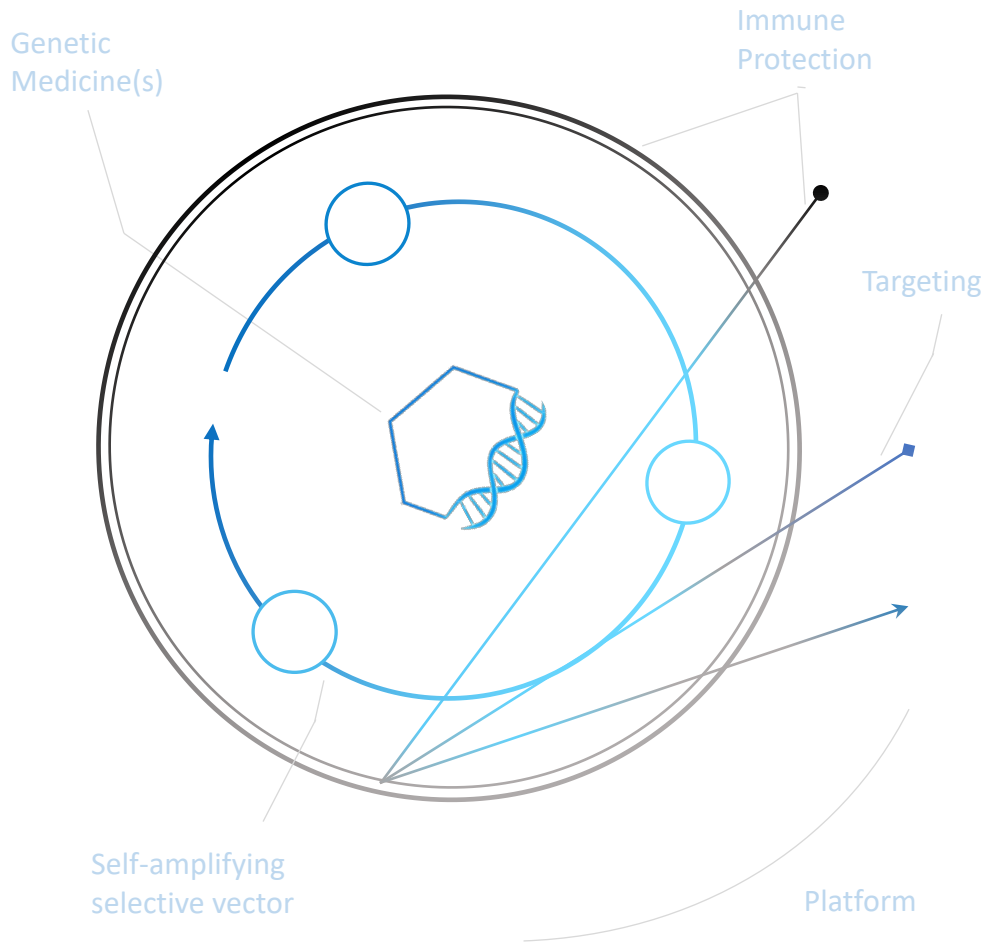
Engineering the Future of Genetic Medicine

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



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NYSE American: CLDI
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CALIDI BIOTHERAPEUTICS

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Calidi Advantages

- **The RedTail platform is the next leap forward in delivering oncolytic viruses**
  - Systemic delivery reaches distal disease sites
  - Ability to express proteins to tumors
  - Designed to avoid immune clearance and home to metastatic tumor sites, induce tumor lysis and immune priming, and deliver genetic medicines to the tumor microenvironment (TME)
  - Allows for higher doses of effective virus with lower levels of innate immune stimulation
  - Development of a proprietary form of vaccinia virus reflects 10 years of research
- **CLD-401 is the first candidate from the RedTail platform**
  - Delivery of IL-15 superagonist to the TME to activate NK and CD8+ T-cells against the tumor
- **Early clinical data will validate the platform and accelerate subsequent work**
  - Partnership and collaboration discussions to advance development of platform programs
  - Potential to move the platform beyond oncology

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- The Systemic Delivery of Oncolytic Viruses
- Our RedTail Technology
- Building the Optimal Viral Platform
- CLD-401: Our Lead Program
- Leadership and Milestones

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Proven Efficacy with Intra-Tumoral Oncolytic Viruses

- **Multiple examples of efficacy with local administration of an oncolytic virus**
  - Amgen: T-Vec approved in 2015 for unresectable lesions in melanoma post surgery
  - CG Oncology: BLA submission for cretostimogene in BCG-unresponsive NMIBC
  - Candel: BLA filing expected for CAN-2409 in localized prostate cancer
  - Replimune: promising data in melanoma
- **Intra-tumoral administration is highly limiting…**
  - Most patients do not have disease amenable to intra-tumoral administration
  - Systemic efficacy is highly dependent on abscopal effects that are clinically rare
- **…but lytic replication and immune priming represent novel MOAs in oncology**
  - Viral lysis of tumor cells is a potent and unique tumoricidal effect
  - Viral replication induces a potent but transient change in the TME

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Can Oncolytic Viruses Be Used as Systemic Therapy?

- **Efficacy in r/r solid tumor Ph I studies with IV admin of Newcastle disease virus**
  - 1 CR, 3 PRs, and 2 minor responses in 18 pts; ~1/3 pts w/ Gr4 AEs; (10^{10} – 10^{11} pfu/dose)[1]
  - 1 CR and 6 PRs in 20 pts with alpha-Gal-NDV (**2025 Cell paper**); (10^{10} – 10^{11} pfu/dose)[2]
    - Concerns around NDV (Avian paramyxovirus) due to USDA designation as a select agent
- **Ph I study with vesicular stomatitis virus expressing interferon-β[3]**
  - 7 pts with TCL: 1 CR, 2 PR; single dose of up to 10^{11} pfu/dose
- **Dosing at higher levels is the current path to allow systemic delivery of oncolytic viruses**
  - Clinical data demonstrating that virus cannot be detected at IV doses lower than 10^{9}/pfu[4]
  - Higher doses are an attempt to overcome the rapid clearance by immune system[2] but…
  - **Higher doses triggers innate immune adverse events, limiting the therapeutic window**
- **Calidi has taken a different strategy based on eliminating immune recognition of virus**
  - Allows for higher doses of effective virus with lower levels of innate immune stimulation
  - **Potential to dramatically expand the therapeutic window for systemic oncolytic viruses**

1. Hotte et al, *Clin Cancer Res* (2007) 13 (3): 977–985.
2. Zhong et al. *Cell.* 2025 188 (4) 1119-1136
3. Cook et al, *Blood Adv*. 2022 Jun 1;6(11):3268–3279.
4. Breitbach et al, *Nature*477 (7362), 99 – 102 (2011)

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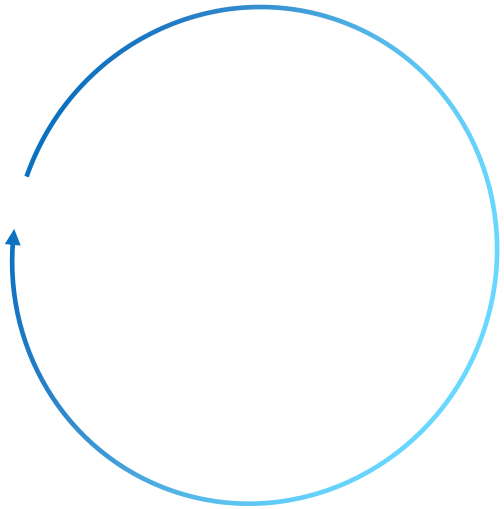
Building the Optimal Viral Platform, Step by Step

- **Vaccinia virus chosen as basis for Calidi's RedTail scaffold**
  - **Large DNA poxvirus that only replicates in the cytoplasm**
    - No potential for host DNA integration
    - Large capacity for payload insertion
  - **Naturally tropic for tumor cells**
  - **Rapid and potent lytic cycle (even under hypoxic conditions)**
  - **Used for decades as the smallpox vaccine**



Vaccinia Virus

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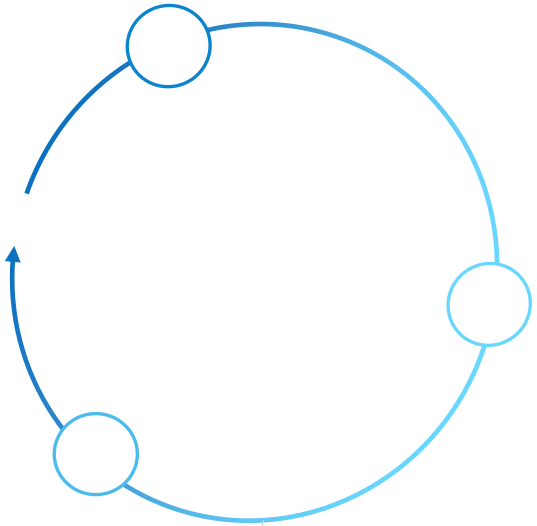
Building the RedTail Scaffold: Step 1

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**

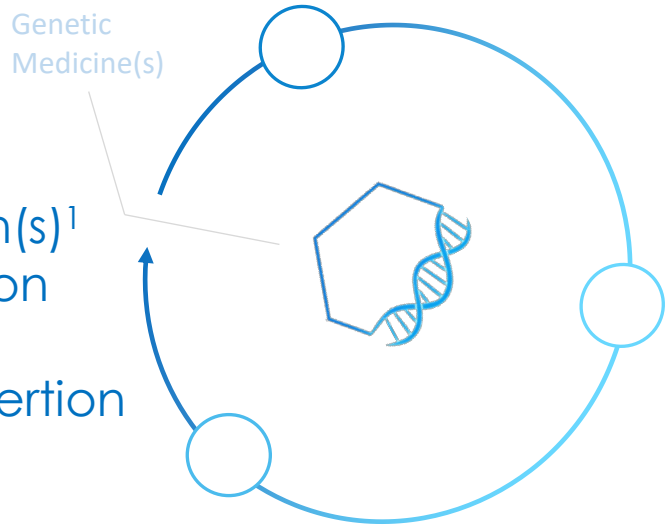
- Triple knockout version of vaccinia virus created that can only replicate in tumor cells
  - TK, VGF, and A46R genes knocked out[3]



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

- 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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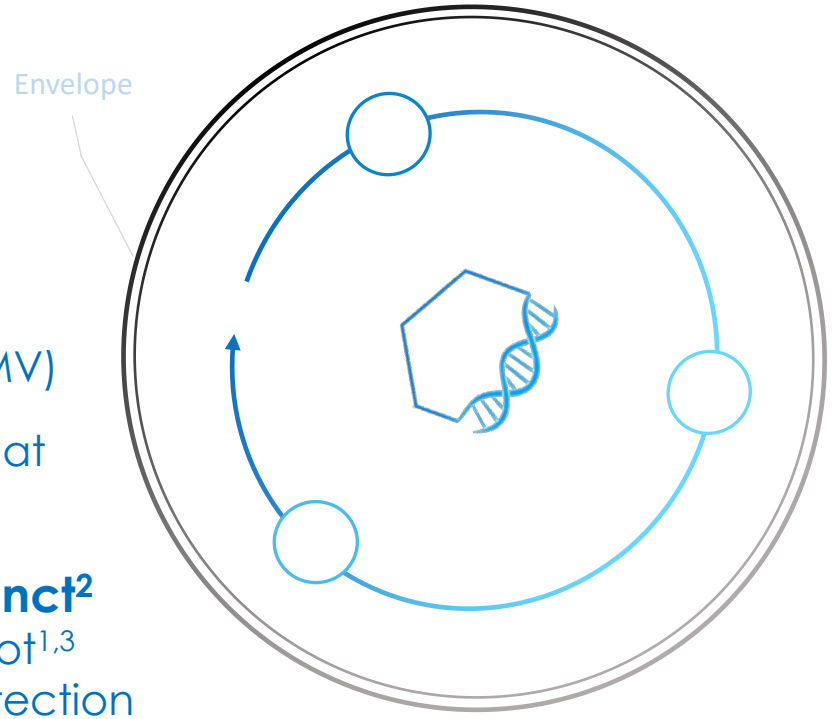
Building the RedTail Scaffold: Step 3

Enveloped Form of Vaccinia Virus

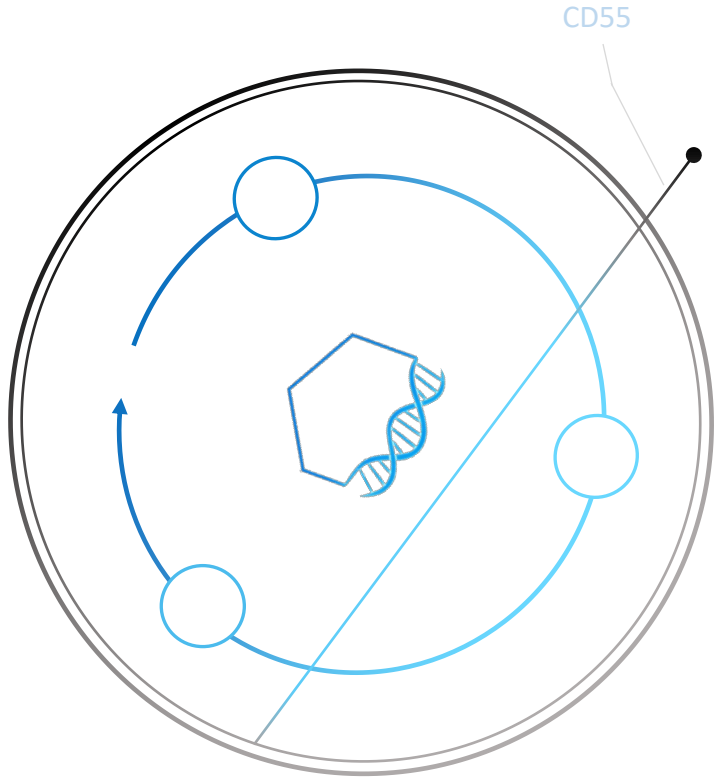


- **Vaccinia virus produces two forms of infectious particles[1]**
  - During infection, >99% of virus is Intracellular Mature Virus (IMV)
  - <1% of virus is the Extracellular Enveloped Virus (EEV) form that takes on the cell membrane (envelope) from its host
- **Forms are structurally, functionally, 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

Building the RedTail Scaffold: Step 4



CD55 Overexpression

- **Complement is pivotal for immune clearance for Vaccinia[1,2]**
  - Complement is the major form of Vaccinia clearance[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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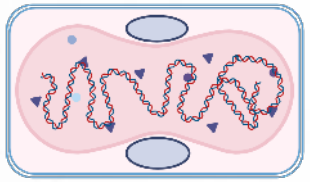
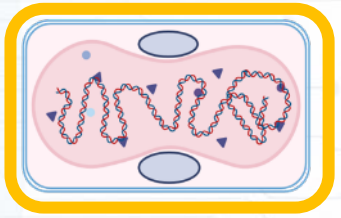
EEV with CD55 Expression Is Highly Resistant to Clearance

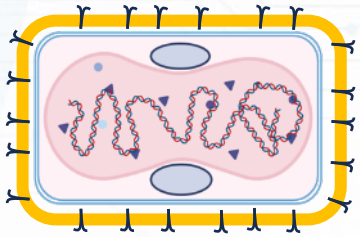
IMV (non-enveloped form)

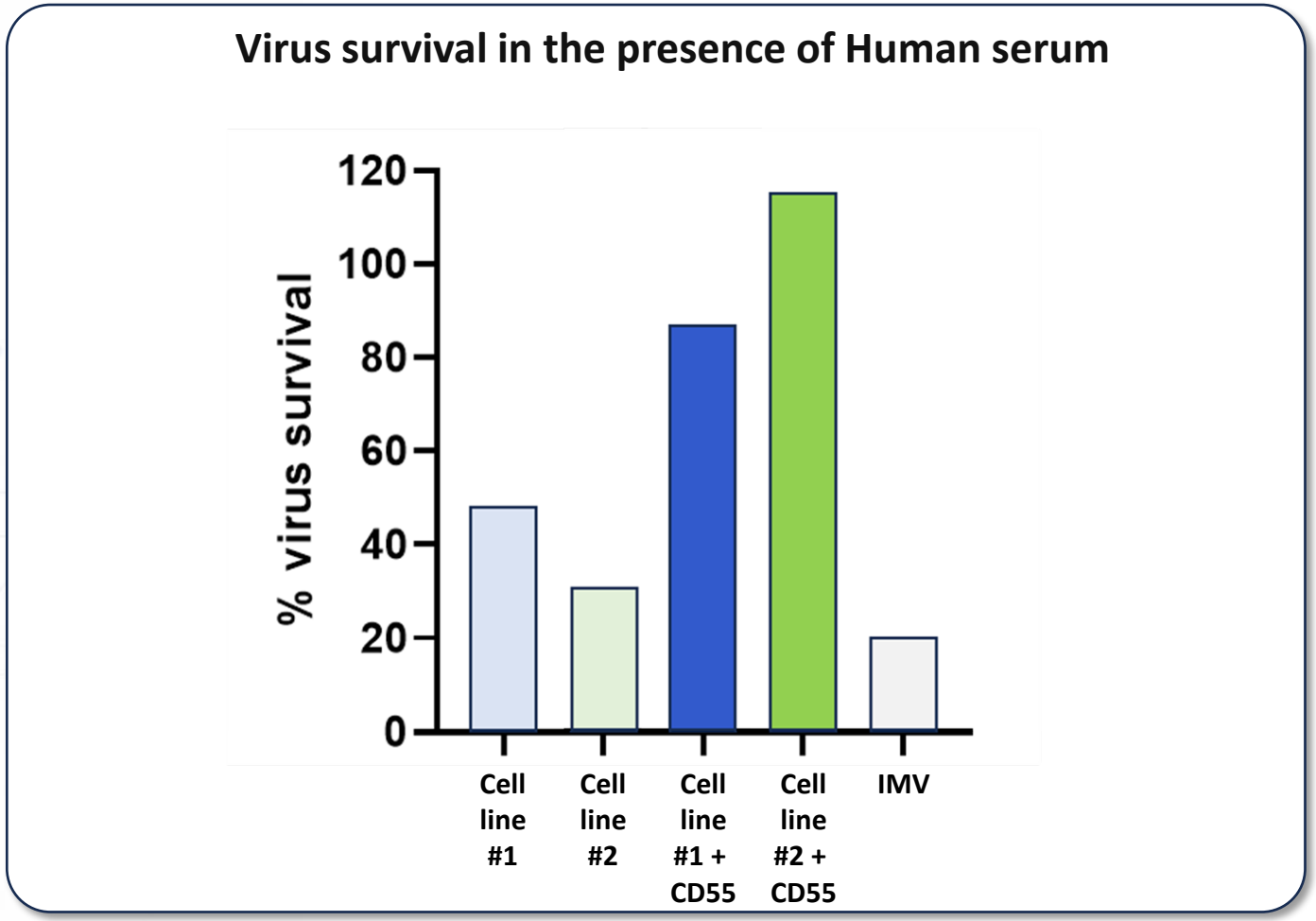


EEV (enveloped form)



EEV with CD55 expression





Overexpression of CD55 on EEV membrane protects against complement inactivation and enhances immune evasion

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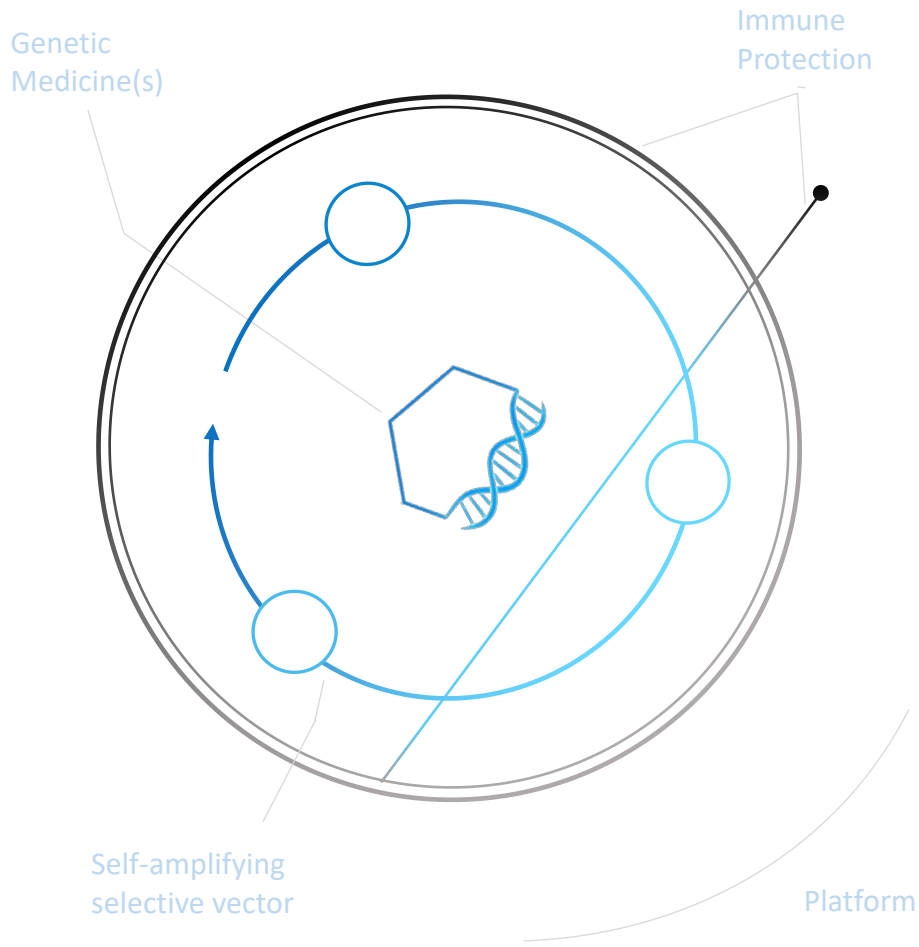
The RedTail Platform

- Systemic administration
- Protected from immune clearance (EEV form / CD55 expression)
- Targeted tumor cell lysis and immune priming
- Genetic medicine payload(s) expression in the TME
- COGS similar to monoclonal antibody
- Broad IP coverage of platform technology



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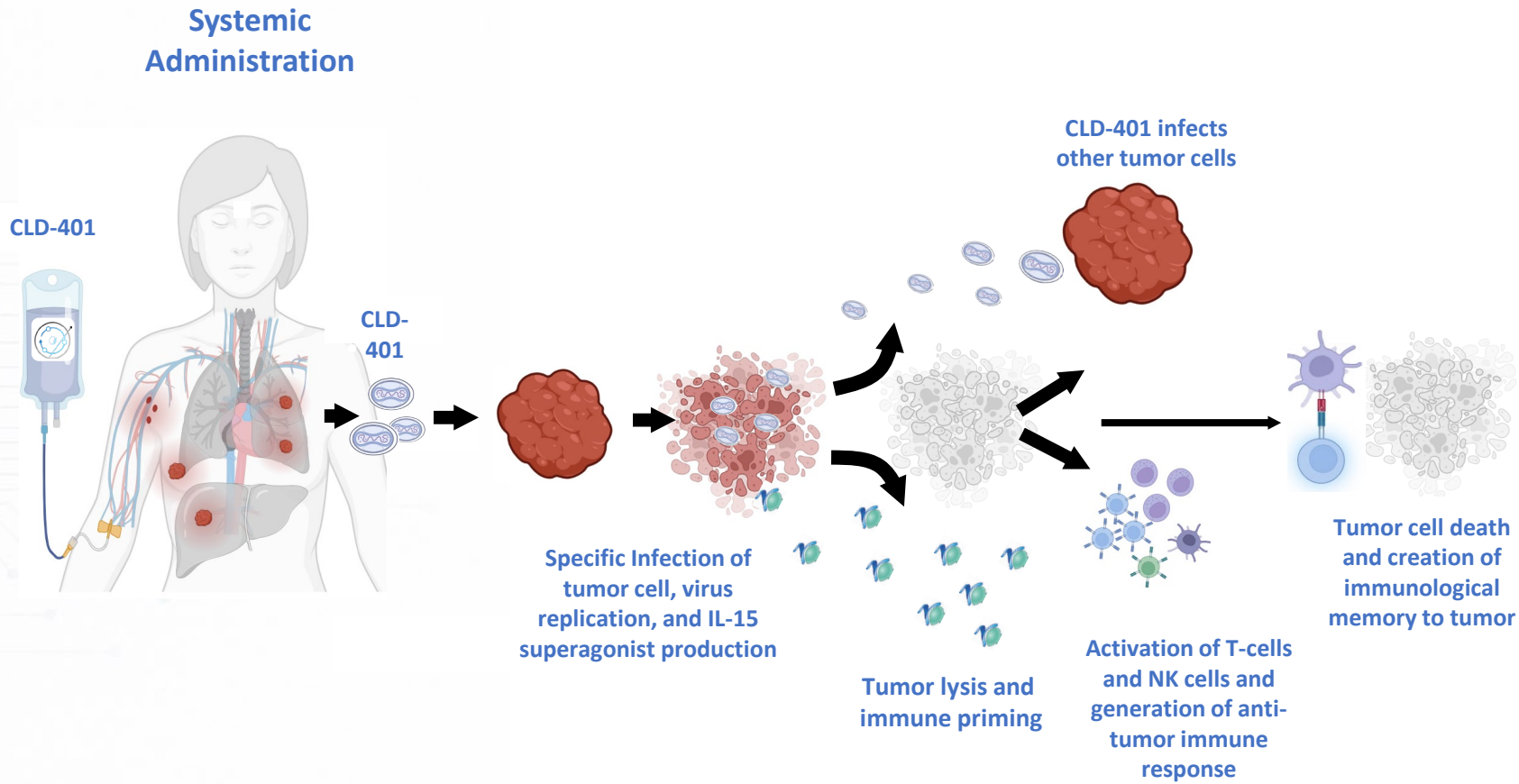
CLD-401: The First Lead From the RedTail Platform

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



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IL-15 Superagonist: Proven Activator of Immunity

- IL-15 is a powerful growth factor for NK cells (innate) and CD8+ T-cells (adaptive)
  - Unlike IL-2, IL-15 does not expand Tregs or induce activation-induced T-cell death
  - IL-15 superagonist is a fusion of IL-15 (N72D) and the Sushi domain IL-15 alpha receptor that dramatically enhances IL-15 activity
- Anktiva (IL-15 superagonist-Fc) approved for the treatment of BCG-non-responsive NMIBC
  - Drug dosed intravesically in bladder cancer at 400 mcg/kg weekly
  - SC dosing in NSCLC is 15 mcg/kg every 3 wks (80-fold lower than intravesical dose)
    - IL-15 agonists: tumor concentrations drive efficacy; systemic concentrations drive tox
      - In situ delivery of IL-15 superagonists maximizes therapeutic window
- IL-15 superagonist chosen as genetic medicine payload for CLD-401

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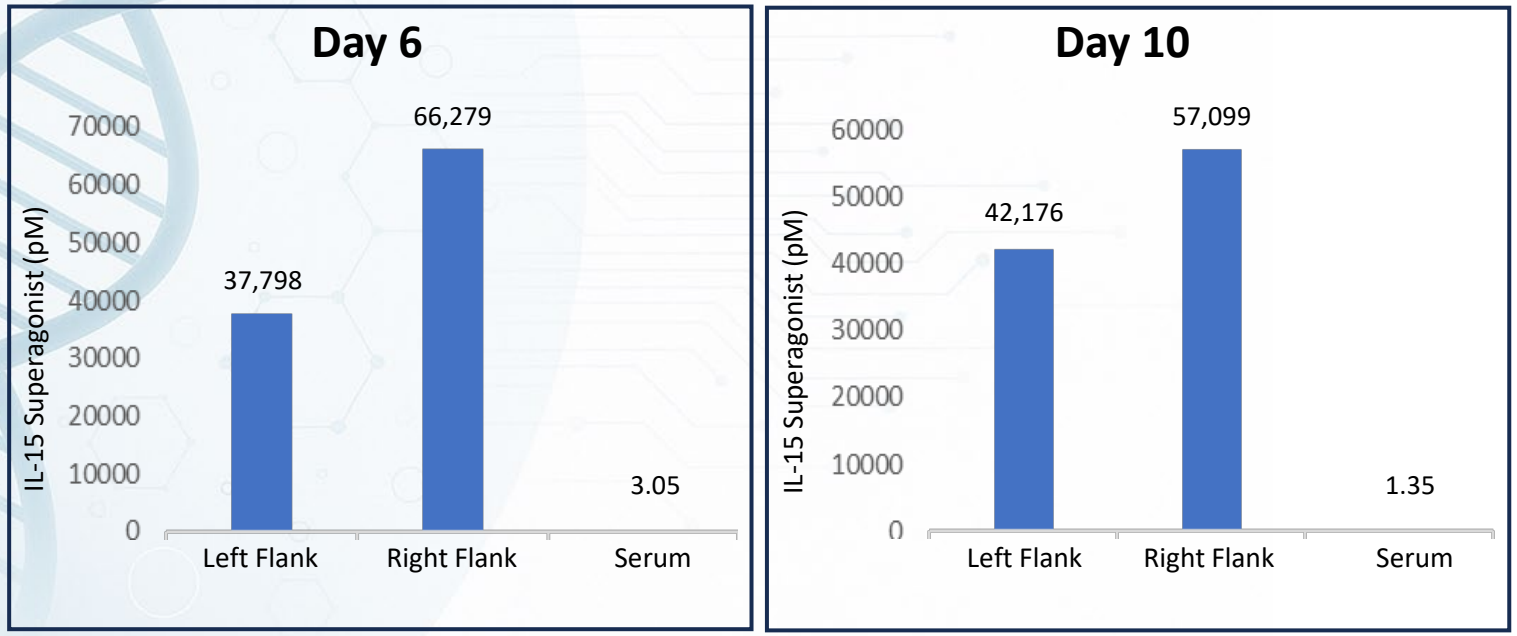
CLD-401 Delivers High Levels of IL-15 SA Only in the Tumor

- Serum concentration in syngeneic murine models is negligible
- Tumor concentration is much higher than achievable with systemic delivery

IL-15 Superagonist Levels in Tumor vs Serum (pM)



RedTail gene therapy delivers IL-15 superagonist directly to tumors, achieving high local concentrations with minimal systemic exposure in mouse models.

- EMT6 model: 1 dose at 10^6 PFU
- Average of 2 animals; each animal had implantations in the left and right flank

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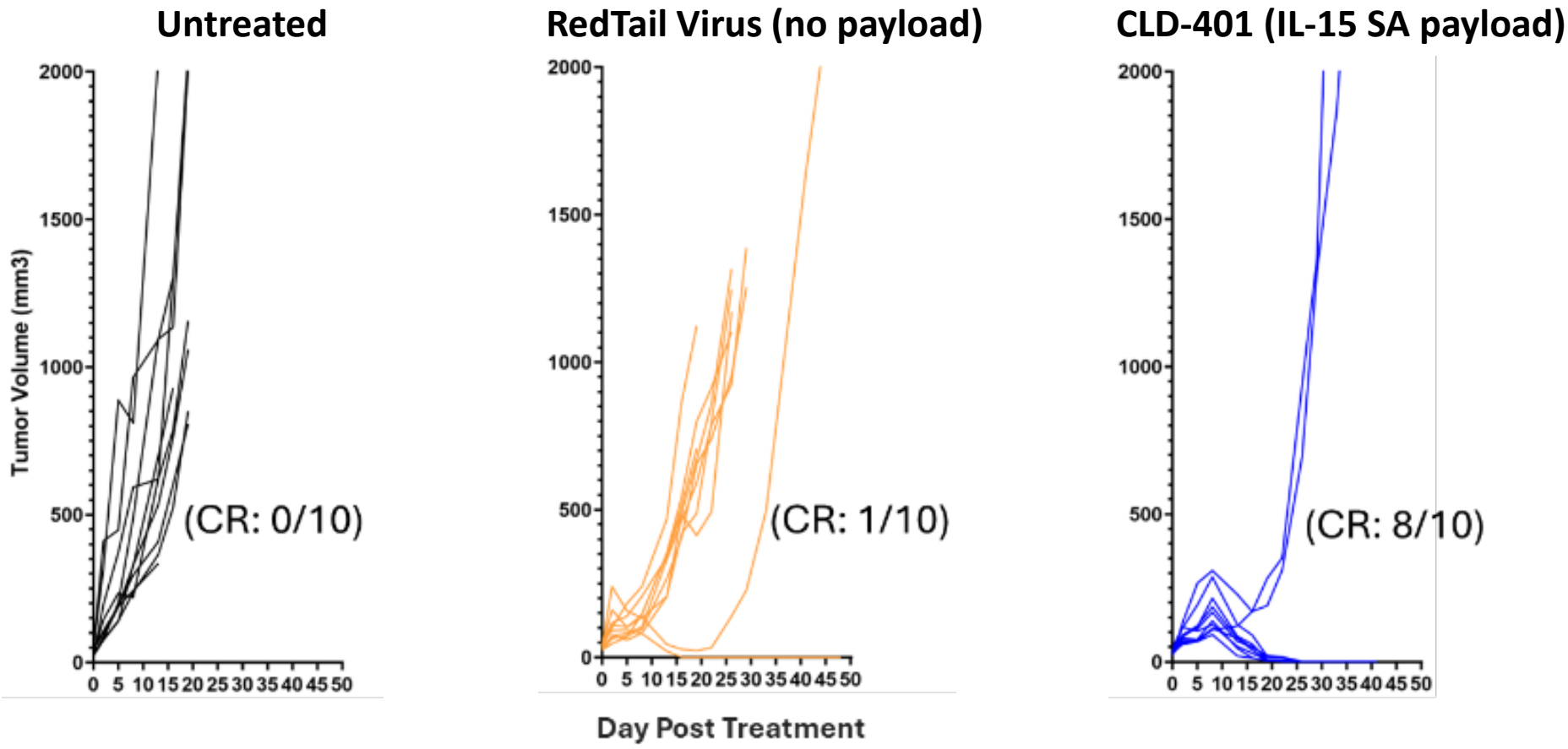
Enhanced Therapeutic Activity With In Situ IL-15 SA Expression

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

Tumor regression in syngeneic EMT6 model after a single administration of 5e6 PFU viral particles



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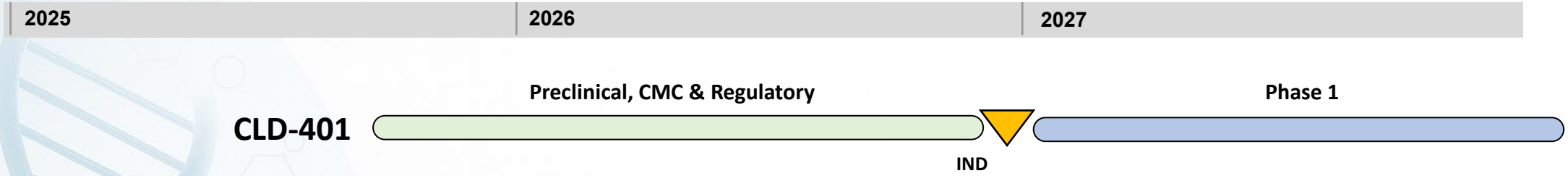
CLD-401 Timeline to Clinic



- **Phase I study to be conducted in a basket of solid tumors (NSCLC, TNBC, Melanoma, etc.)**
  - Rapid dose escalation study with limited # of doses to be tested
  - Early demonstration of systemic delivery of oncolytic virus in a metastatic setting
  - Early demonstration *in situ* delivery of genetic medicine payload (IL-15 superagonist)

- **Responses early in Ph I I would validate the RedTail platform**
  - **Demonstration of activity would create enormous value in the platform**

- **Potential to create first-in-class / best-in-class novel modality for use in oncology and potentially other indications**

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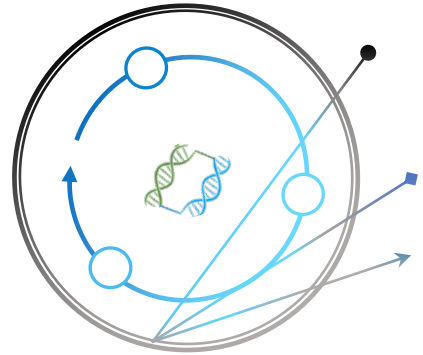
Evolving the RedTail Platform

Lead: CLD-401

Oncology

- Tumor tropism and replication restricted to tumor cells
- Envelope and CD55 expression facilitate survival in the complement-rich bloodstream, enabling systemic delivery
- IL-15 superagonist payload expression drives potent innate and adaptive immune responses to the tumor

Next-Generations



Precision Oncology and Other Diseases

- Envelope engineering for “programmable” targeting
  - Targeting proteins (scFvs, VHHs, etc.) expressed in envelope
- Replication in other proliferating cells (i.e., activated immune cells)
- Additional payload(s) to impart new biology
  - Immunosuppressive payloads for I&I disease

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Capitalization Table

Securities Outstanding (as of September 30, 2025)	Common Stock Equivalents
Common stock outstanding	7,056,312
Warrants (WAEP $34.97)	5,026,613
Options (WAEP $59.56)	251,036
Forward Purchase Agreements	5,501
Fully Diluted	12,339,462

Cash position:

- $5.3M in cash as of June 30, 2025
- Raised gross proceeds of $11.5M through public offerings in July and August 2025

Cash burn of ~$4-5M/quarter

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New Leadership Driving Strategic Progress

❖ **New management team**	✓ New CEO, CMO and Chairman with industry experience to drive value
❖ **Improving the balance sheet**	✓ Debt reduced from >$8M to $1.4M (2Q25); projected to be $0.6M by end of 2025
❖ **Reducing operating costs**	✓ G&A expenses reduced by 25% 1H24-1H25; plans to further reduce costs
❖ **Rapidly advancing the pipeline**	✓ CLD-401 program to be rapidly advanced as proof-of-concept for RedTail platform
❖ **Potential for non-dilutive capital**	✓ Pharma partnerships discussions around the RedTail platform

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Near-term Milestones

CLD-401: SITC presentation — Demonstration of IL-15 SA production in tumors versus serum; benefit in animal models inducing complete responses

CLD-401: IND-enabling pharmacology and toxicology studies completed

RedTail Platform: Preclinical data supporting platform utility beyond solid tumors

CLD-401: Open IND for r/r solid tumor

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