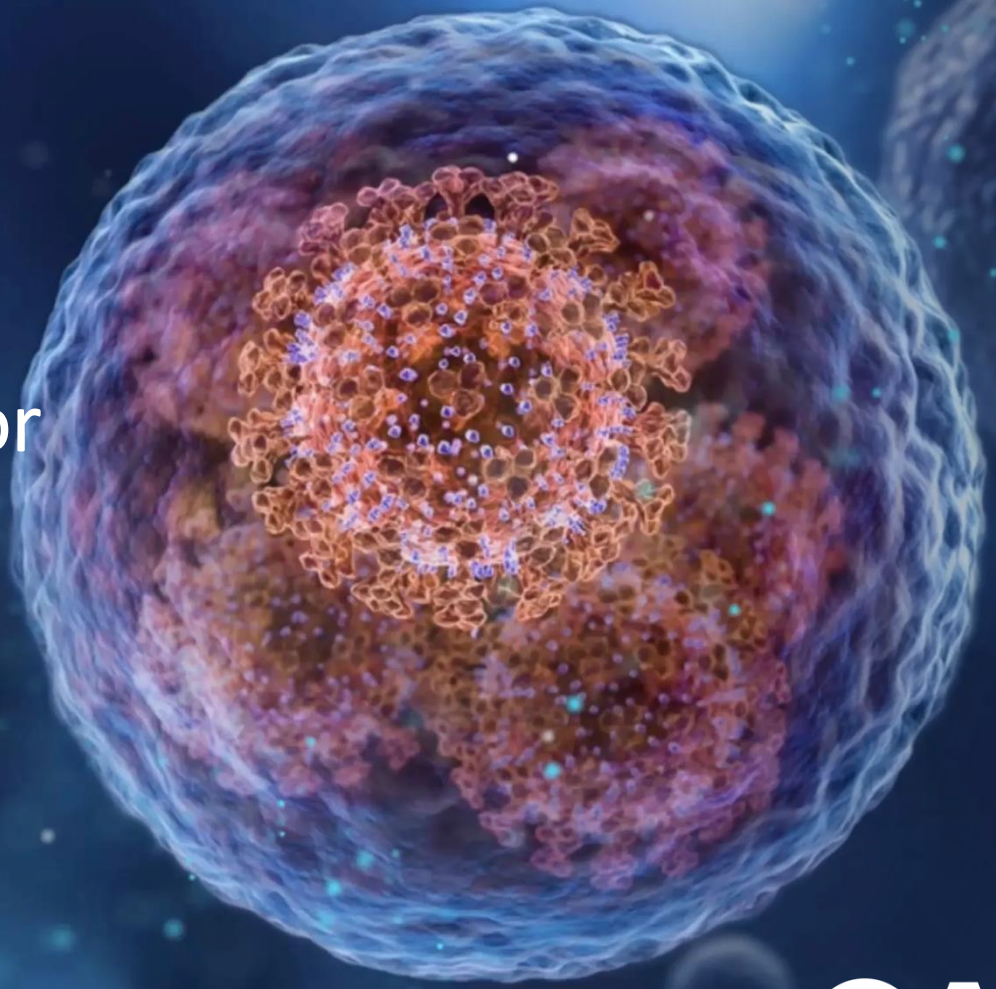
Systemic and Localized Antitumor Virotherapies



Designed to attack every tumor and arm the immune system

October 17th , 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 (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, and (iii) Form 10-Q filed on August 13, 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)**.

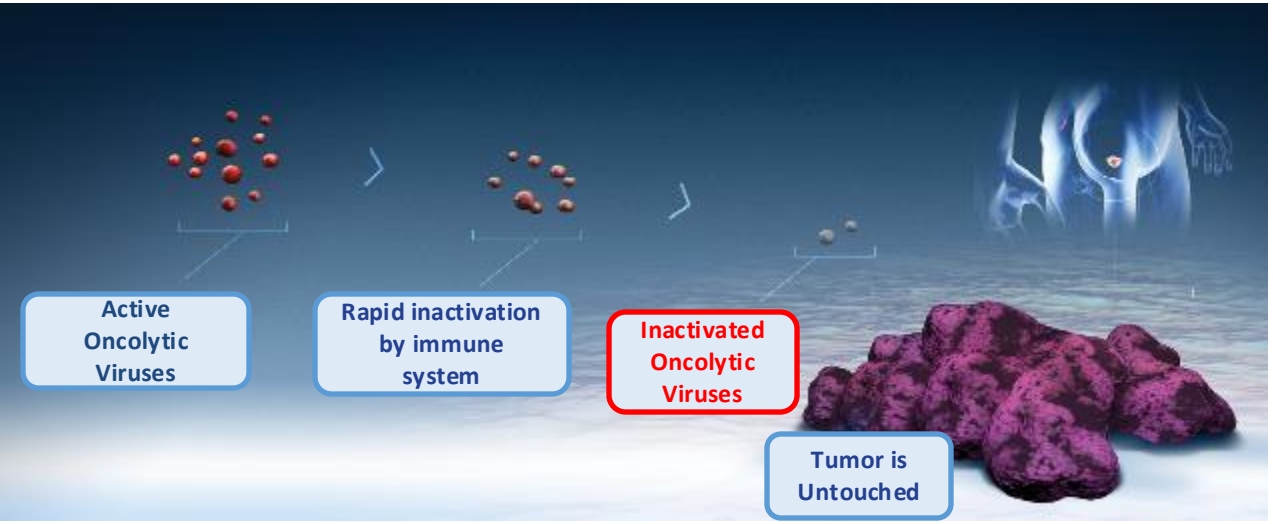
Our cutting-edge **cell-based technologies protect** and deliver oncolytic virotherapies into tumor sites, effectively **overcoming the clinical challenge of rapid elimination by the patient's immune system.**

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

Calidi Overcomes the Obstacles to Oncolytic Viral Therapy

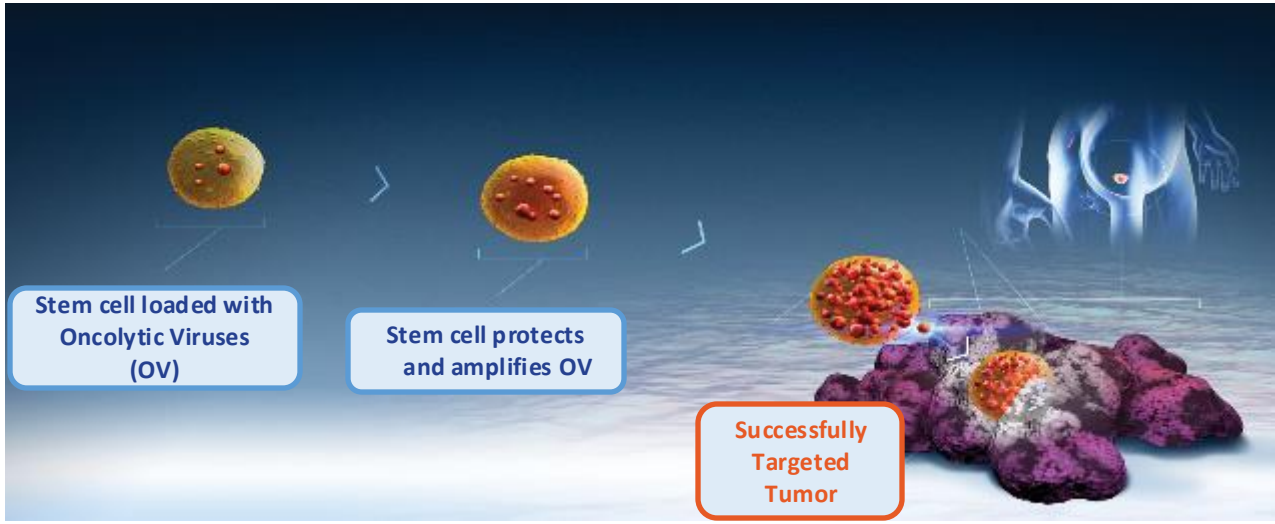
Challenges with Naked OV Therapy

Unprotected Oncolytic Virus



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 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

Upcoming Planned Milestones (2024-2025)

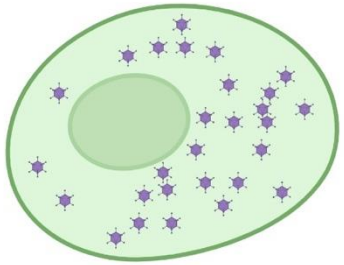
	2024		2025	
	1H	2H	1H	2H
CLD-101 (NNV1: multiple doses newly diagnosed HGG)		✓ In FDA communication to dose first patient ✓ **Open IND**	**1st patient dosed**	Clinical trial enrollment update (ASCO meeting)
CLD-101 (NNV2: Multiple doses recurrent HGG)	✓ CIRM Grant: continued support (partner: COH)	✓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

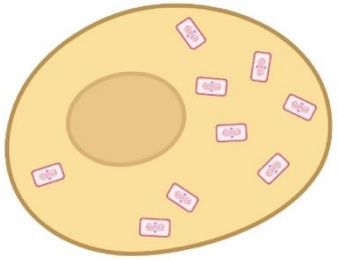
Delivery vehicle/potentiator:
Allogeneic Neuronal Stem Cells

Product type:
Off-the-shelf
Localized administration

CLD-201 (SuperNova)

Targeting clinic 2H 2024

Indication: Advanced Solid Tumors:



Tumor selective Virotherapy:
Vaccinia virus: CAL1

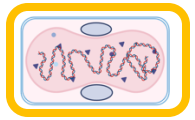
Delivery vehicle/potentiator:
Allogeneic Adipose-derived Mesenchymal Stem Cells

Product type:
Off-the-shelf
Intratumoral administration

CLD-400 (RTNova)

Pre-clinical

Indication: Lung Cancer, and Metastatic Cancer

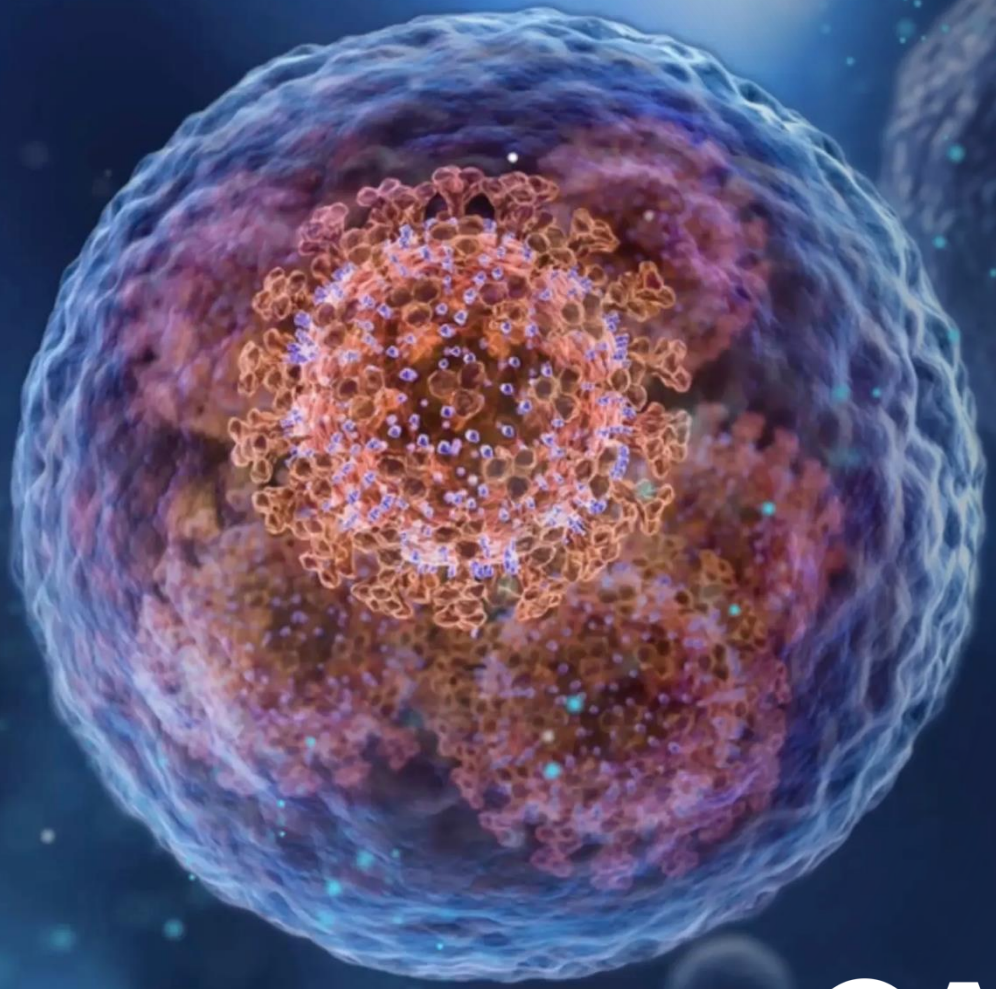


Tumor selective Virotherapy:
Extracellular Enveloped Vaccinia virus: envRT-01

Product type:
Off-the-shelf
Systemic administration

CLD-101 (NeuroNova)

Designed to Attack High Grade Glioma Brain Cancer



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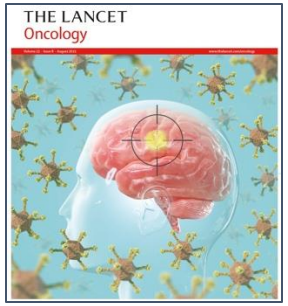
CLD-101 (NeuroNova) in High Grade Glioma (HGG)

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

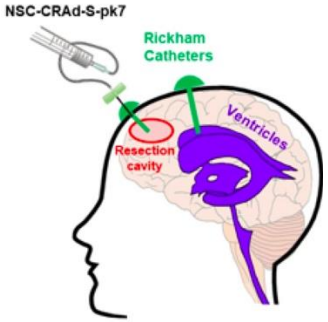
- Treatment was well tolerated
- In the subset of patients containing an unmethylated MGMT promoter, the median **PFS** was **8.8** vs. 5.3 months and **Overall Survival** was **18** vs. 12.7 months.



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).



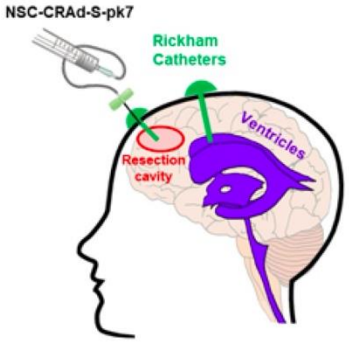
In preparation: Phase 1b/2 (NWU)
multiple dose
in newly diagnosed HGG

- Primary Objective: analyze safety and feasibility of multiple intracerebrally administering in newly diagnosed HGG.
- IND opened (4Q 2024)
- Target to start 1Q 2025

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 • Tumor resection • Manual administration of NSC-CRAd-S-pk7 • Placement of 2 Rickham catheters[b] • CSF[c] and blood collection **Day 2** • CSF[d] and blood collection	**Day 1** • CSF and blood collection • NSC-CRAd-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity **Day 2** • CSF and blood collection	**Day 1** • CSF and blood collection • NSC-CRAd-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity **Day 2** • CSF and blood collection	**Day 1** • CSF and blood collection • NSC-CRAd-S-pk7 slowly administered through the Rickham catheter placed in the resection cavity **Day 2** • 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.

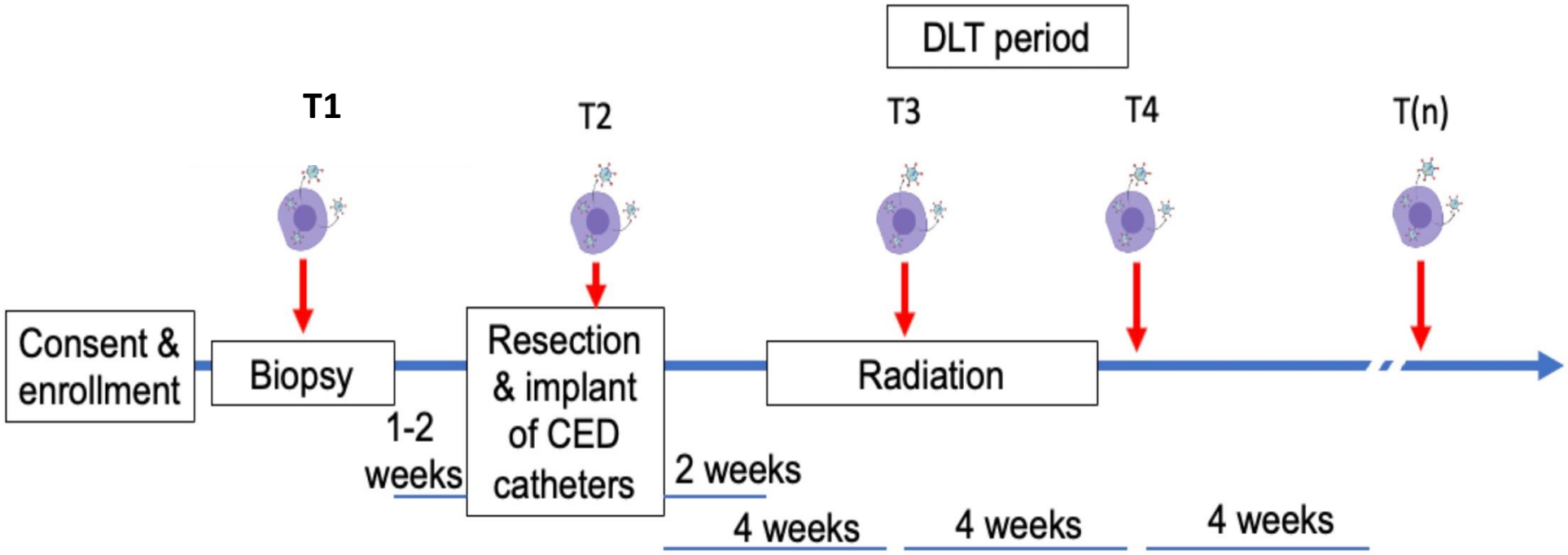
City of Hope®

$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



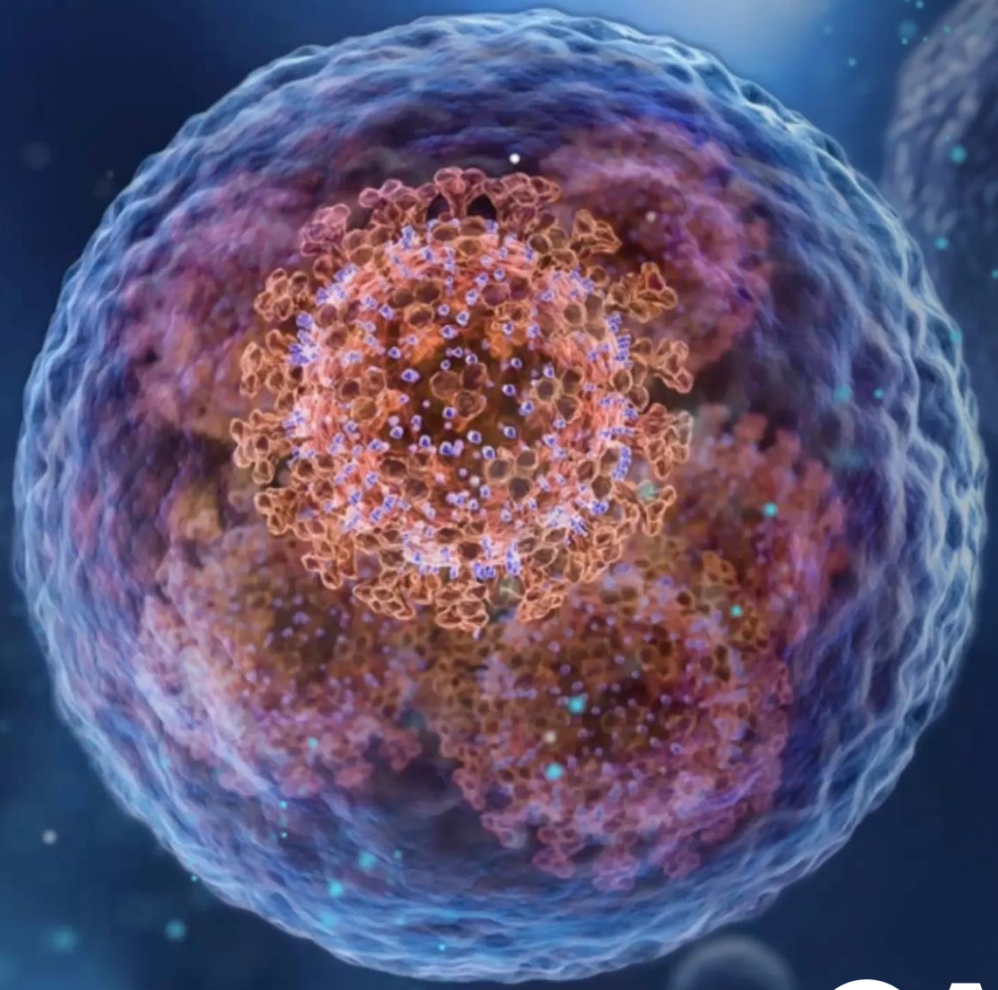
First Patient In:

1Q 2025

CLD-201 (SuperNova)

- Localized administration

For Head & Neck, TNBC, and Soft Tissue Sarcomas



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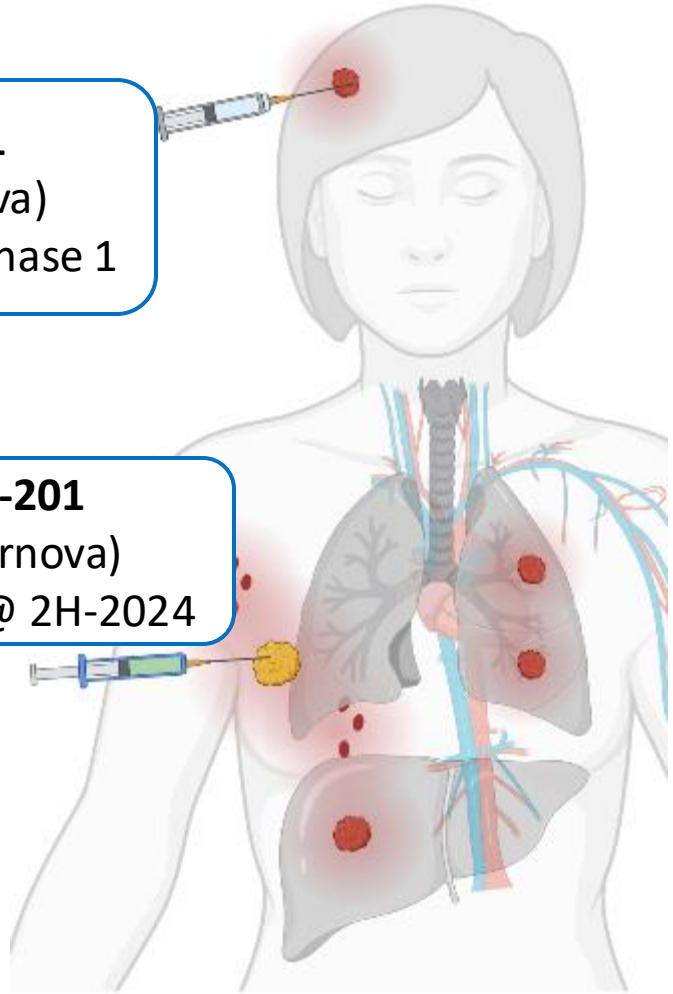
Maximizing Therapeutic Responses with Directed Localized Administration

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 completed in 2Q 2024
- **Phase 1 initiation in 1Q 2025**

  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

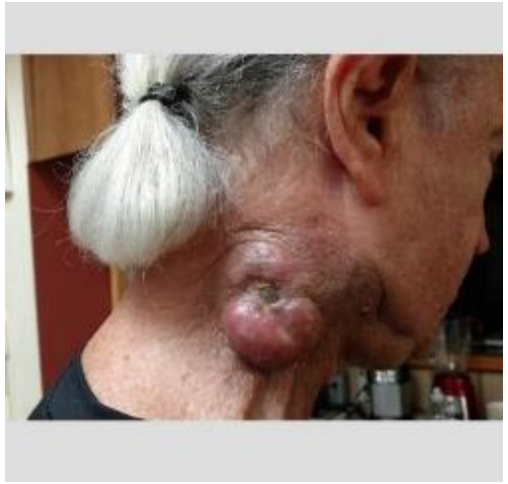
Durable Tumor Regression and Survival

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

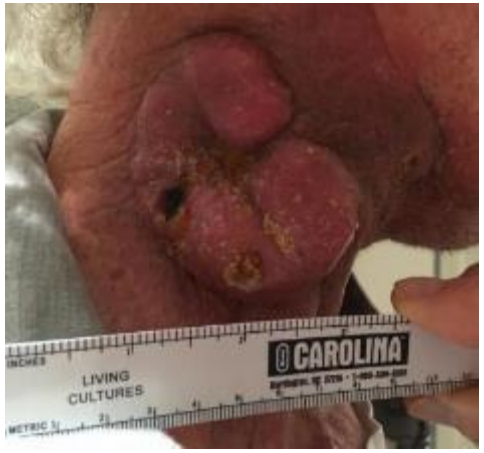
- Age/Sex: 70/M
- Diagnosis: Metastatic Head & Neck SCC
- Stage IV_B
- Injected tumor was previously resistant to chemo- and radio-therapy

Patient Case: Patient #SI01-021

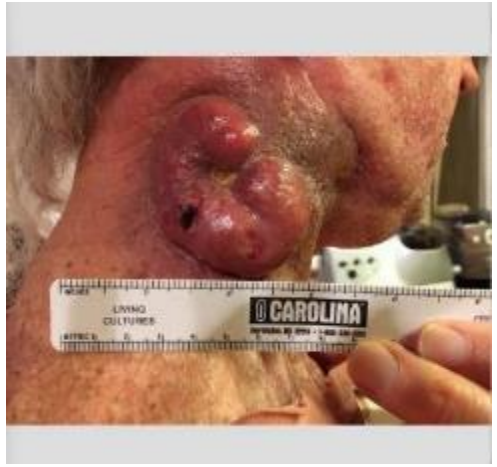
Day 17 post-treatment



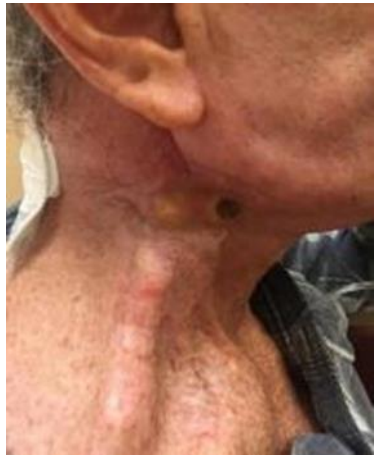
Day 45 post-treatment



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

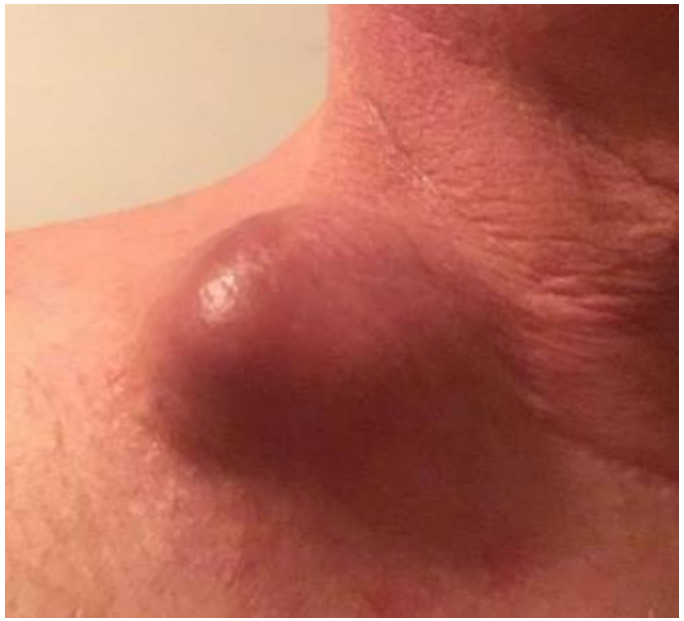
Durable Tumor Regression and Survival (continued)

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

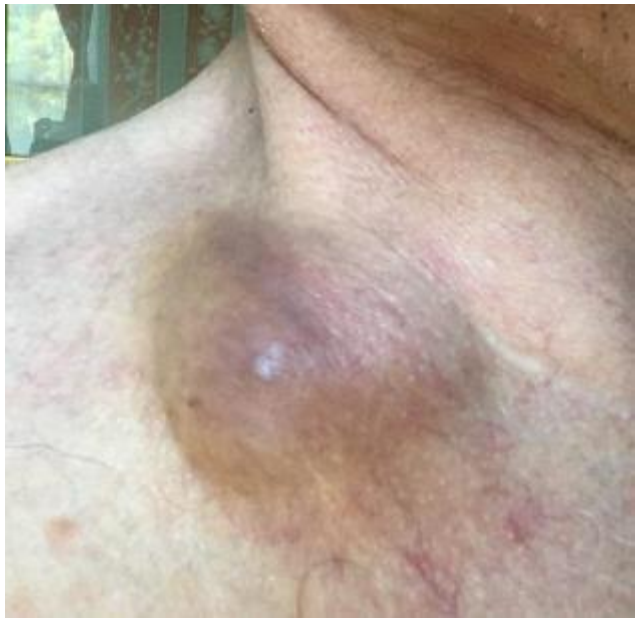
Calidi Autologous Safety Study

Patient Case: Patient #SI01-047

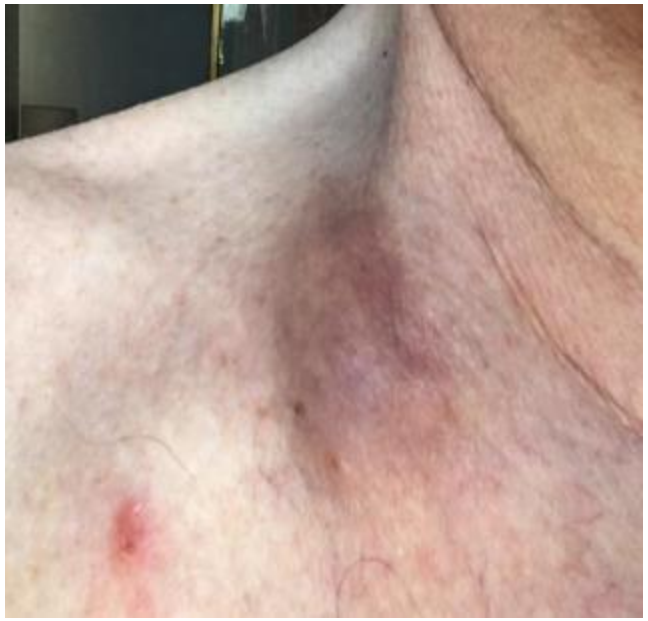
Day 30 post-treatment



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

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.

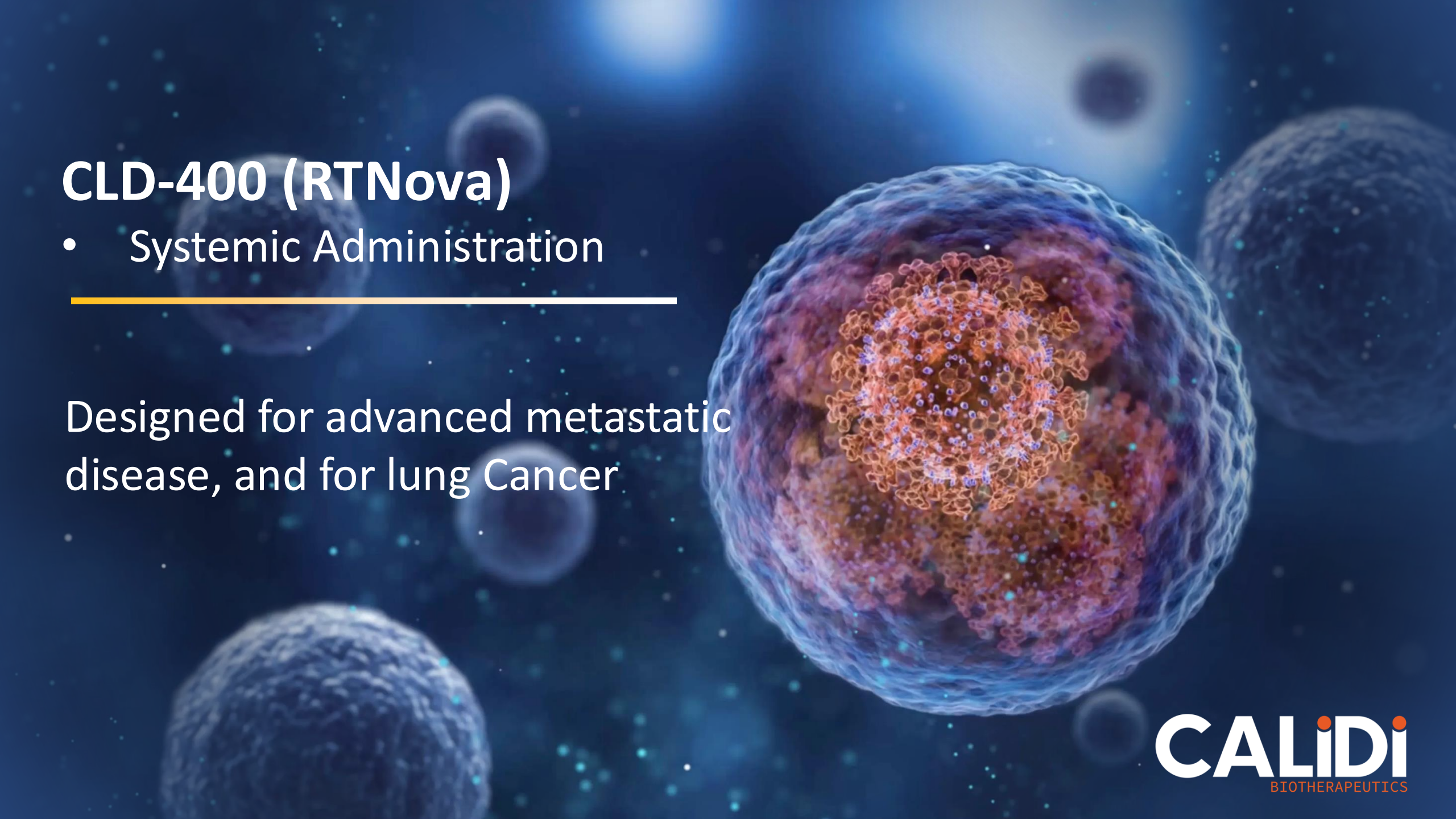
PART 3:
Expansion in Best-Responding Indication – Phase 2

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

CLD-400 (RTNova)

- Systemic Administration

Designed for advanced metastatic disease, and for lung Cancer



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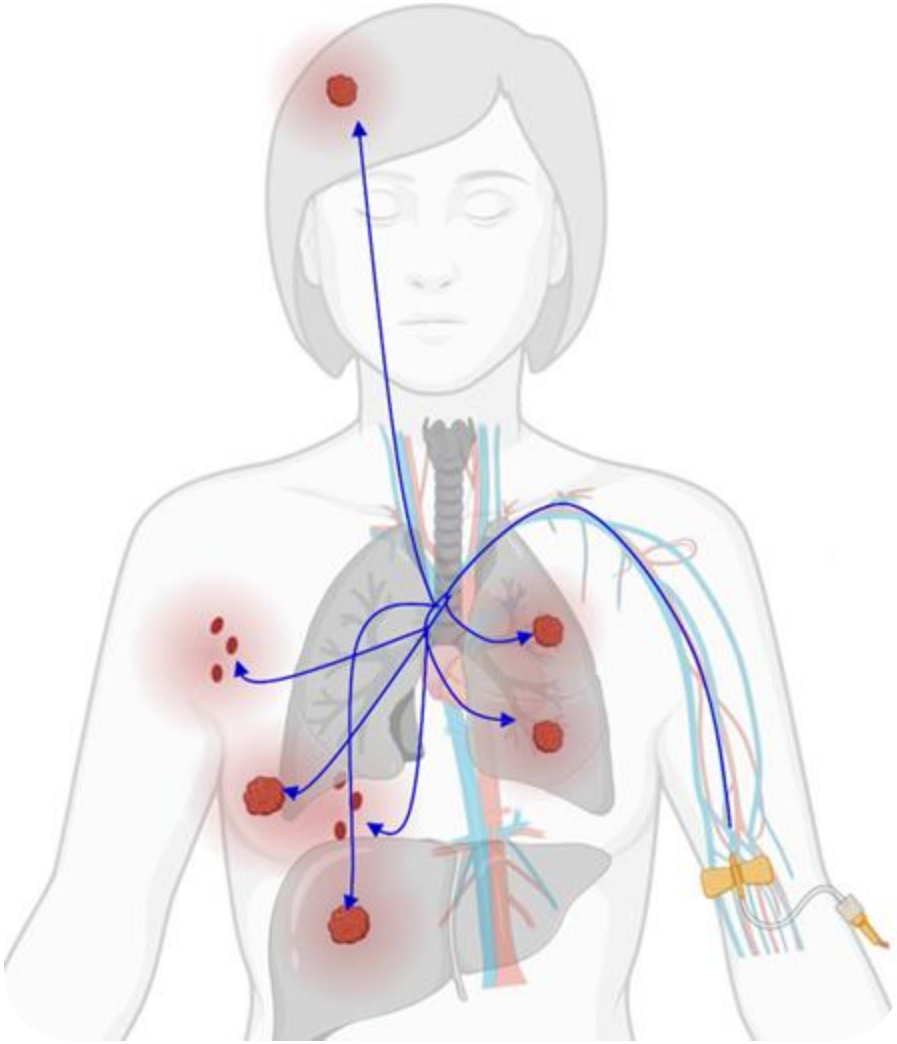
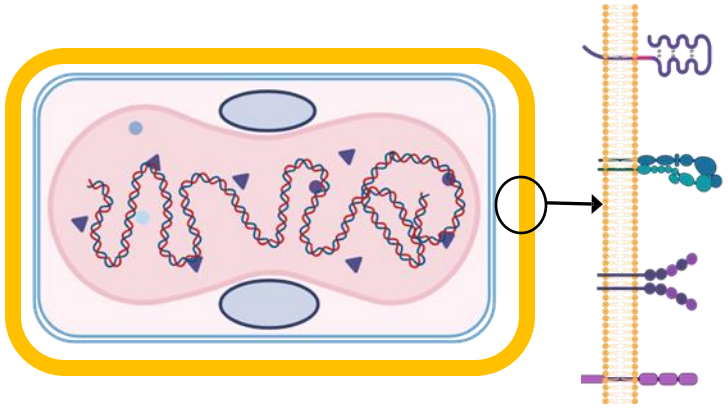
Calidi's Systemic Approach (CLD-400 – RTNova program)



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

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:

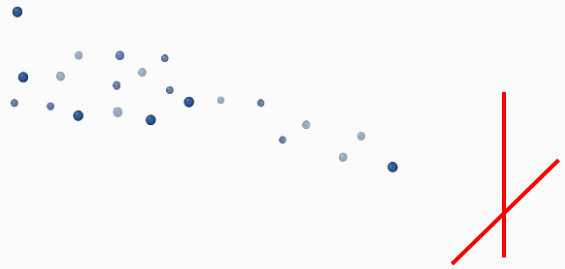
1- New **engineered tumor selective vaccinia virus**

2- Does not integrate into human genome.

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

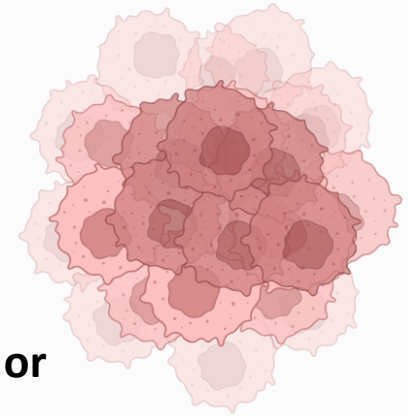
Challenges and Solutions of Systemic Antitumor Virotherapies

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



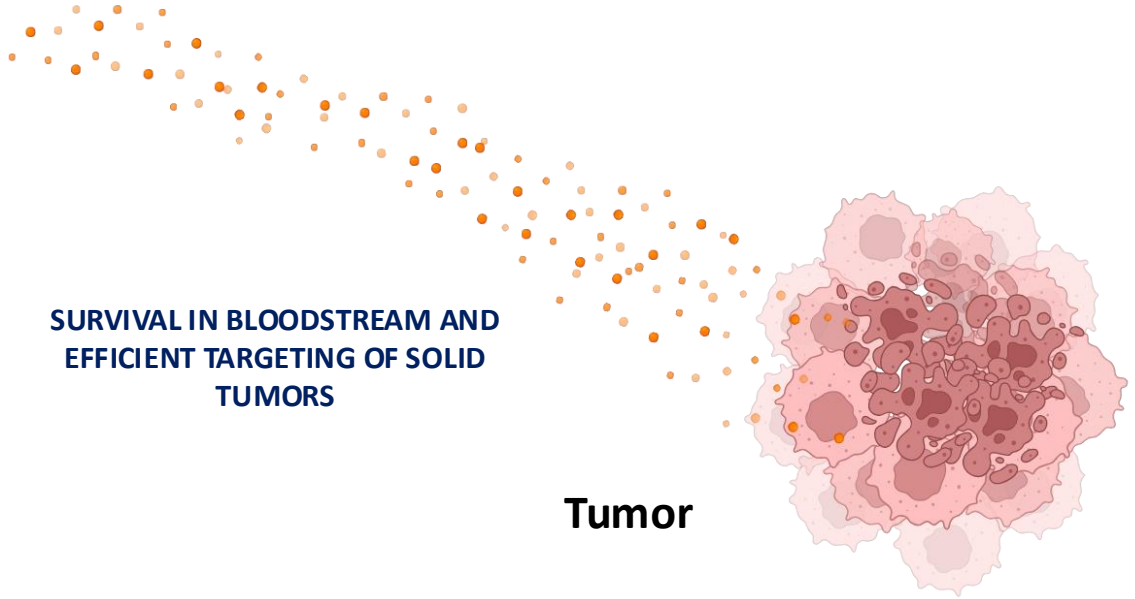
RAPID INACTIVATION
BY THE PATIENT'S IMMUNE SYSTEM

Unfortunately, many companies have claimed systemic delivery, but their virus is primarily eliminated within minutes



Tumor

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

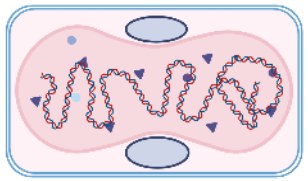


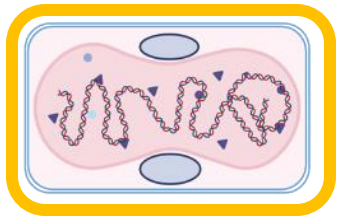
SURVIVAL IN BLOODSTREAM AND EFFICIENT TARGETING OF SOLID TUMORS

Tumor

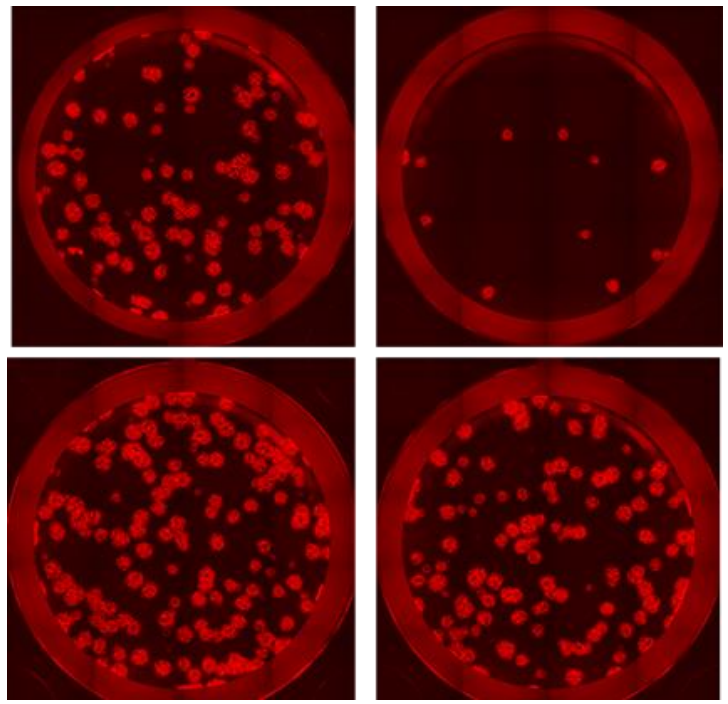
(*) depending on virus type, strain and dose. a) Nguyen DH et al Cancers. 2022 Dec; b) Evgin, L., et al., Mol Ther, 2015. 23(6) c) Martinez-Quintanilla, J et al J. Clin. Investig. 2019, 129

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





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.**

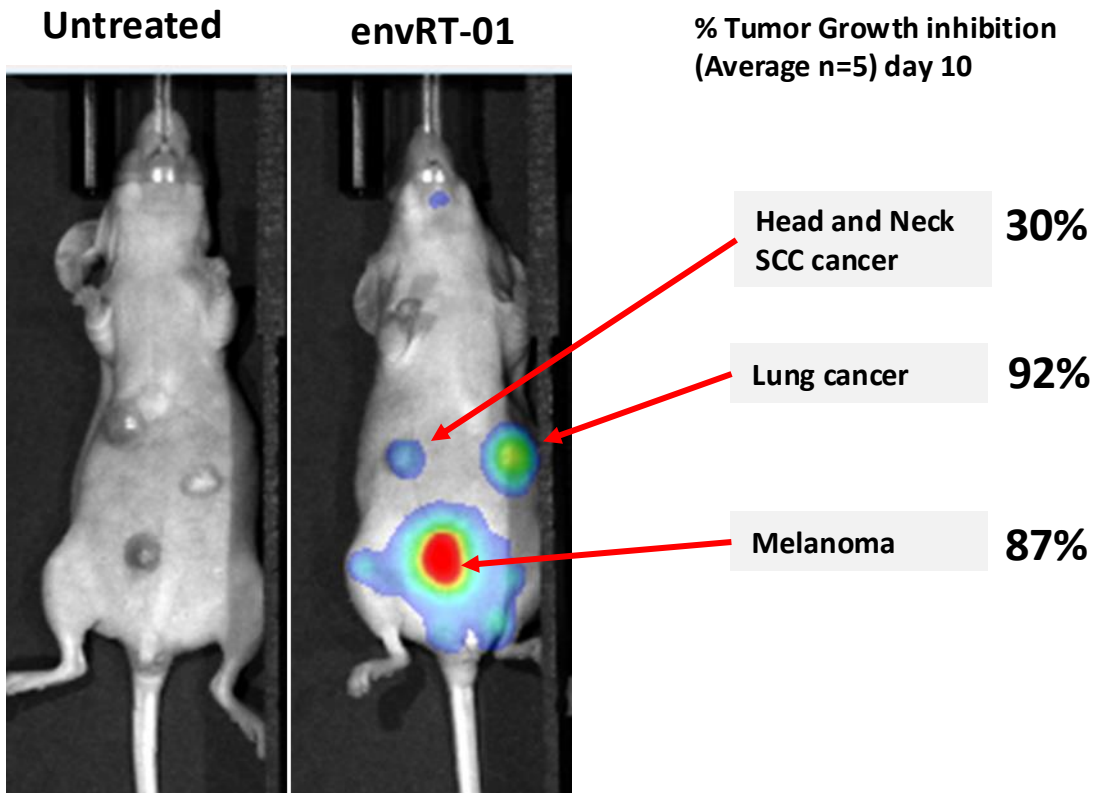
This completes a critical step to achieving systemic delivery in clinical scenarios

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)

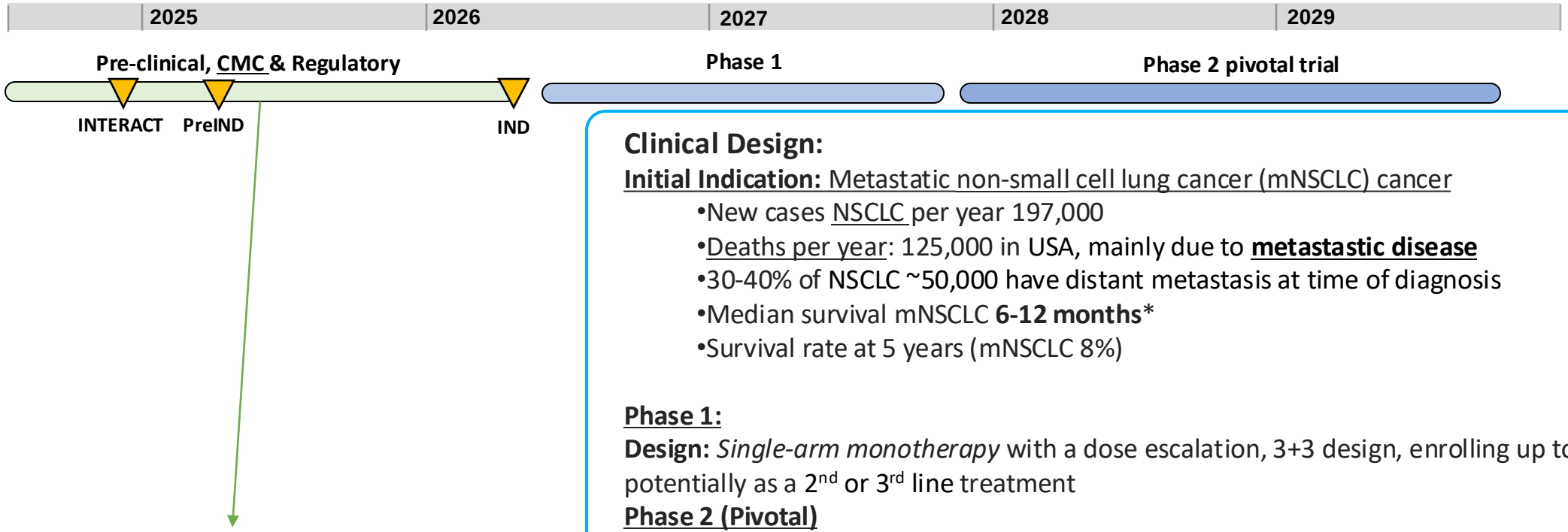
Remarkable Versatility: Ability to address **diverse tumor types** and adapt to the unique **tumor microenvironment** within the organism.

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.

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

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)

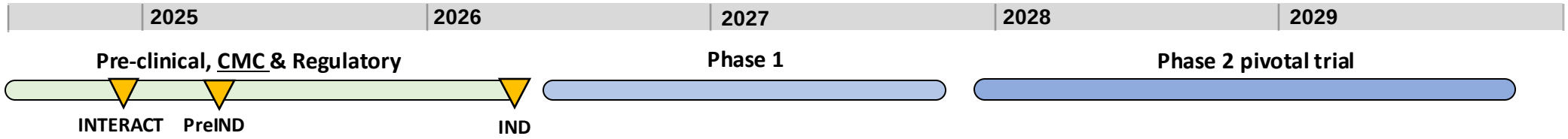
- **Regulatory approval:** targeting late 2029

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

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

* OS may increase with new investigational treatments

Planned Clinical and Regulatory Path for Lead Candidate



Q3 2024 to Q2 2025

- **Key Milestones:**
  - Finalize selection of **Lead Candidate**
  - IND-enabling **pharmacology** studies
  - **Process and analytical** development
  - **CDMO technology transfer**

Q3 2025 to Q2 2026

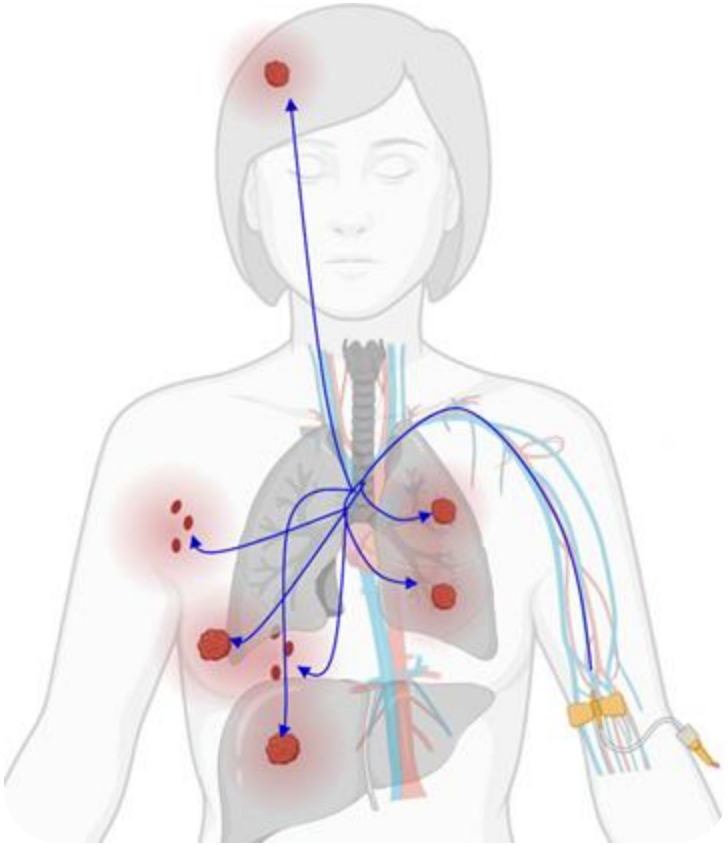
- **Key Milestones:**
  - **Final drug product (FDP**) manufacturing
  - IND-enabling **toxicology** studies
  - Develop the **Biomarkers Clinical program**
  - Prepare **clinical sites** and **CRO**
  - Open **IND**

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 reprograming and Killing. • Payload undisclosed	Target indication undisclosed			

Seeking early partnership with large cap bio-pharma at platform and/or asset 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 **Q2 2026**.

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

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