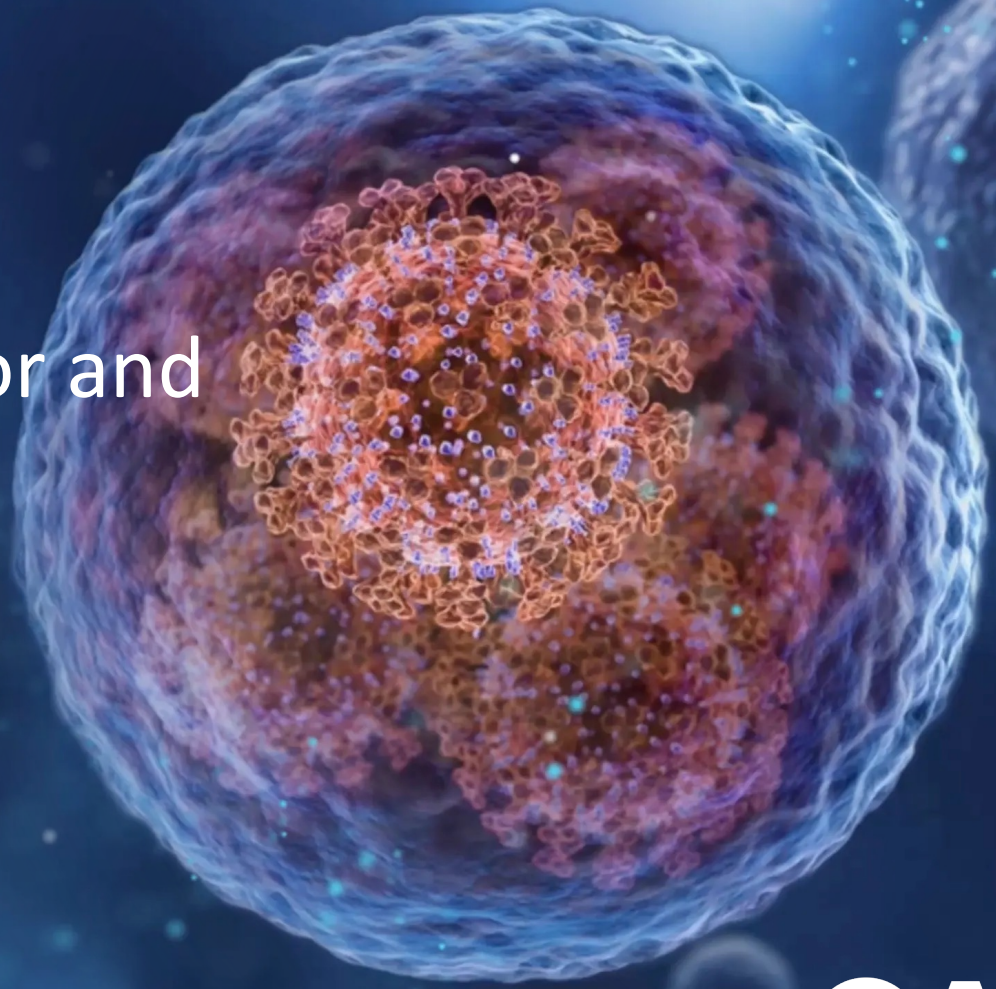
Systemic and Localized Antitumor Virotherapies

Designed to attack every tumor and arm the immune system

Technology Update Webinar

September 11, 2024



CALIDI BIOTHERAPEUTICS

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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 their rapid elimination by the patient's immune system.**

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

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Introducing Dr. George Peoples, MD, FACS

- Founder and Director of the Cancer Vaccine Development Program (CVDP)
- Founder of LumaBridge (formerly Cancer Insight), an oncology-focused Contract Research Organization (CRO) and development partner currently engaged with over 25 pre-clinical and clinical trial sponsors.
- Serves as a Professor of Surgery at the Uniformed Services University of the Health Sciences (USUHS) and an adjunct Professor of Surgical Oncology at MD Anderson Cancer Center. Former Chair of the Cancer Care Program at San Antonio Military Medical Center and Military Director of the United States Military Cancer Institute.
- Graduate of the United States Military Academy at West Point and the Johns Hopkins School of Medicine. Completed his surgical training at Harvard's Brigham and Women's Hospital and a surgical oncology fellowship at MD Anderson Cancer Center.
- Calidi Board Member since June 2024

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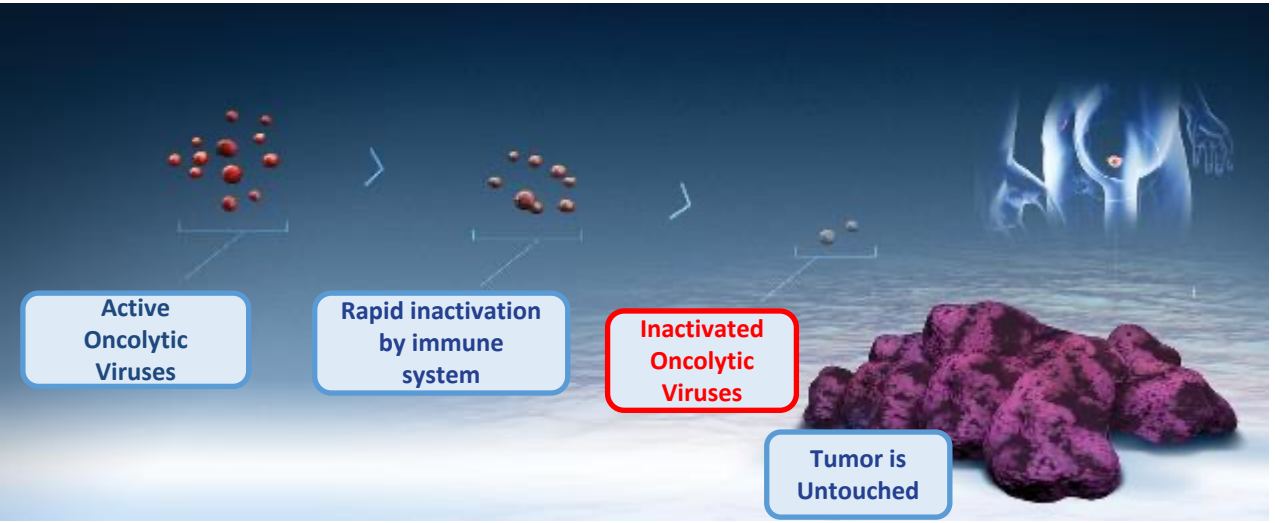
Calidi Overcomes the Obstacles to Oncolytic Viral Therapy

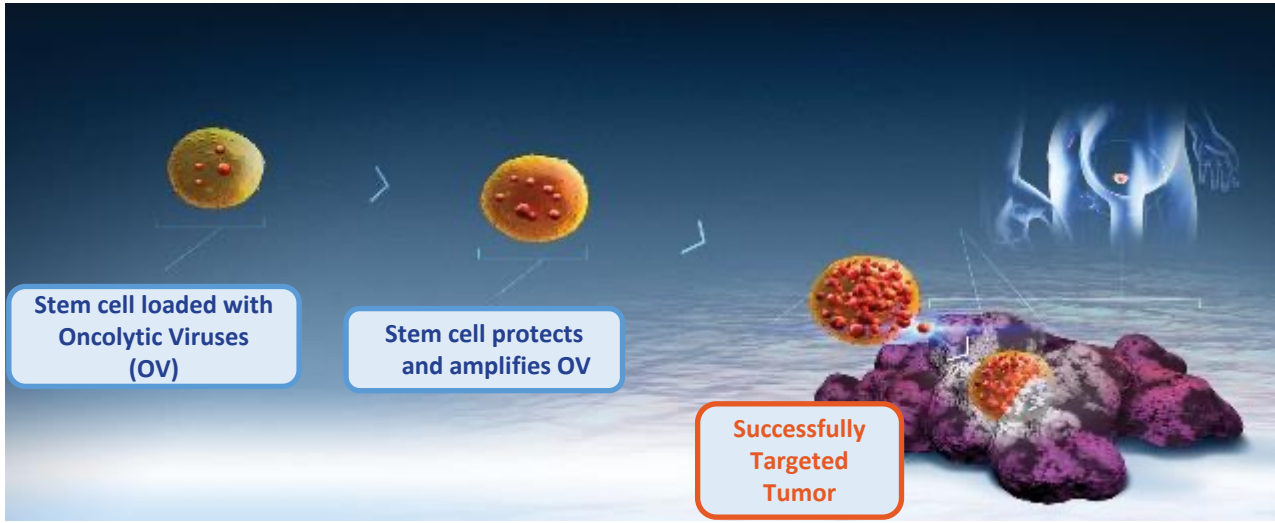
Challenges with Naked OV Therapy

Unprotected Oncolytic Virus



Calidi's Solution

Allogeneic Oncolytic Virus-Loaded Stem Cells



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

Calidi's Allogeneic Stem Cell Platforms

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

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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					NIH National Cancer Institute; Northwestern University
		Recurrent High Grade Glioma	Phase 1 started				$12M	CIRM; City of Hope
CLD-201	SuperNova	Advanced Solid Tumors: Head & Neck, TNBC, Soft tissue Sarcoma (Localized administration)	FDA Pre-IND – Planned Phase 1				$3M	CIRM
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

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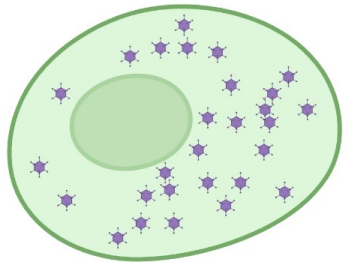
Calidi's Three Lead Programs

CLD-101 (NeuroNova)

Clinical trial Phase 1b/2

Indication: Recurrent and newly diagnosed High Grade Glioma



Tumor selective Virotherapy:
Adenovirus: CRAD-s-Pk7

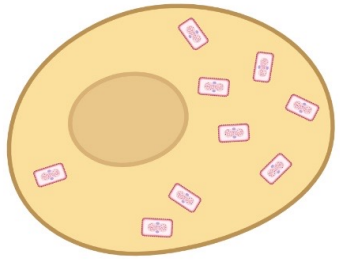
Delivery vehicle/potentiator:
Allogeneic Neuronal Stem Cells

Product type:
Off-the-shelf
Directed administration

CLD-201 (SuperNova)

Targeting clinic Q1 2025

Indication: Advanced Solid Tumors:



Tumor selective Virotherapy:
Vaccinia virus: CAL1

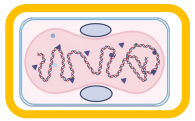
Delivery vehicle/potentiator:
Allogeneic Adipose-derived Mesenchymal Stem Cells

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

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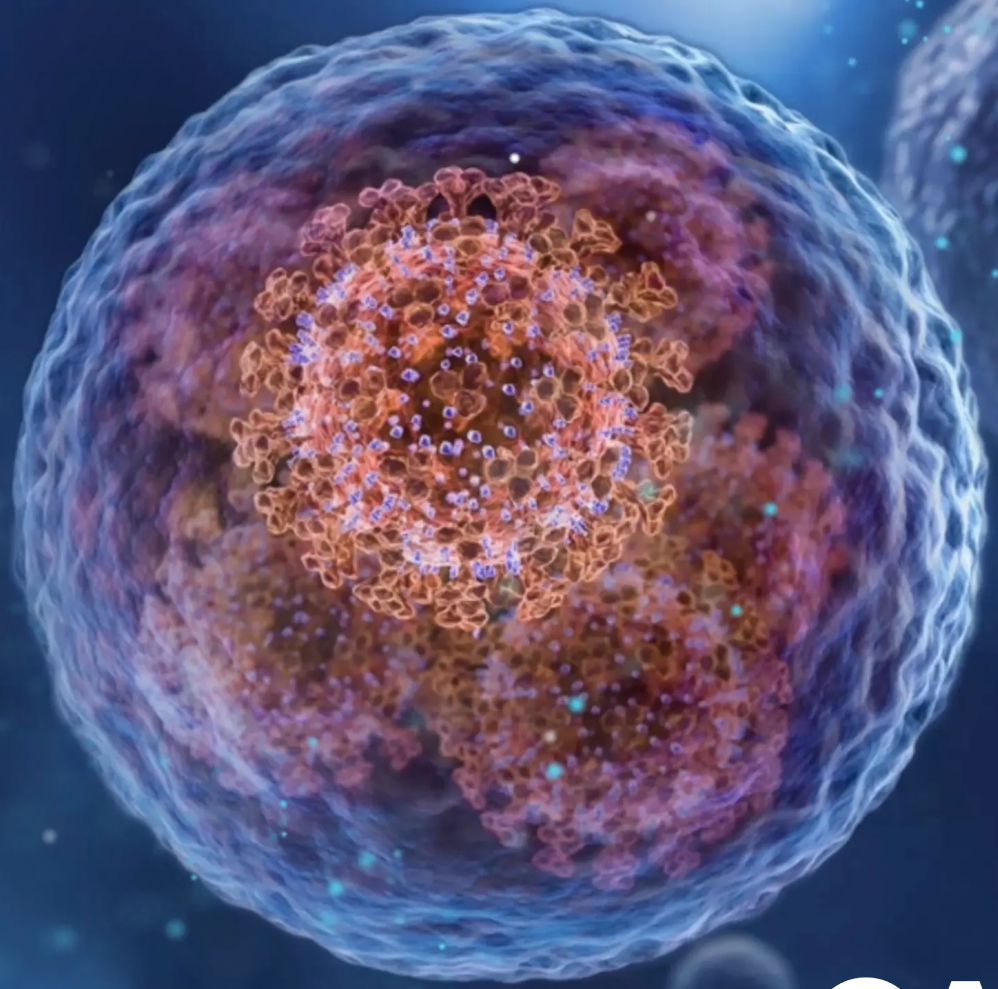
CLD-201 (SuperNova)

- Intratumoral administration

For Head & Neck, TNBC, and Soft Tissue Sarcomas



CALIDI BIOTHERAPEUTICS

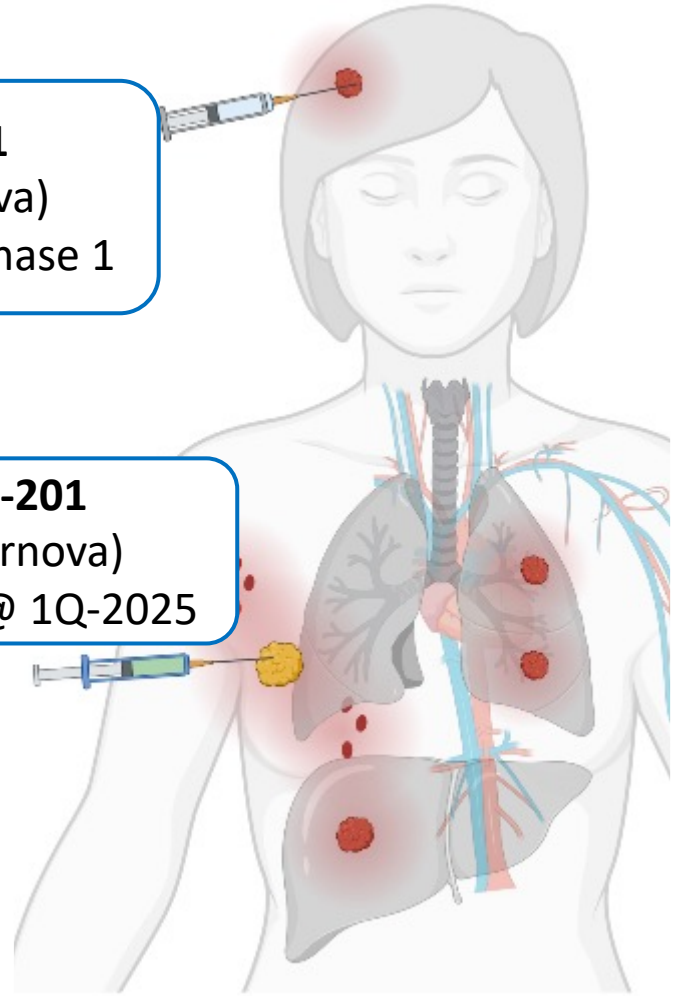
Maximizing Therapeutic Responses with Intratumoral Administration

Intratumoral administration

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

CLD-101
(Neuronova)
Completed Phase 1

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



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CLD-201 (SuperNova) in Advanced Solid Tumors

Completed: Safety Study
Autologous settings - single dose

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

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

- **New allogeneic program developed to reach wider cancer population**
- cGMP Final Drug Product Manufacturing completed in 2Q 2024
- **Phase 1 initiation in 1Q 2025**

  Head & Neck, TNBC, soft tissue Sarcoma

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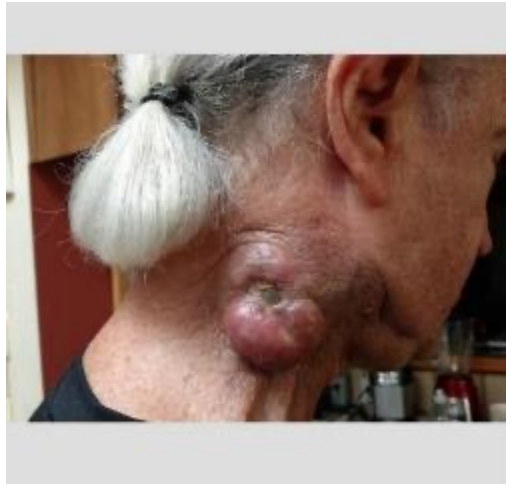
Durable Tumor Regression and Survival

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

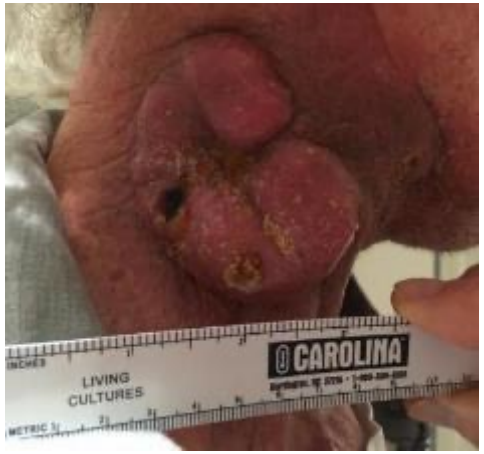
- Age/Sex: 70/M
- Diagnosis: Metastatic Head & Neck SCC
- Stage IV_B
- Injected tumor was previously resistant to chemo- and radio-therapy

Patient Case: Patient #SI01-021

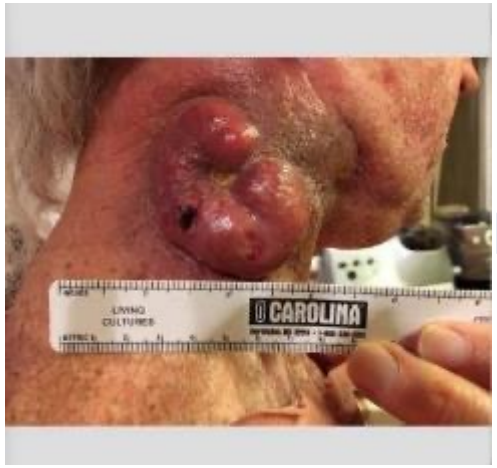
Day 17 post-treatment



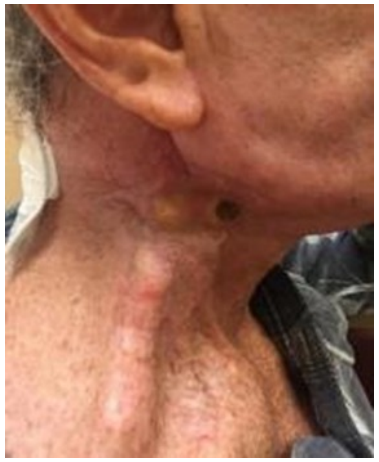
Day 45 post-treatment



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

Minev, et al. Journal of Translational Medicine (2019) 17:271

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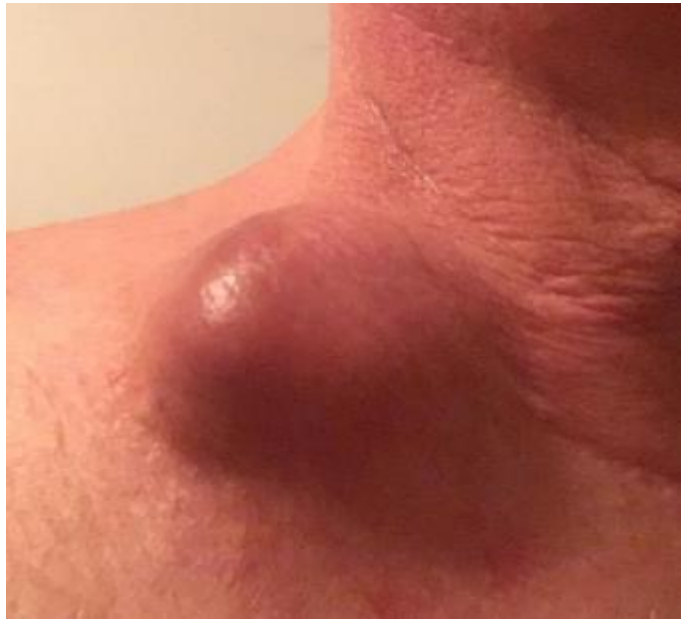
Durable Tumor Regression and Survival (continued)

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

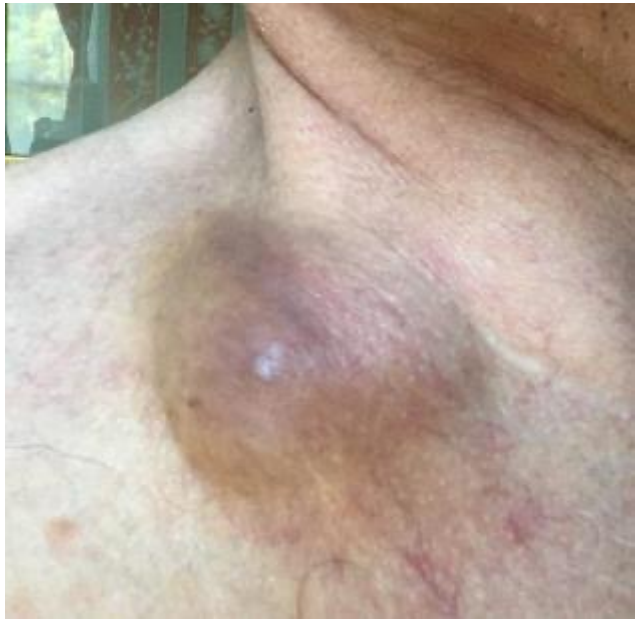
Calidi Autologous Safety Study

Patient Case: Patient #SI01-047

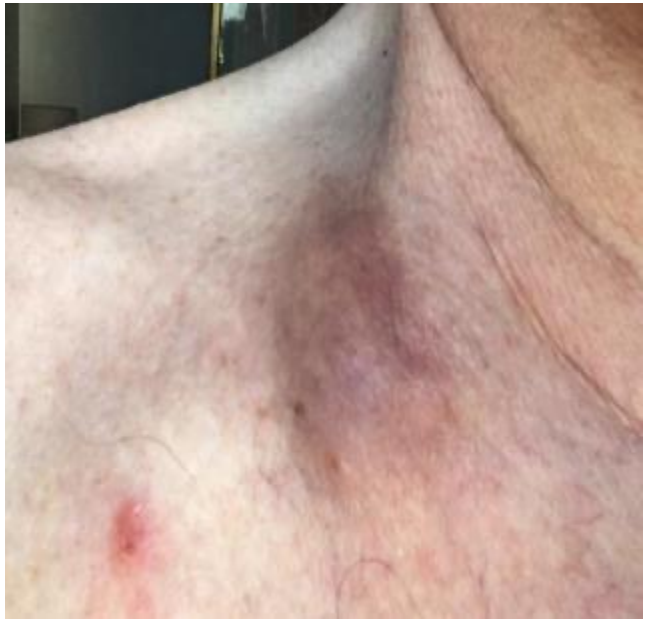
Day 30 post-treatment



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

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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 Three indications

- Classical 3+3 trial design. Four 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

- CLD-201 dose is identified in Part 1 of this trial
- Ten patients from each of the 3 indications will be treated with a fixed dose identified in part 1 of this study

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

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

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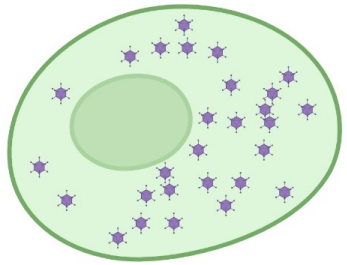
Calidi's Three Lead Programs

CLD-101 (NeuroNova)

Clinical trial Phase 1b/2

Indication: Recurrent and newly diagnosed High Grade Glioma



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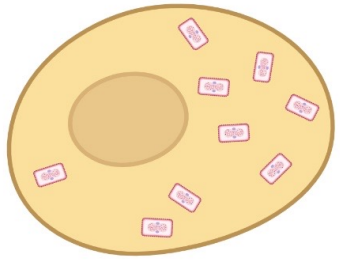

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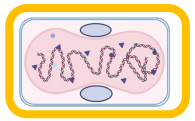

Tumor selective Virotherapy:
Extracellular Enveloped Vaccinia virus: envRT-01

Product type:
Off-the-shelf
Systemic administration

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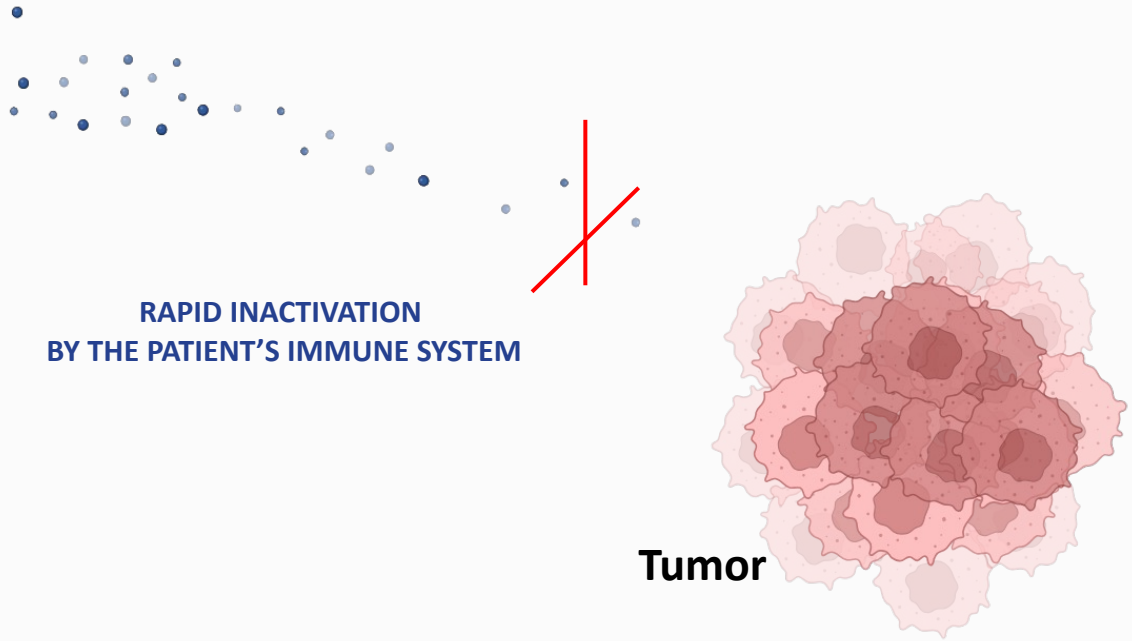
Systemic Antitumor Virotherapies

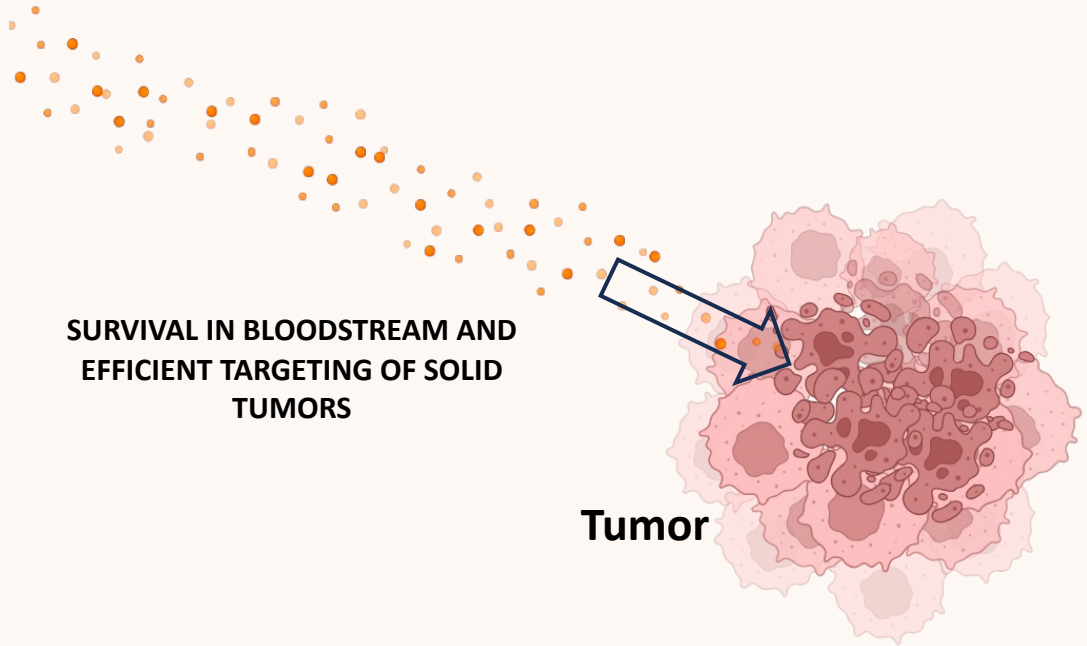
Designed to target and attack every tumor, empowering the immune system

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

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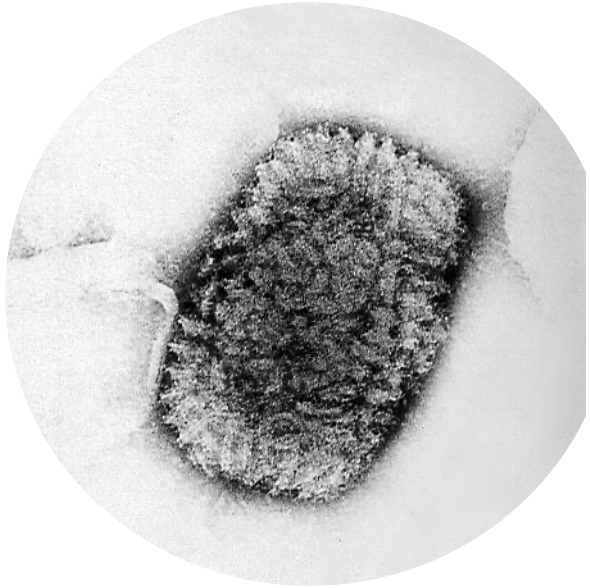
Vaccinia Virus as a Systemic Antitumor Virotherapy and Viral Vector



1- RT Vaccinia virus is a **highly cytolytic virus** - tumor agnostic.

2- Genetically stable. 200kB dsDNA virus.

3- Large insertion capacity (25-45Kb), allowing delivery of existing therapeutic proteins into the tumor, potentiating antitumor systemic virotherapy efficacy.

- Cytokines.
- Checkpoint inhibitors, agonists, (multiple types of therapeutic antibodies).
- Other TME modifiers.

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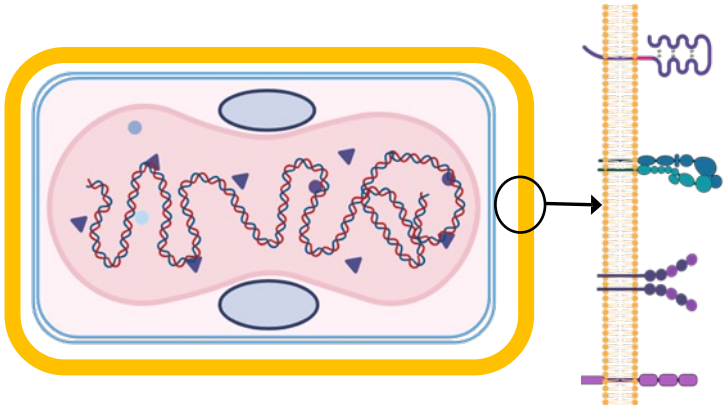
Redtail: An Extracellular Enveloped Vaccinia (EEV) Strain Designed for Systemic Delivery



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.

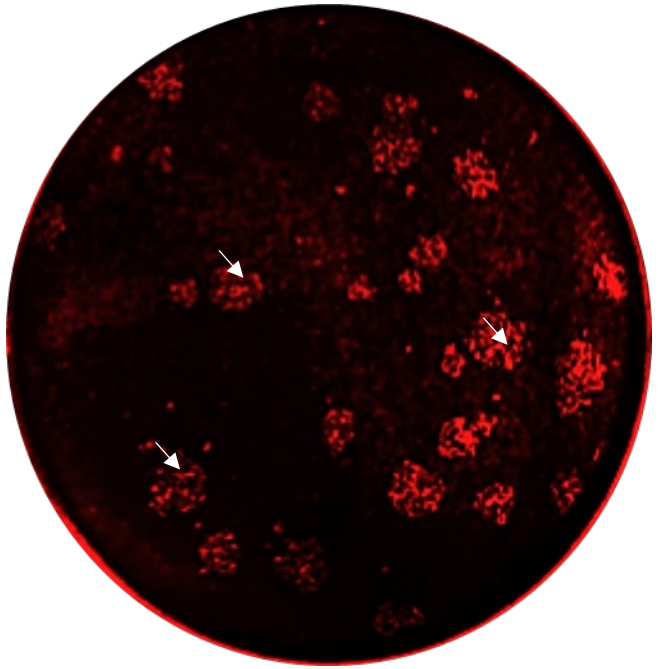
3- *Platform has a* ***safety-switch*** (antiviral, FDA approved)

Redtail (RT): A New Vaccinia Virus Strain Which Produces High Levels of EEV Particles

Comet assay of two distinct vaccinia viruses

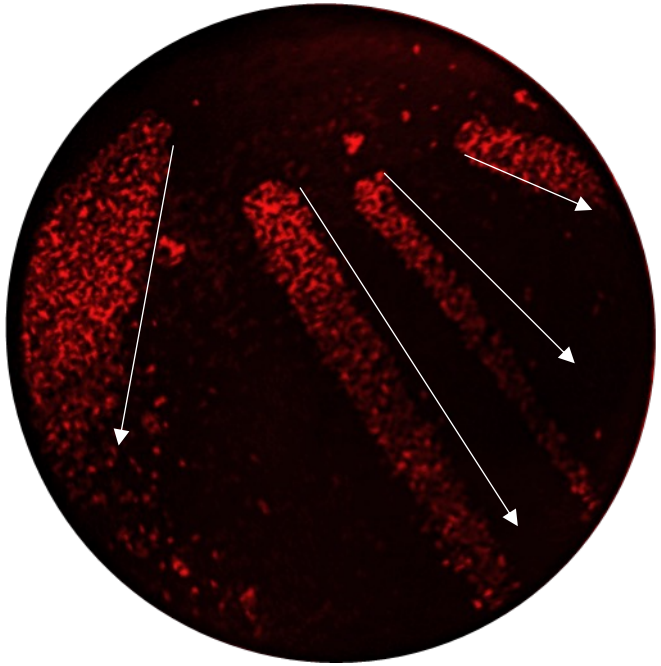
Vaccinia Viruses are genetically engineered to express TurboFP635 (red fluorescence).

Vaccinia virus strain CAL2 producing low EEV particle



A short and round plaque signifies that the virus mainly spreads from cell to cell.

Redtail Vaccinia virus envRT-01 producing high levels of EEV particles



A long “tail” in a comet assay indicates that the virus can produce high levels of EEV **leading to further spread.**

Redtail (RT) Strain

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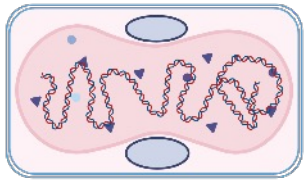
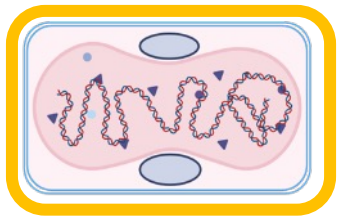
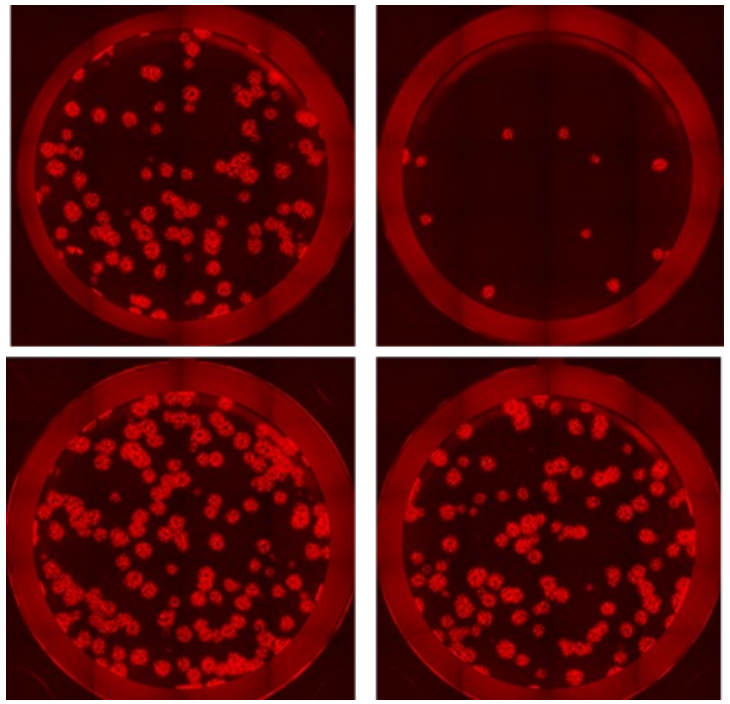
New Manufacturing Process Ensures Second Membrane Integrity, and Maximized Resistance Against Humoral Immunity





envRT-01



12.4% Survival

79.3% Survival

- **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

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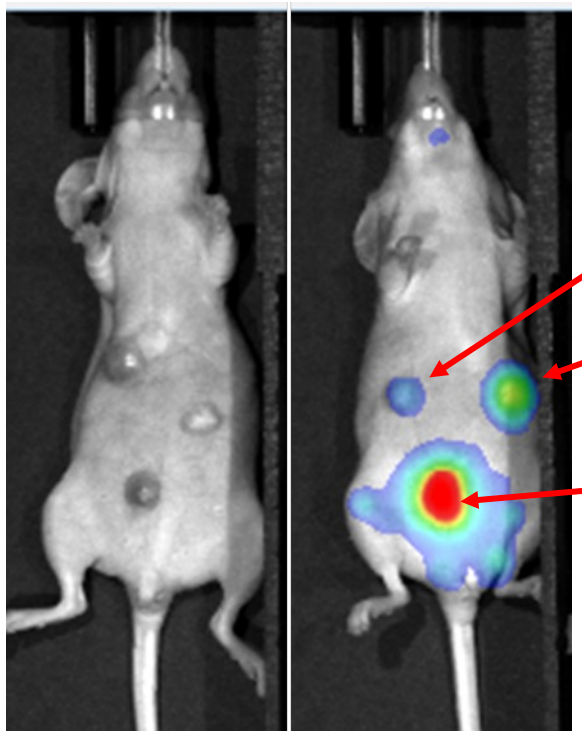
Systemic Administration of envRT01 Can Target and Eliminate Multiple Tumors

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



% Tumor Growth inhibition (Average n=5) day 10

Head and Neck SCC cancer	30%
Lung cancer	92%
Melanoma	87%

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.

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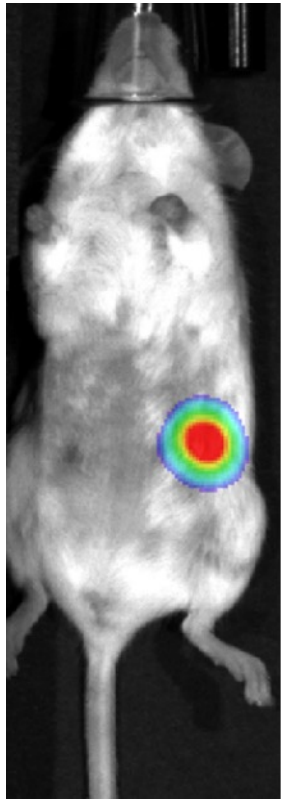
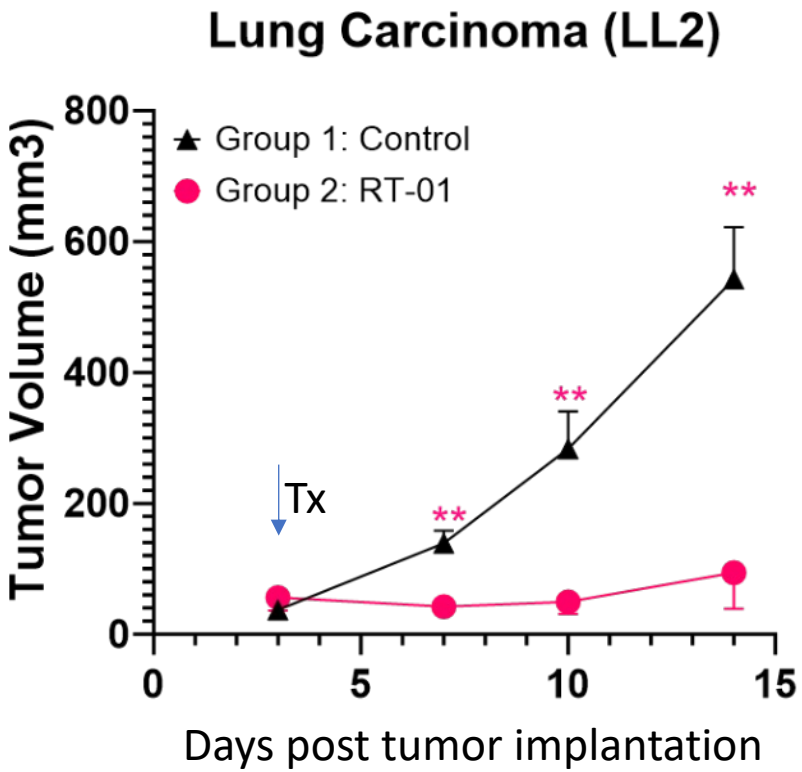
Systemic Administration of Enveloped Virotherapies (envRT-01) in Immunocompetent Lung Tumor-Bearing Models





10-100 times lower dose (compared to other vaccinia viruses) can inhibit tumor growth effectively in immunocompetent animals.

<u>Remarkable tumor selectivity.</u>

envRT-01 Virus: TurboFP635 is represented as Rainbow signal

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.

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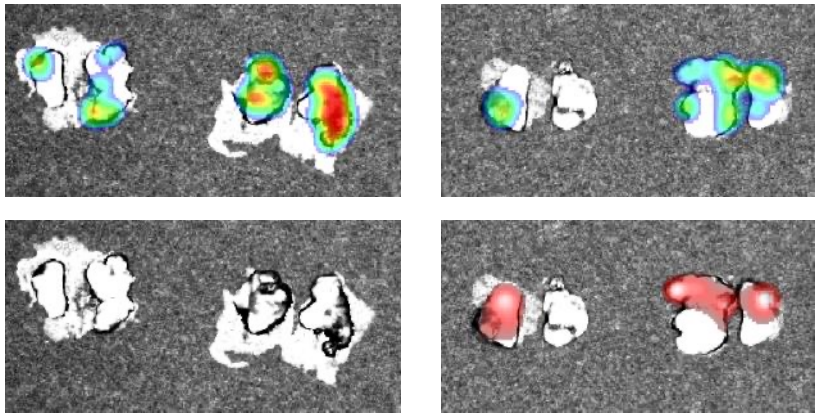
Systemic Administration of envRT-01 Targets Lung Cancer and Metastatic Sites

Tumor signal:
Rainbow
(Bioluminescence)

Virus location:
Red
(Fluorescence)

Lungs:

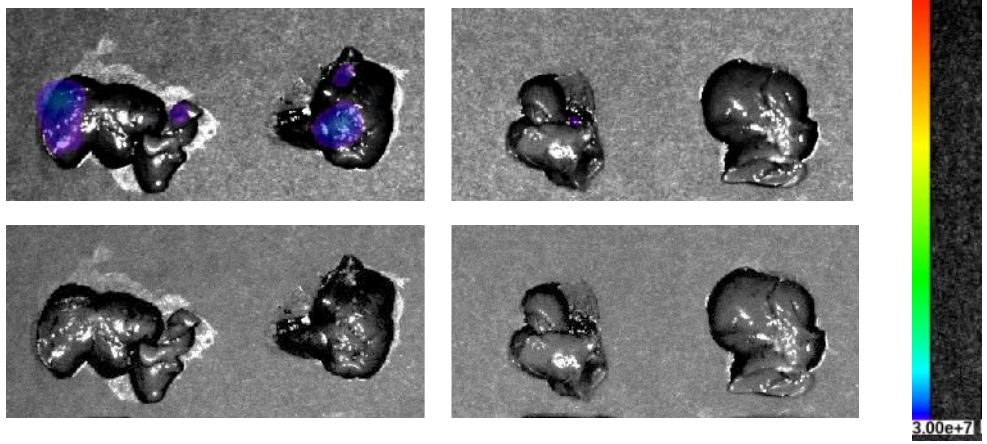
Control		envRT-01	
# 1	# 2	# 3	# 4



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

Liver:

Control		envRT-01	
# 1	# 2	# 3	# 4



- 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.

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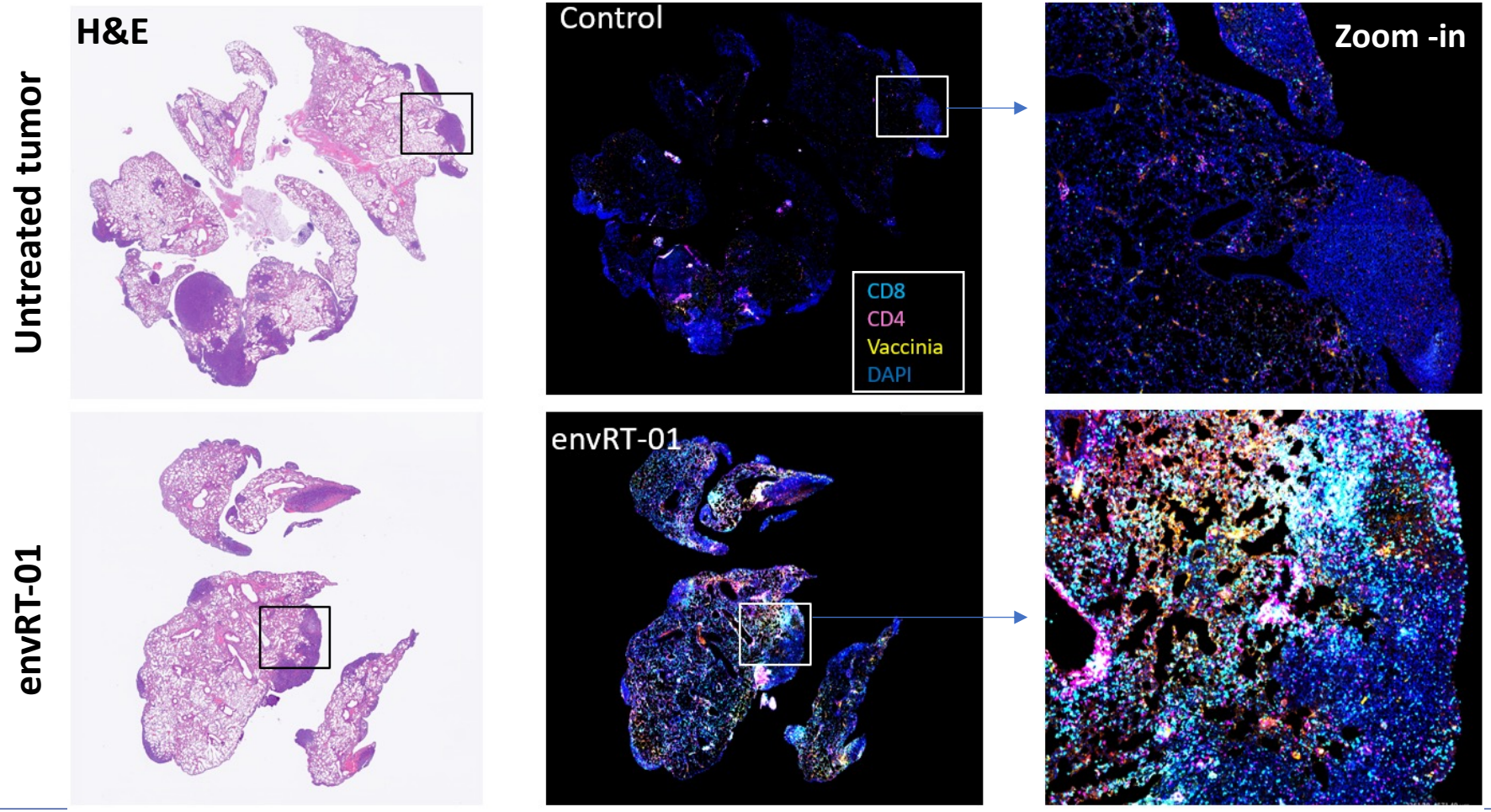
envRT-01 Targets All Disseminated Tumor Sites Inducing Major Immune Modulation

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)



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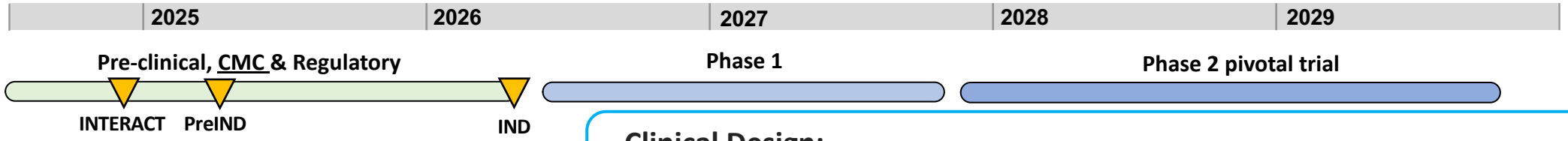
Clinical and Regulatory Path Lead Candidate



Clinical Design:

Initial Indication: Metastatic non-small cell lung cancer (mNSCLC) cancer

- New cases NSCLC per year 197,000
- Deaths per year: 125,000 in USA, mainly due to **metastastic disease**
- 30-40% of NSCLC ~50,000 have distant metastasis at time of diagnosis
- Median survival mNSCLC **6-12 months***
- Survival rate at 5 years (mNSCLC 8%)

Phase 1:

Design: *Single-arm monotherapy* with a dose escalation, 3+3 design, enrolling up to 30 patients, potentially as a 2nd or 3rd line treatment

Regulatory: Aim to secure Fast-Track, Priority Review, and other expedited pathways

Phase 2 (Pivotal)

Design: Accelerated single-arm study focusing on unmet needs 2nd or 3rd line treatment, involving <100 patients The approach and number of patients, will be re-evaluated after Phase 1 Plan Approval endpoints; primary: Objective Response Rate (ORR), secondary: Duration Of Response (DOR)

- **Regulatory approval:** targeting late 2029

https://seer.cancer.gov/statfacts/html/lungb.html

* OS may increase with new investigational treatments

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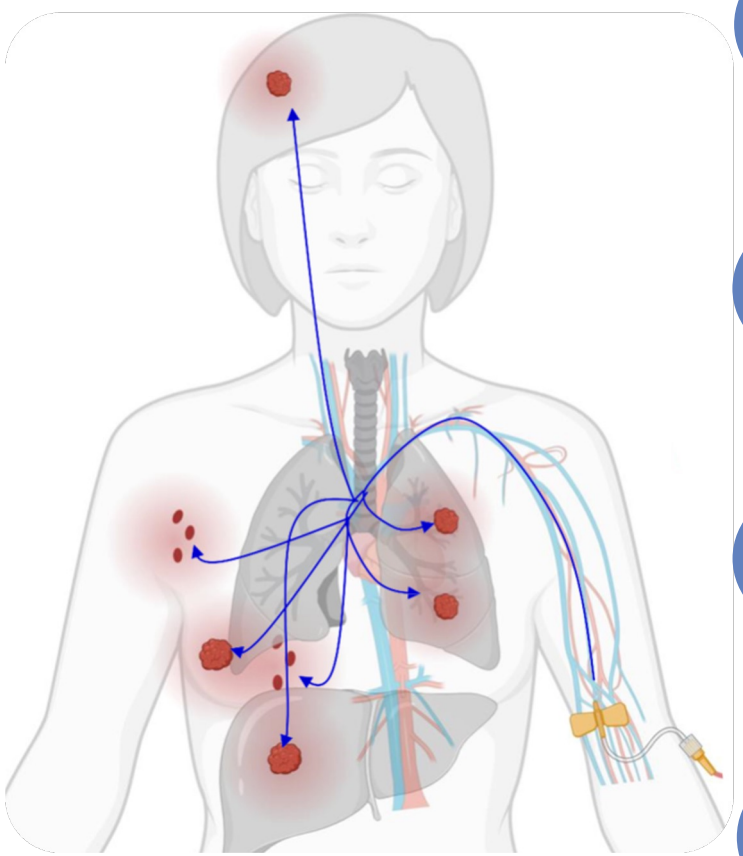
Building the Future of Systemic Virotherapies



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 **Q2 2026**.

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

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

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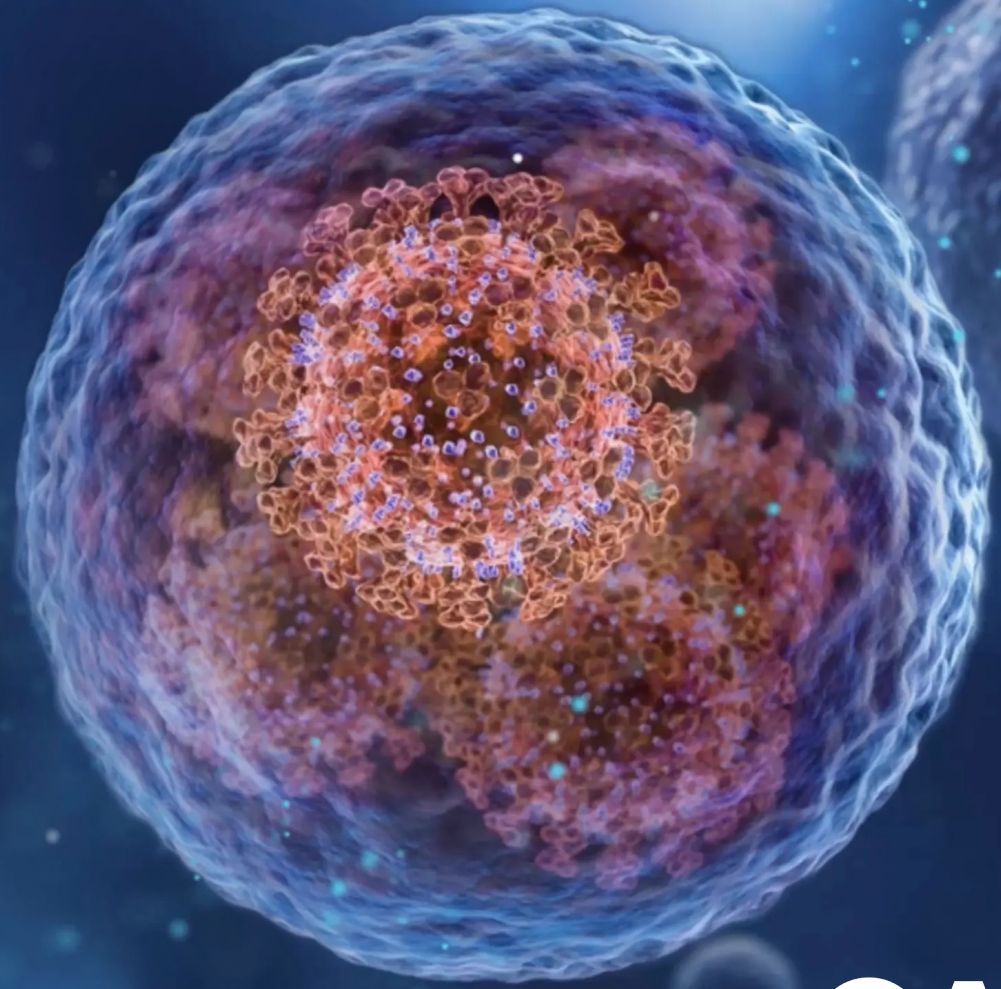
THANK YOU!



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BIOTHERAPEUTICS