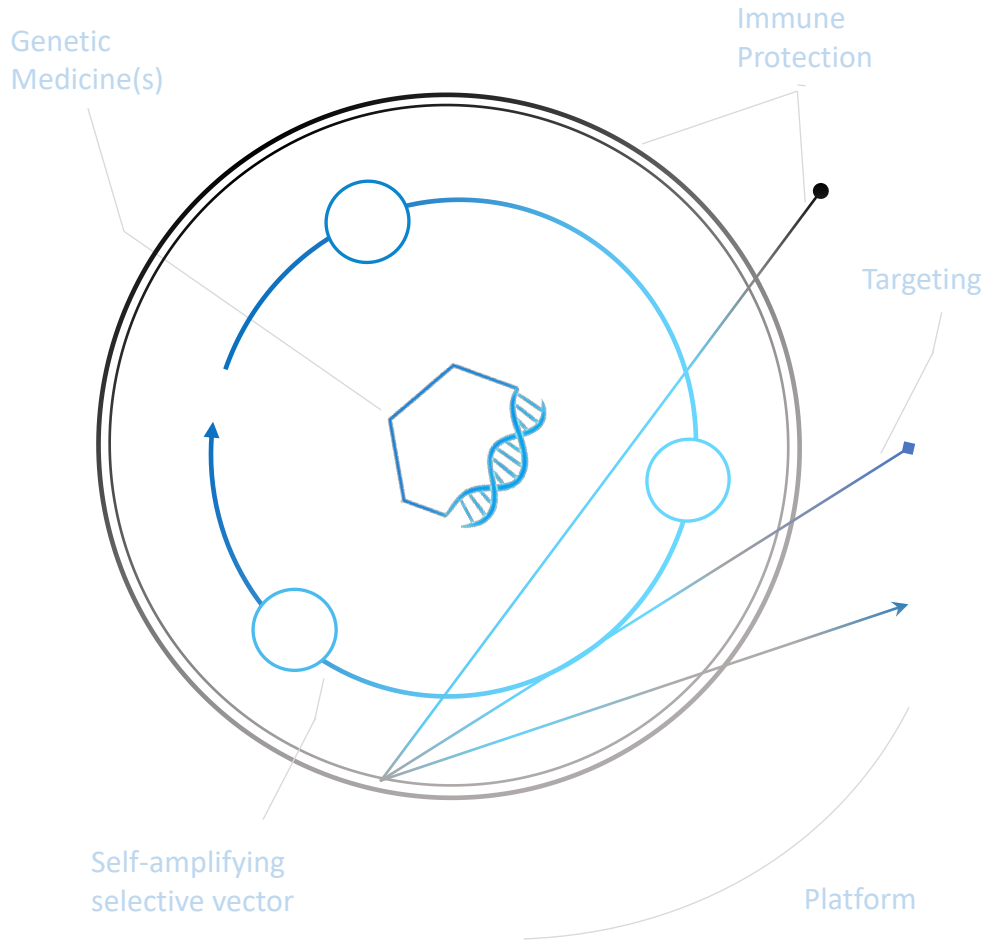
Engineering the Future of Genetic Medicine

From cancer to other complex diseases, Calidi's RedTail platform can precisely deliver genetic medicine to distal sites of disease



April 2026

NYSE American: CLDI
Calidibio.com

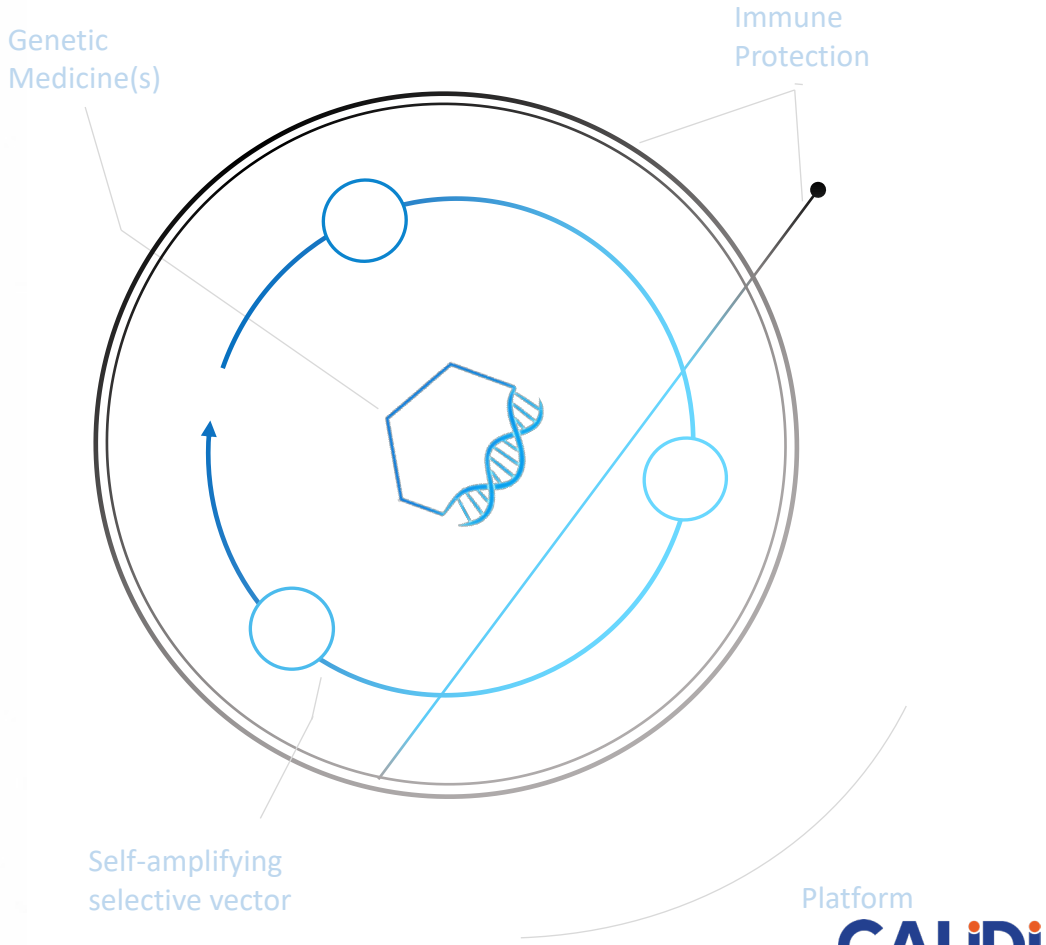
CALIDI BIOTHERAPEUTICS

Calidi Biotherapeutics: precise delivery of genetic medicine to the site of disease

Calidi Biotherapeutics
(NYSE American: CLDI)

- **Engineering the Future of Genetic Medicine to treat cancer and complex disease**
  - Calidi technology expresses high levels of genetic payload(s) only at the sites of disease, marshaling the body's natural immune response
- **Proprietary RedTail Platform**
  - Systemic administration
  - Protected from immune clearance (EEV form / CD55 expression)
  - Targeted tumor cell lysis and immune priming
  - COGS similar to monoclonal antibody
- **Broad IP protection covering 2 patent families**

The RedTail Platform



Efficacy Established with Intra-Tumoral Oncolytic Viruses: Systemic Delivery Would Expand Access to Most Patients

Legacy Attempts / Local Efficacy

- **Multiple examples of efficacy with local administration**
  - Amgen, CG Oncology, Replimmune, Candel
- **Intra-tumoral administration is limiting**
  - Most patients do not have disease amenable to intra-tumoral administration
- **Nevertheless, lytic replication and immune priming represent novel MOAs in cancer**
  - Potent tumor cell lysis and transient immune activation

Calidi's Systemic Solution

- **<u>The challenge:</u> the immune system clears systemically injected viruses**
- **<u>Prior attempts:</u> failed on toxicity**
  - Utilized high dosing to overcome immune clearance; approach limited by toxic AEs
- **<u>Our solution:</u> Calidi's virus designed to evade immune clearance and target only the tumor microenvironment**
  - 10+ years in development
  - Novel enveloped / CD55 overexpressing form of Vaccinia virus prevents immune clearance
  - Replication competent only in tumor cells; potently lytic
  - High levels of genetic payload(s) expression only in the tumor microenvironment

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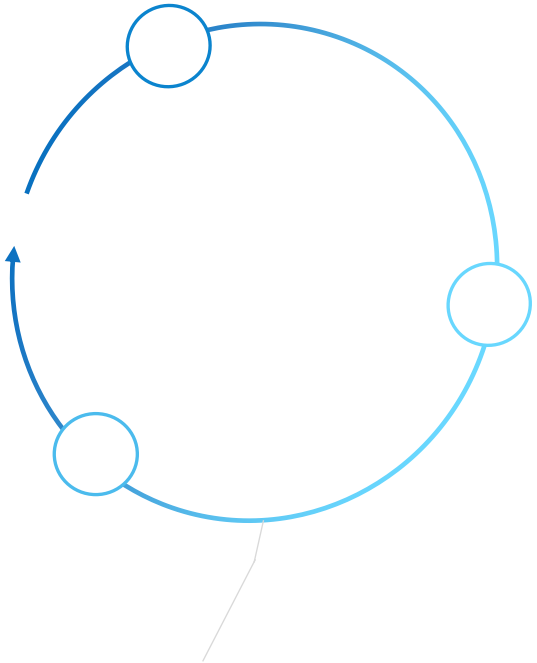
Building the RedTail Scaffold: Step 1
Tumor Tropism

- **Tumor Tropism and Replication Selectivity**
  - Vaccinia virus has inherent tropism for tumor cells[1]
  - Vaccinia virus cell entry is not receptor dependent[2]

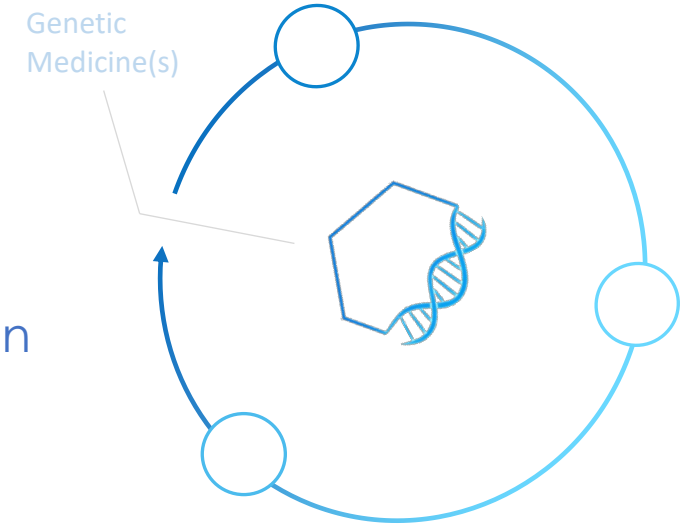
- **Virus genetically engineered to replicate only in tumor cells**
  - Triple knockout version of vaccinia virus created that can only replicate in tumor cells
    - TK, VGF, and A46R genes knocked out[3]



Tumor selective form of vaccinia virus

1. Yu et al, *Nat Biotechnol* (2004) 22(3):313–20..
2. Xu et al, Front. Immunol., 11 January 2024
3. Calidi Biotherapeutics, ASCO 2025

Building the RedTail Scaffold: Step 2
Genetic Medicine Payload



- **Genetic Medicine Payload**
  - Vaccinia has a large genome with high capacity for insertion(s)[1]
    - ~200kbp with >200 ORFs; up to 25kbp capacity for insertion
  - Calidi has identified proprietary sites in RedTail for gene(s) insertion

- **Vaccinia follows a cascade temporal gene expression pattern[2]**
  - Promoters associated with early, intermediate, and late expression allow for better control of gene expression

- **Vaccinia blocks host cell production and favors viral protein production**
  - Allows for extremely high levels of payload expression

1. McCraith et al, *PNAS* 2000 97(9) 4879-4884
2. Deng et al. *Virology*. March 2025
3. Dhungel et al. *Pathogens* **2020**, *9*(5), 40

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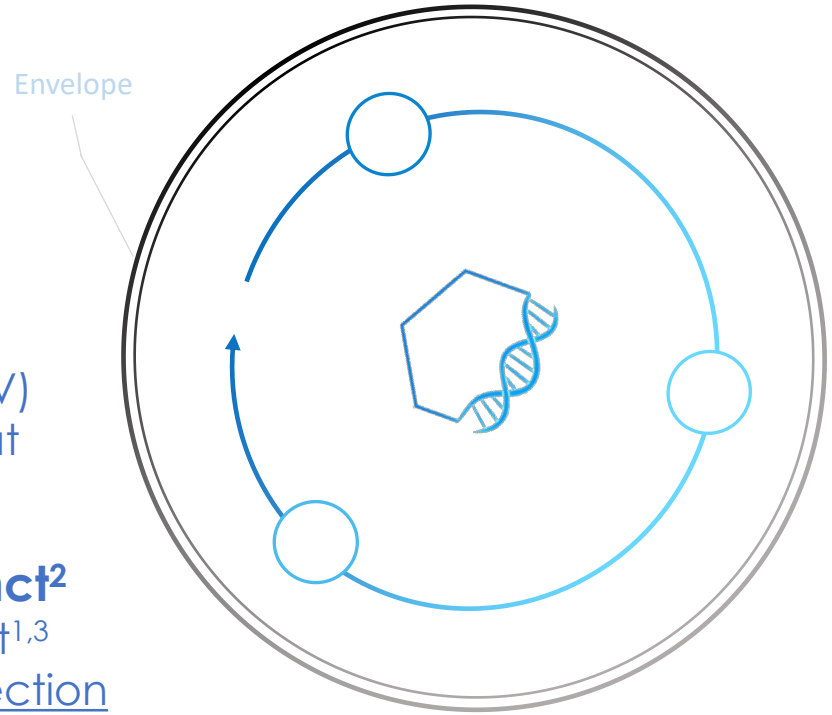
Building the RedTail Scaffold: Step 3
Viral Envelope



- **Enveloped Form of Vaccinia Virus**
  - **Vaccinia virus produces two forms of infectious particles[1]**
    - During infection, >99% of virus is Intracellular Mature Virus (IMV)
    - <1% of virus is the Extracellular Enveloped Virus (EEV) form that takes on the cell membrane (envelope) from its host
  - **Forms are structurally, functionally, and antigenically distinct[2]**
    - EEV form is resistant to antibody neutralization; IMV form is not[1,3]
      - ➢ Cell line virus is produced in can affect the level of protection
    - EEV form mediates dissemination of virus during infection[4]
      - ➢ Viral dissemination is a biological proxy for systemic administration

Calidi has used genetic engineering, strain selection, and process development to, for the first time, manufacture the EEV form at high levels[5]

1. Smith et al, Advances in Experimental Medicine and Biology AEMB,volume 440
2. Roberts et al, *Trends in Micro* 2008 16(10)
3. Vanderplasschen et al, *PNAS* 1998, 95 (13) 7544-7549
4. Payne et al, *J of Gen Virology* Sep;50(1):89-100
5. Calidi Biotherapeutics, ASCO 2025

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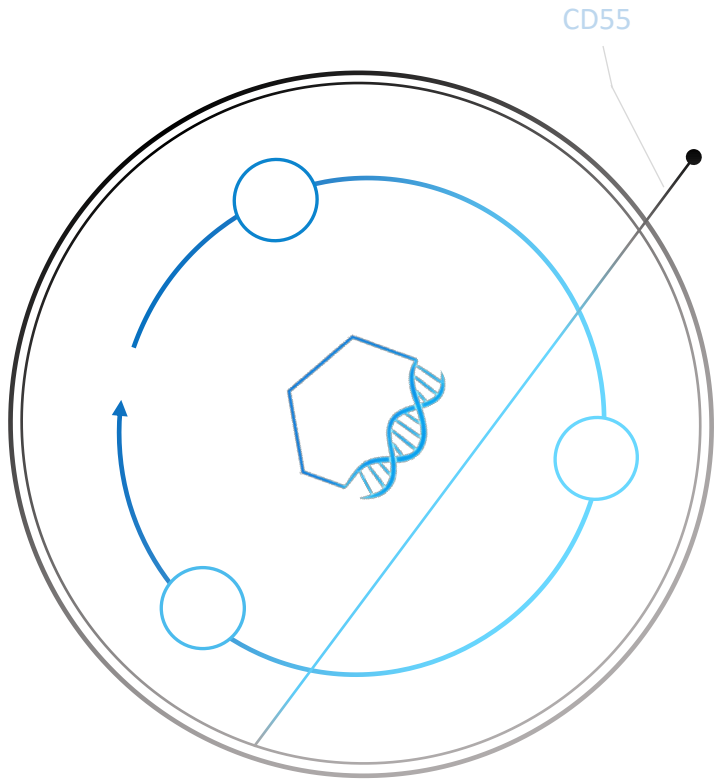
Building the RedTail Scaffold: Step 4
CD55 Overexpression



- **CD55 Overexpression**
  - **Complement is pivotal for immune clearance for Vaccinia[1,2]**
    - Complement is the major mechanism for clearance of Vaccinia[3]
  - **CD55 expression inhibits complement activation[4]**
    - RedTail scaffold genetically engineered to express CD55 at high levels
    - CD55 expression on the RedTail envelope further inhibits immune clearance

Therapeutic use of the EEV form of Vaccinia virus with CD55 expression is a groundbreaking step for systemic administration

1. Evgin et al, *Molecular Therapy* 2015 23(6)
2. Magge et al, *Caner Gene Therapy* 2013 20:342-350
3. Lustig et, *Virology* 2004 Oct 10;328(1):30-5
4. Theresa et al *The Complement FactsBook* (2018)

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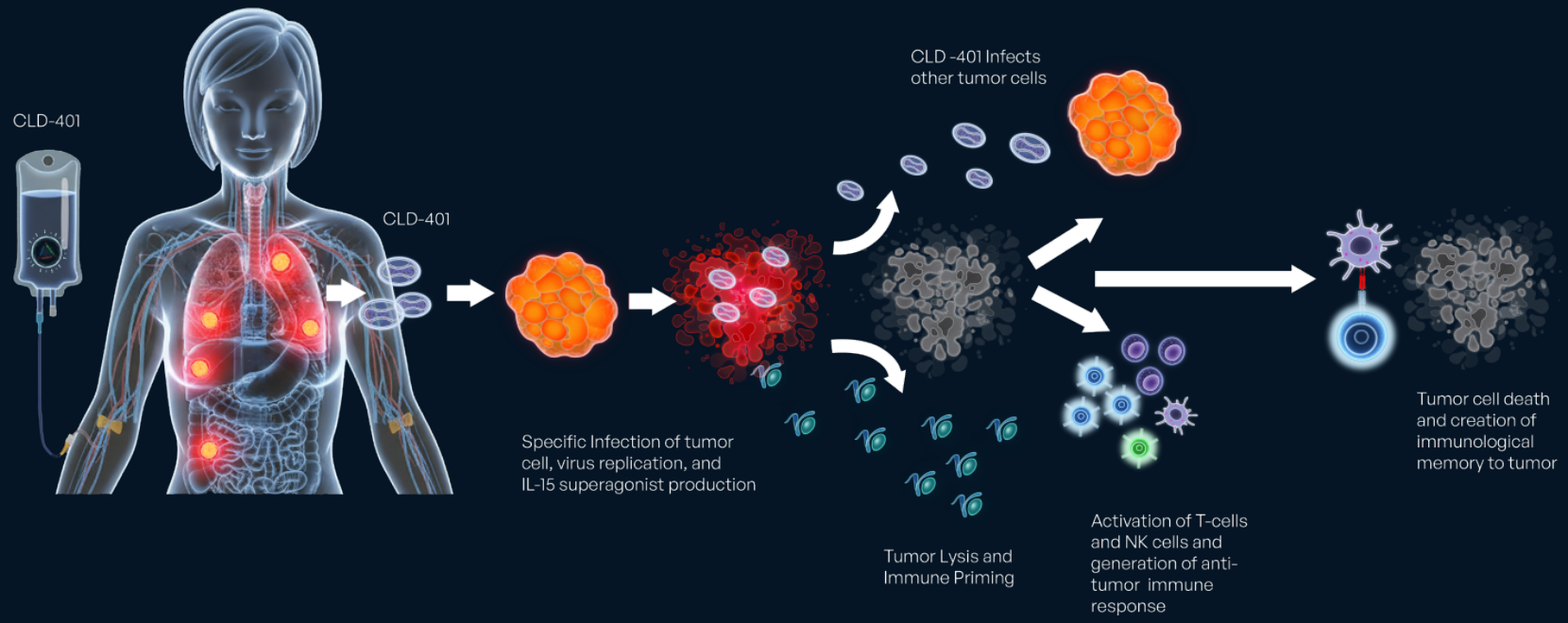
CLD-401: The First Lead From the RedTail Platform

- Systemic administration
- Protected from immune clearance (EEV/CD55)
- Targeted tumor cell lysis and immune priming
- <u>IL-15 superagonist production at the tumor</u>
- Induces innate and adaptive response to the tumor



IND filing expected 2026; Phase I monotherapy study in rel/ref patients (NSCLC, TNBC, Melanoma, etc.). Parallel tracking rapid opening of Phase I study in Australia.

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CLD-401: Tumor-specific IL-15SA expression

- IL-15 SA concentrations in the tumor are similar to concentrations with locally-administered Anktiva in bladder cancer
  - Expression in serum or other tissues is >1,000 times lower

IL-15 SA concentrations (pM) in tumor and organs at multiple time points

Tumor-bearing model:

Timepoint	Tumor		Liver		Ovary		Lung		Plasma	
	pM	sd	pM	sd	pM	sd	pM	sd	pM	sd
Day 6	62,073.9	16,671.7	13.8	4.6	51.0	85.5	12.7	3.5	15.0	0.8
Day 17	264.6	196.9	3.1	0.4	-	-	-	-	-	-
Day 21	36.4	49.0	2.1	1.0	-	-	-	-	-	-

Non-tumor-bearing model:

Timepoint	Liver		Ovary		Lung		Plasma	
	pM	sd	pM	sd	pM	sd	pM	sd
Day 6	2.7	2.2	1.3	1.5	1.2	1.9	3.6	4.3

- IL-15 SA concentrations (pM) detected by ELISA after CLD-401 treatment. High tumor concentrations; minimal in liver, ovary, lung, and plasma. Data from EMT6 breast cancer model (Days 6, 17, 21) and non-disease controls (Day 6). Mean ± SD; "–" = not detected.
- **Tumor concentrations are similar to expected concentrations of Anktiva after intravesicalar delivery; concentrations of Aktiva after subcutaneous administration are ~20pM**

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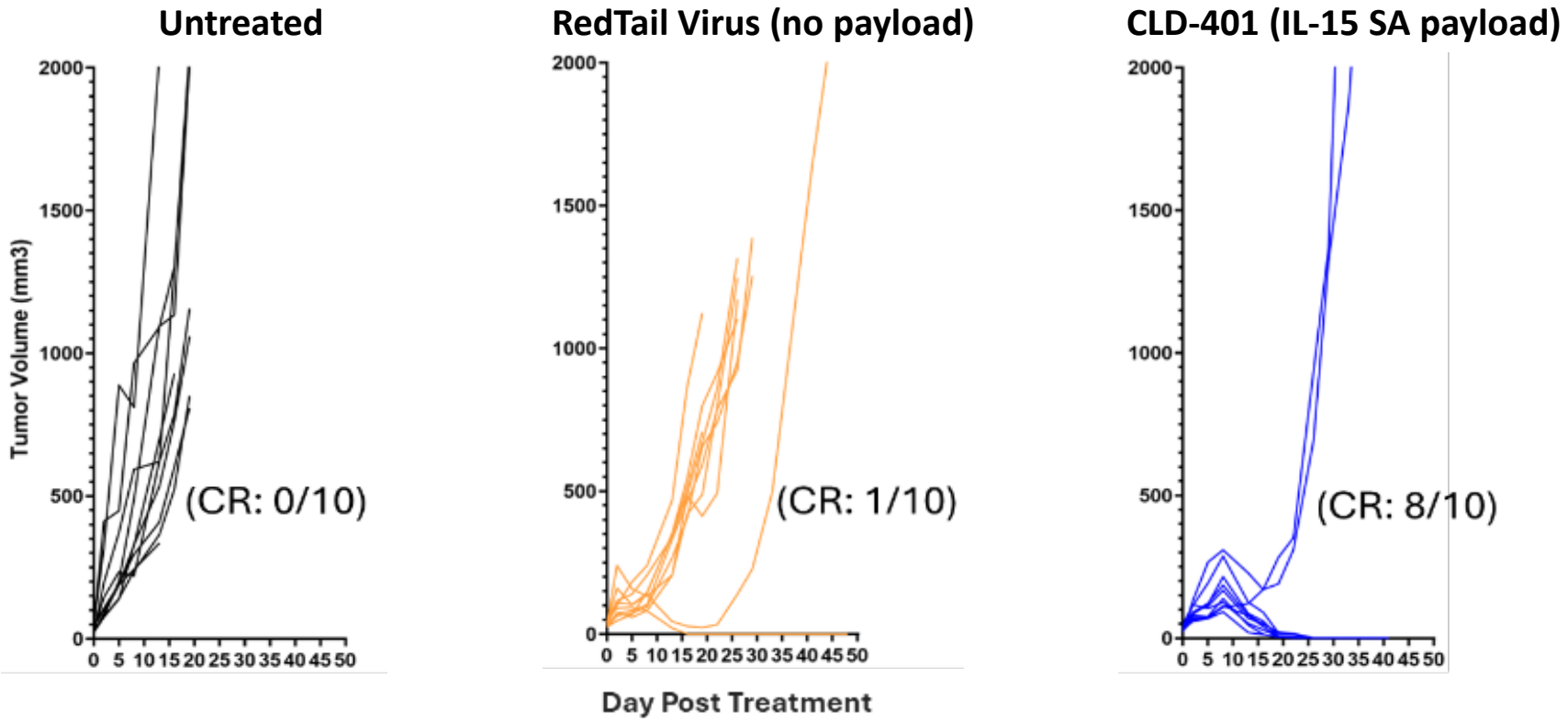
Enhanced Therapeutic Activity With In Situ IL-15 SA Expression

RedTail virus with IL-15 SA payload (CLD-401) dramatically improves treatment efficacy

Tumor regression in syngeneic EMT6 model after a single administration of $5x10^6$ PFU viral particles



Profound changes noted in the TME with CLD-401 vs RedTail Virus

- Dramatic increase in NK, NK-T, and gamma delta T-cells with CLD-401
- Elimination of Tregs and large increase in CD8/Treg ratio

EMT6 tumor cells (5E6) were subcutaneously implanted on both flanks of Balb/c mice, and five days post-implantation, animals received a single intravenous dose of 5e6 PFU RedTail, either unarmed or armed with IL-15 superagonist, or buffer control (n=10 per group).

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RedTail: Potential to Enhance Platform and Expand Outside of Oncology

Next-Generations

Precision Oncology & Other Diseases

- **Cancer:**
  - Expand **payload options** – up to three genetic payloads
  - Proof-of-concept established with in situ TCEs: simultaneous expression of a T-cell engager and a T-cell activating genetic payload(s)
  - Engineer specificity for a given extracellular marker

- **Outside Oncology:**
  - Depletion of activated B- and T-cells via viral lysis
  - New **payloads for inflammatory & immune diseases** (I&I)
    - High levels of expression of immunosuppressive payloads at sites of disease, not systemically

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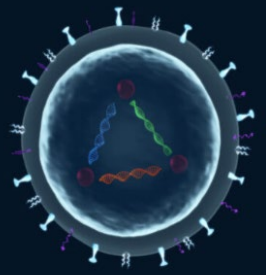
Expanding the RedTail Platform: In Situ T-Cell Engagers

T-cell engagers (TCEs) have faced obstacles in the treatment of solid tumors

1. On-target, off-tumor binding drives toxicity
2. Low concentration of TCEs in the TME limits efficacy
3. Low concentration and impaired T-Cells in the TME limit efficacy

In Situ T-cell Engagers were specifically designed using the RedTail platform to overcome these challenges

1. RedTail is only active in tumor cells, limiting the potential for on-target, off-tumor toxicity

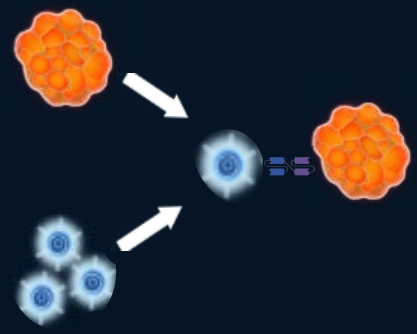


2. In situ expression of high levels of T-cell engager in the TME

T-Cell engagers bind tumor cell and activated T-cells in the TME

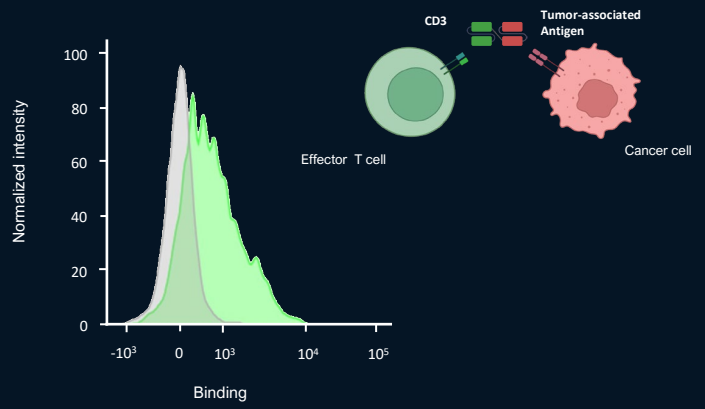
3. In situ expression of high levels of IL-15 SA in the TME

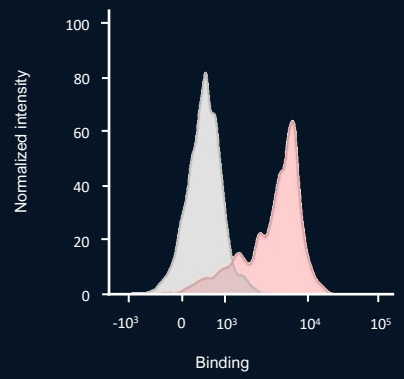
IL-15 SA induces the recruitment and activation of T-cells in the TME

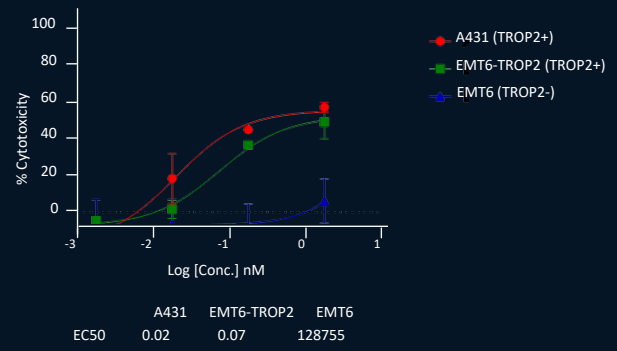


T-Cell –mediated tumor cell destruction

CLD-501: Functional TROP2 TCE and IL-15 SA Expression







	A431	EMT6-TROP2	EMT6
EC50	0.02	0.07	128755

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Calidi's Partnership / Licensing Goals

- **Mutual opportunity in collaboration**
- **Calidi seeks partners with expertise in oncology or autoimmune disease to expand the reach of its RedTail platform**
- **Calidi can design vectors**
  - Targeted to a specific extracellular marker, and / or
  - Carrying up to 3 genetic payloads
- **Licensing can be defined by extracellular marker and / or genetic payloads**
- **Calidi can ensure manufacturing through early phase clinical development**