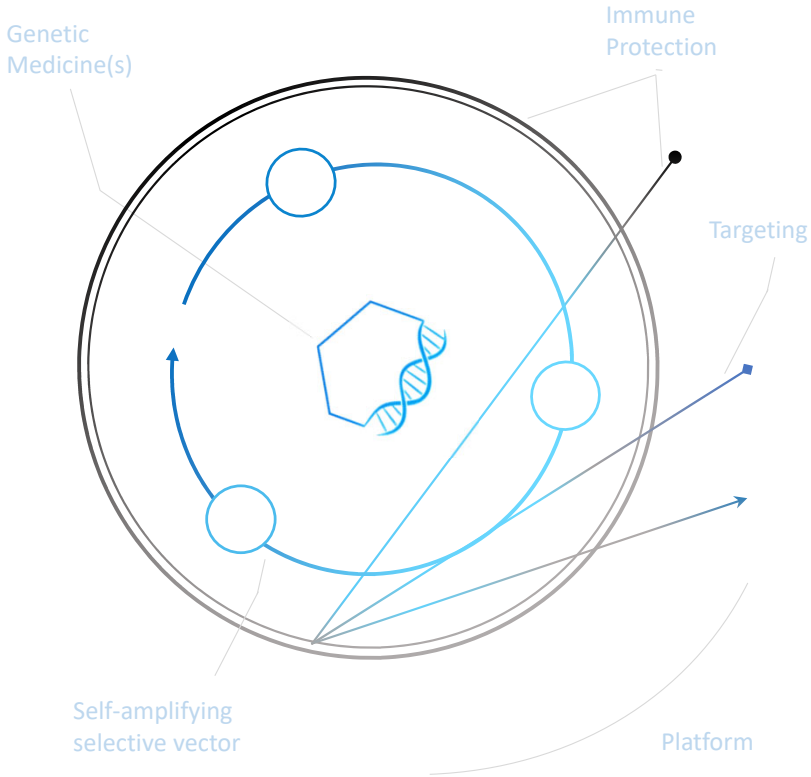
Engineering the Future of Genetic Medicine

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



February 2026

NYSE American: CLDI
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CALIDI BIOTHERAPEUTICS

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Any forward-looking statements contained in this discussion are based on Calidi's current expectations and beliefs concerning future developments and their potential effects and are subject to multiple risks and uncertainties that could cause actual results to differ materially and adversely from those set forth or implied in such forward-looking statements. Other risks and uncertainties are set forth in the section entitled "Risk Factors" and "Cautionary Note Regarding Forward-Looking Statements" in the Company's Form 10-K filed on March 31, 2025, as may be amended or supplemented by subsequent filings we make with the SEC from time to time.

New Technology / New Leadership

❖ **RedTail platform and CLD-401 recently presented**	✓ First data presented on RedTail and CLD-401 in 2025
❖ **New management team with focus on execution**	✓ New CEO, CMO and Chairman with the industry experience to drive value
❖ **Revamped Scientific Advisory Board to support RedTail platform**	✓ Mace Rothenberg (former CMO of Pfizer), Dr. John Wrangle (pioneered systemic dosing of Anktiva)
❖ **Improved balance sheet**	✓ Debt reduced from >$8M to $0.7M
❖ **Reduced operating costs**	✓ ~70% of forecasted spend on R&D in 2026
❖ **Rapidly advancing the pipeline**	✓ CLD-401 program to be rapidly advanced as proof-of-concept for RedTail platform

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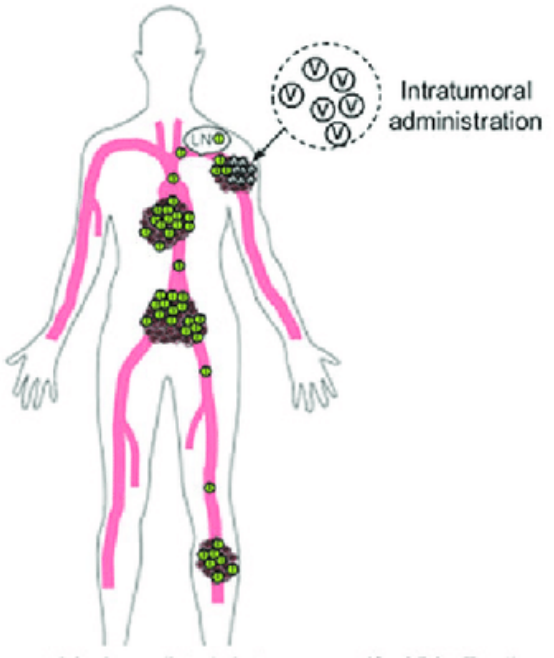
Proven Efficacy with Intra-Tumoral Oncolytic Viruses

- **Multiple examples of efficacy with local administration**
  - Amgen: T-Vec approved in 2015 for melanoma
  - CG Oncology: BLA submission for bladder cancer
  - Candel: BLA filing expected in localized prostate cancer
  - Replimune: BLA submitted for melanoma
- **Intra-tumoral administration is highly limiting…**
  - Most patients do not have disease amenable to intra-tumoral administration
- **…but lytic replication and immune priming represent novel mechanisms of action in oncology**
  - A potent and unique way of killing tumor cells
  - A potent (but transient) immune signal



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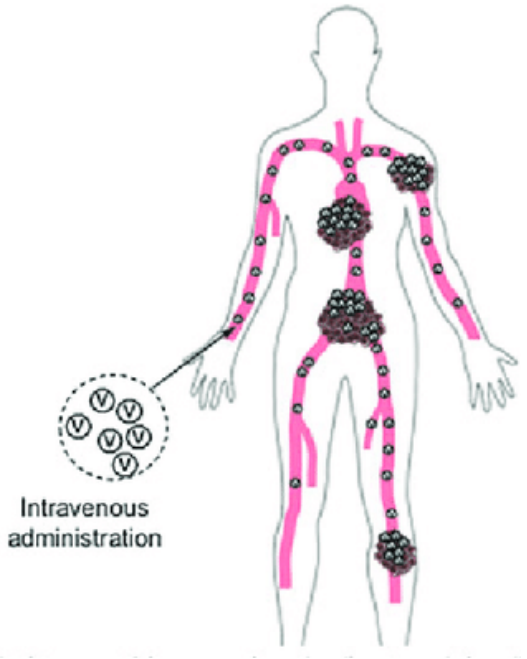
Can Oncolytic Viruses Be Used as Systemic Therapy?

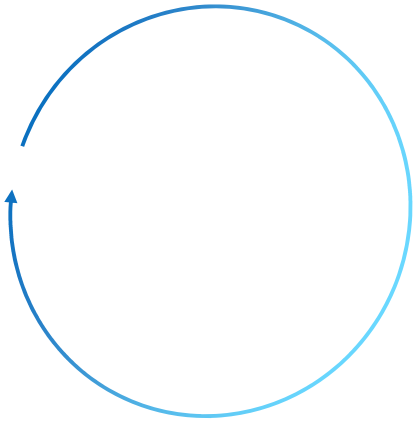
- **Immune system quickly clears virus injected systemically into the bloodstream**
- **Some limited success with systemic delivery of viruses[1,2,3,4]**
  - Strategy is based largely on dosing very high levels of virus to overcome immune clearance
- **Calidi has spent the last decade working on a virus that can be delivered systemically and access metastatic sites**
  - Creating a virus that can evade the immune system
  - Creating a virus that can only destroy tumor cells
  - Creating a virus that can deliver potent genetic medicines to tumor cells



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)

Building the Optimal Viral Platform, Step by Step

- **Calidi has created a new strategy for systemic delivery based on eliminating immune recognition of virus**
  - Allows for higher doses of effective virus with lower levels of innate immune stimulation; i.e., better therapeutic window
- **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
  - **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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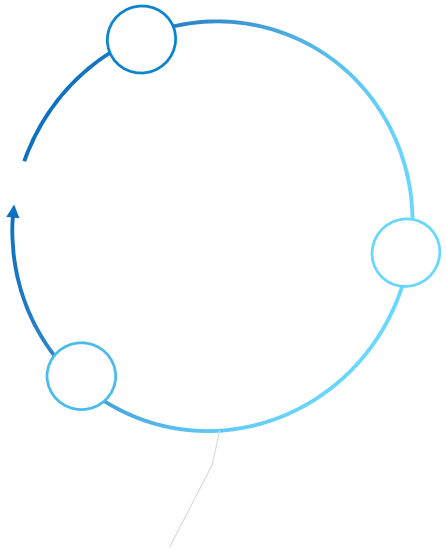
Building the RedTail Scaffold: Step 1

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

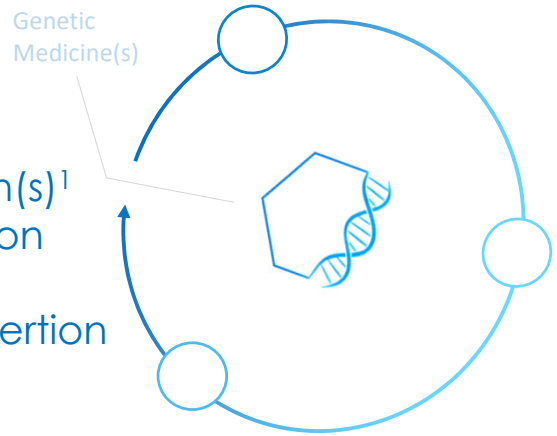
- Triple knockout version of vaccinia virus created that can only replicate in tumor cells
  - TK, VGF, and A46R genes knocked out[3]



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

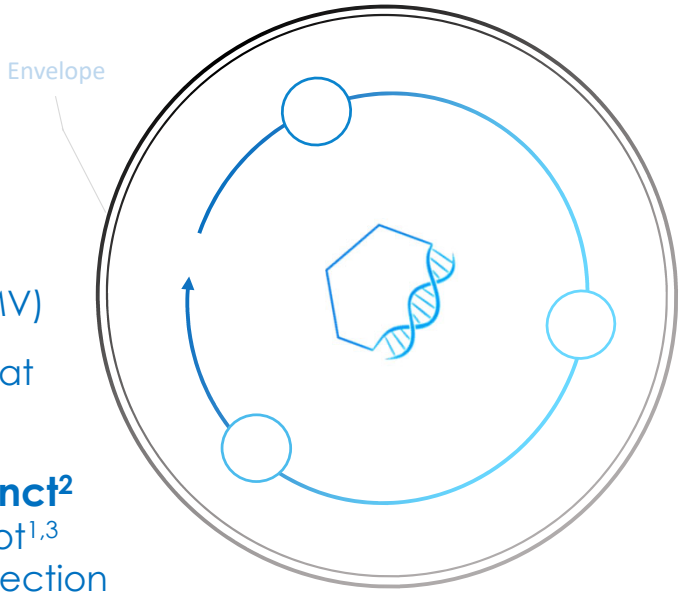
❖ **Vaccinia blocks host cell production and favors viral protein production**

- 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

Building the RedTail Scaffold: Step 3

Enveloped Form of Vaccinia Virus

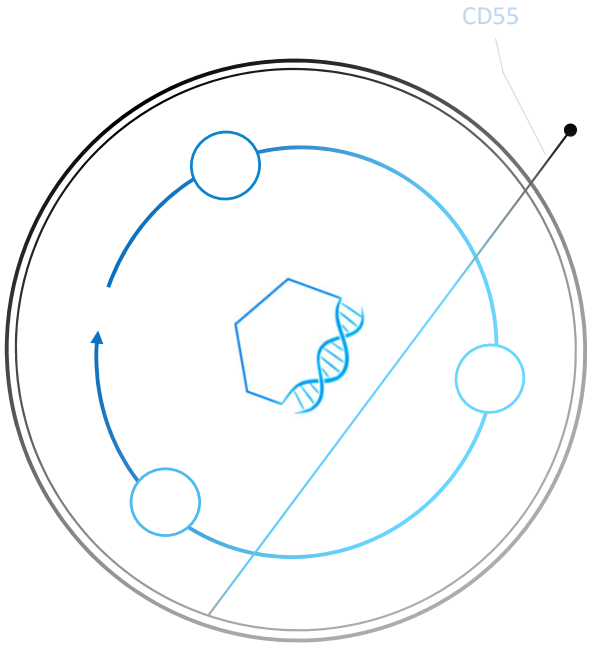


- **Vaccinia virus produces two forms of infectious particles[1]**
  - During infection, >99% of virus is Intracellular Mature Virus (IMV)
  - <1% of virus is the Extracellular Enveloped Virus (EEV) form that takes on the cell membrane (envelope) from its host
- **Forms are structurally, functionally,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

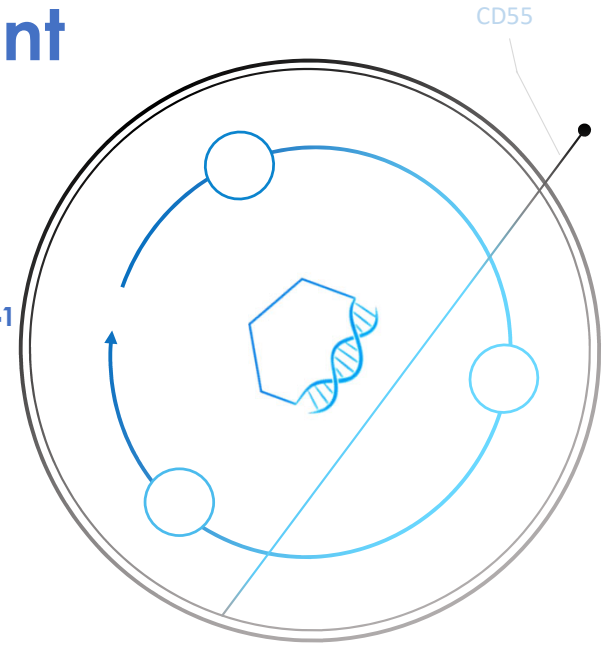
Building the RedTail Scaffold: Step 4



- **CD55 Overexpression**
  - **Complement is pivotal for immune clearance for Vaccinia[1,2]**
    - Complement is the major 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)

CD55 as a Protector Against Complement



- **CD55 expression and erythrocytes (red blood cells, RBCs)**
  - **RBCs are normally protected from clearance by complement**[1]
  - **Paroxysmal Nocturnal Hemoglobinuria (PNH)**
    - Mutation in CD55; RBCs are cleared by complement system[1]
  - **Parasite induces a loss of CD55 on RBCs**
    - Extent of CD55 loss correlates with severity of anemia[2]
- **CD55 expression and resistance to Mab therapy**
  - **MOA for mAbs in hematologic malignancies dependent on complement**
    - Resistance to Daratumumab and Rituxan is associated with CD55 upregulation[3,4]

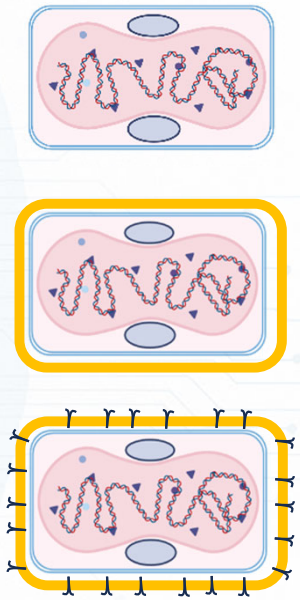
1. Ruiz-Delgado, *Hematology.* 2009 Feb;14(1):33-7.
2. Fendel et al. *PLOS One.* 2010 April; 5(4)
3. Nijhof et al. *Blood.* 2016 Aug; 18(1)
4. Rezvani et al Best *Pract Res Clin Haematol.* 2011 Apr 13;24

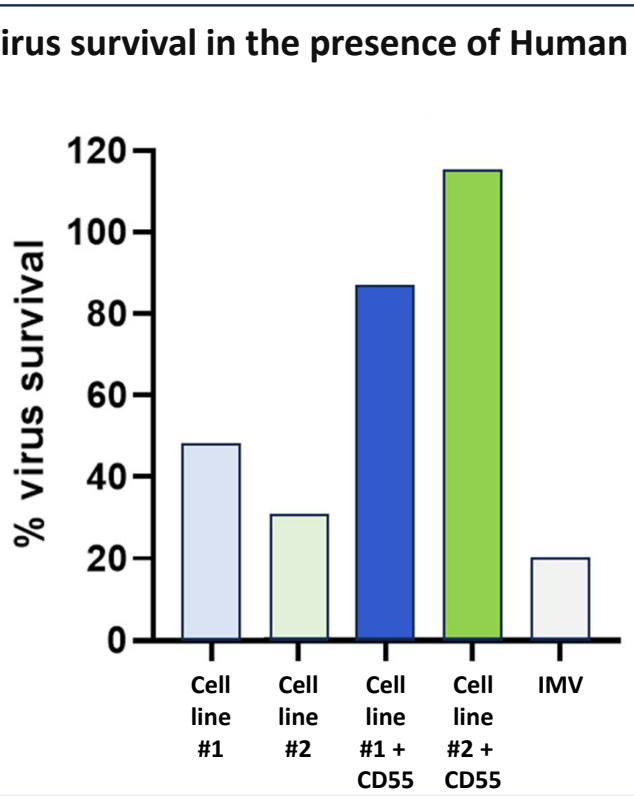
EEV with CD55 Expression Is Highly Resistant to Clearance

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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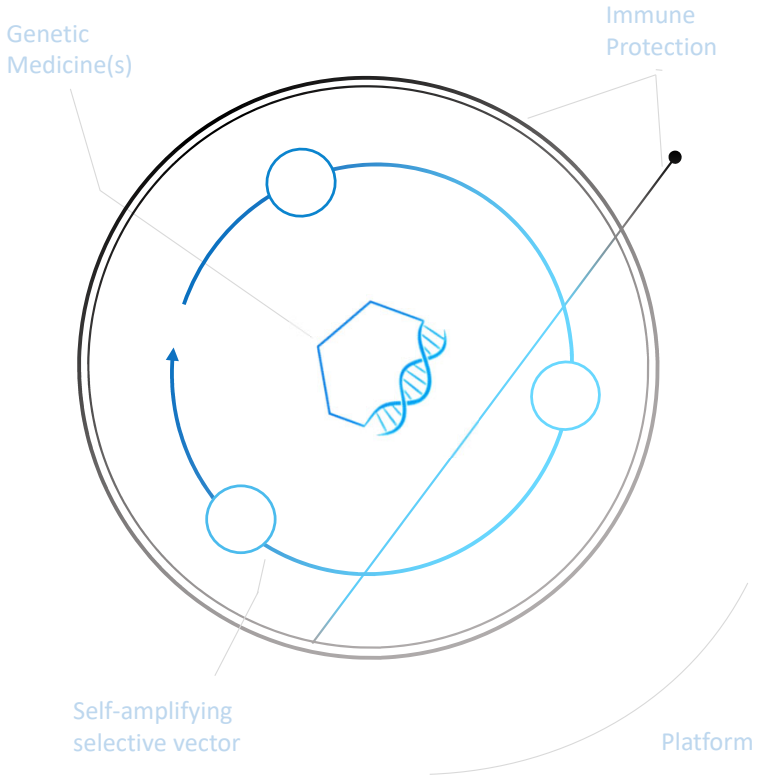
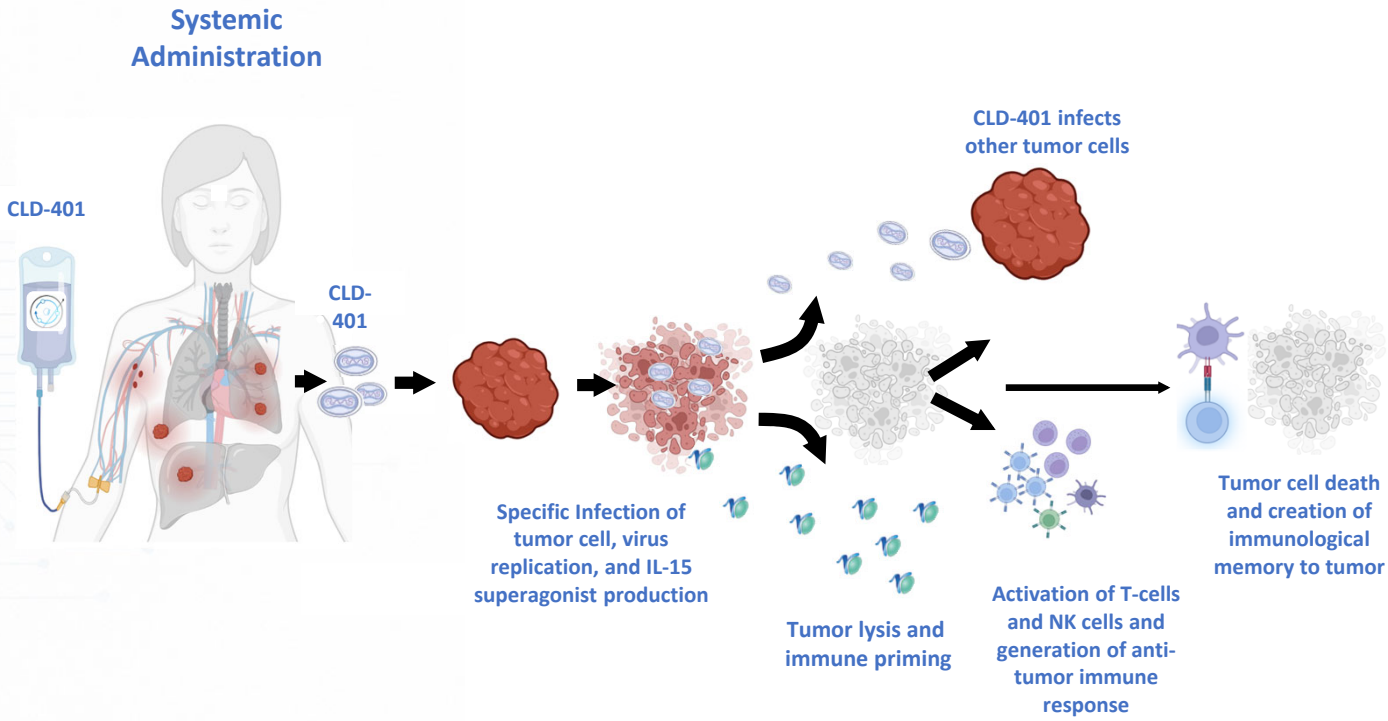
The RedTail Platform

- 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



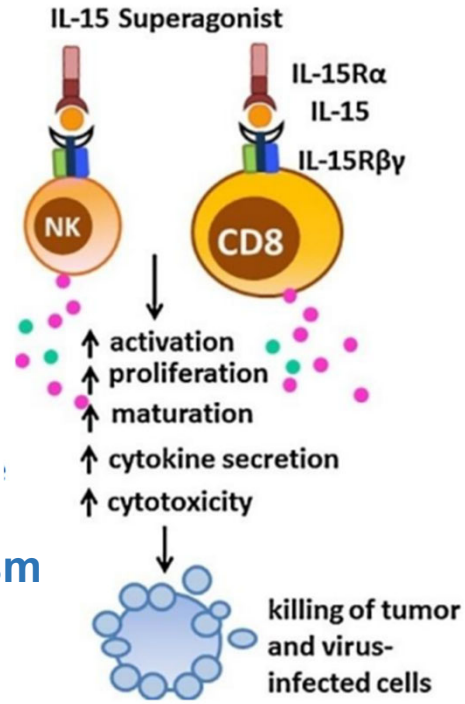
CLD-401: The First Lead From the RedTail Platform

- 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



IL-15SA: Proven Activity At High Doses and With an Immune Primer

- IL-15 is a powerful growth factor for NK cells (innate) and CD8+ T-cell (adaptive)
  - Unlike IL-2, IL-15 does not expand Tregs or induce T-cell death
- A major mechanism of resistance to PD-1 therapy is B2M mutation / HLA loss
  - B2M/HLA loss prevents CD8 T-cell recognition of tumors
  - IL-15 activation of NK cells may overcome this resistance mechanism
    - NK cells can recognize and destroy cells with B2M/HLA loss
- IL-15 superagonist (IL-15SA) is an engineered form of IL-15 with enhanced potency over IL-15



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IL-15SA: Proven Activity At High Doses and With an Immune Primer

- **Anktiva (IL-15 SA) is approved in bladder cancer for local delivery:**
  - Extraordinary levels of IL-15 SA in the TME (~80K pM)
  - Given with BCG as an immune priming mechanism
  - Low systemic IL-15 SA exposure (<20pM)
- **Anktiva is being explored for systemic delivery in metastatic patients**
  - Dosing is limited due to toxicity potential; no priming mechanism is included
  - Systemic levels of IL-15 SA exposure are <20pM
- **ImmunityBio (Anktiva) has >$5B market cap**

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

- **IL-15 SA concentrations in the tumor are similar to Anktiva in bladder cancer**
  - **Expression in serum or other tissues is >1,000 times lower**
  - **Virus is acting as an immune primer in the tumor**

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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CLD-401: Tumor-specific viral replication

- **Viral expression detected only in tumor tissue**
  - **Replication in other tissues is ~1,000 times lower or non-detectable**
  - **Tumor-specific replication allows for systemic delivery**

CLD-401 showed high tumor presence with minimal detection in other organs:

Tumor-bearing model:

Timepoint	Tumor		Liver		Ovary		Lung	
	copies/ug DNA	sd	copies/ug DNA	sd	copies/ug DNA	sd	copies/ug DNA	sd
Day 6	96,436	12,558	-	-	121	210	-	-
Day 17	10,489	5,741	-	-	-	-	-	-
Day 21	5,085	2,766	-	-	-	-	-	-

Non-tumor-bearing model:

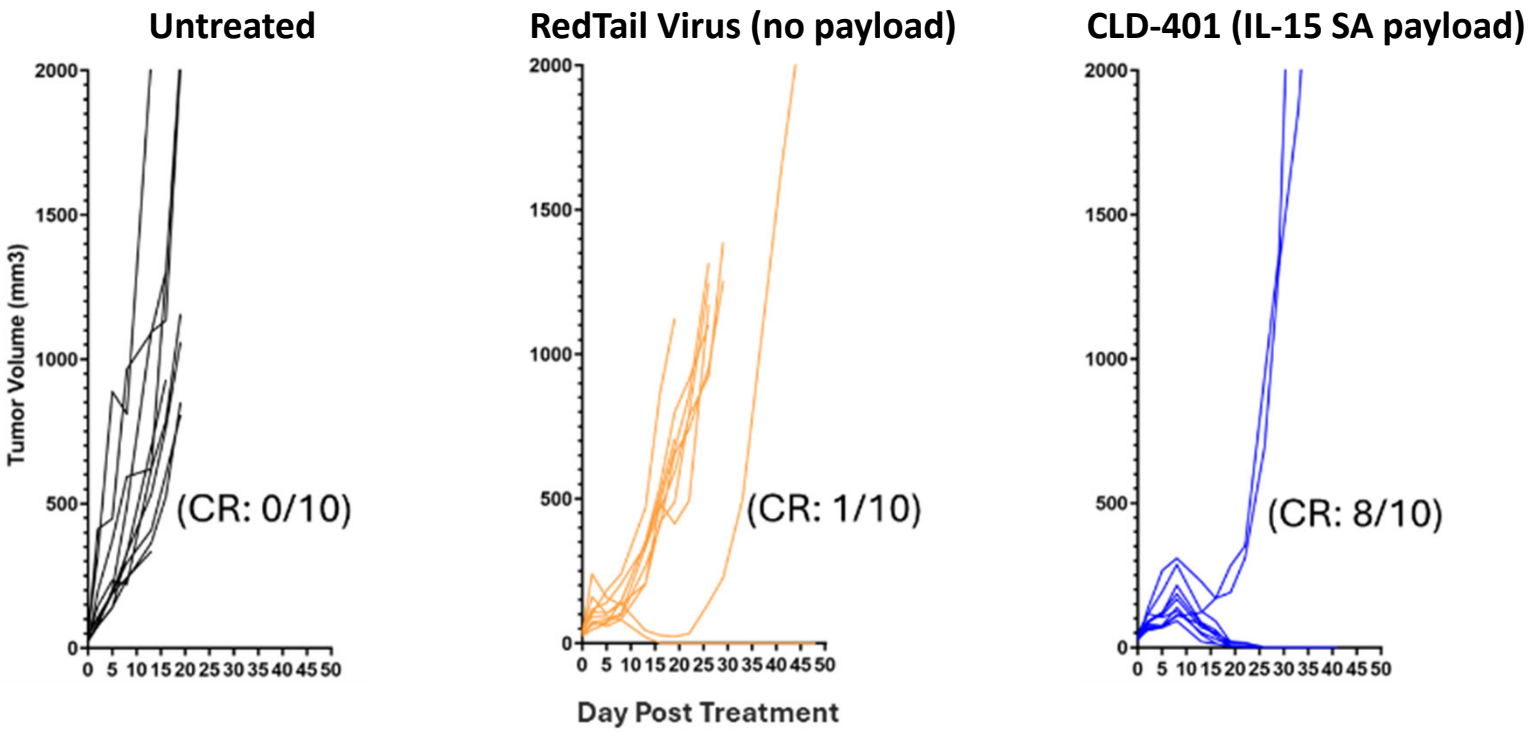
Timepoint	Liver		Ovary		Lung	
	copies/ug DNA	sd	copies/ug DNA	sd	copies/ug DNA	sd
Day 6	-	-	51	79	-	-

Vaccinia virus amplification (copy number) detected by qPCR

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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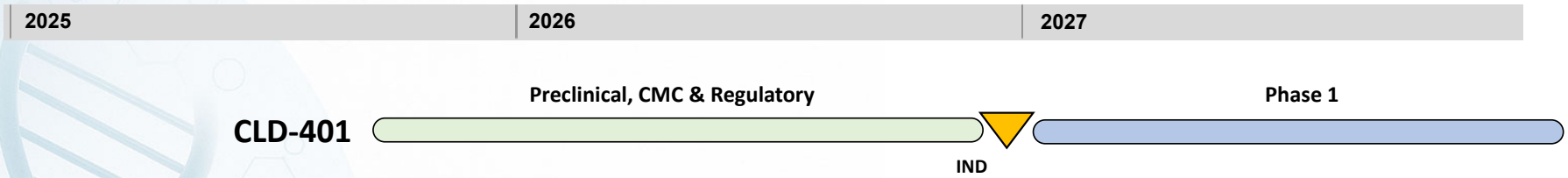
CLD-401 Timeline to Clinic



- **Phase I study to be conducted in a basket of solid tumors (NSCLC, TNBC, Melanoma, etc.)**
  - Streamlined 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 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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RedTail: Potential to Enhance Platform and Expand Outside of Oncology

Next-Generations

Precision Oncology and Other Diseases

Cancer:

- Expand **payload** options (**e.g BiTEs)**
- Engineer envelope for **programmable targeting** (e.g. HER2, TROP2, CD38, etc)

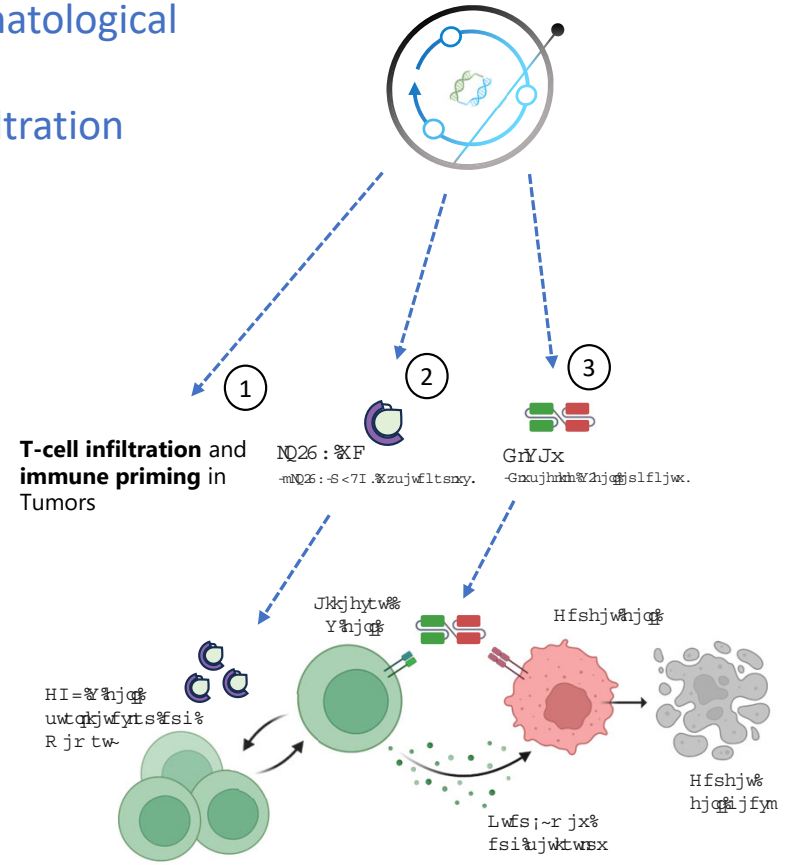
Outside Oncology:

- New **payloads for inflammatory & immune diseases** (I&I)
- Target other cell types via envelope engineering (e.g CD38, BCMA etc)
- Leverage viral replication in proliferative cells (e.g., activated B cells)

Delivering High Concentrations of BiTEs and T-cell Amplifier to the TME

- **BiTEs (Bi-specific T-cell engagers) have been transformative** in hematological malignancies but have not shown success in solid tumors
  - The tumor microenvironment in solid tumors inhibits T-cell infiltration and T-cell effector activity

- **RedTail platform can be used to simulataneously increase T-cell infiltration into the TME and deliver both a BiTE and a T-cell activating cytokine(s) to the TME**
  - Can deliver a BiTE along with high concentrations of cytokine(s) that activate and/or recruit T-cells
  - Potential to overcome hostile TME and with monotherapy



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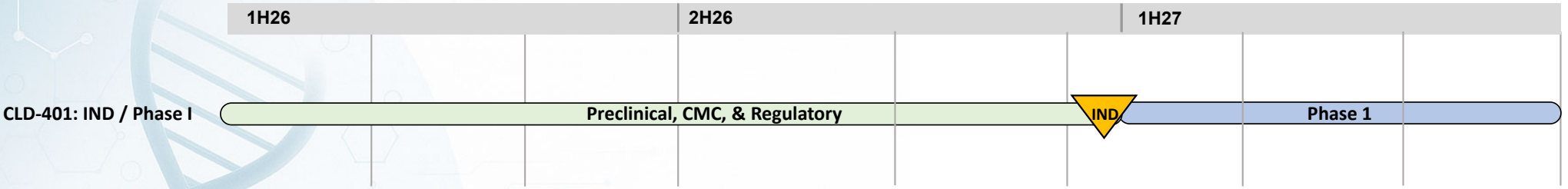
Upcoming Milestones



Data presentations	AACR	ASCGT	ASCO	ESMO	SITC	AACR	ASCGT	ASCO
CLD-401	• Data on TME remodeling in immunocompetent animal models	• Presentation of RedTail platform to non-oncology community	• Data on repeat dosing in immuno-competent models	• Tox and efficacy data supporting IND filing	• Biodistribution data from IND enabling-studies	• Combination data with CLD-401	• Update on non-oncology programs	• Combination data with CLD-401
Additional Pipeline	• First data presented on RedTail BiTE approach: in situ simultaneous expression of BiTE and T-cell activator		• Additional data on BiTE platform across multiple targets		• In vivo BiTE data • Data on programs outside oncology	• Pipeline updates • Pipeline updates		• Pipeline updates • Pipeline updates

- ❖ IND filing planned for end of 2026 with first patient treated planned for 1Q27
- ❖ Multiple pre-clinical data presentations for CLD-401, BiTE, and non-oncology programs throughout 2026 and 2027
- ❖ Press release updates on clinical trial in real-time; robust presence at banking and partnering conferences

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