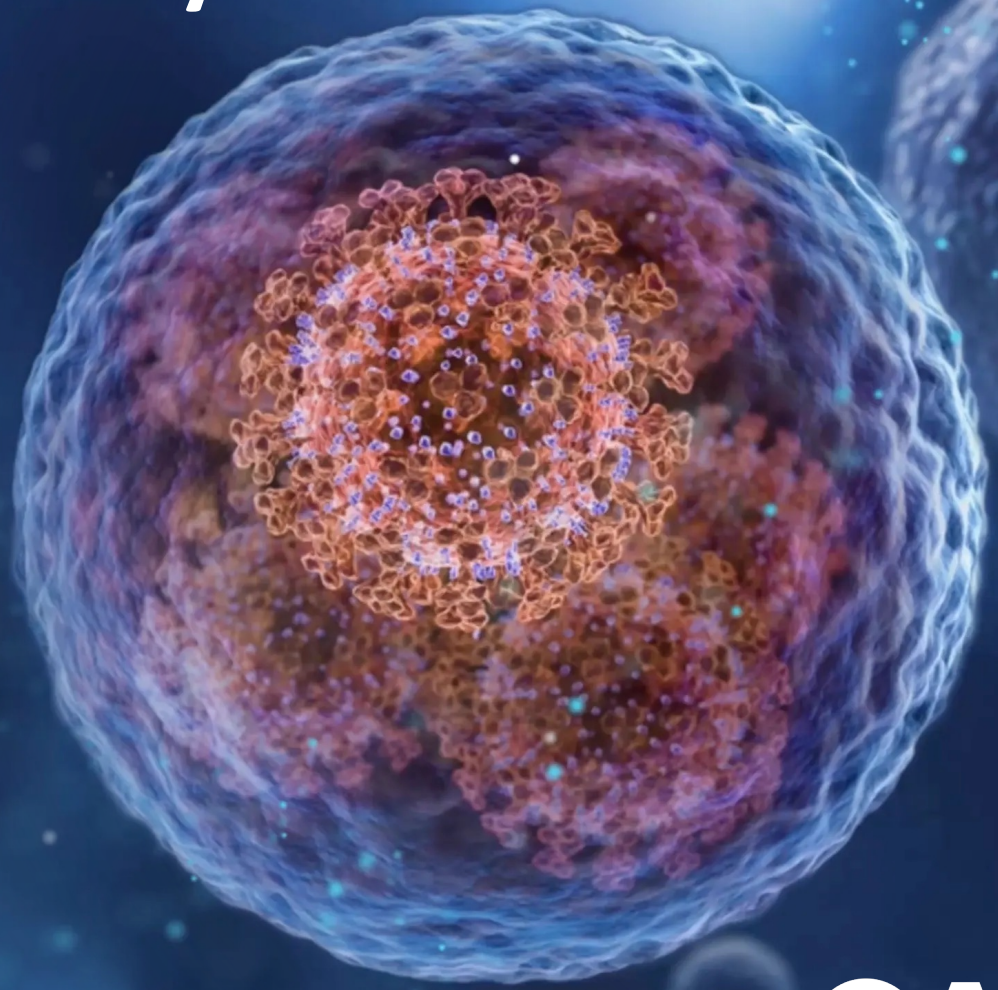
Systemic and Localized Oncolytic Virotherapies



Designed to attack every tumor and arm the immune system

Biocom Global Life Science Partnering & Investor Conference - February 28, 2024

CALIDI BIOTHERAPEUTICS

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.

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Rapidly Growing OV Market With High Unmet Medical Needs

Large total addressable market

- Large total addressable market across current indications of focus: **Melanoma, GBM, TNBC, Head & Neck, Lung**
- ~56k patients across all Calidi indications* (U.S. only)
- **$13B - $15B** (U.S. TAM)**

Rapidly **growing** OV **market** with **high unmet needs**

2021	2030
1 approved OV	**6-8 approved OVs**
$150M in US* **	**$2.4B in US*** **

Differentiated technology with **early signals of efficacy**

Cell-based & enveloped technologies protect and deliver oncolytic virotherapies into tumor sites, effectively overcoming clinical challenges

(*) Types of Cancer | Cancer.Net
(**) Oncology Cancer Drugs Market Size is projected to reach USD (globenewswire.com), and lung cancer: Insights10 report
(***) Oncolytic Virus Immunotherapy Market Size is Predicted to Hit US$ 2.4 Billion by 2030 | BioSpace

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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 Skin cancers, 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)						

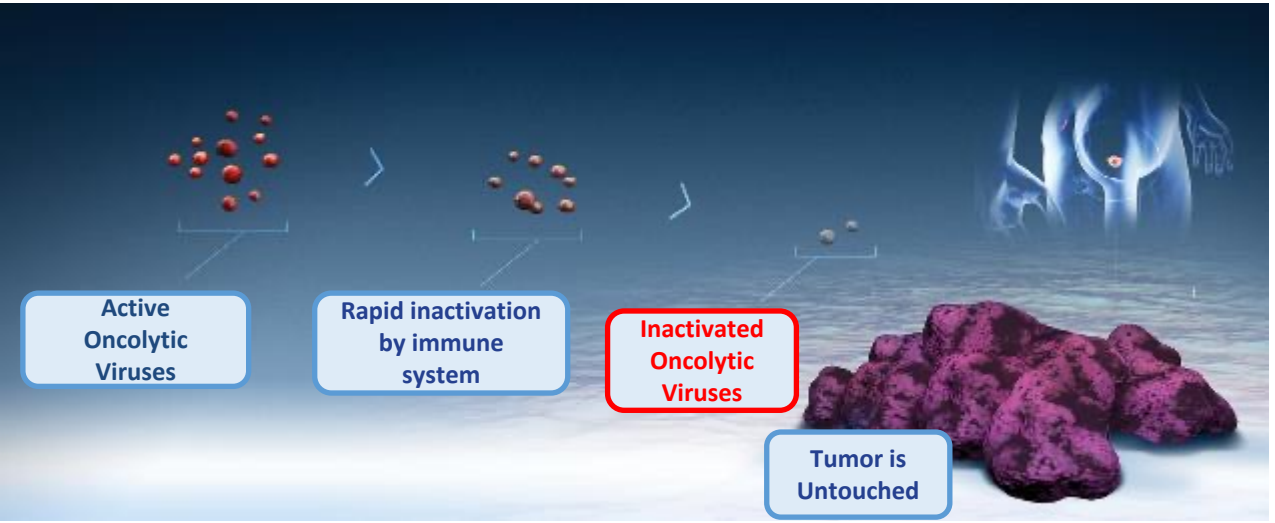
Multiple partnership opportunities to potentiate and deliver other existing OV's, combination therapies, and joint development of next generation therapies

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Calidi Overcomes the Obstacles to Oncolytic Viral Therapy

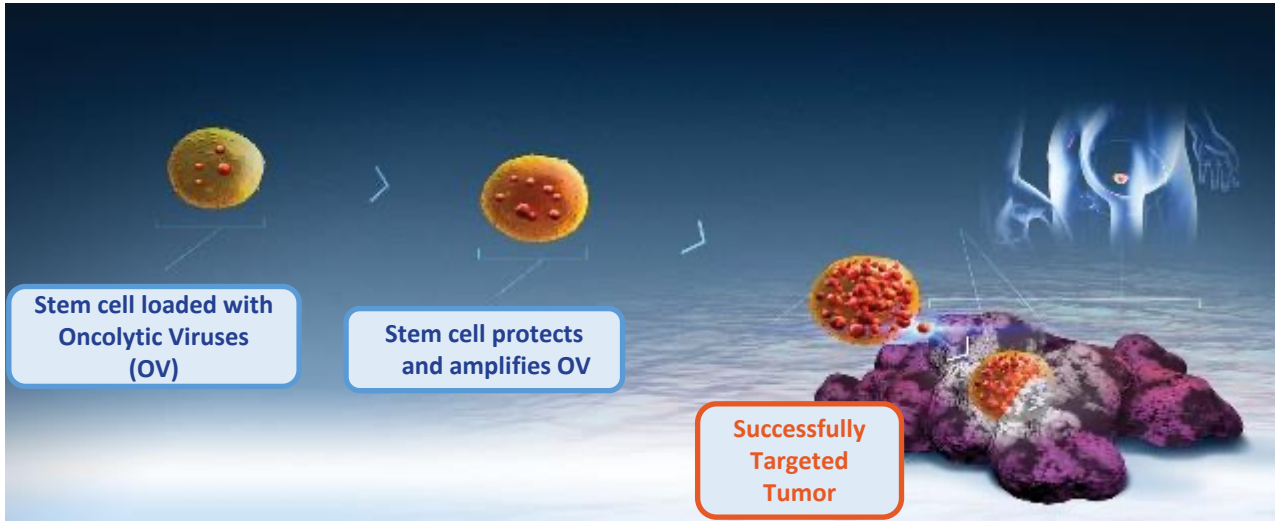
Challenges with Naked OV Therapy

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

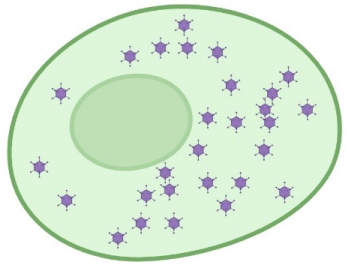
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Calidi's Three Lead Programs

CLD-101 (NeuroNova)

Clinical trial Phase 1/1b

Indication: Recurrent and newly diagnosed High Grade Glioma



Tumor selective Virotherapy:
Adenovirus: CRAD-s-Pk7

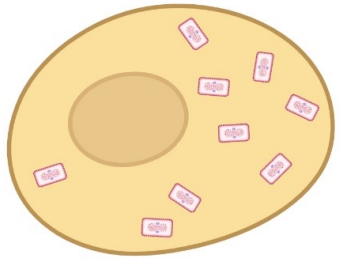
Delivery vehicle/potentiator:
Allogeneic Neuronal Stem Cells

Product type:
Off-the-shelf
Localized administration

CLD-201 (SuperNova)

Targeting clinic 2H 2024

Indication: Advanced Solid Tumors:



Tumor selective Virotherapy:
Vaccinia virus: CAL1

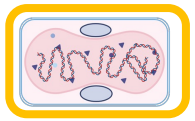
Delivery vehicle/potentiator:
Allogeneic Adipose-derived Mesenchymal Stem Cells

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

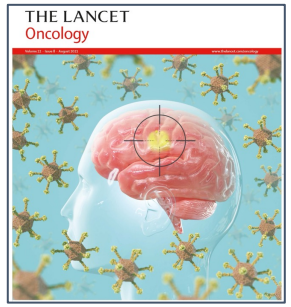
Product type:
Off-the-shelf
Systemic administration

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CLD-101 (Neuronova) in High grade Glioma (HGG)

Completed: Phase 1 (NWU)
Single dose
in newly diagnosed HGG

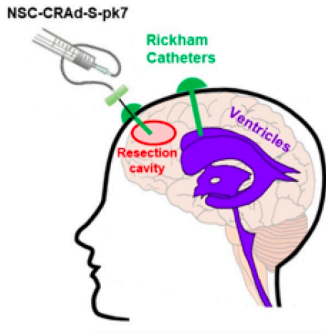
- Treatment was safe and tolerable.
- In the subset of patients containing an unmethylated MGMT promoter, the median **PFS** was **8.8** vs. 5.3 months and **Overall Survival** was **18** vs. 12.7 months.



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

Ongoing: Phase 1 (COH)
multiple dose
in recurrent HGG

- 1ari Objective: analyze safety and feasibility of intracerebrally administering up to 4 weekly doses
- Currently enrolling participants to Treatment Schedule 4 (4 doses).



In preparation: Phase 1b (NWU)
multiple dose
in newly diagnosed HGG

- 1ari Objective: analyze safety and feasibility of multiple intracerebrally administering in newly diagnosed HGG.
- Target to start 1H 2024

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CLD-201 (Supernova) in Advanced Solid Tumors

Completed: Safety Study
Autologous settings - Single dose

- Treatment was safe and tolerable.
- **Strong initial signals of efficacy documented** (in combination with Checkpoint Inhibitors)



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

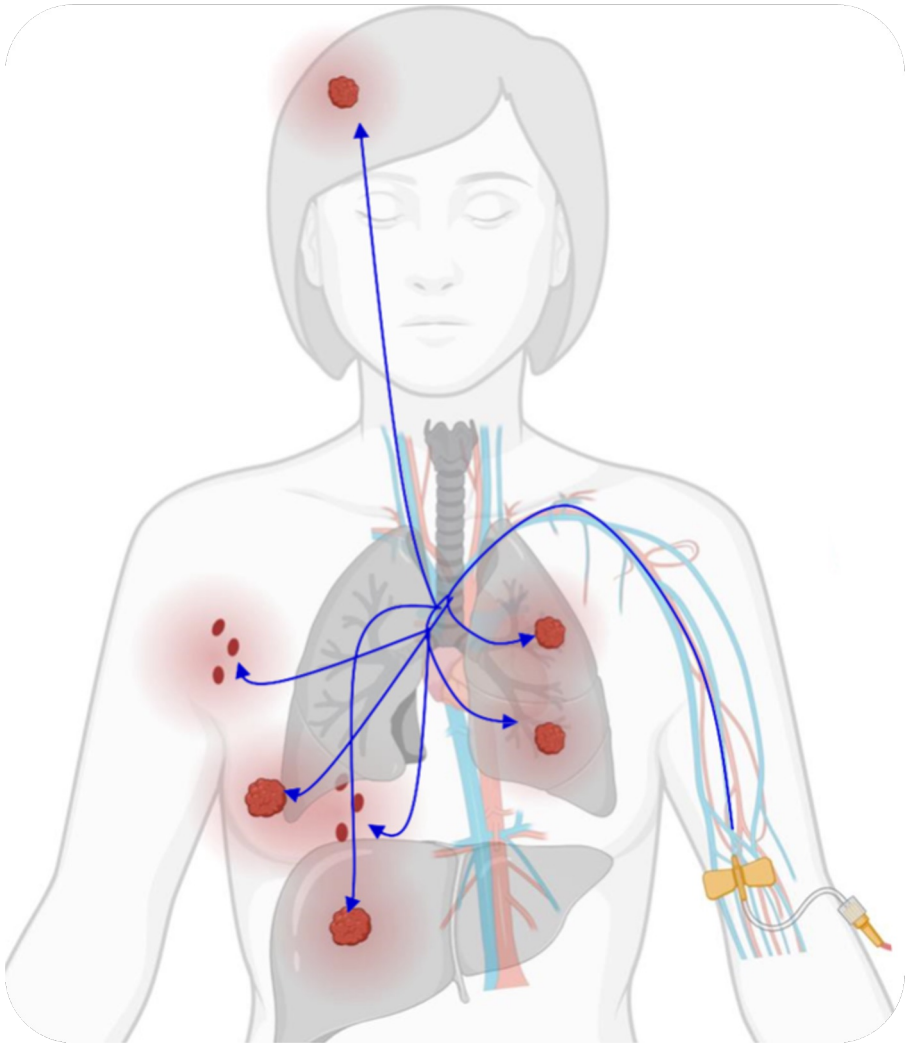
- **New allogeneic program developed to reach wider cancer population**
- cGMP Final Drug Product Manufacturing to be completed in 2Q 2024
- **Phase 1 initiation in 2H 2024**

Skin cancers, Head & Neck, TNBC, soft tissue Sarcoma

Minev B, et al. Journal of Translational Medicine (2019) 17:271 | & Nguyen DH, et al Cancers. 2022 Dec 13;14(24):613

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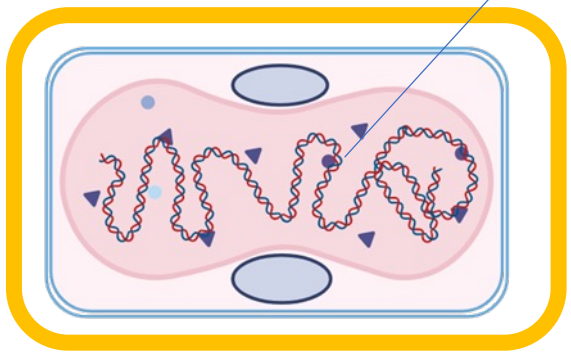
Calidi's Systemic Approach (CLD-400 – RT Nova program)



- ✓ New treatment option for advanced metastatic disease, or lung Cancer
- ✓ Simple, cost-effective IV administration avoiding the need for image-guided delivery.

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Development of a New Enveloped Vaccinia (EEV) Backbone Designed for Systemic Delivery



Virotherapy:

1- New **engeneered tumor selective Vaccinia virus (RT)**

2- A large insertion capacity (25-45Kb), allowing delivering of existing therapeutic proteins into the tumor.

Enveloped:

***1- High production of* enveloped viruses** by manufacturing human cell and at tumor site. Genetically encoded in virus genome.

2- Protection is given by second membrane originated by human cell

3- Targeting: Mediates the long-range dissemination. (Contains human surface receptors).

4- Immunomodulation: Surface proteins regulate immunosuppression

Safety:

1- Does not integrate into human genome.

2- *Platform has a* ***Safety-switch***

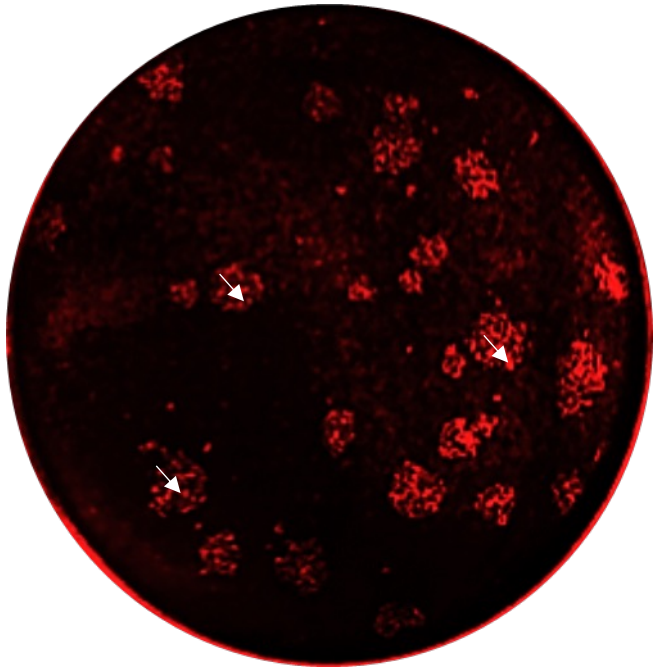
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Dissemination: Vaccinia Virus Strain ("Redtail") Produces High Levels of EEV Particles

Comet assay of two distinct vaccinia viruses.

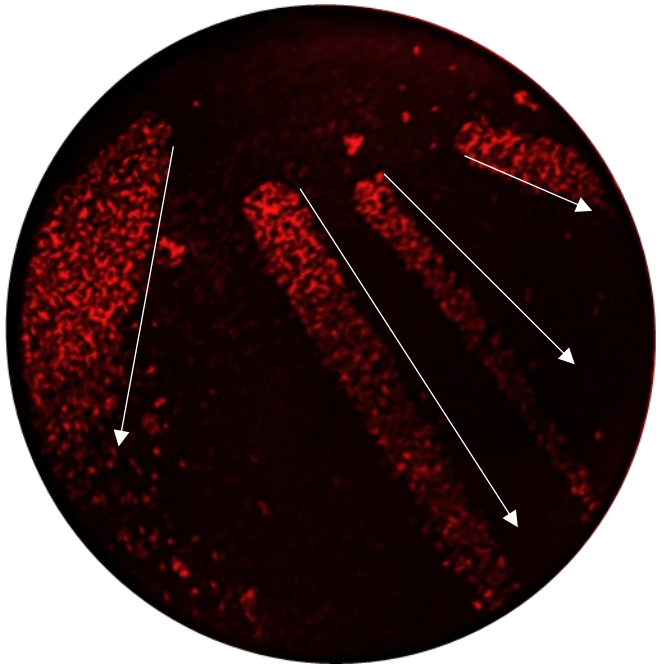
Vaccinia Viruses are genetically engineered to express TurboFP635 (red fluorescence).

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 particle



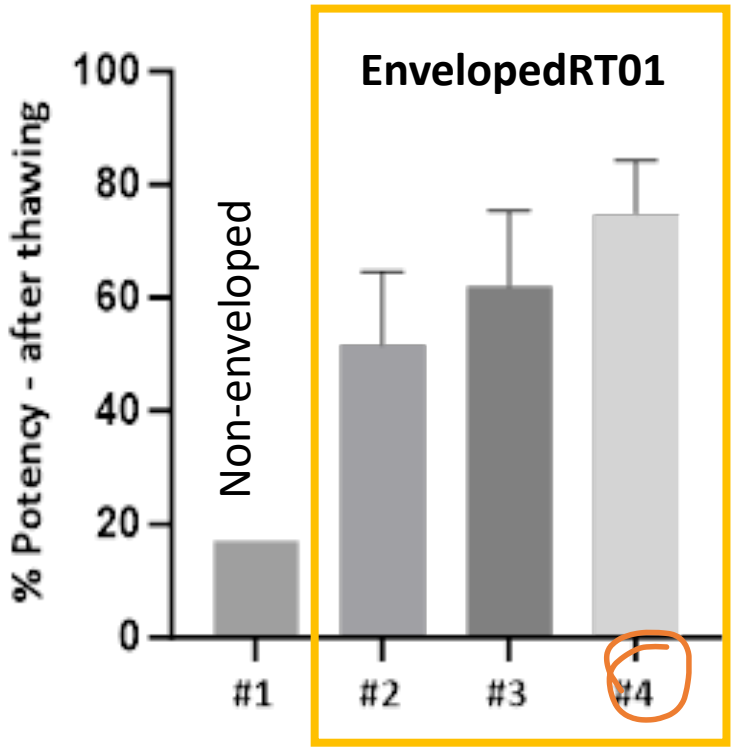
A long "tail" in a comet assay indicates that the virus can produce high levels of EEV **leading to further spread.**

Redtail (RT) Strain

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

Potency of EEV after different manufacturing protocol.



⇨ **A novel technique for purifying <u>extracellular enveloped viruses</u> (EEVs), was required.**

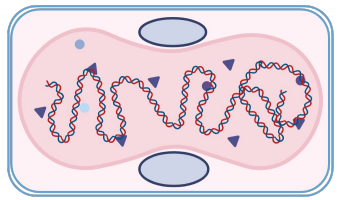
⇨ **Clinically relevant manufacturing process is critical, as the virus' functionality depends on having a scalable manufacturing process that maintains the integrity of the 2nd membrane.**

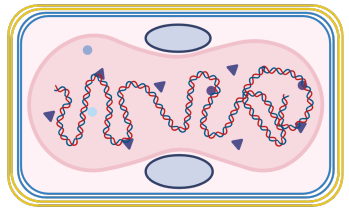
- Potency is defined as % EEV that are active after incubation with human serum

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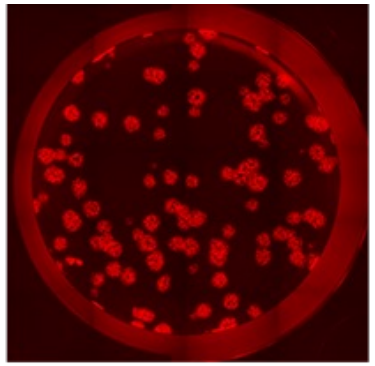
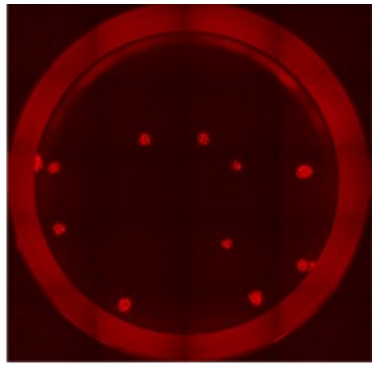
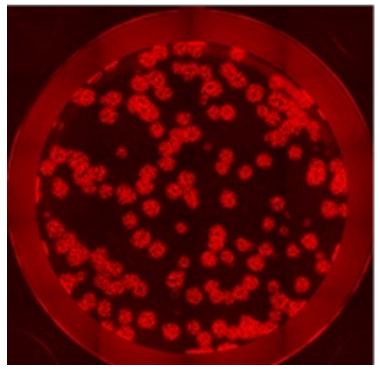
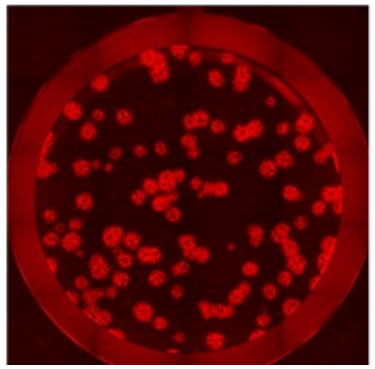
Protection: Only Enveloped Vaccinia Particles Are Resistant to Humoral Immunity

Only Enveloped virotherapies can survive inactivation by human serum.
Critical step to achieve systemic delivery





envRT-01

	Standard media	Human Serum	
Non-enveloped Vaccinia virus			12.4% Survival
Enveloped Vaccinia virus			79.3% Survival

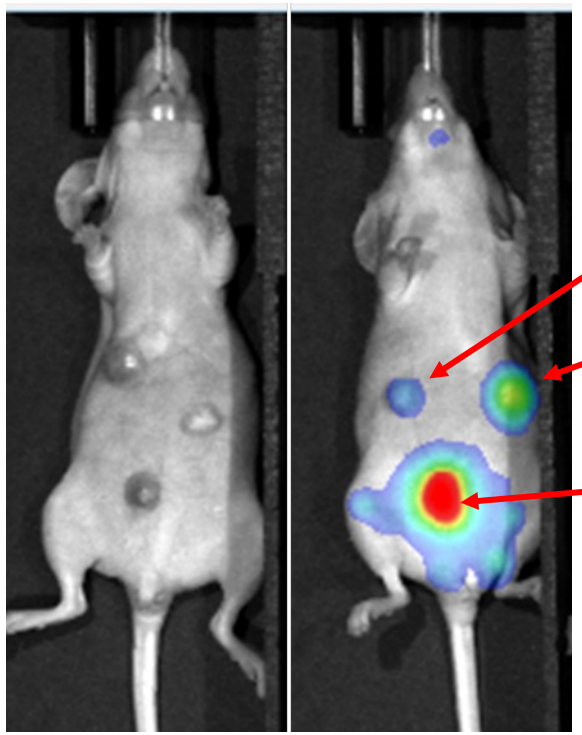
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Systemic Administration of envRT01 Can Target and Eliminate Multiple Tumors

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

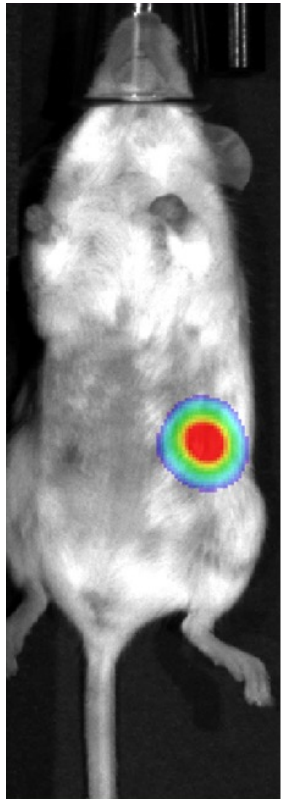


% Tumor Growth inhibition (Average n=5) day 10

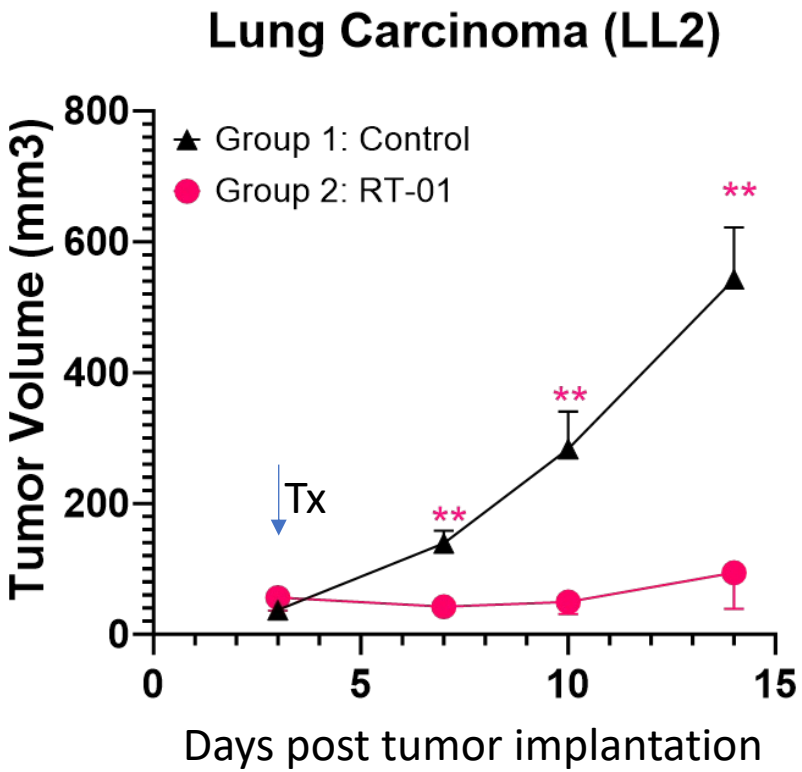
Head and Neck SCC cancer	30%
Lung cancer	92%
Melanoma	87%

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



envRT-01 Virus: TurboFP635 is represented as Rainbow signal



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

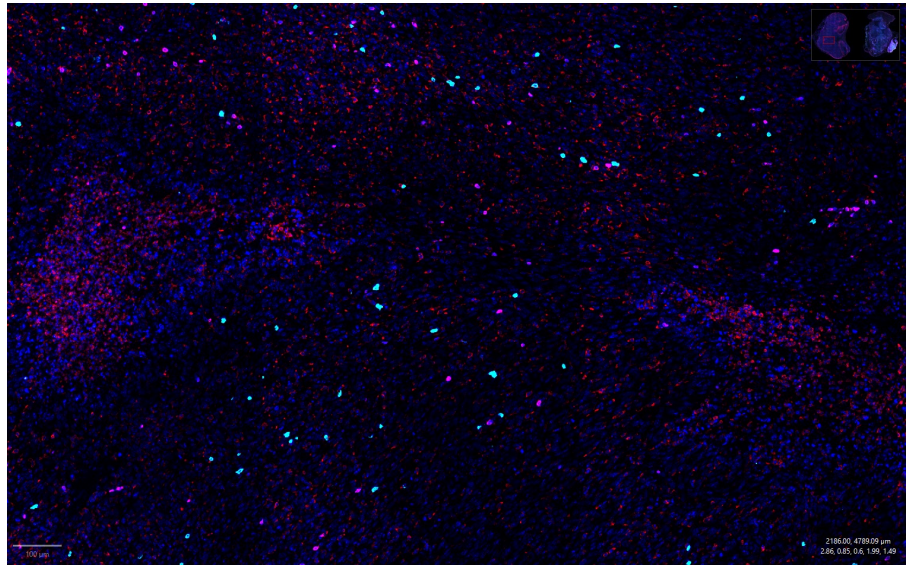
Remarkable tumor selectivity.

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envRT-01 Induces Major Modulation of Tumor Immune Microenvironment

Immunohistochemistry data indicates envRT-01 treatment induces major infiltration of CD8 and CD4 T cells and reduction of myeloid population (Breast cancer tumors).

Untreated tumor

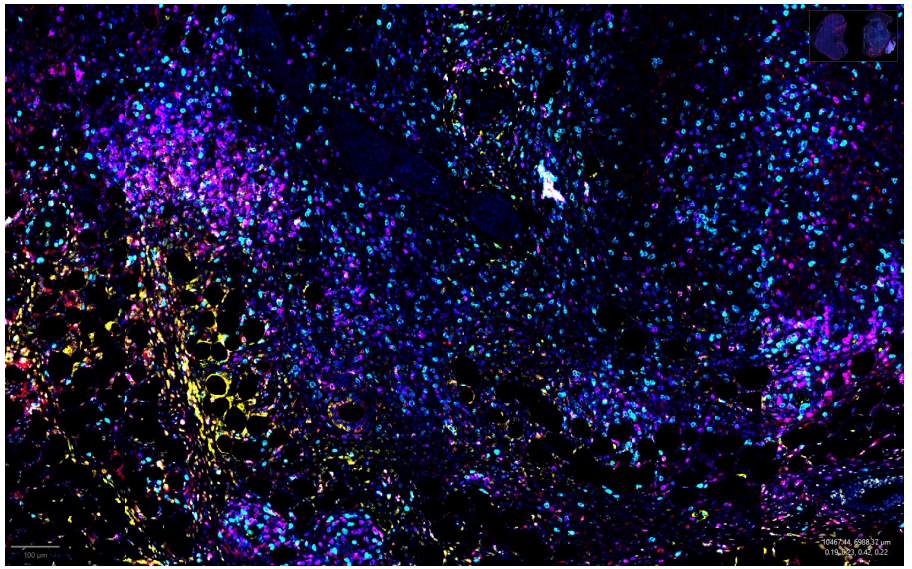


CD8 T, CD4 T ↓ Myeloid ↑

Color legend

CD8 T
CD4 T
CD11b
(Myeloid)
Vaccinia
DAPI
(tumor)

envRT-01

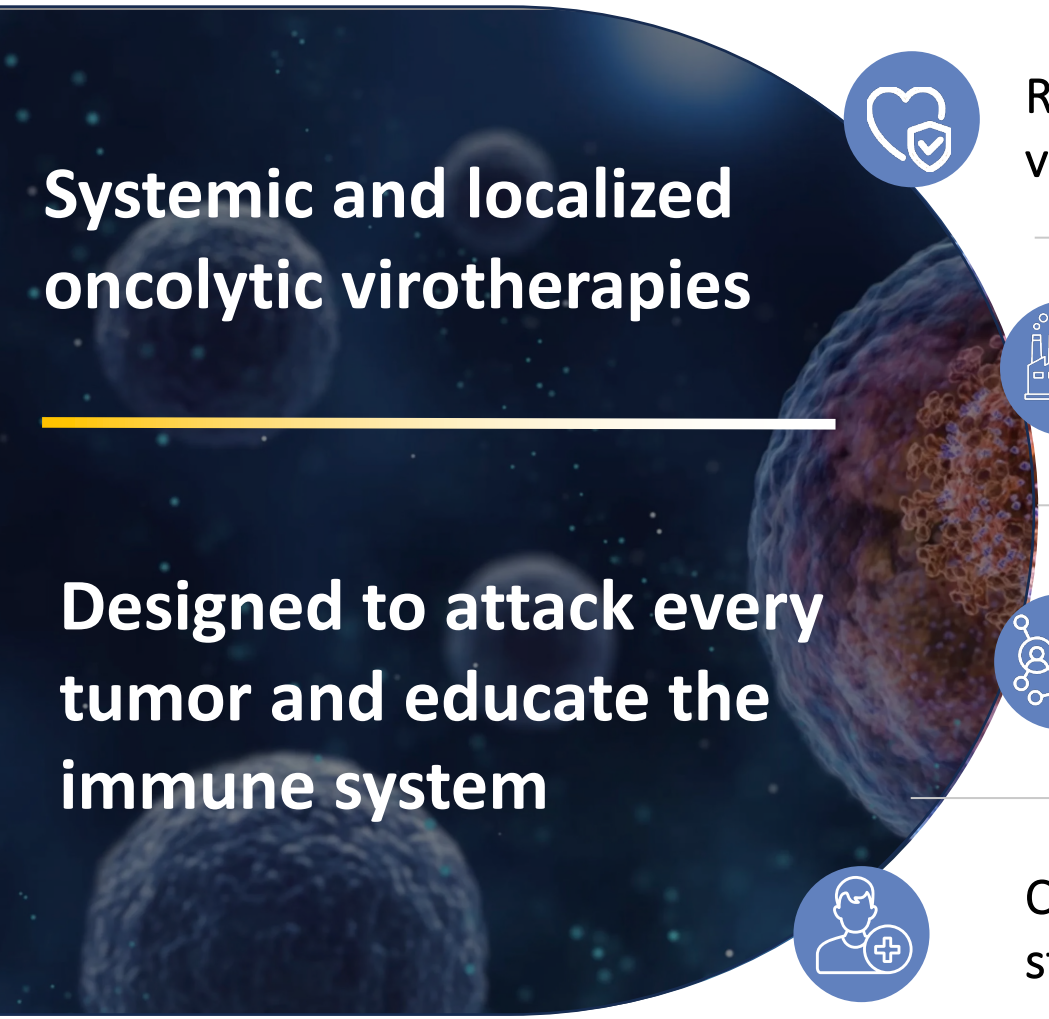


CD8 T, CD4 T ↑ Myeloid ↓

Enhancement of anti-tumor efficacy is linked with increased infiltration of CD8 & CD4 T immune cells.

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Driving Clinical Revolution Using Cells, or Cell-Membranes to Advance Oncolytic Virotherapies to a New Therapeutic Level



Systemic and localized oncolytic virotherapies

Designed to attack every tumor and educate the immune system

RTNova delivers a breakthrough in true systemic oncolytic virotherapy

Delivering on a vision for off-the-shelf platforms that are scalable, and commercially viable

Oncolytic virotherapies that target local and distant tumors

Cell-based delivery platforms: Initial clinical trials showed strong signals of efficacy with favorable safety profile

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Allan J. Camaisa
CEO/Chair of the Board

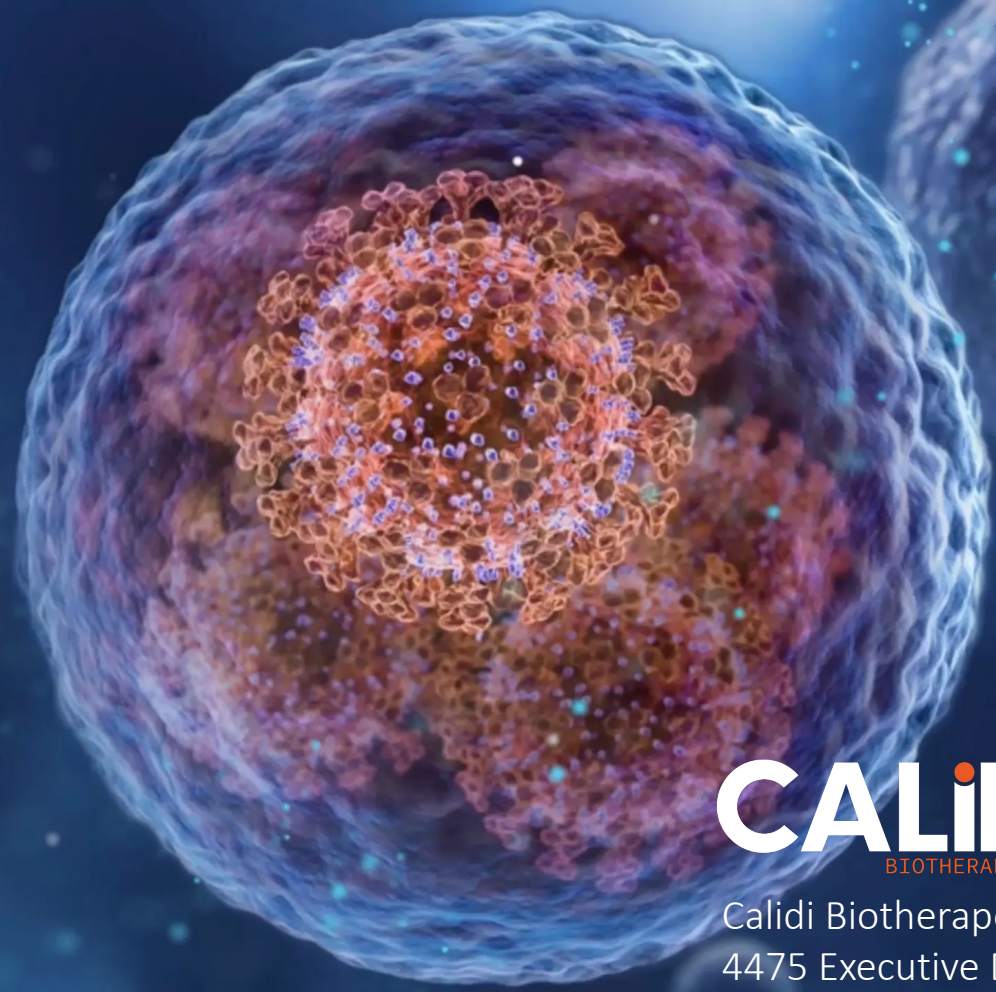
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