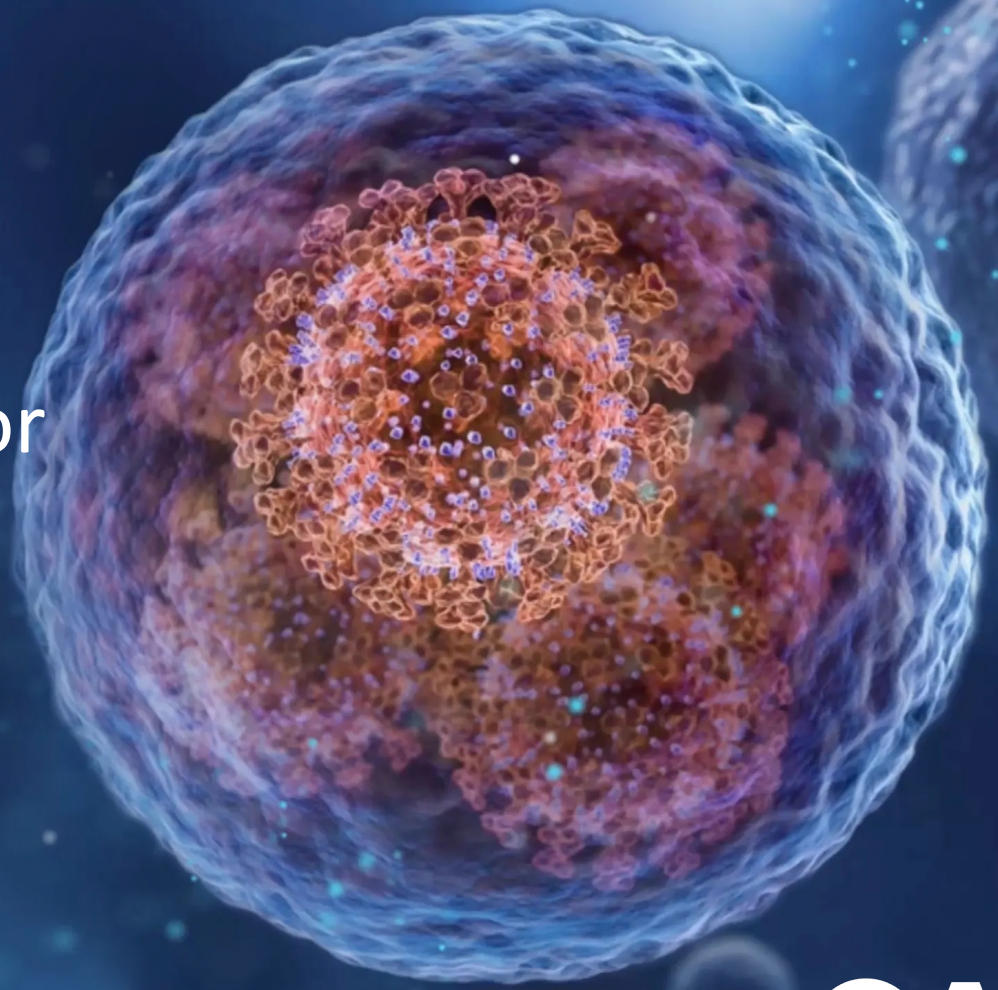
# Systemic and Localized Antitumor Virotherapies



## Designed to attack every tumor and arm the immune system

June 13, 2024

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, 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 Form S-4 filed on August 2, 2023, on Form S-1 filed on October 6, 2023, our Form 10-Q filed on November 14, 2023 and our Form S-1 filed on January 29, 2024.

# 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)**.

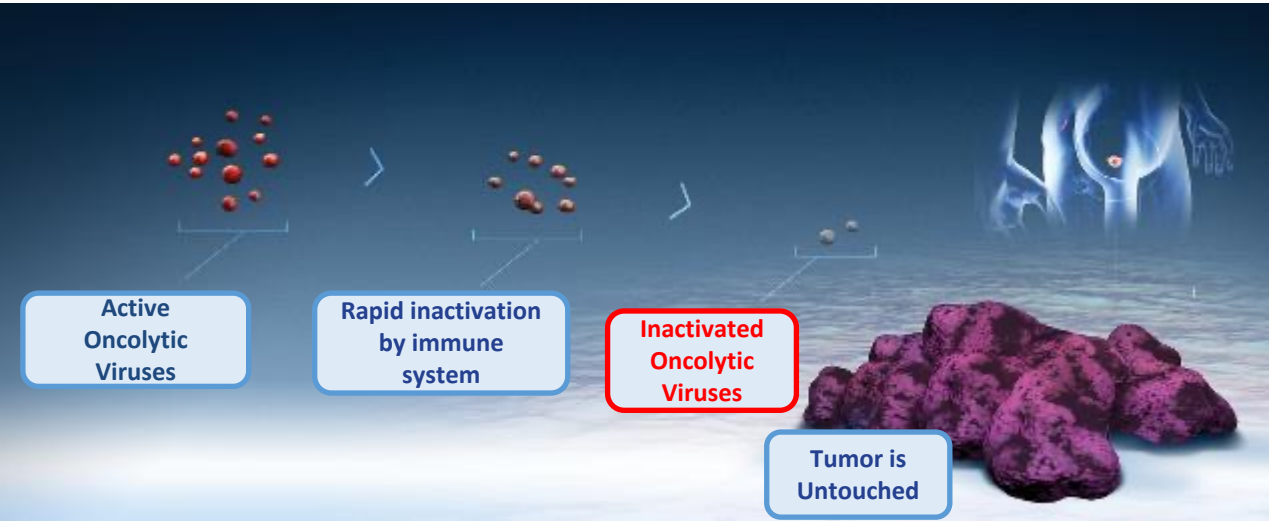
Our cutting-edge **cell-based technologies protect** and deliver oncolytic virotherapies into tumor sites, effectively **overcoming the clinical challenge of rapid elimination by the patient's immune system.**

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

# Calidi Overcomes the Obstacles to Oncolytic Viral Therapy

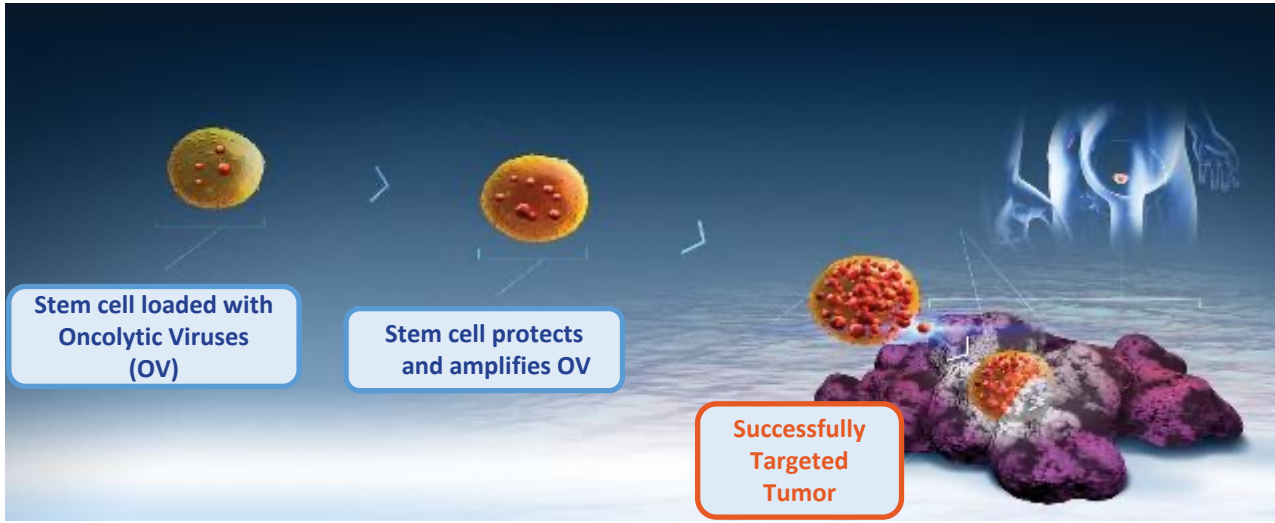
## Challenges with Naked OV Therapy

### Unprotected Oncolytic Virus




## 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**

# Calidi's Platform Advantages (NeuroNova and SuperNova)

| | CALIDI BIOTHERAPEUTICS | Replimune | GENELUX | ONCOLYTIC BIOTECH INC | CANDEL THERAPEUTICS | CG ONCOLOGY | IMUGENE |
|---|---|---|---|---|---|---|---|
| **Ticker Symbol** | NYSEAM:CLDI | NASDAQ:REPL | NASDAQ:GNLX | NASDAQ:ONCY | NASDAQ:CADL | NASDAQ:CGON | ASX:IMU |
| **Stage of Development** | Phase 1 | Phase 3 | Phase 3 | Phase 3 | Phase 3 | Phase 3 | Phase 2 |
| **Market Caps** (6/12/24) | $14.1M | $579.7M | $80.6M | $79.0M | $223.4M | $2.3B | $433.9M |
| **Oncolytic Virus Platform** | Cell Protected: Vaccinia Virus Adenovirus | Herpes Virus | Vaccinia Virus | Reovirus | Adenovirus Herpes Virus | Adenovirus | Vaccinia Virus |
| **Engineered Virus** | ✓ | ✓ | ✓ | X | ✓ | ✓ | ✓ |
| **Reduced viral elimination by the immune system** | ✓ | X | X | X | X | X | X |
| **Virally-encoded therapeutic expressed at administration** | ✓ | X | X | X | X | X | X |
| **Stem cell-derived immune modulators** | ✓ | X | X | X | X | X | X |

# 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) | Preclinical | | | | | |

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

# Upcoming Planned Milestones (2024-2025)

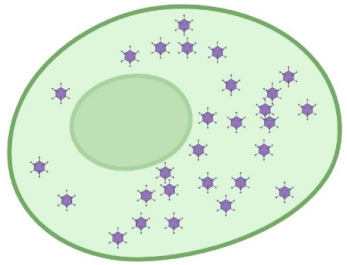
| | 2024 | | 2025 | |
|---|---|---|---|---|
| | 1H | 2H | 1H | 2H |
| **CLD-101** (NNV1: multiple doses newly diagnosed HGG) | | In FDA communication to dose first patient | Clinical trial enrollment update (SITC or ESMO meeting) | Clinical trial Update (ASCO meeting) | Clinical trial Update (SITC or ESMO meeting) |
| **CLD-101** (NNV2: Multiple doses recurrent HGG) | ☑ CIRM Grant: continued support (partner: COH) | Clinical trial enrollment update – 4th Cohort (ASCO meeting) | Completion of dose escalation (SITC or ESMO meeting) | Clinical trial & biomarker studies update (ASCO meeting) | Clinical trial Update (SITC or ESMO meeting) |
| **CLD-201** (SNV1) | cGMP FDP Manufactured; IND-enabling studies completed | IND Submission | First patient dosed (dose escalation) | Clinical trial Update (ASCO meeting) | First patient expansion phase 1 |
| **CLD-400** (RTNova) | ☑ Biocom partnering meetings | Presentation Systemic Platform (ASCO meeting) | Update development Systemic Platform (SITC meeting) | Update (AACR meeting) | PRE-IND Submission. Lung cancer; Update (ASCO meeting) | Update (SITC meeting) |

# 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

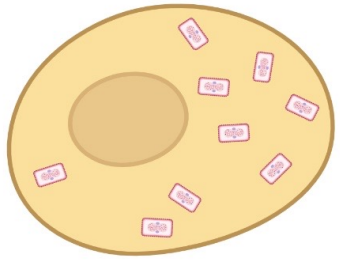
**Delivery vehicle/potentiator:**
Allogeneic Neuronal Stem Cells

**Product type:**
Off-the-shelf
Localized administration

## **CLD-201** (SuperNova)

**Targeting clinic 2H 2024**

**Indication:** Advanced Solid Tumors:



**Tumor selective Virotherapy:**
Vaccinia virus: CAL1

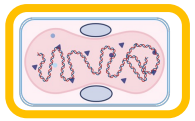
**Delivery vehicle/potentiator:**
Allogeneic Adipose-derived Mesenchymal Stem Cells

**Product type:**
Off-the-shelf
Intratumoral administration

## **CLD-400** (RTNova)

**Pre-clinical**

**Indication:** Lung Cancer, and Metastatic Cancer

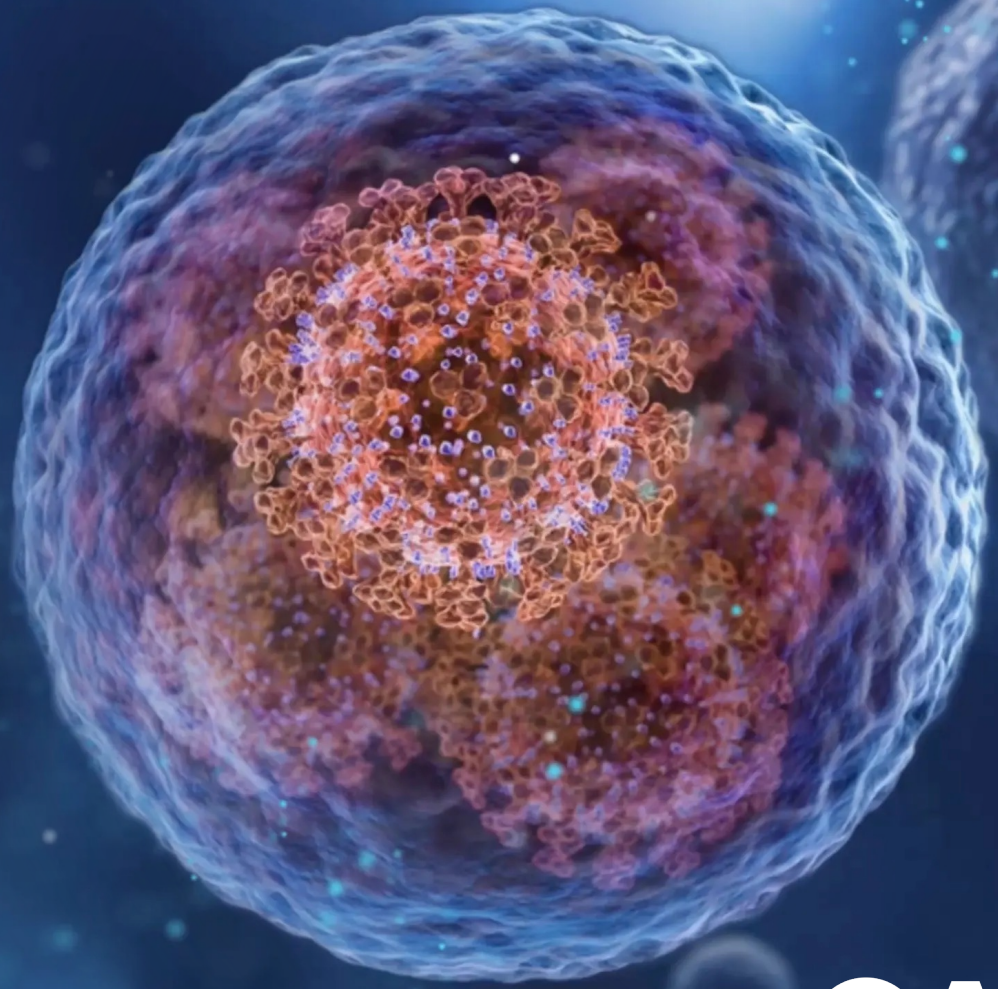


**Tumor selective Virotherapy:**
Extracellular Enveloped Vaccinia virus: envRT-01

**Product type:**
Off-the-shelf
*Systemic* administration

# CLD-101 (NeuroNova)

Designed to Attack High Grade Glioma Brain Cancer



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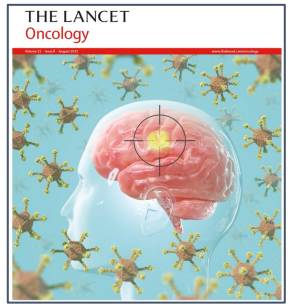
# CLD-101 (NeuroNova) in High Grade Glioma (HGG)

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

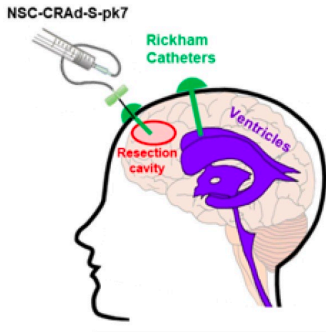
- Treatment was well tolerated
- In the subset of patients containing an unmethylated MGMT promoter, the median **PFS** was **8.8** vs. 5.3 months and **Overall Survival** was **18** vs. 12.7 months.




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

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

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



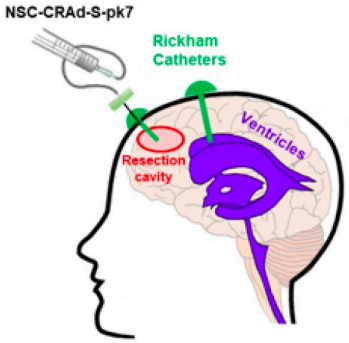

**In preparation:** Phase 1b/2 (NWU)
multiple dose
in newly diagnosed HGG

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

# CLD-101: Recurrent High-Grade Glioma Clinical Pathway

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

**STUDY PROCEDURES:**




| Cycle[a] 1 | Cycle 2 | Cycle 3 | Cycle 4 |
|---|---|---|---|
| **Day 1**<br>• Tumor resection<br>• Manual administration of NSC-CRAd-S-pk7<br>• Placement of 2 Rickham catheters[b]<br>• CSF[c] and blood collection<br>**Day 2**<br>• CSF[d] and blood collection | **Day 1**<br>• CSF and blood collection<br>• NSC-CRAd-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity<br>**Day 2**<br>• CSF and blood collection | **Day 1**<br>• CSF and blood collection<br>• NSC-CRAd-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity<br>**Day 2**<br>• CSF and blood collection | **Day 1**<br>• CSF and blood collection<br>• NSC-CRAd-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity<br>**Day 2**<br>• 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 Starting Schedule | 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.**

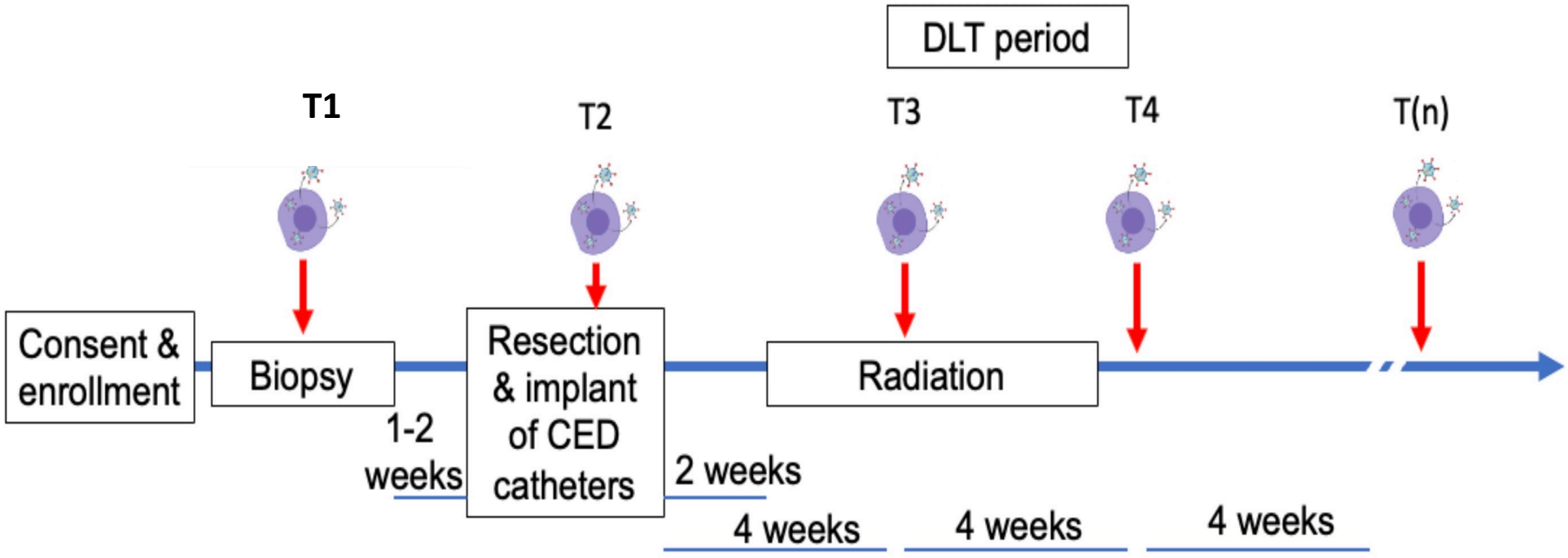
City of Hope®

$12M CIRM CALIFORNIA'S STEM CELL AGENCY

**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



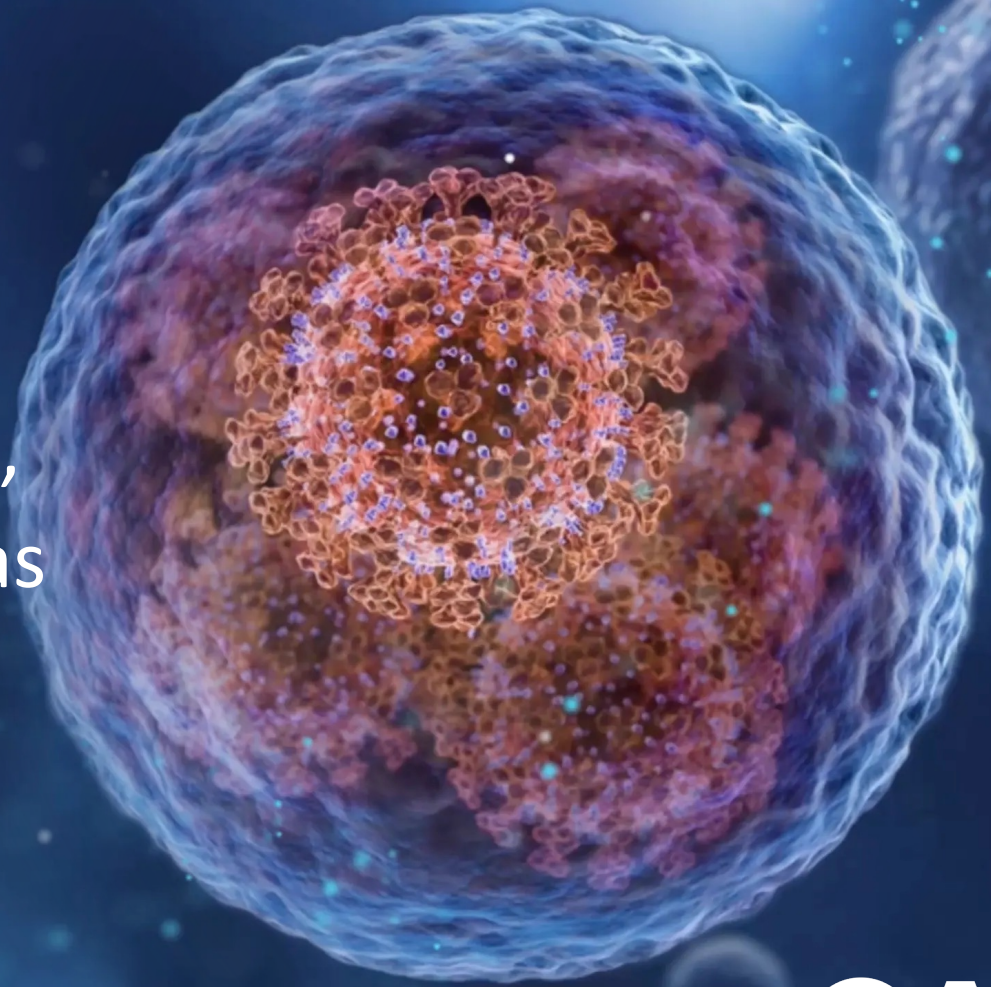

First Patient In:

**1H 2024**
**In FDA communications**

# CLD-201 (SuperNova)

- Localized administration

For Skin Cancers, Head & Neck, TNBC, and Soft Tissue Sarcomas



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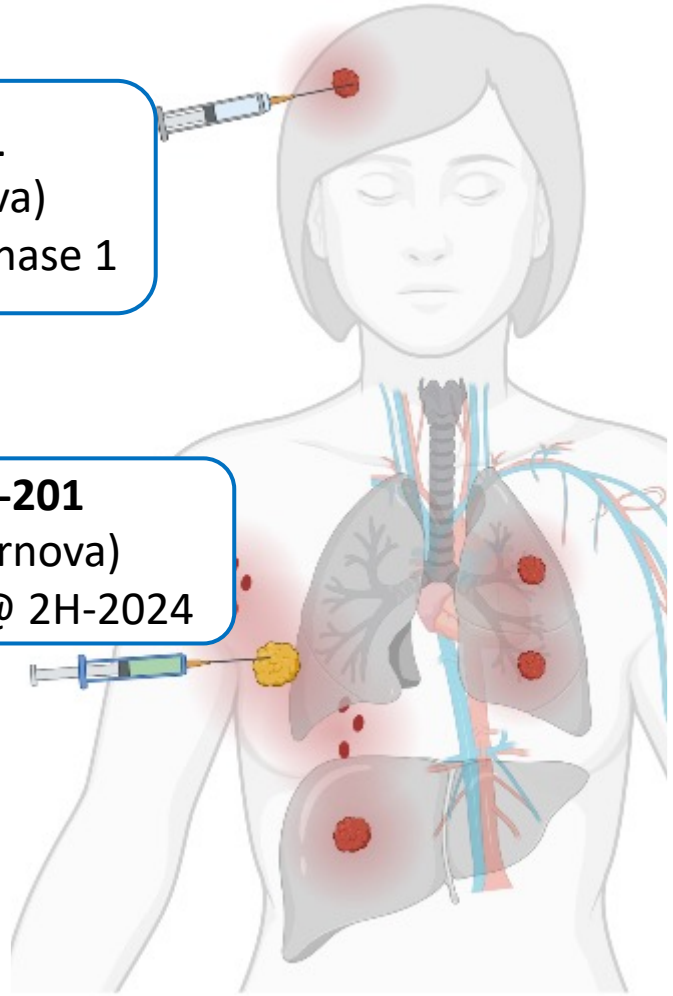
# Maximizing Therapeutic Responses with Directed Localized Administration

## Directed – Localized administration

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

**CLD-101**
(Neuronova)
Completed Phase 1

**CLD-201**
(Supernova)
Phase 1 @ 2H-2024



# 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 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*

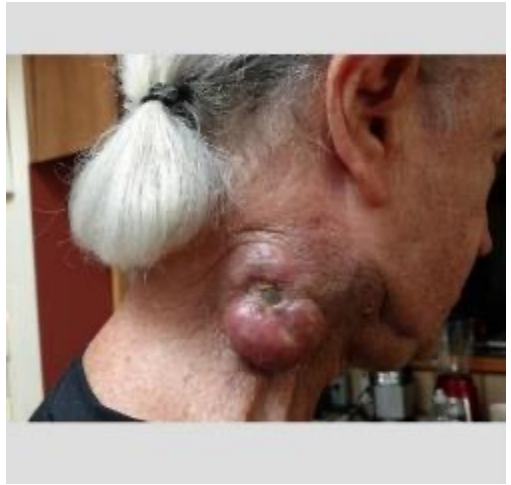
# Durable Tumor Regression and Survival

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

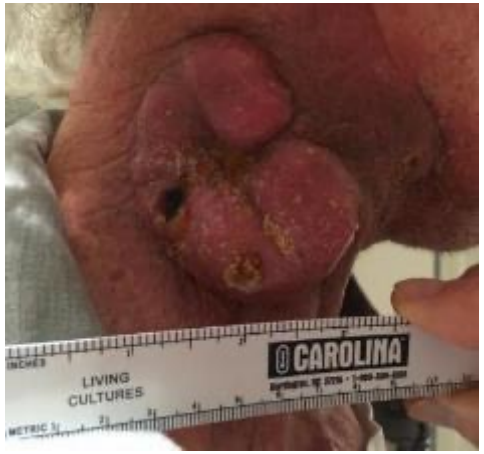
- Age/Sex: 70/M
- Diagnosis: Metastatic Head & Neck SCC
- Stage IV_B
- Injected tumor was previously resistant to chemo- and radio-therapy

**Patient Case: Patient #SI01-021**

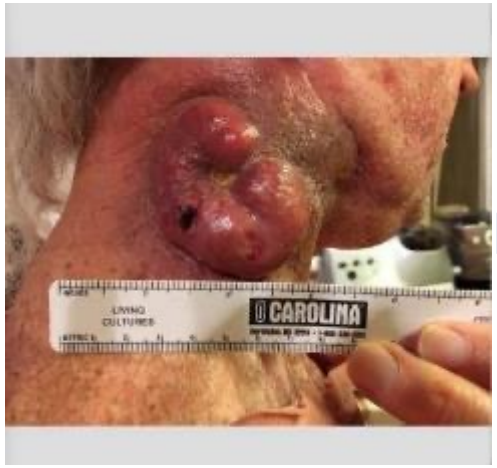
**Day 17 post-treatment**



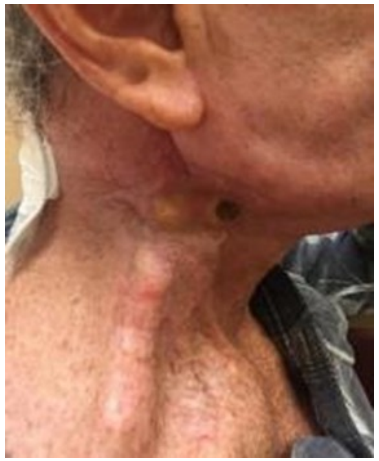
**Day 45 post-treatment**




**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

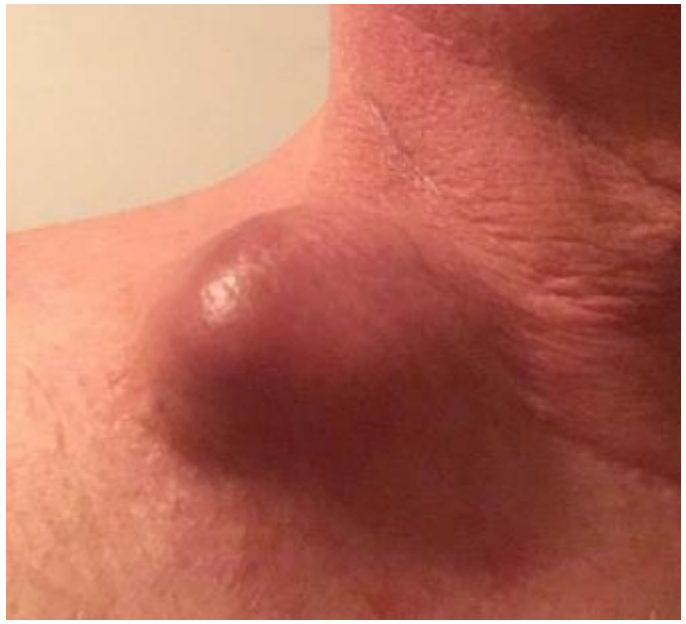
# Durable Tumor Regression and Survival (continued)

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

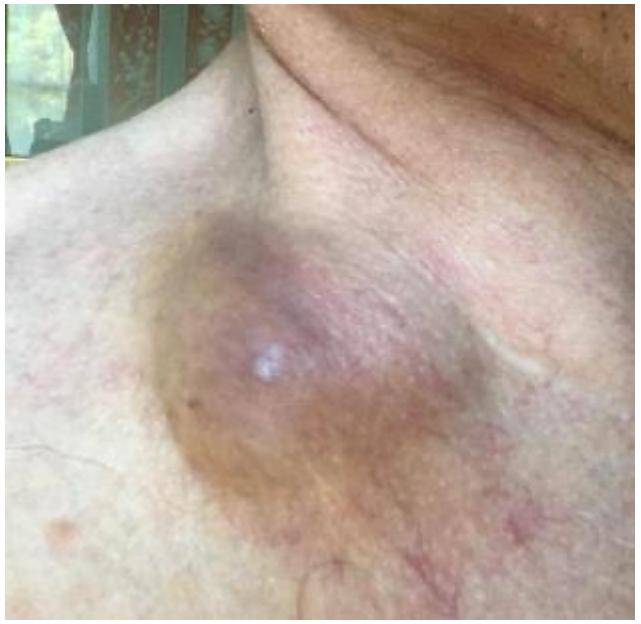
**Calidi Autologous Safety Study**

## Patient Case: Patient #SI01-047

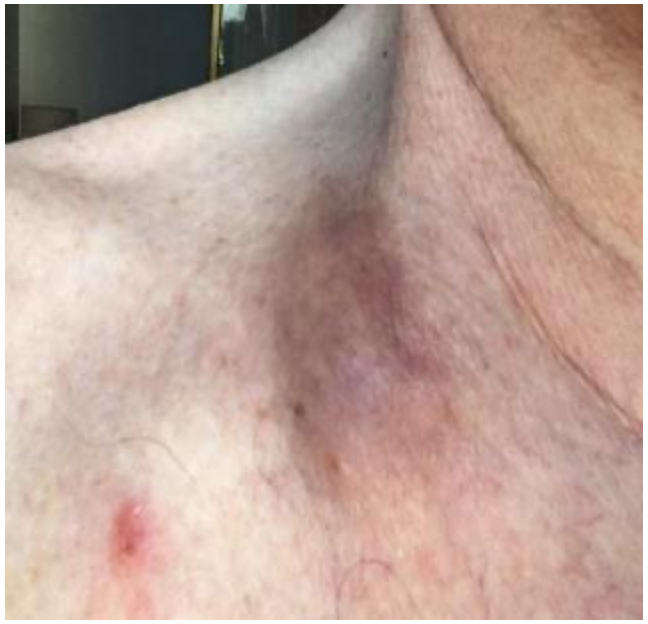
**Day 30 post-treatment**



**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

# Platform with Therapeutic Potential in Multiple Indications

| Tumor Type | Age (M/F) | Diagnosis | Date of Diagnosis | Stage | Date of Treatment | Known Survival Post Treatment (Months) |
|---|---|---|---|---|---|---|
| Head & Neck | 76/F | Left parotid pleomorphic adenoma | 2011 | IVA | 12/16/2015 | 29 |
| Head & Neck | 33/M | Salivary Gland CA & Lung Mets | 2013 | IVC | 6/10/2016 | 23 |
| Thyroid | 67/M | Thyroid CA | 1985 | IVC | 7/19/2017 | 24 |
| Prostate | 62/M | Prostate CA | 2008 | IV | 3/24/2016 | 26 |
| Prostate | 85/M | Prostate CA | 2012 | III | 3/30/2016 | 26 |
| Breast | 43/F | Breast CA | 2015 | IIIC | 5/11/2016 | 24 |
| Colorectal | 59/F | CRC (Colo-Rectal CA) | 2012 | III | 3/10/2016 | 22 |
| Bronchial Carcinoid | 58/F | Bronchial Carcinoid | 2012 | III | 3/30/2016 | 20 |
| Adrenal | 53/F | Adrenal CA | 2013 | IV | 5/11/2016 | 22 |
| Ovarian | 67/F | Ovarian Cancer | 2012 | IV | 1/15/2016 | 23 |

**Discontinued monitoring of patients 1 year following their treatment**

Calidi Autologous Safety Study

# 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 (Skin cancers, 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.

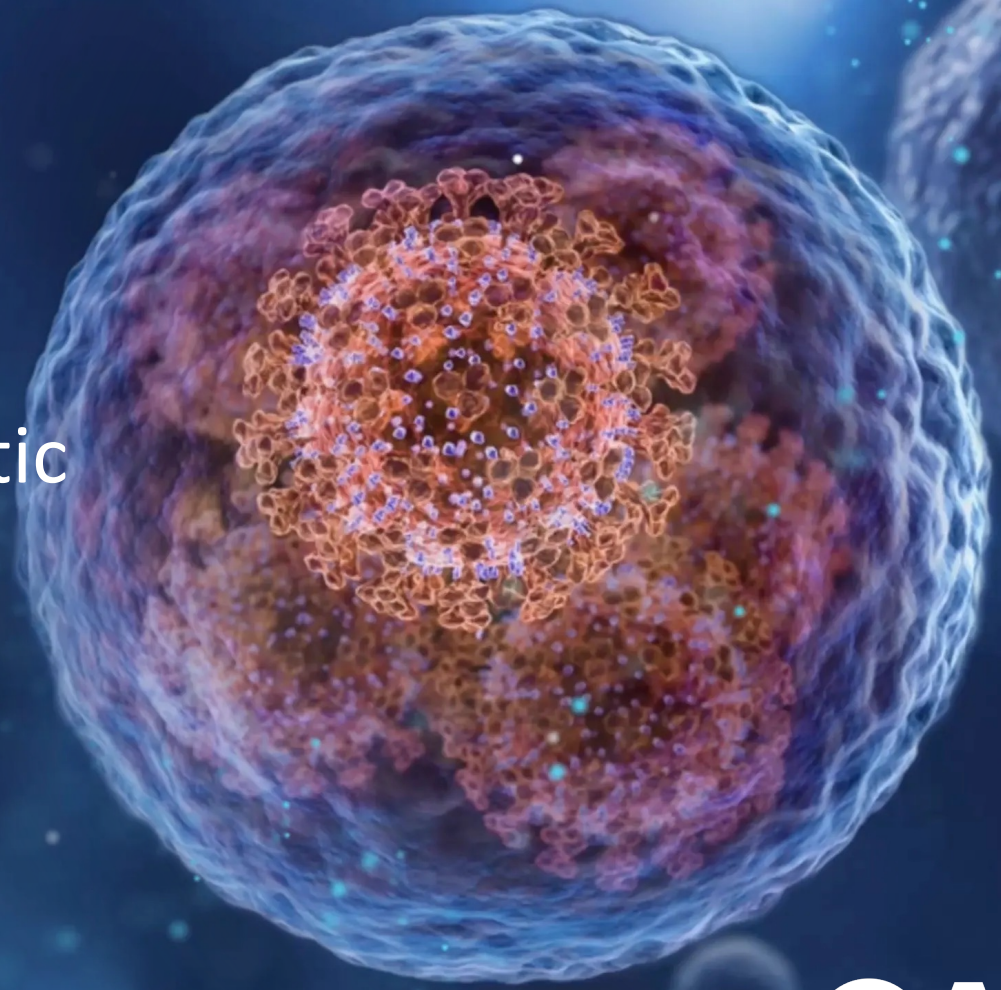
**PART 3:**
**Expansion in Best-Responding Indication – Phase 2**

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

# CLD-400 (RTNova)

- Systemic Administration

Designed for advanced metastatic disease, and for lung Cancer



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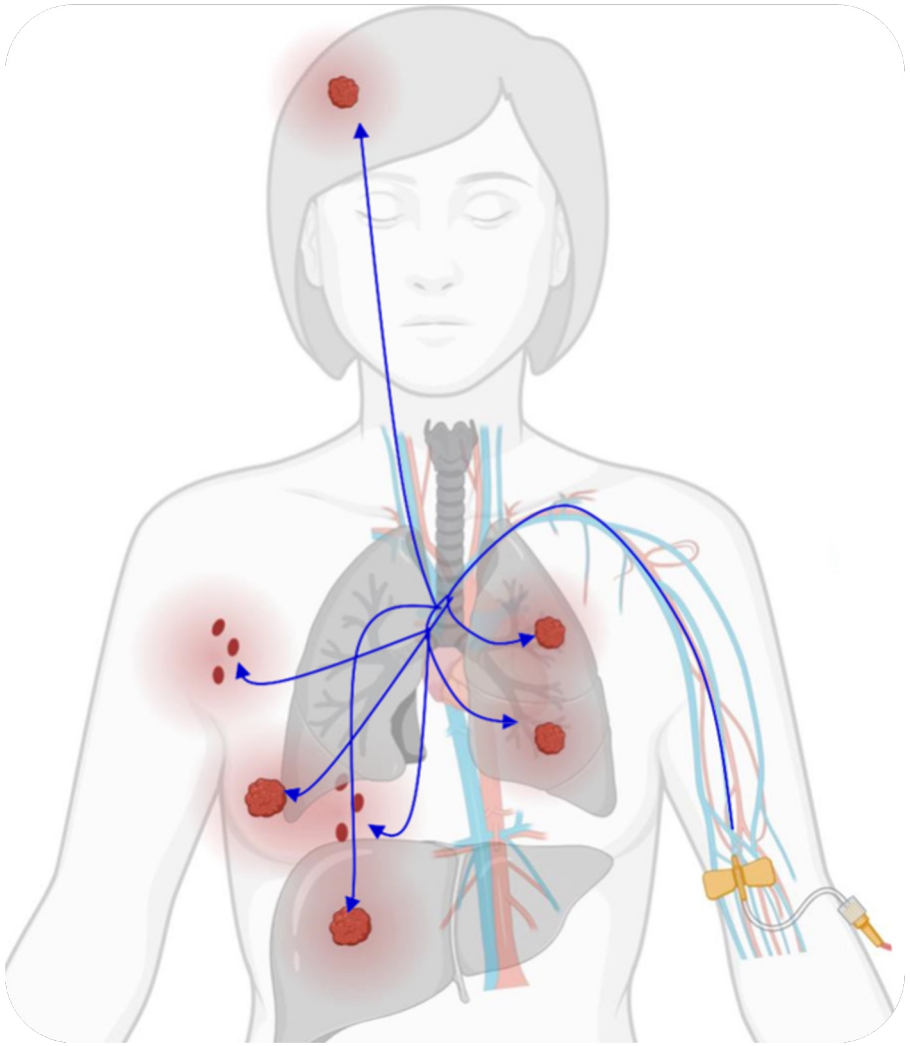
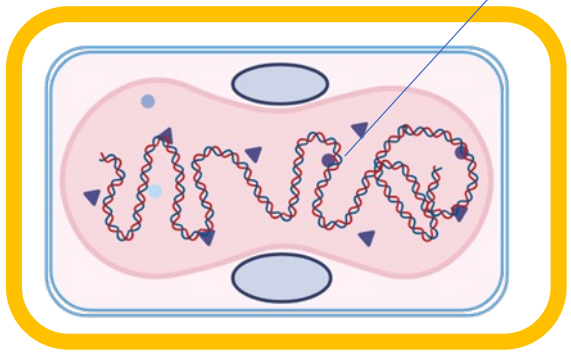
# Calidi's Systemic Approach (CLD-400 – RTNova program)



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

# Extracellular Enveloped Vaccinia (EEV) Backbone Designed for Systemic Delivery



**Virotherapy:**

**1-** New **engineered 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**.

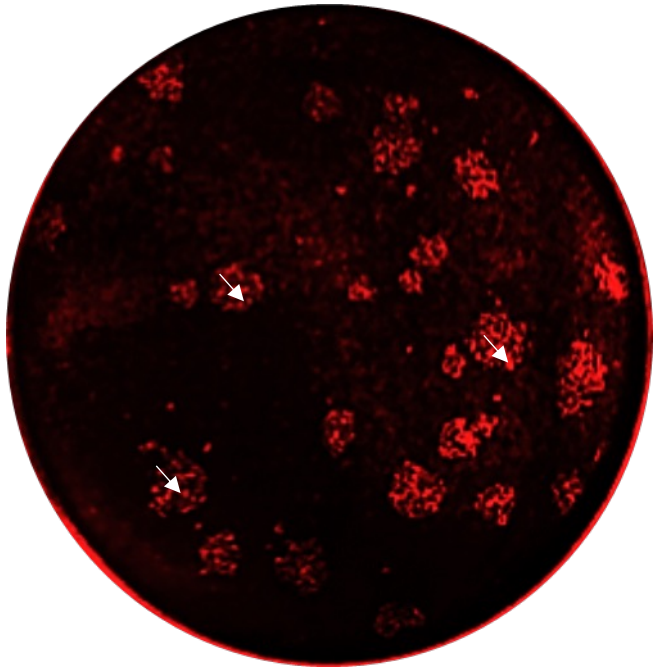
***2-*** *Platform has a* ***Safety-switch***

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

Comet assay of two distinct vaccinia viruses.

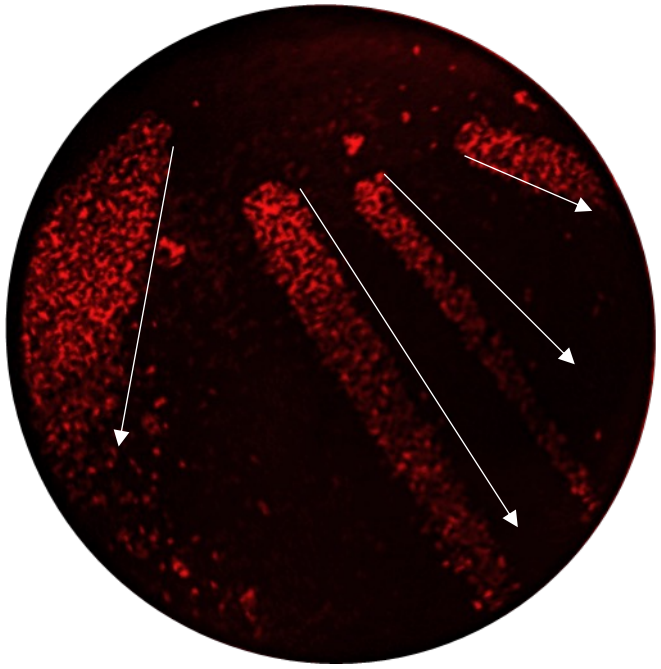
Vaccinia Viruses are genetically engineered to express TurboFP635 (red fluorescence).

**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**

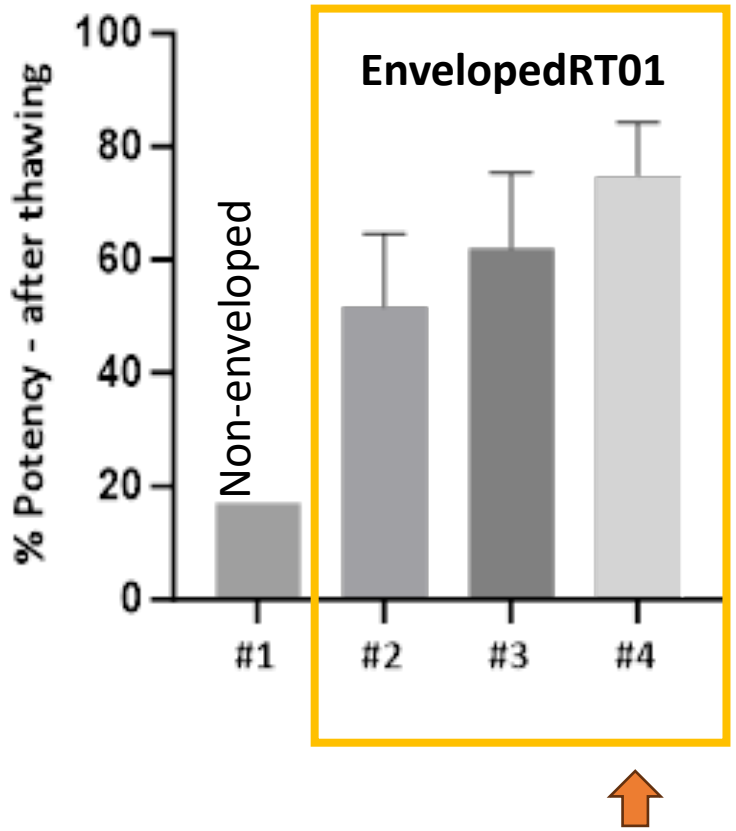


A long "tail" in a comet assay indicates that the virus can produce high levels of EEV **leading to further spread.**

**Redtail (RT) Strain**

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

**Potency of EEV after different manufacturing protocol.**

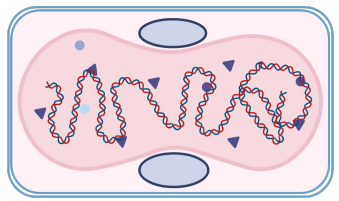



- **A novel technique for purifying <u>extracellular enveloped viruses</u> (EEVs), was required.**
- **Clinically relevant manufacturing process is critical, as the virus' functionality depends on having a scalable manufacturing process that maintains the integrity of the 2nd membrane.**

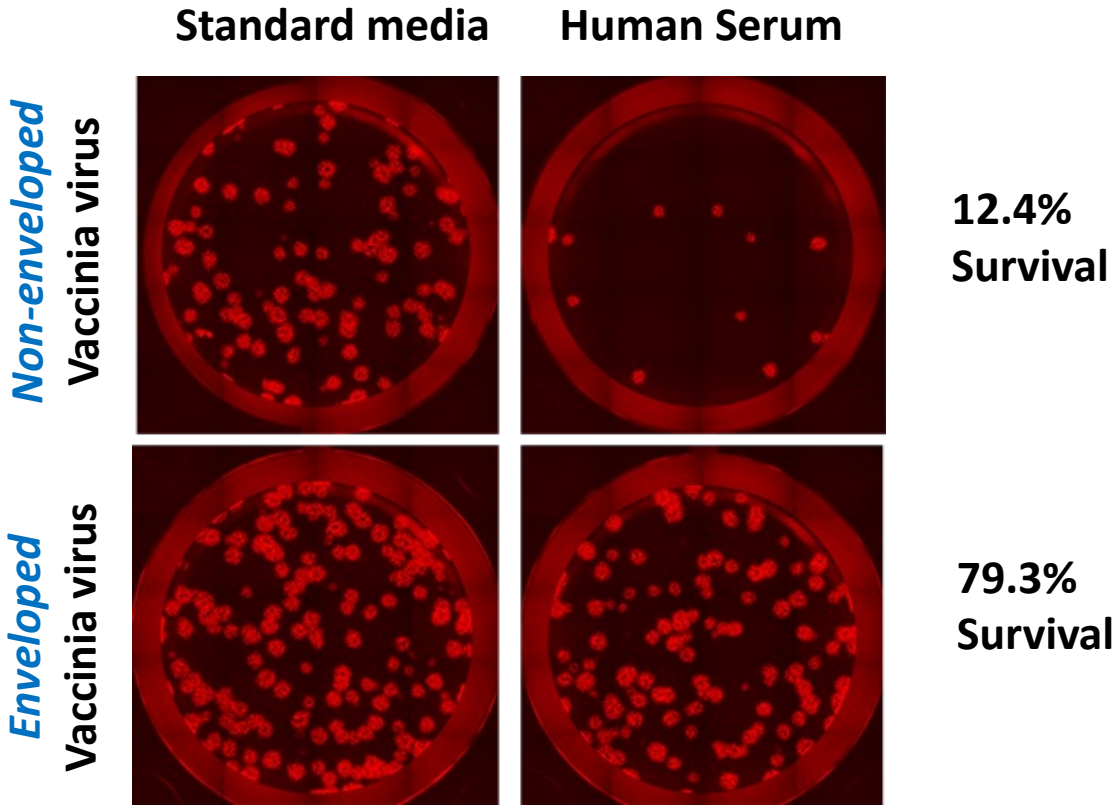
**- Potency is defined as % EEV that are active after incubation with human serum**

# Protection: Only Enveloped Vaccinia Particles Are Resistant to Humoral Immunity

**Only Enveloped virotherapies can survive inactivation by human serum.**
**A critical step to achieving systemic delivery**



envRT-01

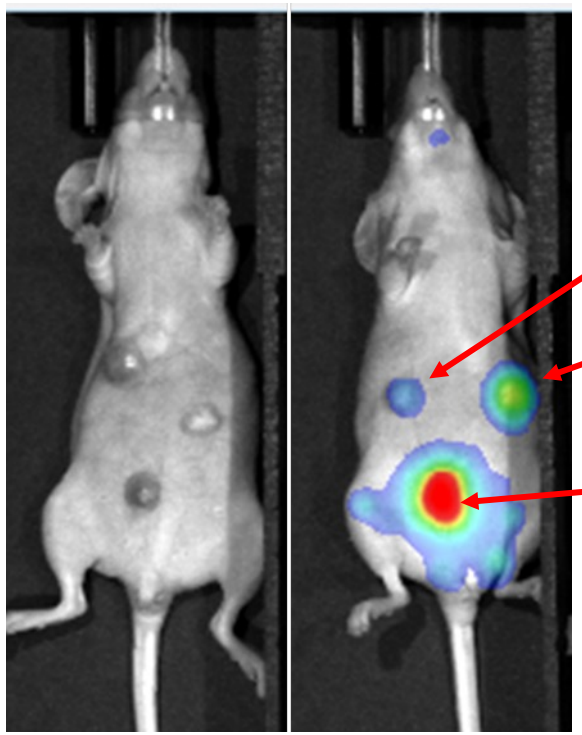


# Systemic Administration of envRT01 Can Target and Eliminate Multiple Tumors

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.

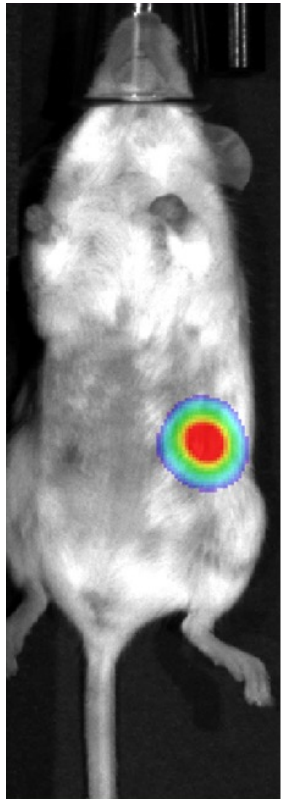
**Mouse model bearing 3 different human solid tumor types**

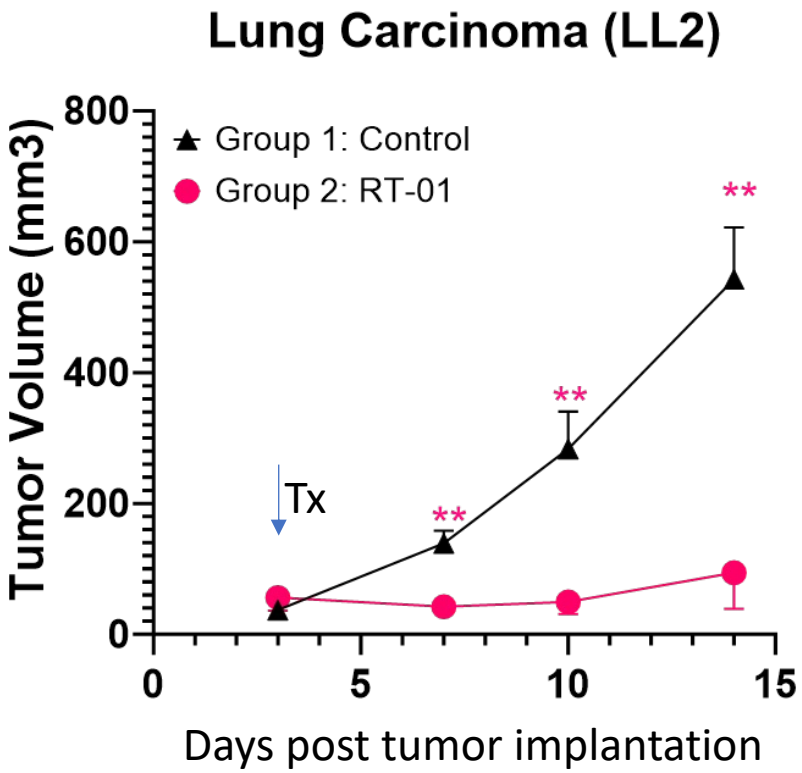



**% Tumor Growth inhibition (Average n=5) day 10**

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

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






**envRT-01 Virus: TurboFP635 is represented as Rainbow signal**

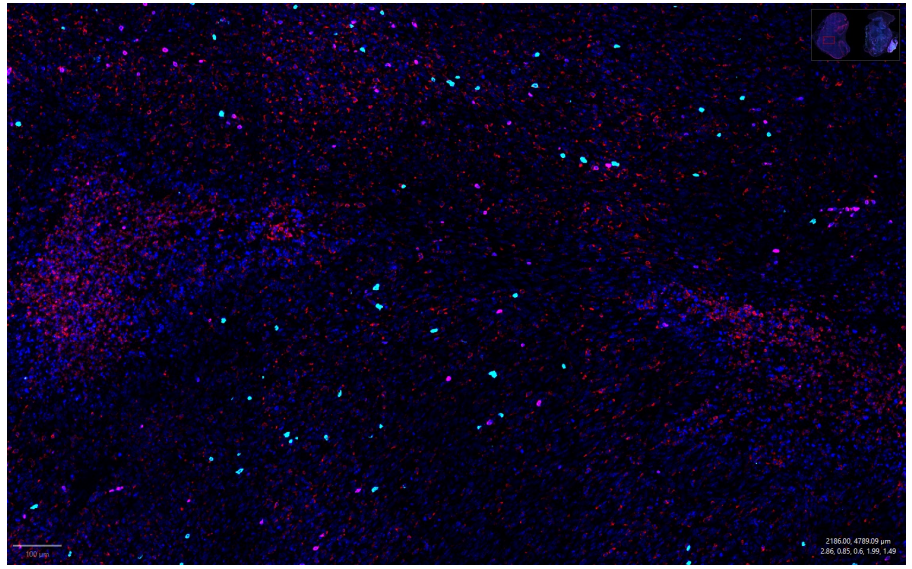
10-100 times lower dose (compared to other vaccinia viruses) can inhibit tumor growth effectively in immunocompetent animals.

<u>Remarkable tumor selectivity.</u>

# 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

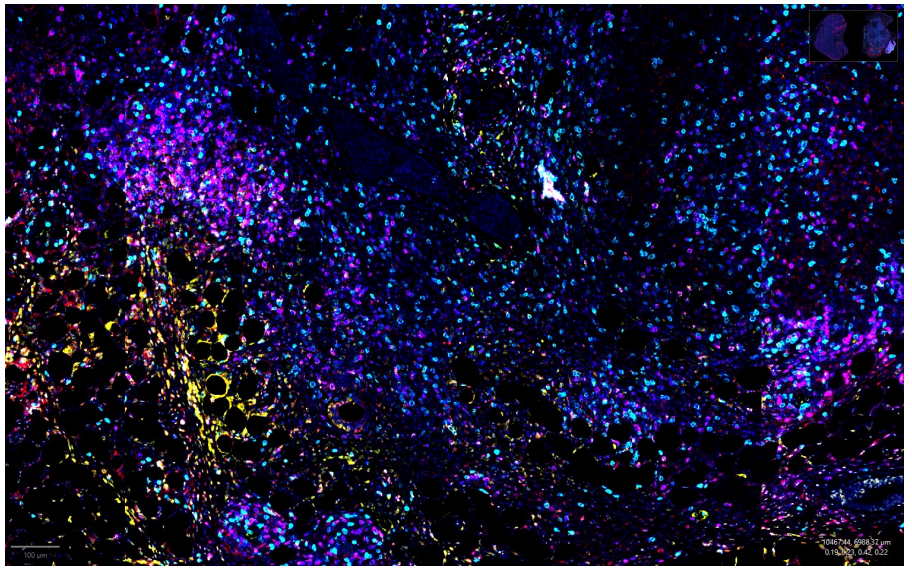


CD8 T, CD4 T ↓ Myeloid ↑

**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.**

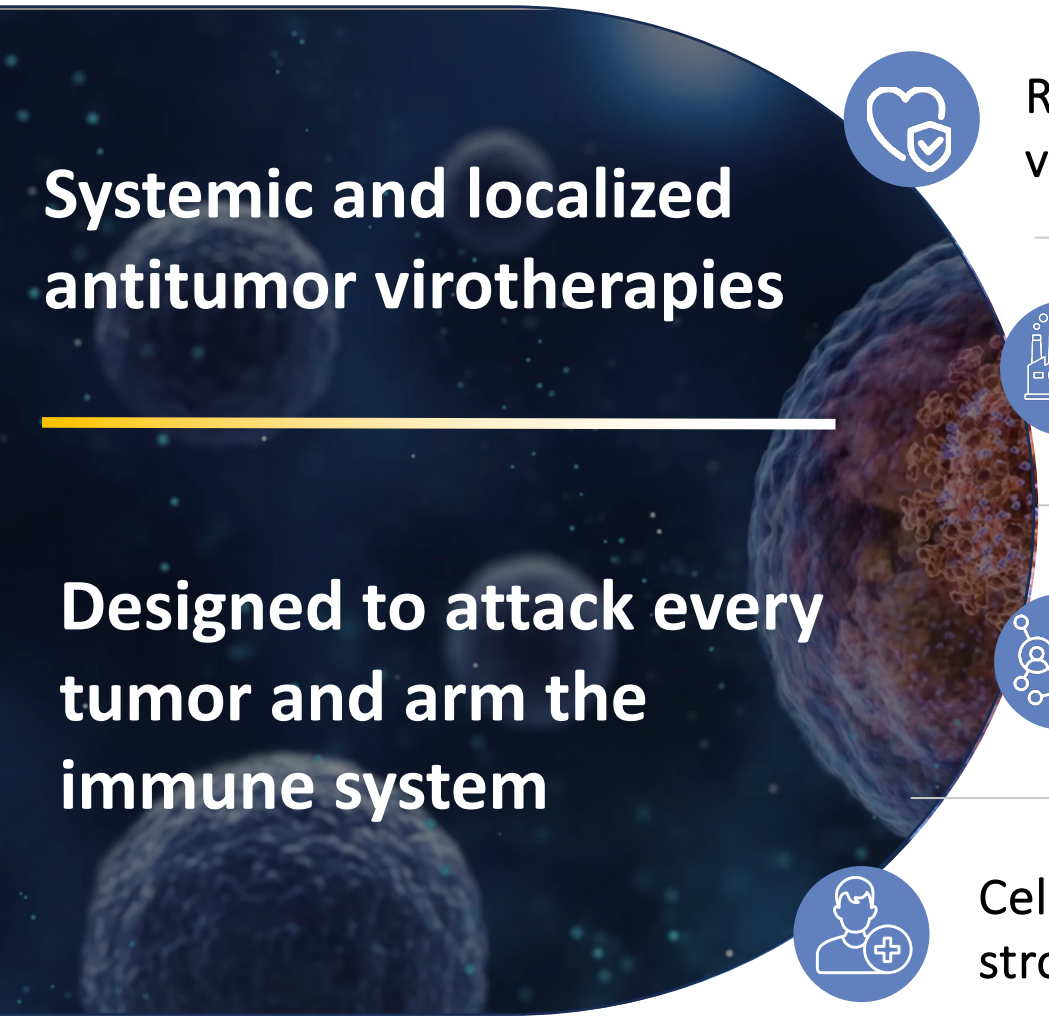
# Market Data for Calidi Biotherapeutics, Inc.

**NYSE American: CLDI**
**Industry: Biopharma**

| | |
|---|---|
| Fiscal Year | Dec. 31 |
| Price[1] | $0.23 |
| Market Cap[1] | $14.1M |
| Shares Outstanding | 64.2M |
| Float | 44.8M |
| Avg. Vol (90-day) | 1.9M |
| Cash[2] | $1.1M |
| Current Debt (proforma)[3] | $0.3M |

*[1] as of June 12, 2024*
*[2] as of March 31, 2024. Raised $6.1M gross proceeds in April 2024 and $2.1M gross proceeds in June 2024*
*[3] principal payments due in 2024, total debt = approx. $4.6M*

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



**Systemic and localized antitumor virotherapies**

**Designed to attack every tumor and arm the immune system**

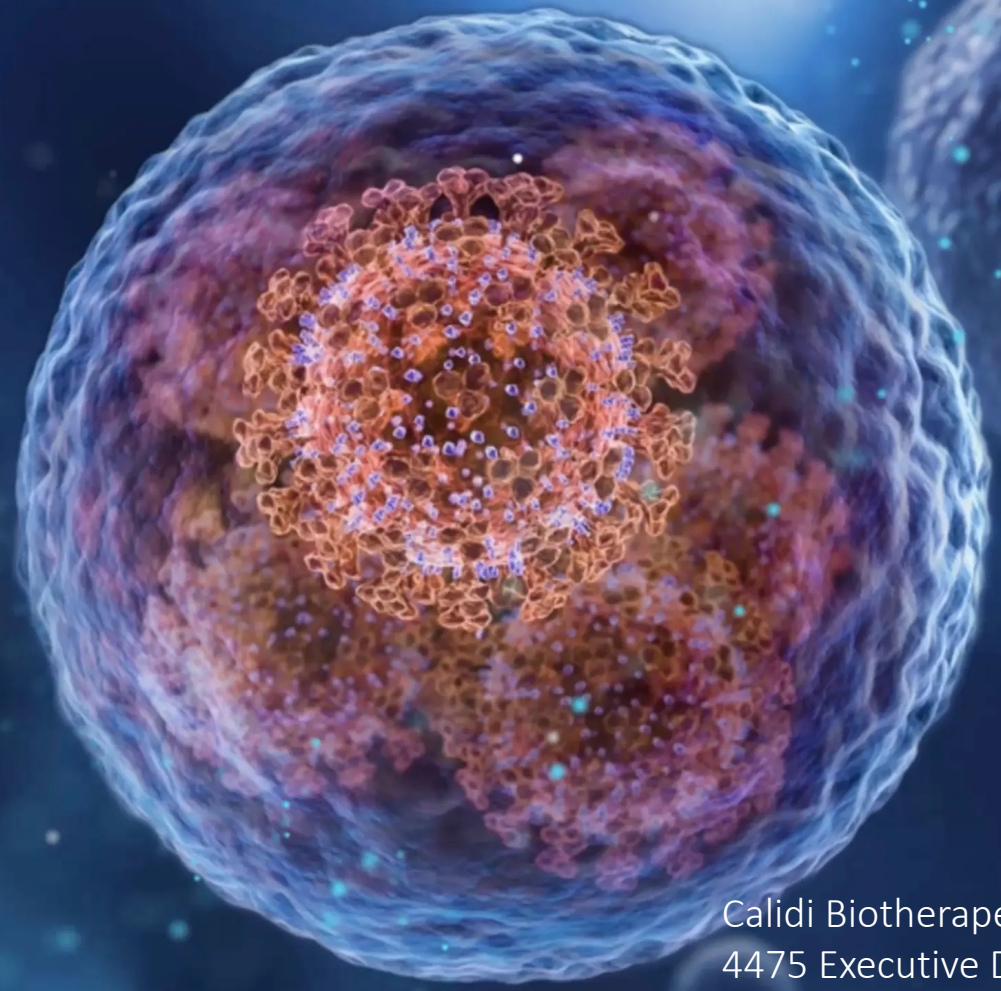
RTNova delivers a breakthrough in true systemic oncolytic virotherapy

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

CALIDI BIOTHERAPEUTICS

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