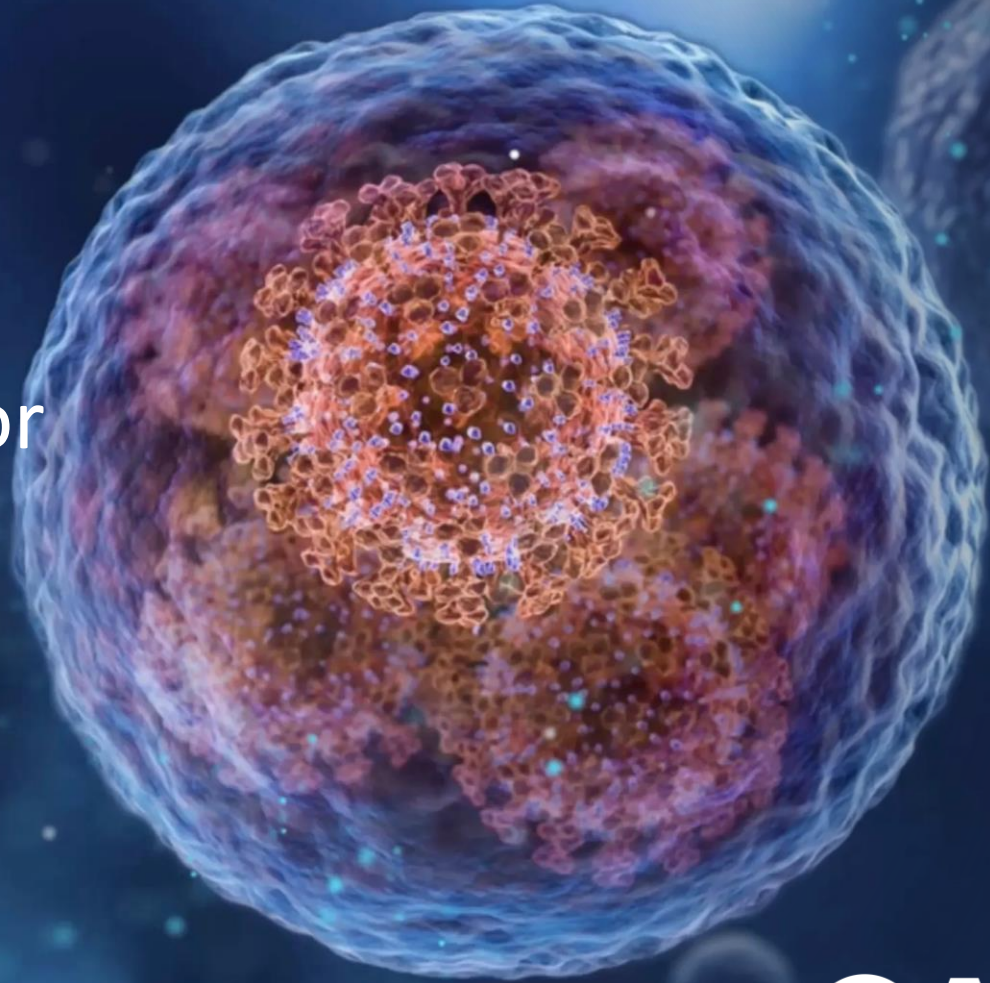


Systemic and Localized Antitumor Virotherapies

Designed to attack every tumor
and arm the immune system

January 2025



CALiDi
BIOTHERAPEUTICS

Forward-Looking Statements and Legal Disclaimer

This presentation may contain forward-looking statements for purposes of the “safe harbor” provisions under the United States Private Securities Litigation Reform Act of 1995. Terms such as “anticipates,” “believe,” “continue,” “could,” “estimate,” “expect,” “intends,” “may,” “might,” “plan,” “possible,” “potential,” “predicts,” “project,” “should,” “towards,” “would” as well as similar terms, are forward-looking in nature, but the absence of these words does not mean that a statement is not forward-looking. These forward-looking statements include, but are not limited to, statements concerning upcoming key milestones (including the reporting of interim clinical results and the dosing of patients), planned clinical trials, and statements relating to the safety and efficacy of Calidi’s therapeutic candidates in development. 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. These risks and uncertainties include, but are not limited to, the risk that Calidi is not able to raise sufficient capital to support its current and anticipated clinical trials, the risk that early results of clinical trials do not necessarily predict final results and that one or more of the clinical outcomes may materially change following more comprehensive review of the data, and as more patient data becomes available, the risk that Calidi may not receive FDA approval for some or all of its therapeutic candidates. Other risks and uncertainties are set forth in the section entitled “Risk Factors” and “Cautionary Note Regarding Forward-Looking Statements” in the Company’s Registration Statements filed with the SEC on (i) Form S-4 filed on August 2, 2023 and the corresponding prospectus filed on August 4, 2023, and (ii) on Form S-1 filed on April 15, 2024, and the Company’s periodic reports filed with the SEC on (i) Form 10-K filed on March 15, 2024, (ii) Form 10-Q filed on May 14, 2024, (iii) Form 10-Q filed on August 13, 2024, and (iv) Form 10-Q filed on November 12, 2024. These reports may be amended or supplemented by other reports we file with the SEC from time to time.

RISK FACTORS

The risk factors summarized below could materially harm our business, operating results and/or financial condition, impair our future prospects and/or cause the price of our common stock to decline. These risks are discussed more fully following this summary. Material risks that may affect our business, operating results and financial condition include, but are not necessarily limited to, the following:

- We are an immuno-oncology company with a limited operating history and have not generated any revenue to date from product sales.
- We have incurred significant operating losses since our inception and anticipate that we will incur continued losses for the foreseeable future.
- We have no products approved for commercial sale and have not generated any revenue from product sales.
- Our engineered allogeneic stem cell product candidates represent a novel approach to cancer treatment that creates significant challenges.
- Adverse publicity regarding stem cell-based immunotherapy could have a material adverse impact on our business.
- We will need to raise substantial additional funding. If we are unable to raise capital when needed, or if at all, we would be forced to delay, reduce or eliminate some of our product development programs or commercialization efforts.
- We may incur significant cash payment obligations under our in-licensing agreements with Northwestern University and City of Hope.
- Mr. Camaisa, an officer and director, and Mr. Leftwich, a director, and their respective affiliates own a significant percentage of common stock and have significant influence over management.
- The company has limited foreign intellectual property rights and may not be able to protect intellectual property rights throughout the world.

Overview



Calidi Biotherapeutics is a **clinical-stage biotechnology** company that is transforming cancer treatment, with innovative **oncolytic virotherapies (OV)**.



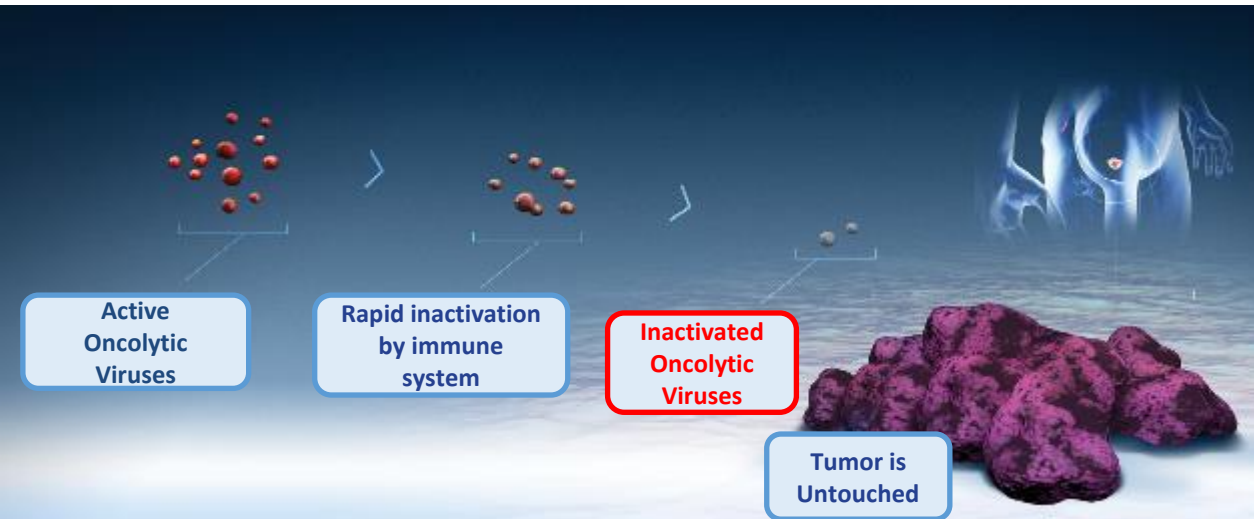
Our cutting-edge **cell-based technologies protect** and deliver oncolytic virotherapies into tumor sites, effectively **overcoming the clinical challenge of rapid elimination by the patient's immune system.**



Both systemic and localized technologies will revolutionize the treatment of solid tumors.

Calidi Overcomes the Obstacles to Oncolytic Viral Therapy

Challenges with Naked OV Therapy Unprotected Oncolytic Virus

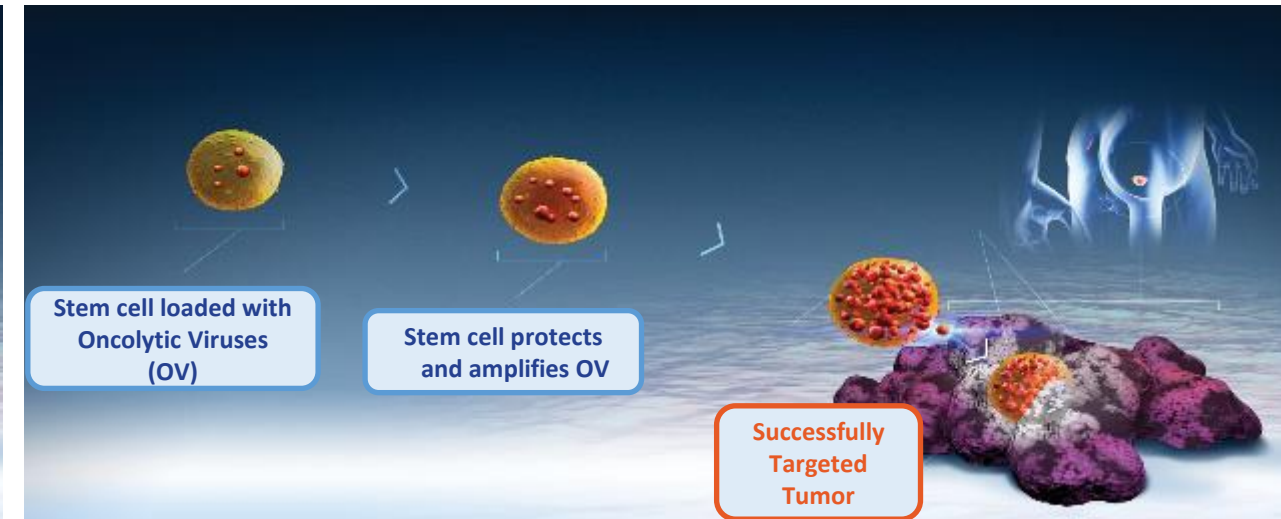


Naked oncolytic viruses are quickly eliminated by the patient's immune system, leading to limited therapeutic potential

Calidi's Allogeneic Stem Cell Platforms

Calidi's Solution

Allogeneic Oncolytic Virus-Loaded Stem Cells



Allogeneic Stem Cells
Protect, Amplify, Deliver
and Potentiate OV's

Calidi Oncology Pipeline

Product	Platform	Target Indications	Discovery	Non-clinical studies	Phase 1	Phase 2	Pivotal Trial	Partner
CLD-101	NeuroNova	Newly Diagnosed High Grade Glioma	Entering Phase 1b/2					 
		Recurrent High Grade Glioma	Phase 1 started				\$12M	 
CLD-201	SuperNova	Advanced Solid Tumors: Head & Neck, TNBC, Soft tissue Sarcoma (Localized administration)	FDA Pre-IND – Planned Phase 1					\$3M 
CLD-400	RTNova	Metastatic Solid Tumors & Lung cancer (Systemic administration)	Preclinical					

Multiple partnership opportunities to potentiate and deliver other existing OV's, combination therapies, and joint development of next generation therapies

Upcoming Planned Milestones (2025-2026)

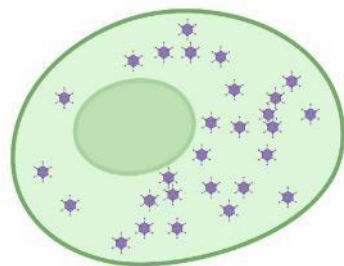
	2025		2026	
	1H	2H	1H	2H
CLD-101 (NNV1: multiple doses newly diagnosed HGG)	 <u>1st patient dosed</u>	 Clinical trial enrollment update	 Clinical trial Update	 Clinical trial Update
CLD-101 (NNV2: Multiple doses recurrent HGG)	 <u>Clinical trial & biomarker studies update</u>	 Phase 1. Dose escalation recruitment completed	 Clinical trial Update	 Clinical trial Update
CLD-201 (SNV1)	 <u>IND Submission</u>	 <u>1st patient dosed (dose escalation)</u>	 Clinical trial Update	 Phase 1. 10 patient expansion starts
CLD-400 (RTNova)	 <u>Platform update (AACR)</u>	 <u>Selection of Lead candidate (ASCO)</u>  <u>FDA: Type D meeting</u>	 FDA: PRE-IND Submission. Type C meeting.	 Scientific meeting: Update IND-enabling studies.  IND Submission

Calidi's Three Lead Programs

CLD-101 (NeuroNova)

Clinical trial Phase 1b/2

Indication: Recurrent and newly diagnosed High Grade Glioma



Tumor selective Virotherapy:

Adenovirus: CRAD-s-Pk7

Delivery vehicle/potentiator:

Allogeneic Neuronal Stem Cells

Product type:

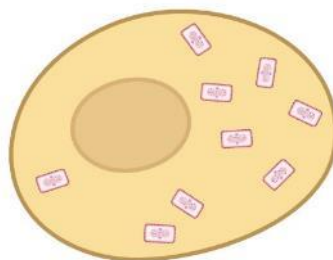
Off-the-shelf

Localized administration

CLD-201 (SuperNova)

Targeting clinic 1H 2025

Indication: Advanced Solid Tumors:



Tumor selective Virotherapy:

Vaccinia virus: CAL1

Delivery vehicle/potentiator:

Allogeneic Adipose-derived

Mesenchymal Stem Cells

Product type:

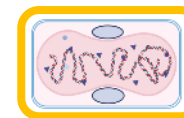
Off-the-shelf

Intratumoral administration

CLD-400 (RTNova)

Pre-clinical

Indication: Lung Cancer, and Metastatic Cancer



Tumor selective Virotherapy:

Extracellular Enveloped Vaccinia virus: envRT-01

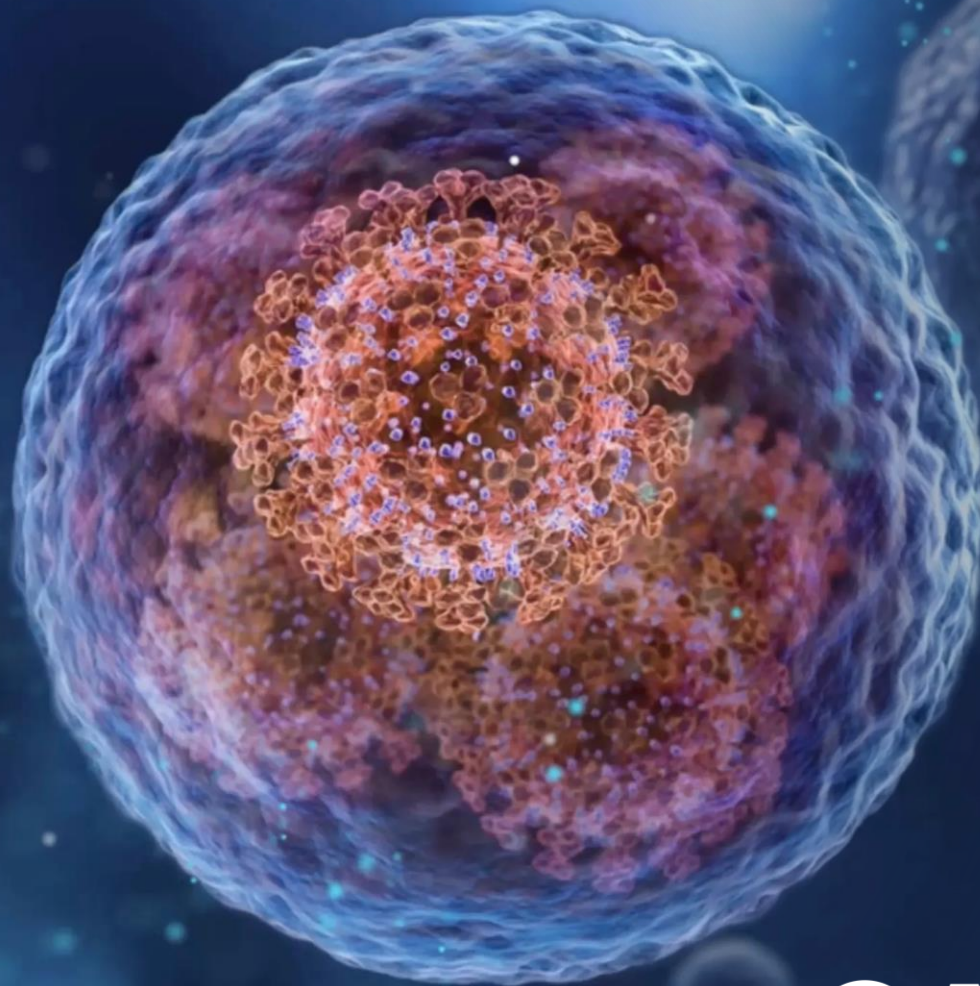
Product type:

Off-the-shelf

Systemic administration

CLD-101 (NeuroNova)

Designed to Attack High
Grade Glioma Brain Cancer



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CLD-101 (NeuroNova) in High Grade Glioma (HGG)

Completed: Phase 1 (NWU)

Single dose

in newly diagnosed HGG

Ongoing: Phase 1 (COH)

multiple dose

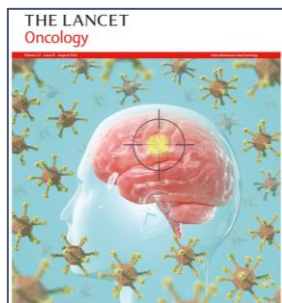
in recurrent HGG

In preparation: Phase 1b/2 (NWU)

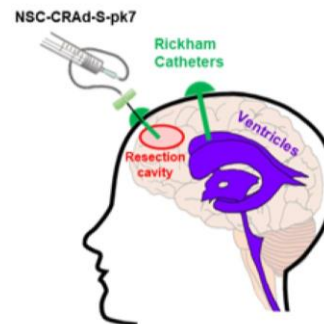
multiple dose

in newly diagnosed HGG

- Treatment was **well tolerated**
- In the subset of patients containing an unmethylated MGMT promoter, the median **PFS was 8.8 vs. 5.3 months** and **Overall Survival was 18 vs. 12.7 months**.
- Primary Objective: analyze **safety and feasibility** of intracerebrally administering up to **4 weekly doses**
- Currently enrolling participants to Treatment Schedule 4 (4 doses).
- Primary Objective: analyze **safety and feasibility** of multiple intracerebrally administering in newly diagnosed HGG.
- **IND opened (4Q 2024)**
- **Target to start 1Q 2025**



*Lancet Oncology, 2021
Aug;22(8):1103-1114*

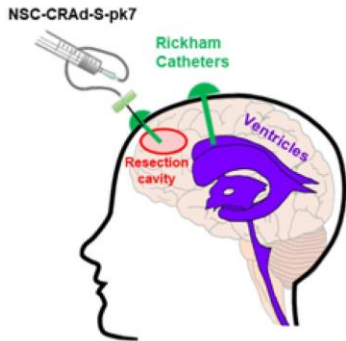


CLD-101: Recurrent High-Grade Glioma Clinical Pathway

- Ongoing Phase 1 trial at City of Hope
- **Indication:** Recurrent High-Grade Glioma
STUDY PROCEDURES:



\$12M **CIRM**
CALIFORNIA / STEM CELL AGENCY



Cycle ^a 1	Cycle 2	Cycle 3	Cycle 4
<u>Day 1</u> • Tumor resection • Manual administration of NSC-CRAD-S-pk7 • Placement of 2 Rickham catheters^b • CSF^c and blood collection <u>Day 2</u> • CSF^d and blood collection	<u>Day 1</u> • CSF and blood collection • NSC-CRAD-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity <u>Day 2</u> • CSF and blood collection	<u>Day 1</u> • CSF and blood collection • NSC-CRAD-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity <u>Day 2</u> • CSF and blood collection	<u>Day 1</u> • CSF and blood collection • NSC-CRAD-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity <u>Day 2</u> • CSF and blood collection

Treatment Schedule	Cycle 1 / Dose 1	Cycle 2 / Dose 2	Cycle 3 / Dose 3	Cycle 4 / Dose 4
1	Treatment ^e (1)	No Treatment	No Treatment	No Treatment
2	Treatment (1)	Treatment (2)	No Treatment	No Treatment
3	Treatment (1)	Treatment (2)	Treatment (3)	No Treatment
4	Treatment (1)	Treatment (2)	Treatment (3)	Treatment (4)
Two weeks after the last treatment with NSC-CRAD-S-pk7, patients will undergo a second surgical procedure to remove the two Rickham catheters and a post-treatment tissue biopsy will be performed.				

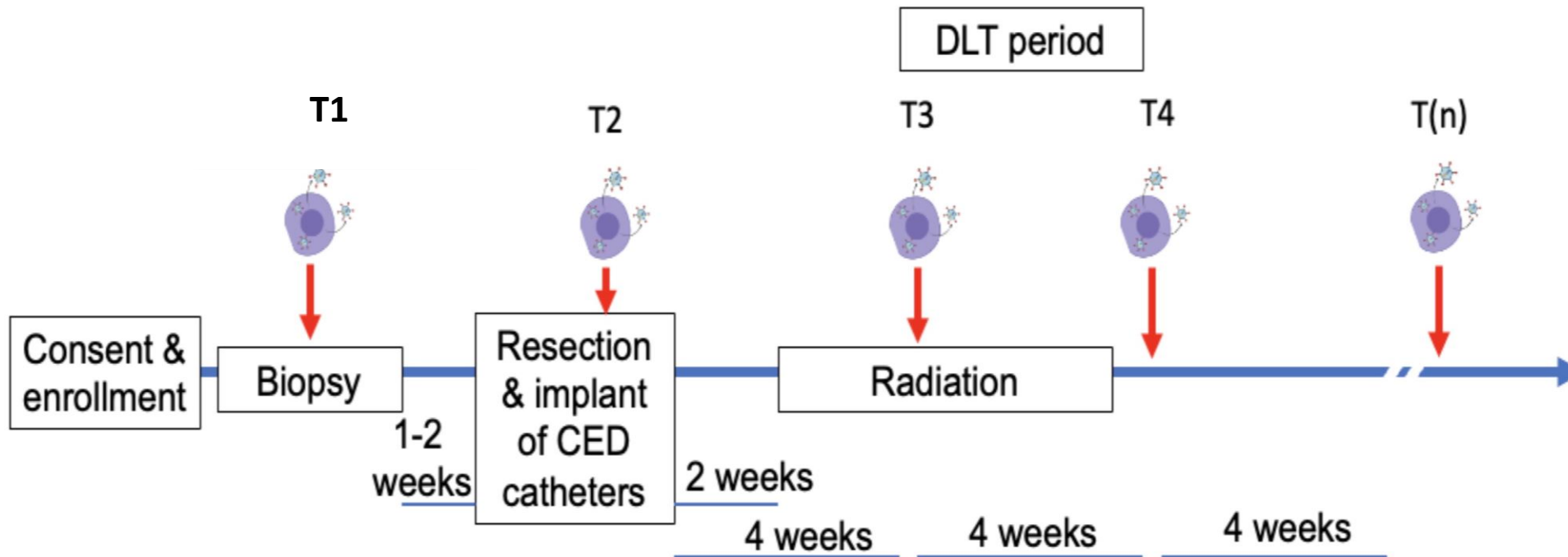
Status:
recruiting 4th cohort

CLD-101: Newly-Diagnosed High-Grade Glioma Clinical Pathway

- Planned Phase 1b/2 Trial at Northwestern University
- Indication:** Newly-Diagnosed High-Grade Glioma



Northwestern
University

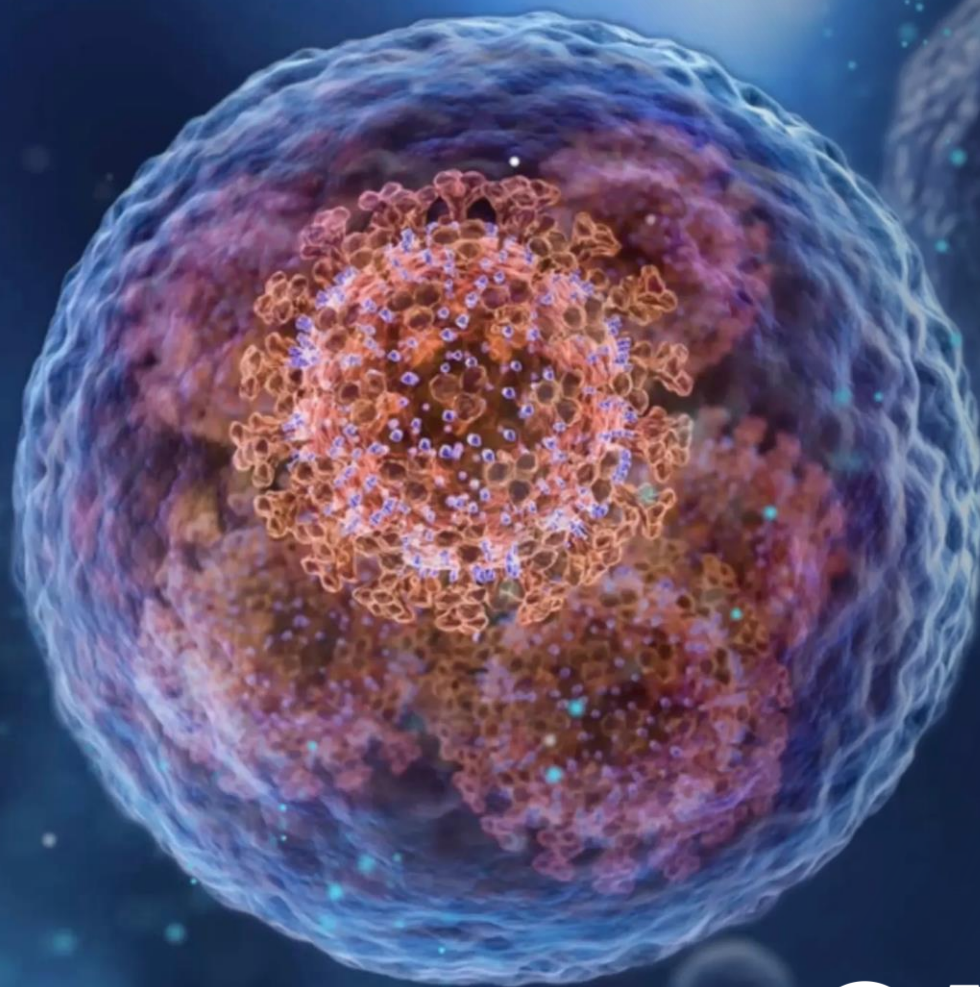


First Patient
In:
1Q 2025

CLD-201 (SuperNova)

- Localized administration
-

For Head & Neck, TNBC, and
Soft Tissue Sarcomas



CLD-201 (SuperNova) in Advanced Solid Tumors

Completed: Safety Study
Autologous settings - **Single dose**

In Preparation: Phase 1 (Calidi)
Allogeneic, off-the shelf - **multiple dose**

- Treatment was **well tolerated**.
- **Strong initial signals of efficacy documented** (in combination with Checkpoint Inhibitors)

- **New allogeneic program developed to reach wider cancer population**
- cGMP Final Drug Product Manufacturing and release completed in 3Q 2024



- **Phase 1 initiation in 1H2025**
Head & Neck, TNBC, Sarcoma

Durable Tumor Regression and Survival

Calidi Autologous Safety Study: Positive Results in Combination With Checkpoint Inhibitor

- Age/Sex: 70/M
- Diagnosis: Metastatic Head & Neck SCC
- Stage IV_B
- Injected tumor was previously resistant to chemo- and radio-therapy

Patient Case: Patient #SI01-021

Day 17 post-treatment



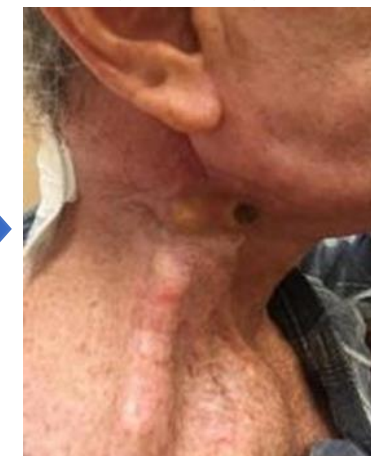
Day 45 post-treatment



Day 52 post-treatment



Day 194 post-treatment:
complete response



**Previously resistant tumor
has fully regressed**

Primary objective - Safety: There were no treatment-related side effects

Secondary objective, Response and Patient Survival:

43 days after treatment the patient received Opdivo (anti-PD-1 treatment) and 76 days after treatment the patient received local radiation therapy. 194 days post treatment the previously resistant tumor had fully regressed.

Durable Tumor Regression and Survival (continued)

- Age/Sex: 68/M
- Diagnosis: Thyroid Papillary Carcinoma
- Stage IV

Calidi Autologous Safety Study

Patient Case: Patient #SI01-047

Day 30 post-treatment



Day 65 post-treatment



Day 85 post-treatment: tumor has fully regressed



Primary objective - Safety: There were no treatment-related side effects

Secondary objective, Response and Patient Survival: 36 hours after treatment, patient received Ipilimumab (anti-CTLA-4), by 85 days tumor fully regressed

CLD-201: Planned Clinical Development of Allogeneic Platform

- A Phase 1/2 study of intra-tumoral administration of CLD-201, in patients with advanced solid tumors (Head & Neck, TNBC, soft tissue Sarcoma)

PART 1: Dose Escalation in Five indications

- Classical 3+3 trial design. Three dose levels will be tested,
- Three to 6 patients will be enrolled at each dose level depending on DLTs observed.

PART 2: Expansion in Three Indications

- Ten patients from each of 3 separate indications will be selected from part 1 based on most favorable biological activity
- CLD-201 dose is identified in Part 1 of this trial.

PART 3: Expansion in Best-Responding Indication – Phase 2

- 30 to 50 patients with the best responding indication determined in Part 2
- CLD-201 dose is identified in Part 1 of this trial.

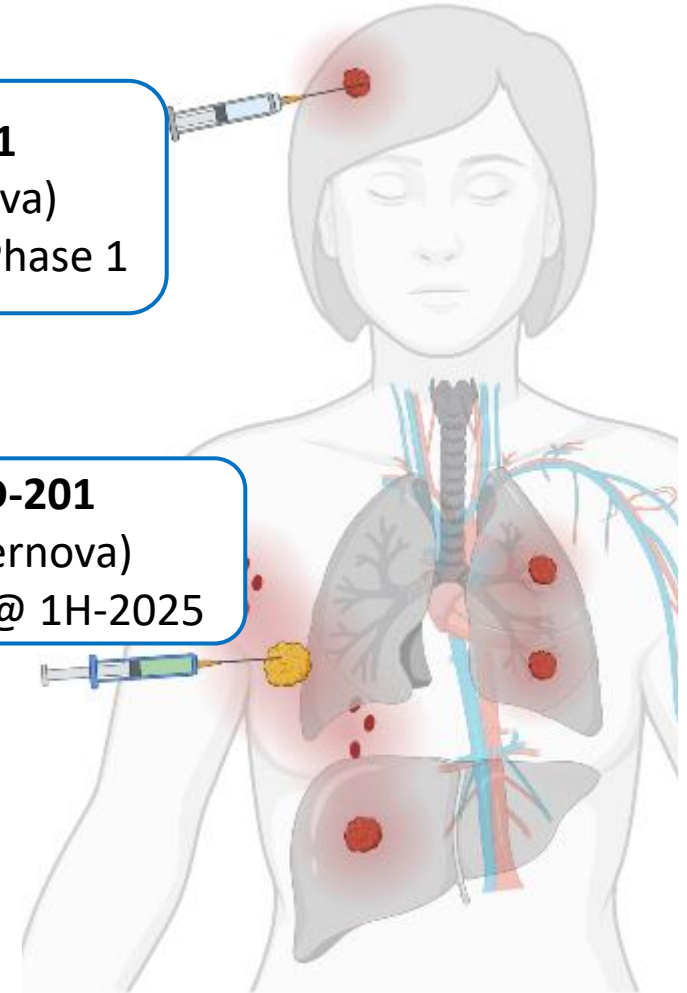
Maximizing Therapeutic Responses with Directed Localized Administration

Directed – Localized administration

- ✓ High therapeutic index of treated lesion/areas
- ✓ Low toxicity
- ✓ Strong activation of local and systemic antitumor immunity
- ✓ In situ vaccination
- ✓ Efficacy of intratumoral approach shown in clinic trials

CLD-101
(Neuronova)
Completed Phase 1

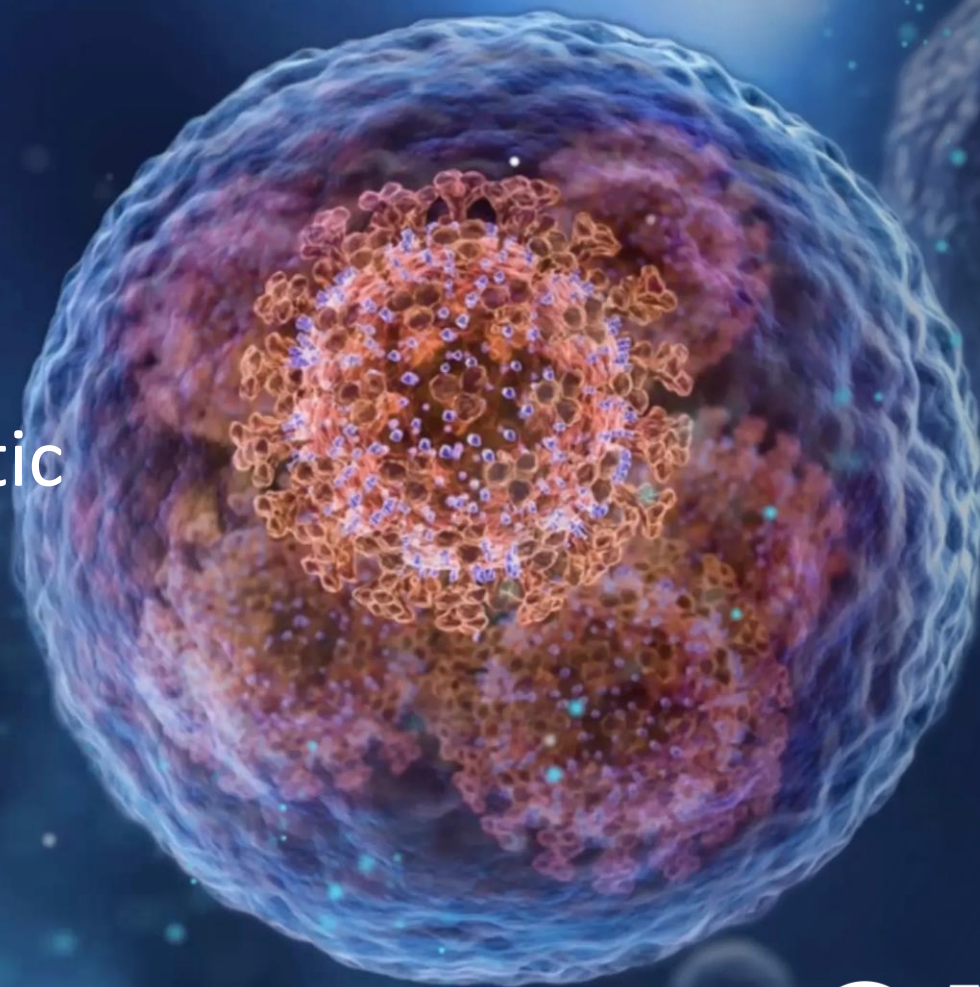
CLD-201
(Supernova)
Phase 1 @ 1H-2025



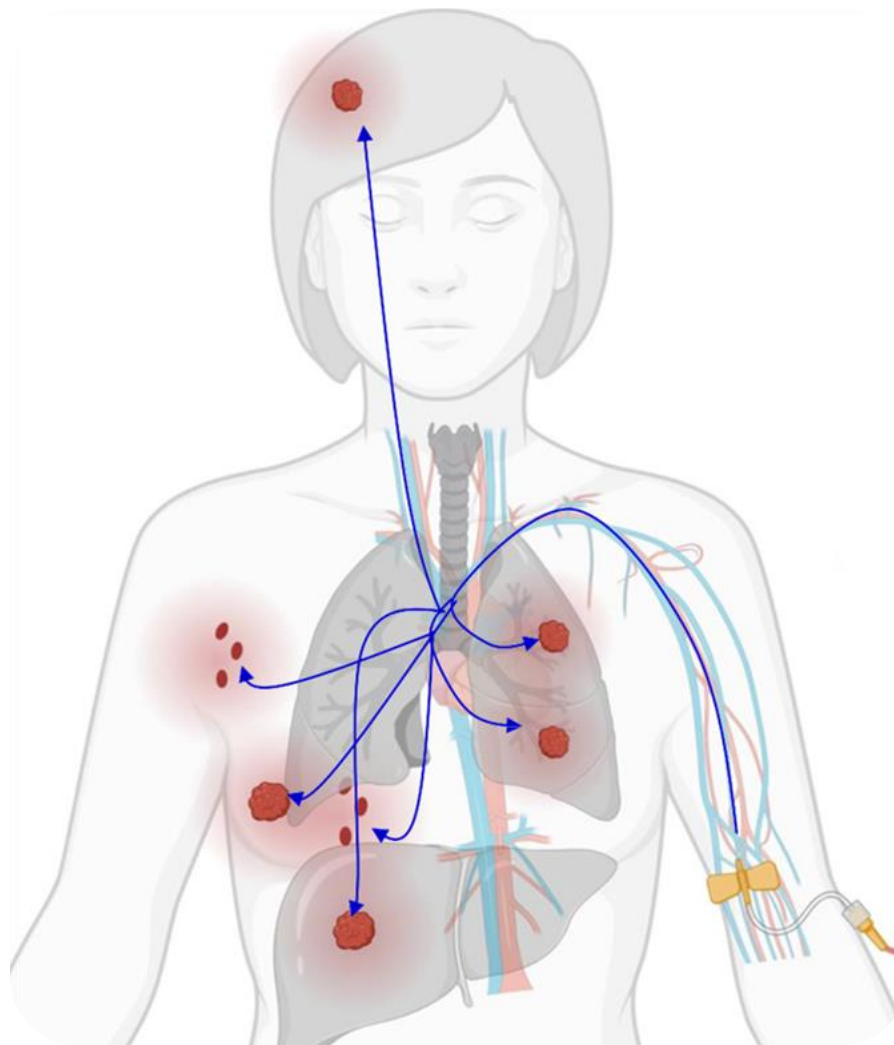
CLD-400 (RTNova)

- Systemic Administration
-

Designed for advanced metastatic disease, and for lung Cancer



Calidi's Systemic Approach (CLD-400 – RTNova program)



- ✓ New treatment option for [advanced metastatic disease](#), or [lung cancer](#)
- ✓ Simple, [cost-effective IV administration](#) avoiding the need for image-guided delivery.
- ✓ Able to survive in circulation and target tumor sites

Why Systemic Virotherapies?

2021

During presentations with several bio-pharma companies, we were **challenged to develop a systemic antitumor virotherapy**

5

Redtail's platform was formally introduced in February 2024 and now in **active discussion with 5 large cap global bio-pharma companies**

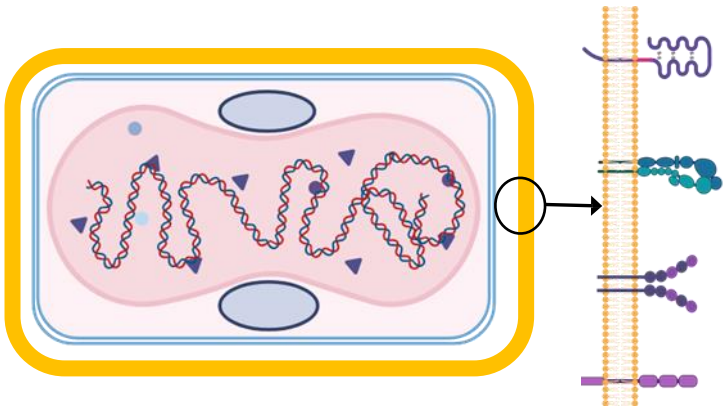
Platform

A systemic virotherapy platform technology with **multiple solid tumor indications**

Team

Seasoned team with decades of experience in oncology and virotherapy drug development

Redtail: An Extracellular Enveloped Vaccinia (EEV) Strain Designed for Systemic Delivery



Enveloped:

1- **High production of enveloped viruses** is genetically encoded in virus genome

2- Virus is ***manufactured*** enveloped with a human cell membrane containing **human surface receptors** offering:

➔ Protection/immunomodulation

➔ Targeting/Tumor Homing

Safety:

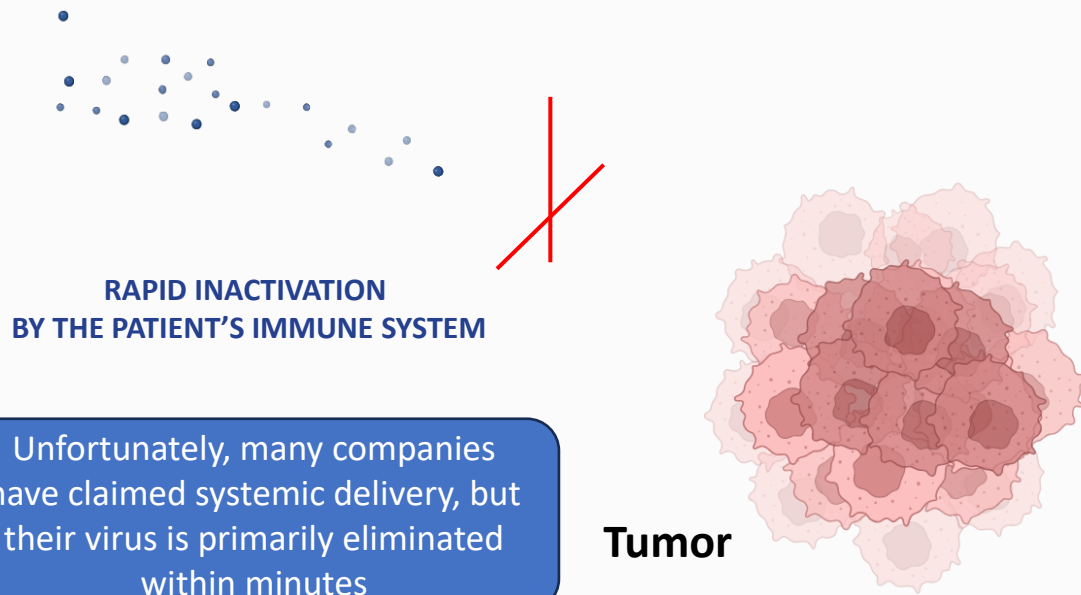
1- New engineered tumor selective vaccinia virus

2- Does not integrate into human genome

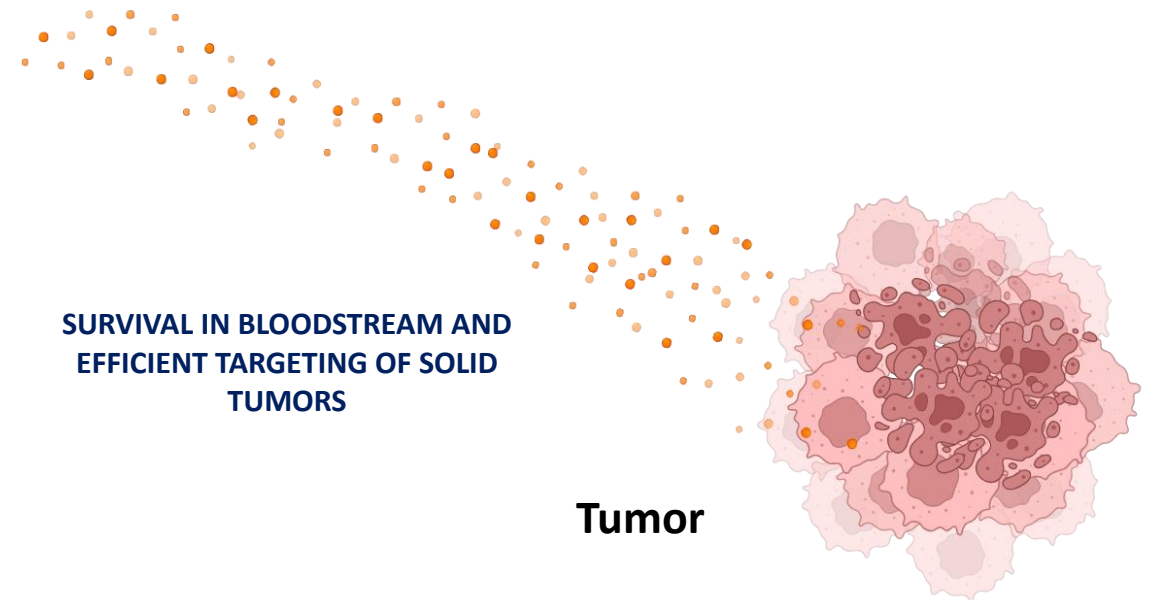
3- Platform has a safety-switch (antiviral, FDA approved)

Challenges and Solutions of Systemic Antitumor Virotherapies

Clinical Challenge: Current systemic **virotherapies** are **rapidly inactivated in minutes by the immune system**, with only 0.1-5%* remaining intact, limiting the ability to reach the tumor

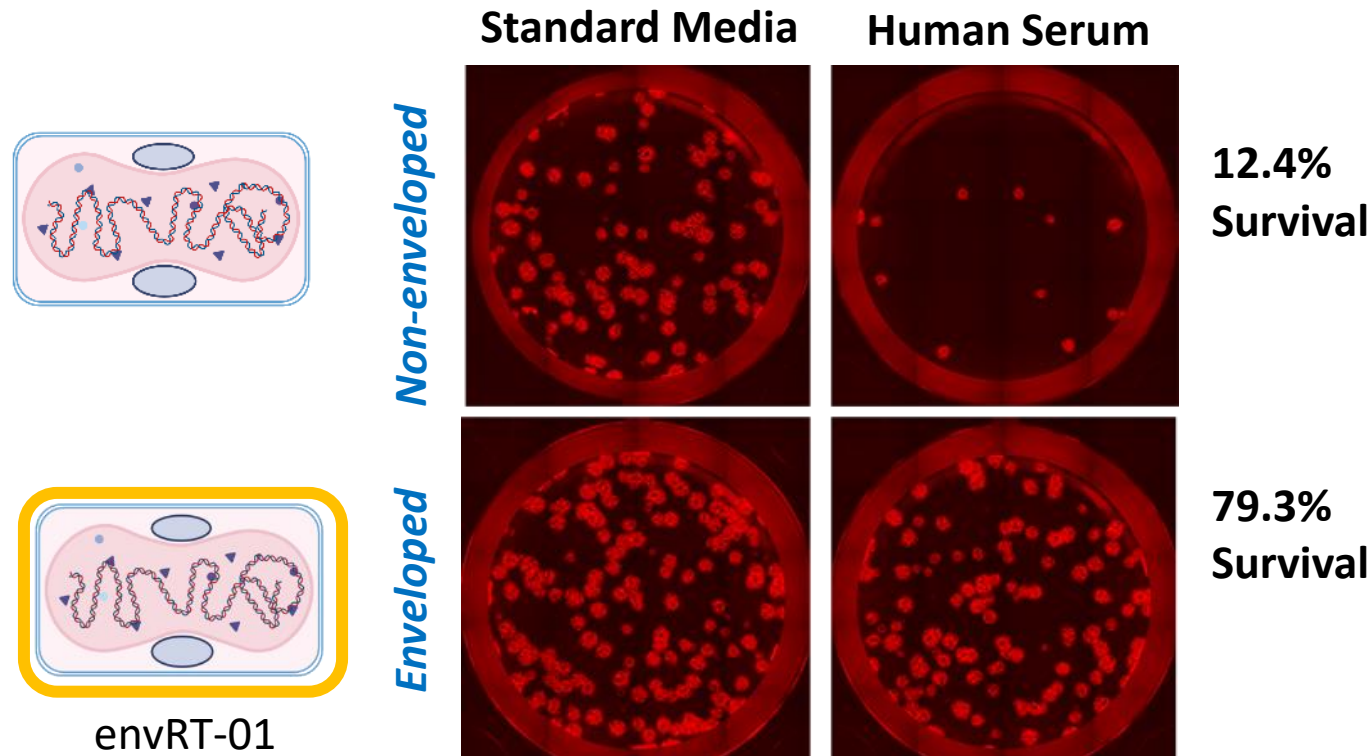


Solution: RTNova (extracellular enveloped virotherapy) best-in-class virotherapy **resistant to quick elimination by humoral immunity**, and able to **target distant tumor sites**



(*) depending on virus type, strain and dose. a) Nguyen DH et al Cancers. 2022 Dec; b) Evgin, L., et al., Mol Ther, 2015. 23(6) c) Martinez-Quintanilla, J et al J. Clin. Investig. 2019, 129

New Manufacturing Process Ensures Second Membrane Integrity, and Maximized Resistance Against Humoral Immunity



➡ A novel technique for purifying extracellular enveloped viruses (EEVs), was required.

➡ Human host cell line: undisclosed

➡ Only enveloped virotherapies can survive inactivation by human serum.

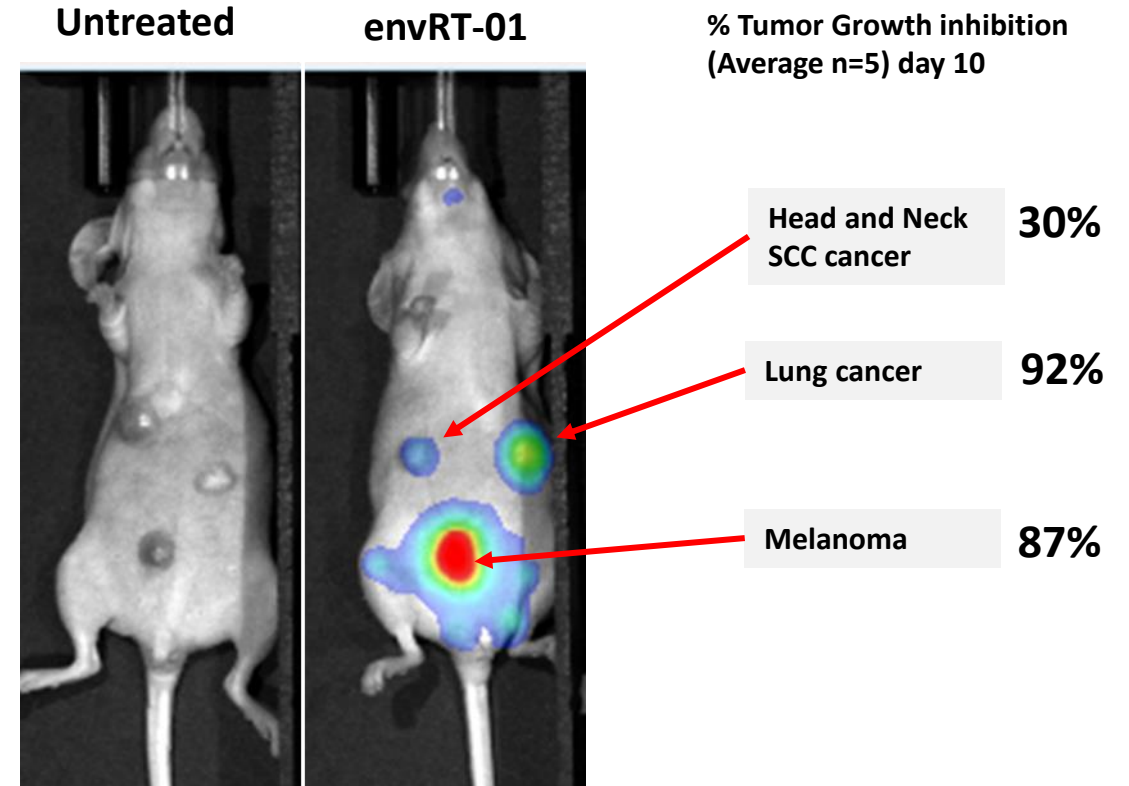
This completes a critical step to achieving systemic delivery in clinical scenarios

Systemic Administration of envRT01 Can Target and Eliminate Multiple Tumors

After systemic administration, envRT-01 (enveloped RT-01) can target all distant tumors and express selected payload (such as TurboFP635)

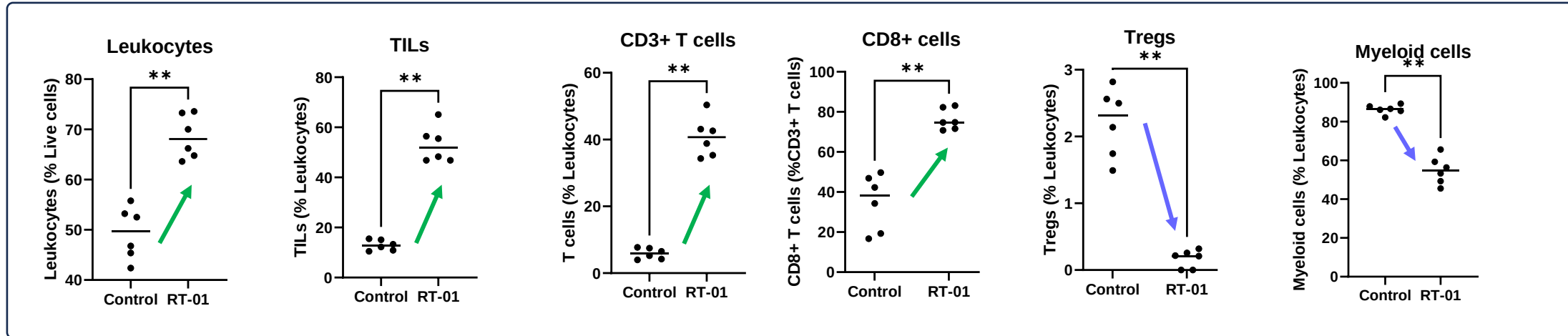
Remarkable Versatility: Ability to address **diverse tumor types** and adapt to the unique **tumor microenvironment** within the organism.

Mouse model bearing 3 different human solid tumor types

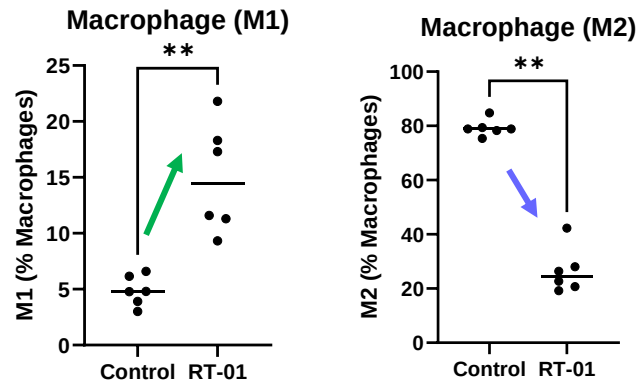


Data indicates that targeting tumors with envRT01 enables the expression of any encoded payload within the tumor, providing an additional MOA to the therapeutic approach.

envRT Induces Major Modulation of Tumor Immune Microenvironment



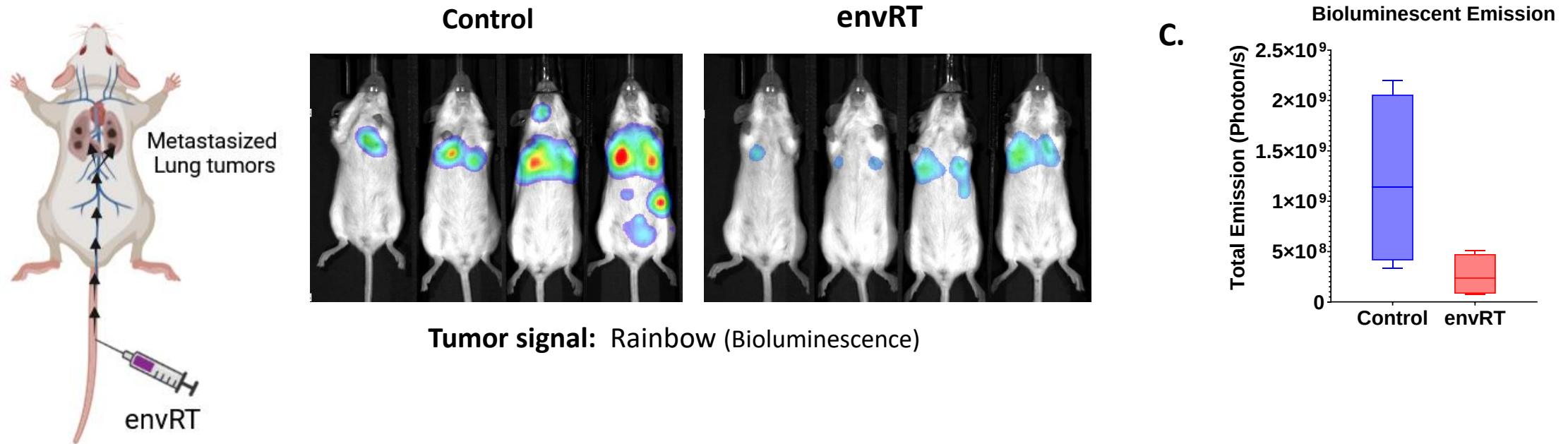
Macrophage subsets



- **envRT-01 induced dramatic changes in the tumor immune microenvironment favorable for the anti-tumor response.**
 - Increased leukocyte, TILs, T cell in the tumors
 - Decreased Treg population and myeloid cells in the tumors
 - Macrophage polarization towards pro-inflammatory subtype (M1) from anti-inflammatory subtype (M2)
- **Confirmed in multiple tumor models:**
 - EMT6 (breast cancer), CT26 (colon cancer), LL2 (lung cancer)

Systemic Administration of envRT01 can eliminate lung cancer and metastasis

One (1) dose (5e6 PFU) was able to decrease and eliminate lung cancer and metastatic tumors into the lung.



Bioluminescence picture (tumor burden) were taken 6 days after treatment

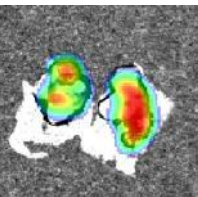
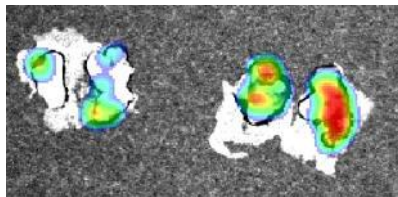
Systemic Administration of envRT Targets Lung Cancer and Metastatic Sites

Lungs:

Control

1

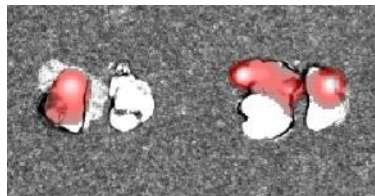
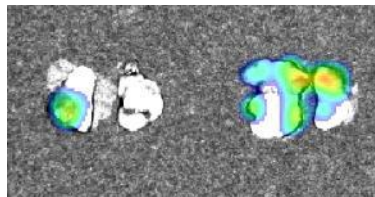
2



envRT-01

3

4

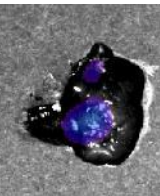
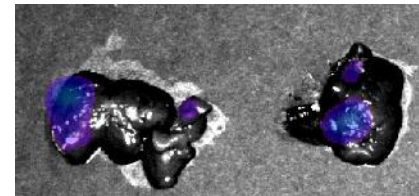


Liver:

Control

1

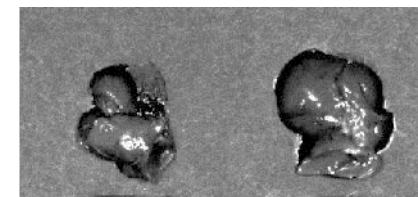
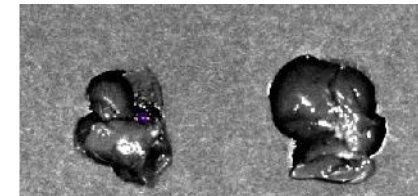
2



envRT-01

3

4



Tumor signal:
Rainbow
(Bioluminescence)

Virus location:
Red
(Fluorescence)

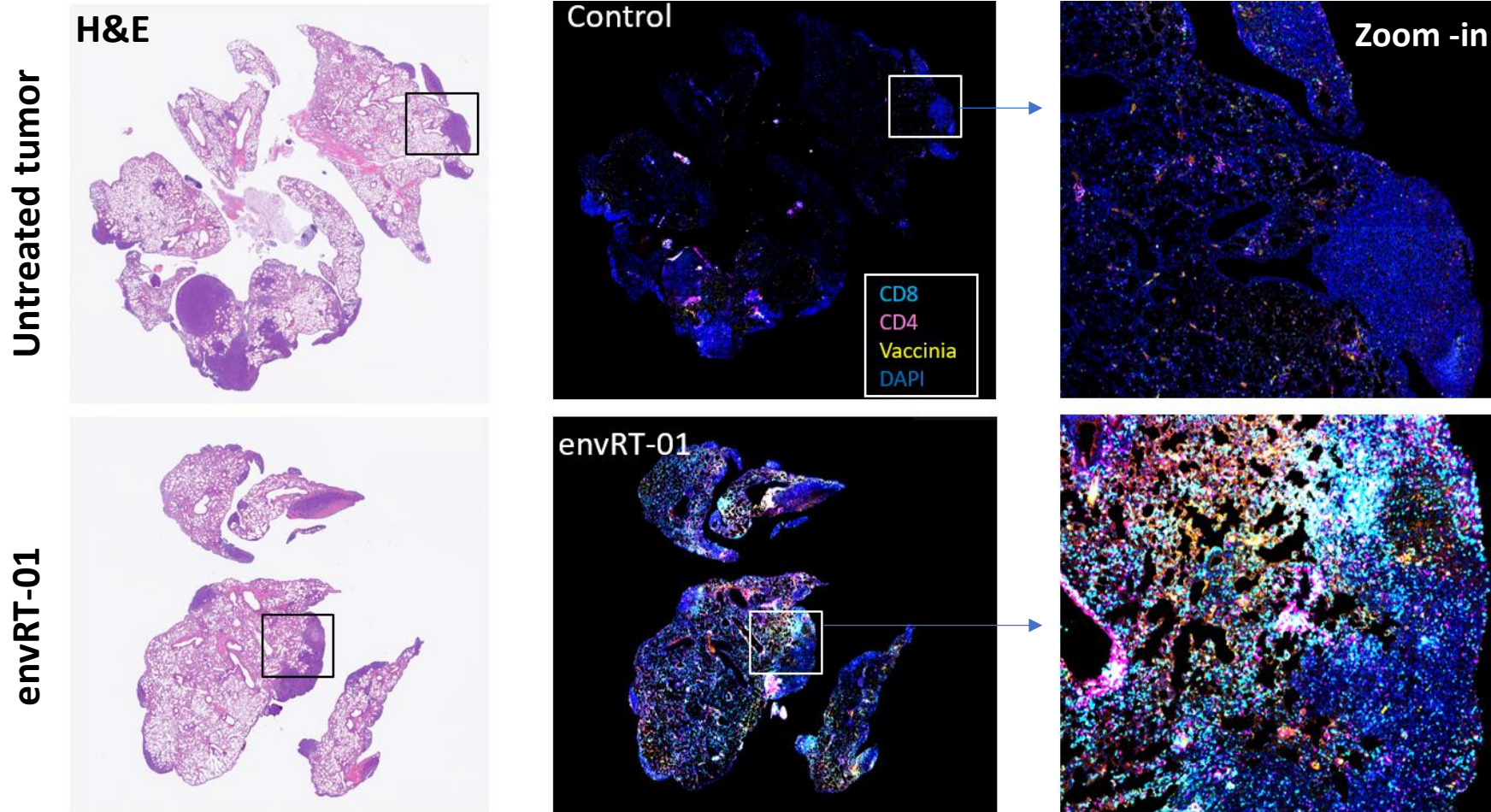
- LL2 lung cancer cells colonize lungs after I.V administration.
- Systemic administration of envRT-01 targets multiple tumor loci.

- LL2 lung cancer cells colonize liver after I.V administration.
- Animals treated with envRT-01 had lower metastatic site in Liver

Note: animals were euthanized, and organs imaged 6 days following 1 single administration of envRT-01 treatment.

envRT-01 Targets All Disseminated Tumor Sites Inducing Major Immune Modulation

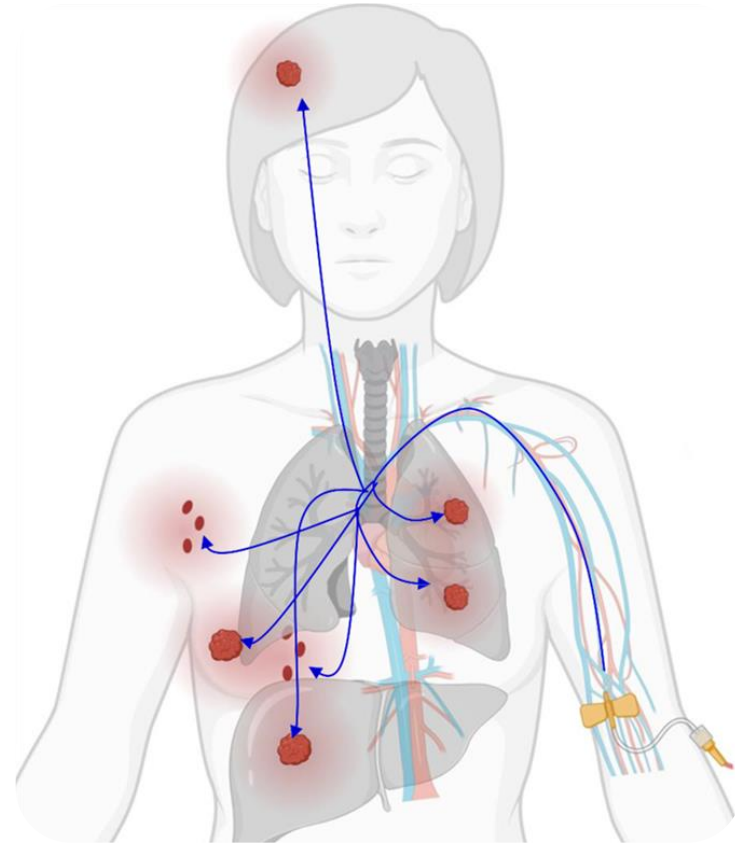
Targeting all metastasis: Immunohistochemistry data indicates systemic envRT-01 treatment targets metastasis inducing major infiltration of immune cells in all tumor loci. ([Experimental metastasis lung cancer tumors](#))



Pipeline and early partnership opportunities

Program	Mode of Action	Target Indication	Discovery/Preclinical	IND-enabling	Phase 1
EnvRT-01s Lead generation	- Tumor killing - TME reprogramming, - Payload undisclosed	Metastatic NSCLC (Lung Cancer)			
EnvRT-02s Combo with Immune cell therapy	- Tumor killing - Prime solid tumors to prepared for combo Tx	Advanced solid tumors (Indication undisclosed)			
EnvRT-03s Novel Payload	- Improved TME reprogramming and Killing. - Payload undisclosed	Target indication undisclosed		Seeking early partnership with large cap bio-pharma at <u>platform</u> and/or <u>asset</u> level	

Building the Future of Systemic Virotherapies



RTNova delivers a breakthrough in **true systemic virotherapy** using enveloped technology to **target** and **attack all tumors**.



Planned **phase 1 clinical trial**, as a monotherapy, targeting metastatic lung cancer solid tumors in **Q3 2026**.



Aiming to secure Fast-Track, Priority Review, or other **expedited regulatory pathway**.



Delivering **off-the-shelf platforms**, scalable, and commercially viable.