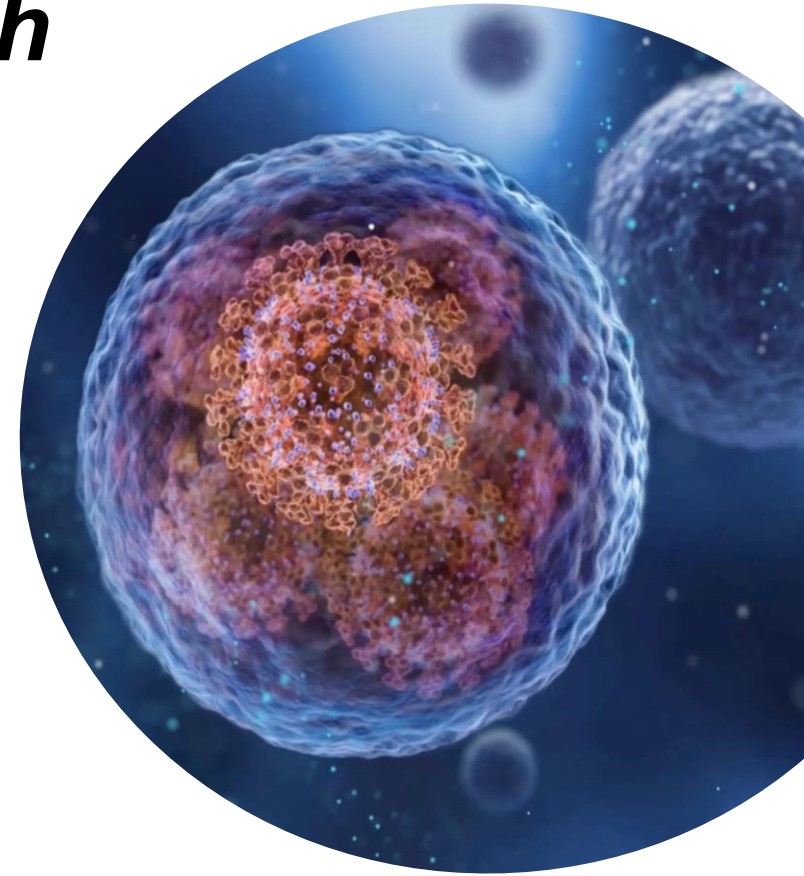


Targeting and Attacking Tumors with Multimodal Virotherapies

A New Era of Systemic and Localized Immuno-Oncology Therapies



NYSE American: CLDI
March 2025

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Forward-Looking Statements and Legal Disclaimer

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

Executive Summary - Overview



Cancer is a complex disease, often leading to patient **mortality due to metastasis**, which underscores the need for innovative solutions.

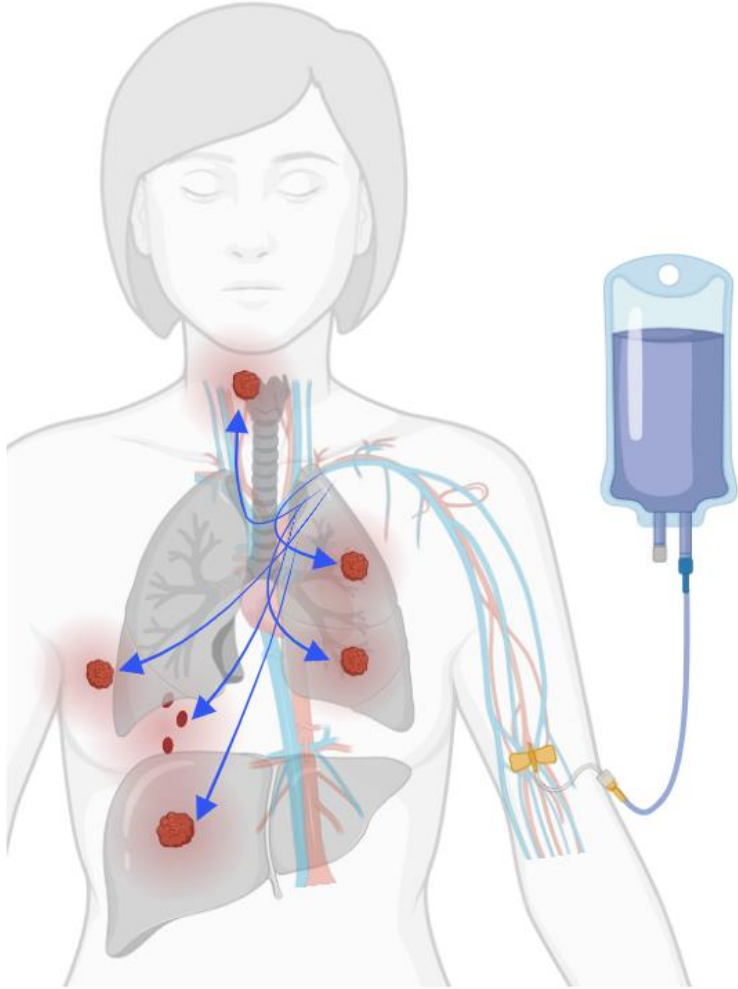


Calidi is transforming immune-oncology treatment by pioneering a new generation of systemic and localized multimodal virotherapies.



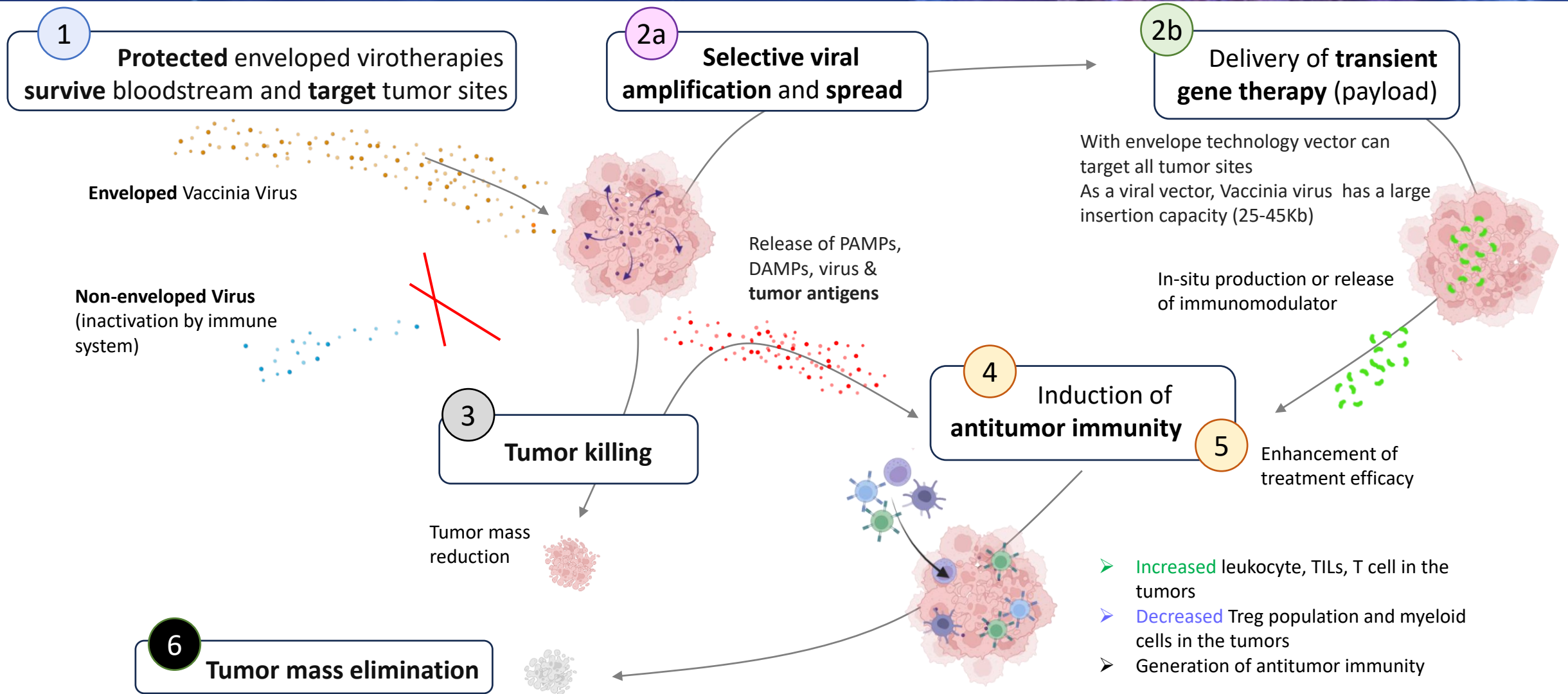
Calidi designed an advanced **protected virotherapies** to effectively **target tumors**. Once within the tumor, these virotherapies are designed with **a multimodal MOA which includes, a) direct killing, b) induction of antitumor immunity and c) the genetic delivery to tumors of additional immunotherapies**

RTNova Program (CLD-400), a Systemic Virotherapy Solution

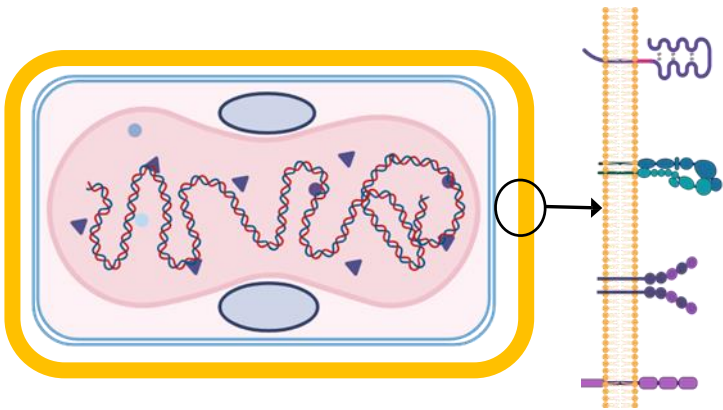


- ✓ New treatment option for **advanced metastatic** disease or **lung cancer**
- ✓ Simple IV administration avoiding the need for image-guided delivery.
- ✓ Able to survive in circulation
- ✓ Designed to home and self-amplify in tumor sites

Multimodal Mechanism of Action of Enveloped RT Virotherapy



RT Vaccinia Virus: An Extracellular Enveloped Vaccinia (EEV) Strain



Enveloped:

1- **High production of enveloped viruses** is genetically encoded in RT 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** (triple knockout, RT-3KO)

2- Does not integrate into human genome

3- Available FDA-approved antiviral

For more information regarding the RT Vaccinia virus, please refer the appendix

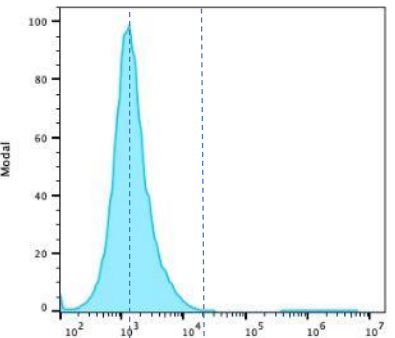
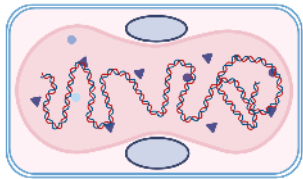
Protection: Envelope Maximizes Resistance Against Humoral Immunity

We developed a novel methodology to manufacturing extracellular enveloped vaccinia viruses (EEVs)

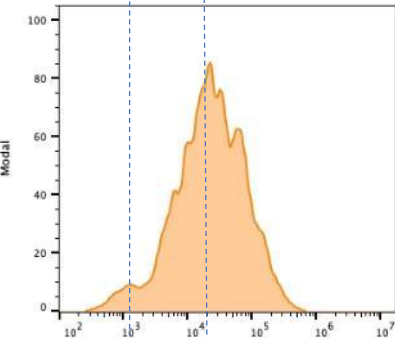
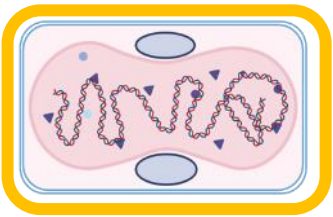
Expression of anti
complement receptor CD55
(DAF) in viral envelop

- +

Non-envelop
RT-virus



Envelop
RT-virus

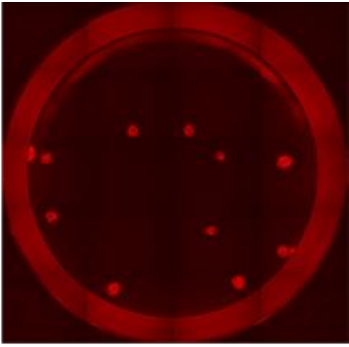
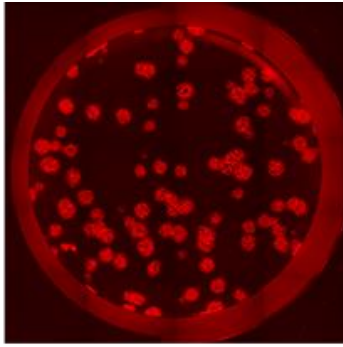


Enveloped Vaccinia virus survives rapid inactivation by human serum **making feasible systemic targeting of tumors**

Standard Media

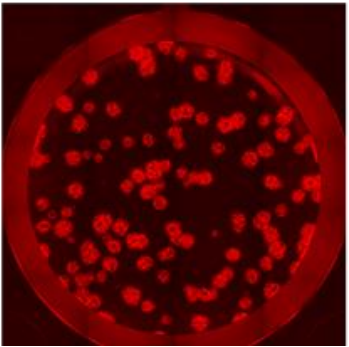
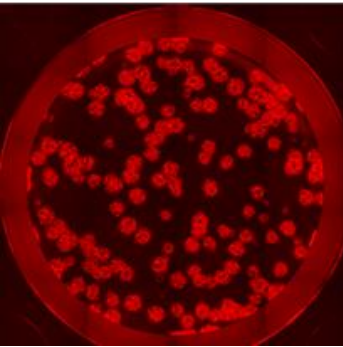
Human Serum

Non-envelop



12.4%
Survival

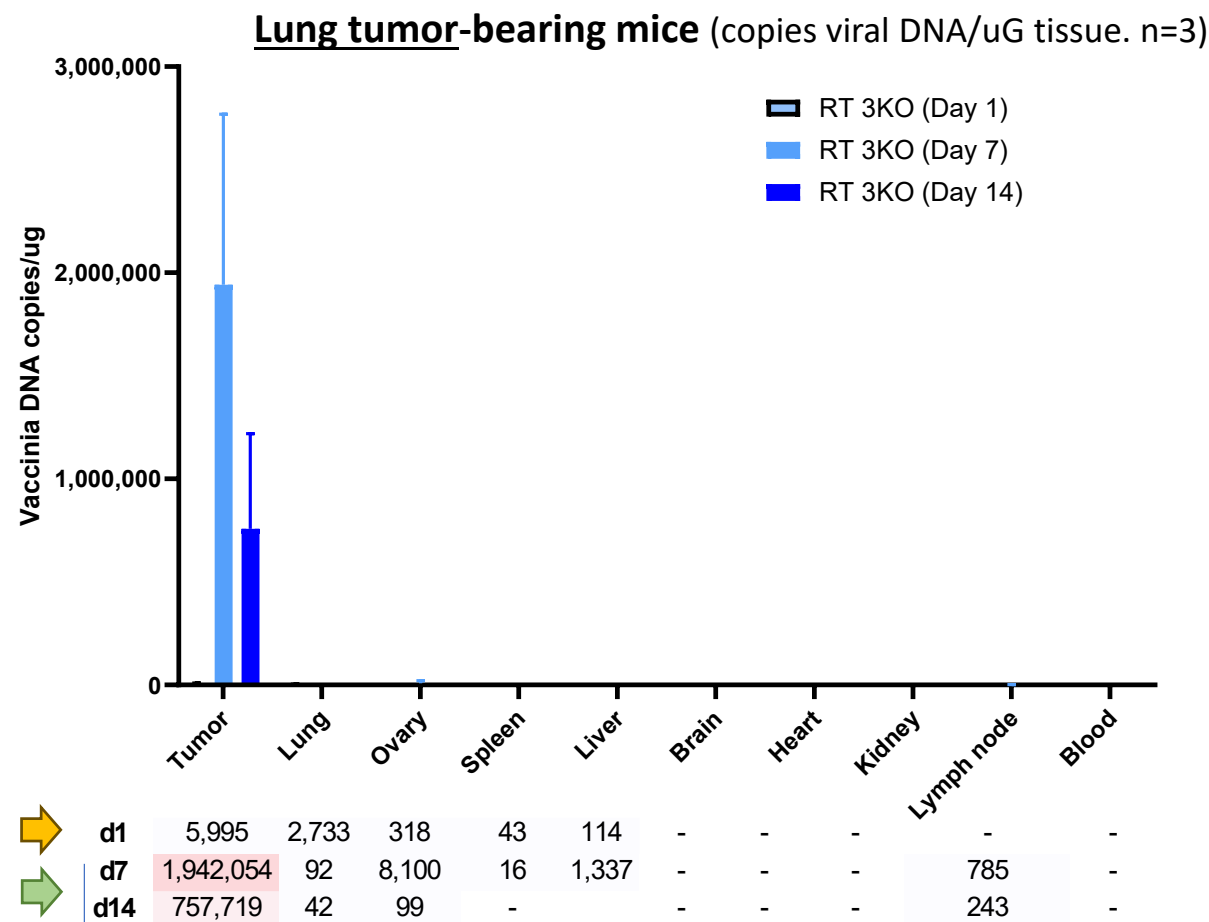
Envelop



79.3%
Survival

Targeting and Tumor-Selective Amplification of RT - Triple Knockout (3KO) - virus

Targeting, amplification & biodistribution analysis after single dose administration of RT-3KO virus



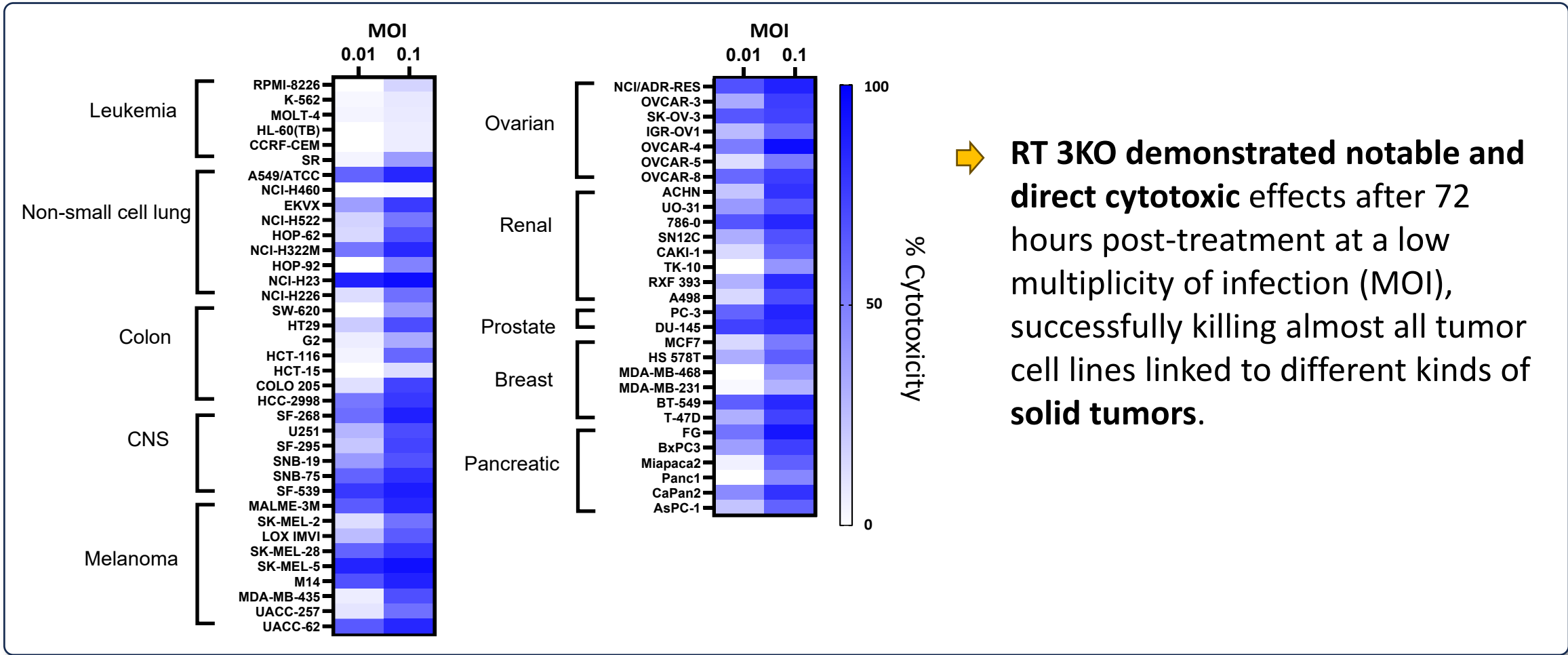
➡ **RT 3KO** virus targets preferentially the tumor with 65% of copies found in tumors in day 1 (compared with major organs) in syngeneic mouse lung cancer model.

➡ **RT 3KO** virus amplifies preferentially in the tumor.

Refer to the appendix for additional details regarding the creation of a tumor-selective RT 3KO vaccinia virus

RT-3KO Induces Direct Killing of Multiple Tumors Cell Types

Analysis of tumor cytotoxicity for RT-3KO across over 60 tumor cell lines using the NCI-60 panel.



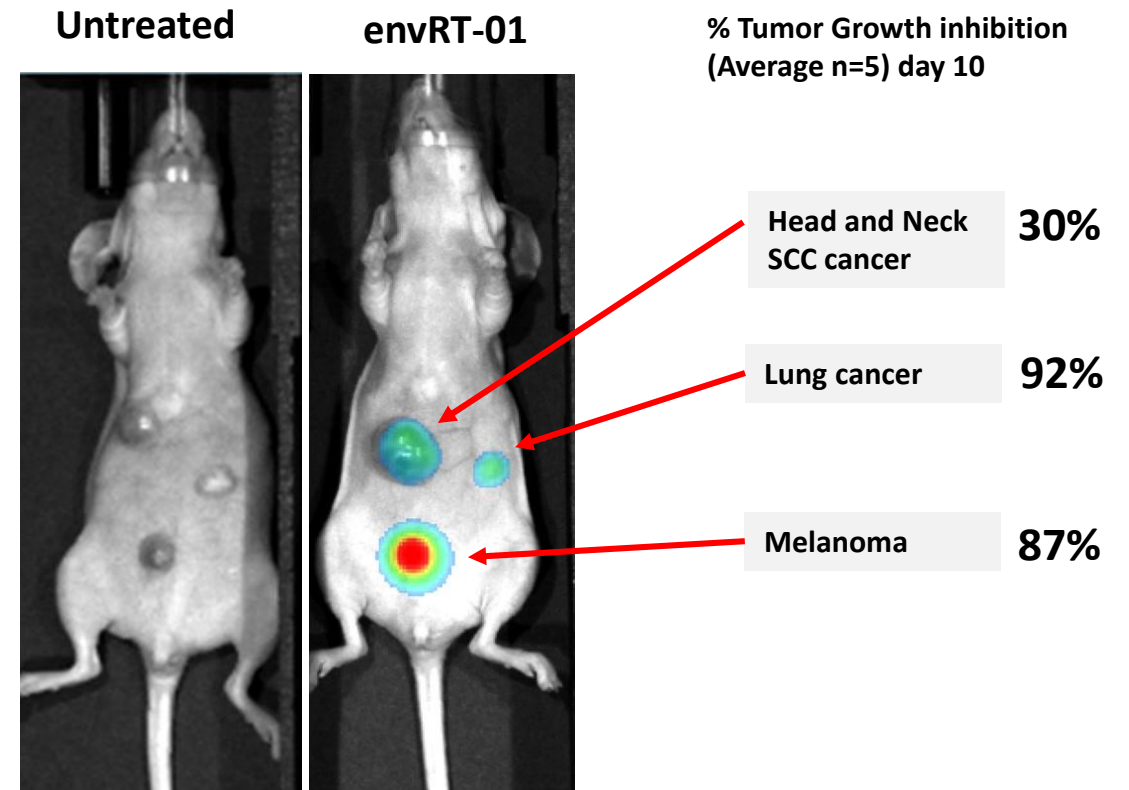
RT Virotherapy Targets and Eliminates Multiple Tumors in Preclinical Models

After one (1) systemic administration, envRT (enveloped RT) can target all distant tumors and express selected payload (i.e imaging protein TurboFP635)

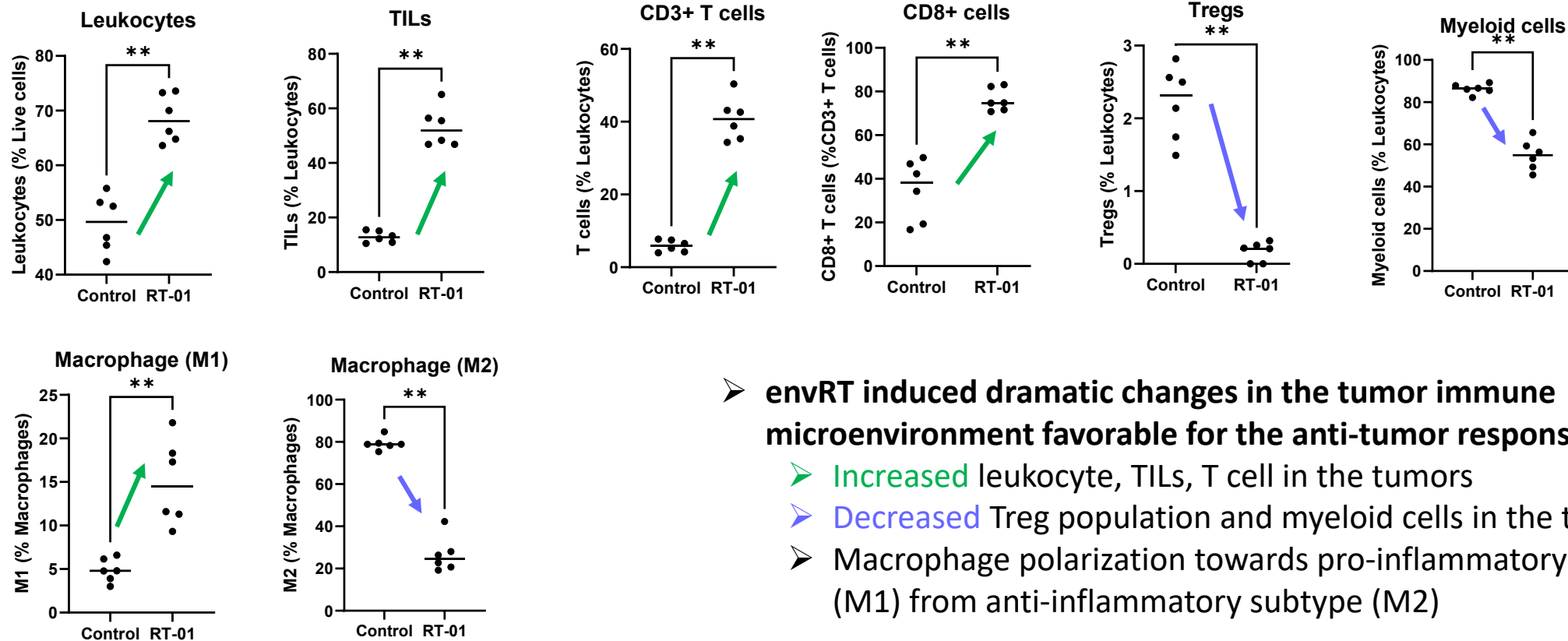
Remarkable Versatility: Ability to address **diverse tumor types** and adapt to the unique **tumor microenvironment** within the organism.

Refer to the appendix for further models, including experimental metastatic lung cancer in immunocompetent mice

Mouse model bearing 3 different human solid tumor types



RT Virotherapy Leads to Significant Modulation of All Tumor Microenvironment Supporting an Anti-Tumor Immune Response



See the appendix for immunohistochemistry studies examining the infiltration of TILs in various lung metastases in the lung

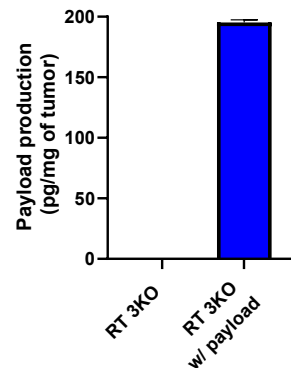
- **envRT induced dramatic changes in the tumor immune microenvironment favorable for the anti-tumor response.**
 - **Increased** leukocyte, TILs, T cell in the tumors
 - **Decreased** Treg population and myeloid cells in the tumors
 - Macrophage polarization towards pro-inflammatory subtype (M1) from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

Maximizing Therapeutic Efficacy Through Delivery of Gene Immunotherapy Payload to All Targeted Tumors

RT 3KO, serving as a viral vector, has the capacity to genetically introduce the in-situ production of immunomodulators (payload) in tumors, drastically improving treatment efficacy.

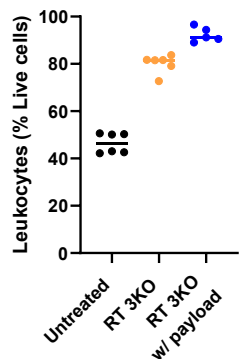
➡ The administration of a single dose of RT 3KO with a specific payload positively alters the tumor microenvironment (TME) and boosts therapeutic effectiveness.

Local production of payload

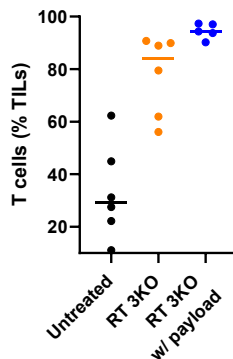


TILs in the tumors

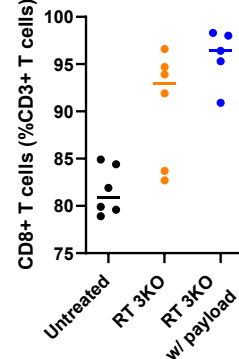
CD45+ Leukocytes



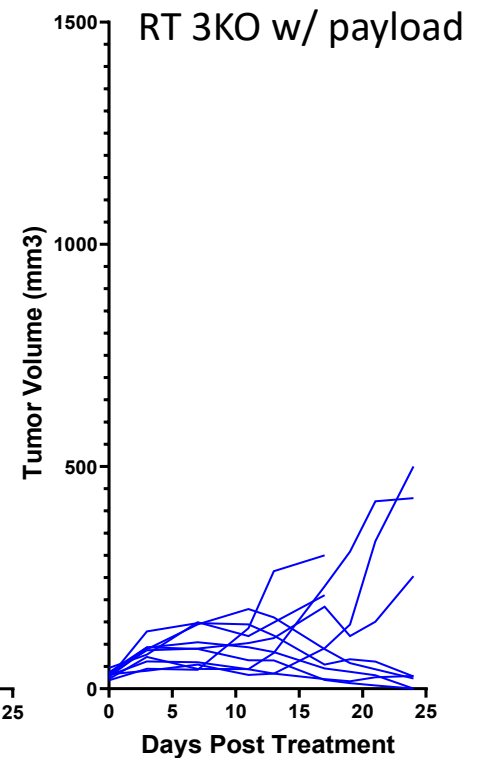
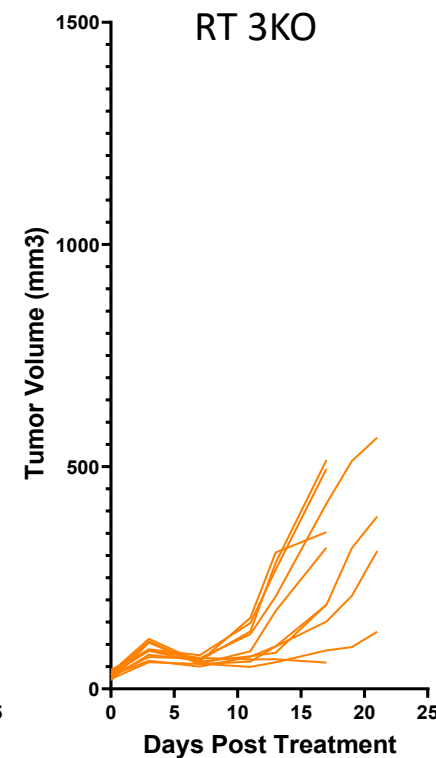
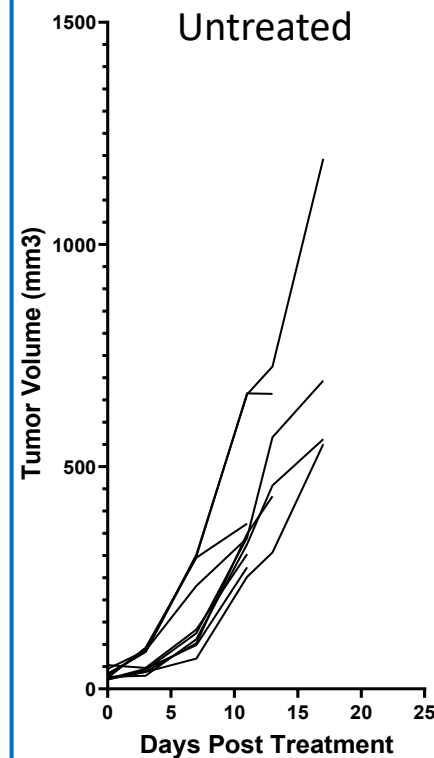
CD3+ T cells



CD8+ cells



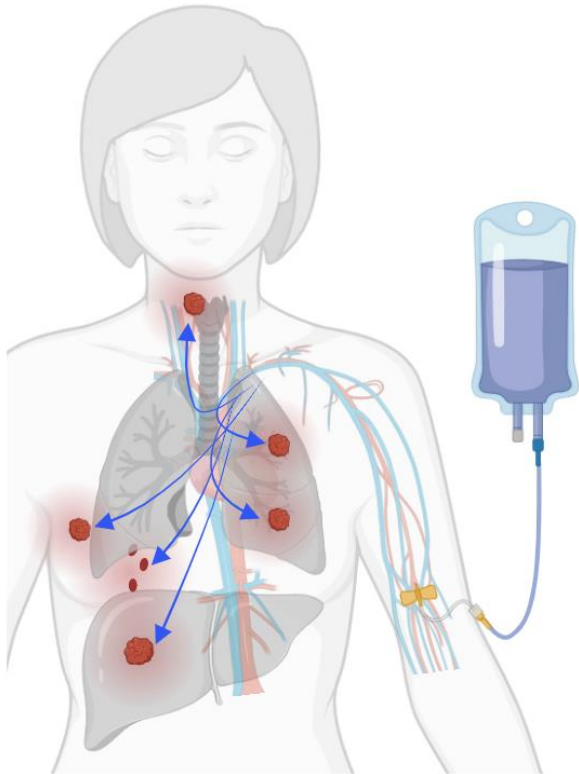
Tumor regression in a preclinical model of lung cancer after one (1) administration of 5e6 PFU viral particles



Pipeline And Early Partnership Opportunities

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

Building the Future of Systemic Virotherapies



RTNova introduces a significant advancement in **true systemic virotherapy** by employing enveloped technology to survive bloodstream and **target all tumors**.



RTNova is designed with a multimodal MOA which includes, a) direct killing, b) induction of antitumor immunity and c) the genetic delivery to tumors of additional immunotherapies.



Planned **phase 1 clinical trial**, as a monotherapy, targeting metastatic lung cancer solid tumors in **Q4 2026**.



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

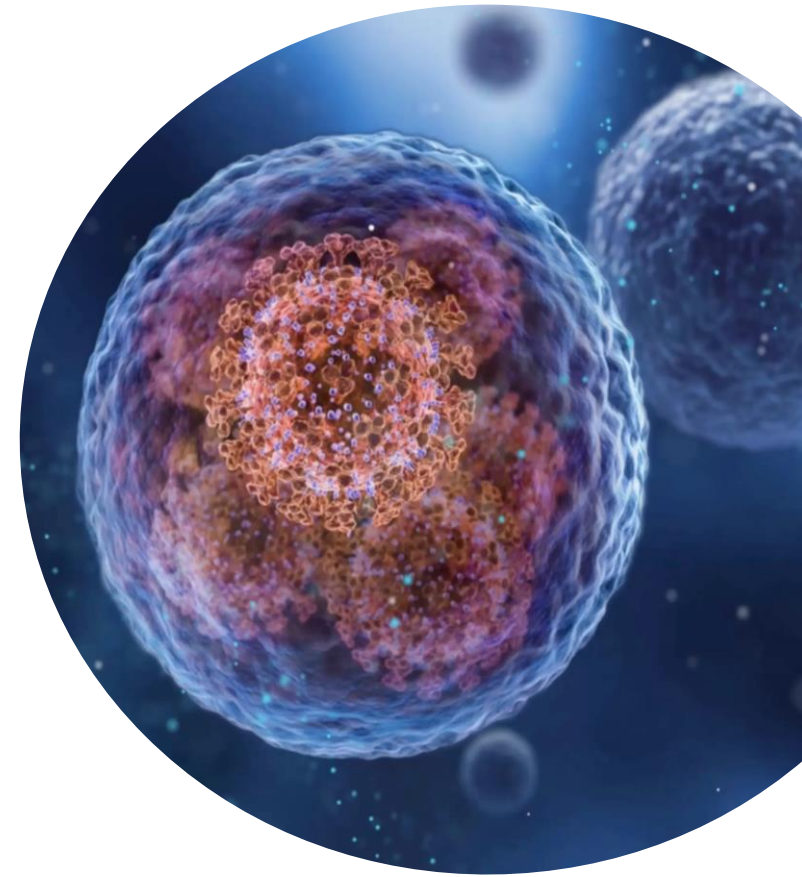


Delivering **off-the-shelf platforms** and able to build targeted multiple assets.

Clinical pipeline

Intratumoral and localized cell-based virotherapies

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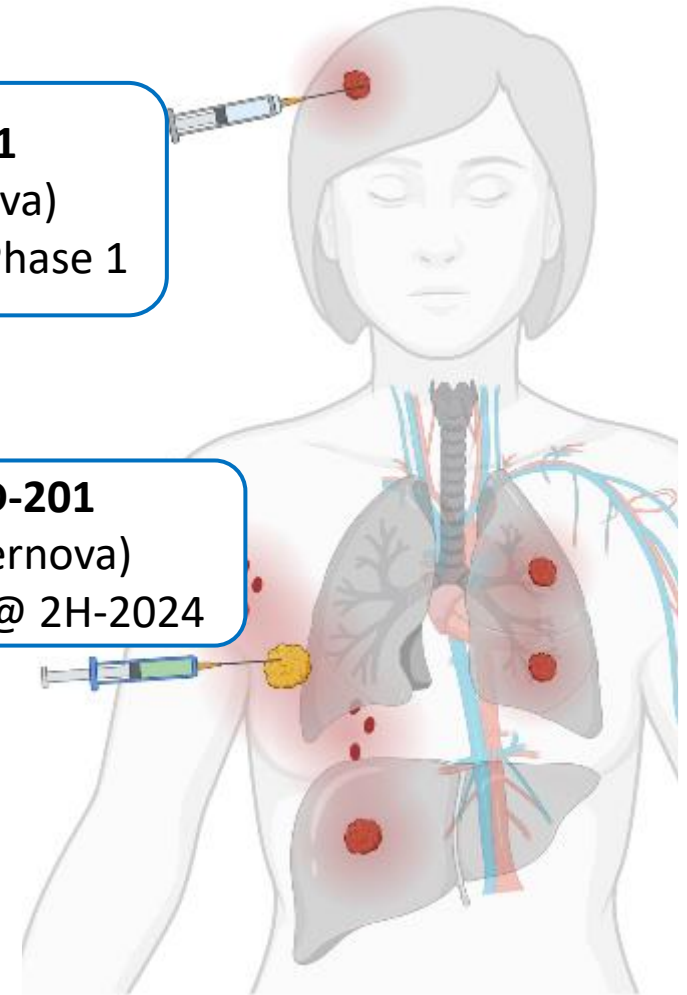
Maximizing Therapeutic Responses with Directed Localized Administration

Directed – Localized Administration

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

CLD-101
(Neuronova)
Completed Phase 1

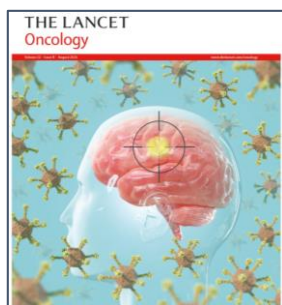
CLD-201
(Supernova)
Phase 1 @ 2H-2024



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

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

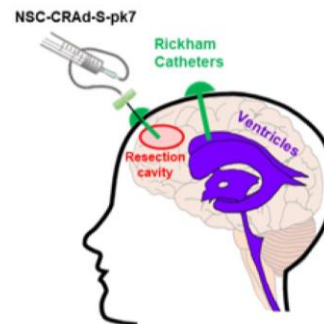
- Treatment was **well tolerated**
- In the subset of patients containing an unmethylated MGMT promoter, the median **progression free survival (PFS)** was **8.8 vs. 5.3 months** and **overall survival (OS)** was **18 vs. 12.7 months**.



*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).**



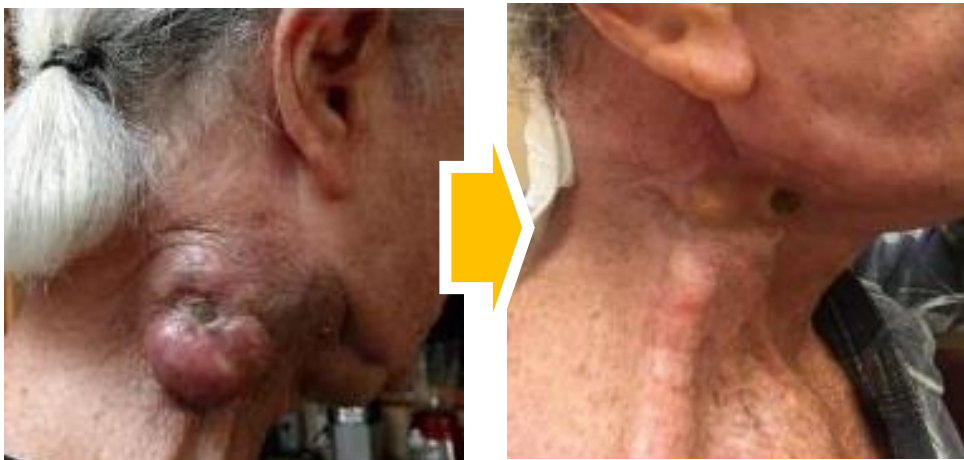
In preparation: Phase 1b/2 (NWU)
multiple dose
in newly diagnosed HGG

- Primary Objective: analyze **safety and feasibility** of multiple intracerebrally administering in newly diagnosed HGG.
- **IND opened (4Q 2024)**
- **Recruitment started February 2025**

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**
- **Phase 1 dose escalation initiation in 1H2025** (indications: Head & Neck, TNBC, Sarcoma)
- cGMP Final Drug Product Manufacturing and release completed in 3Q 2024

Upcoming Planned Milestones (2025-2026)

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

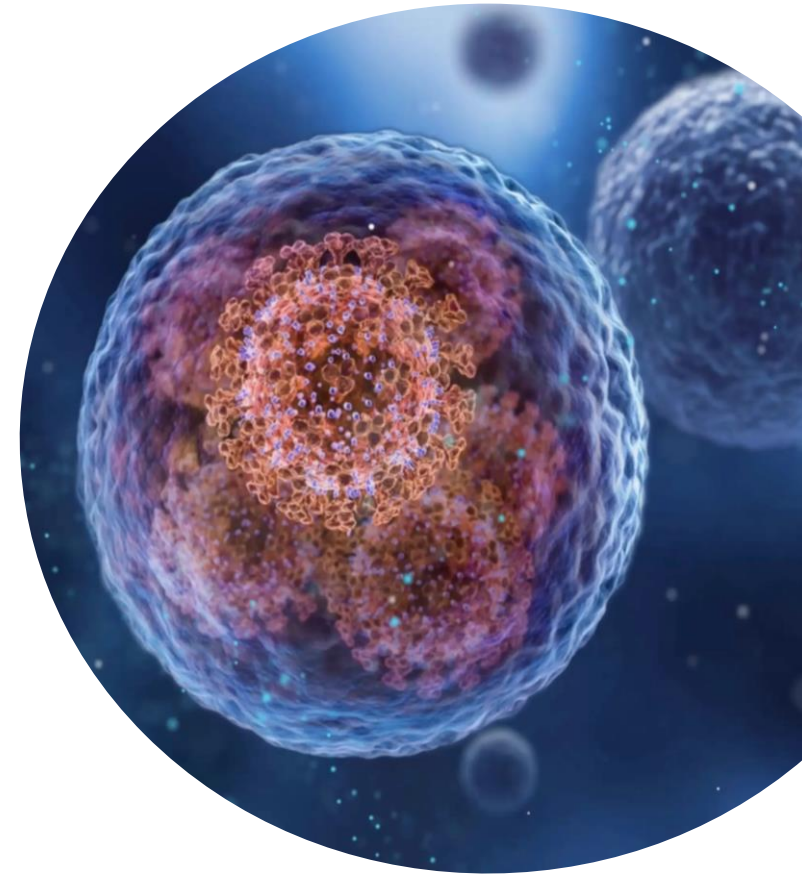
Appendix

CLD-400

Additional Scientific information

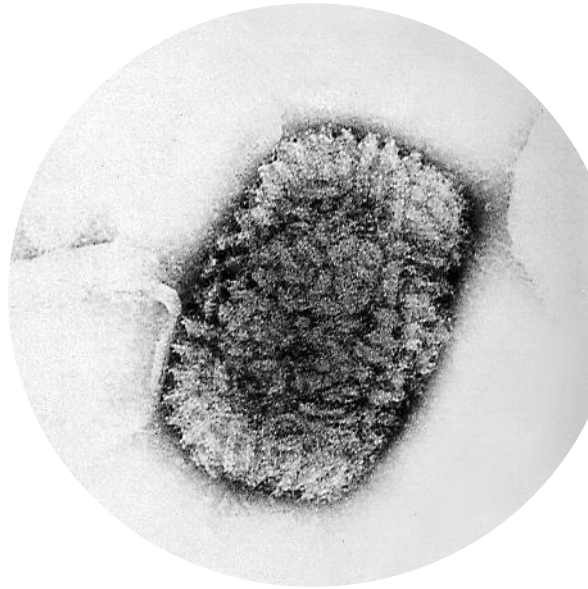
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Vaccinia Virus as a Systemic Antitumor Virotherapy and Viral Vector



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

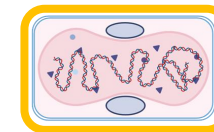
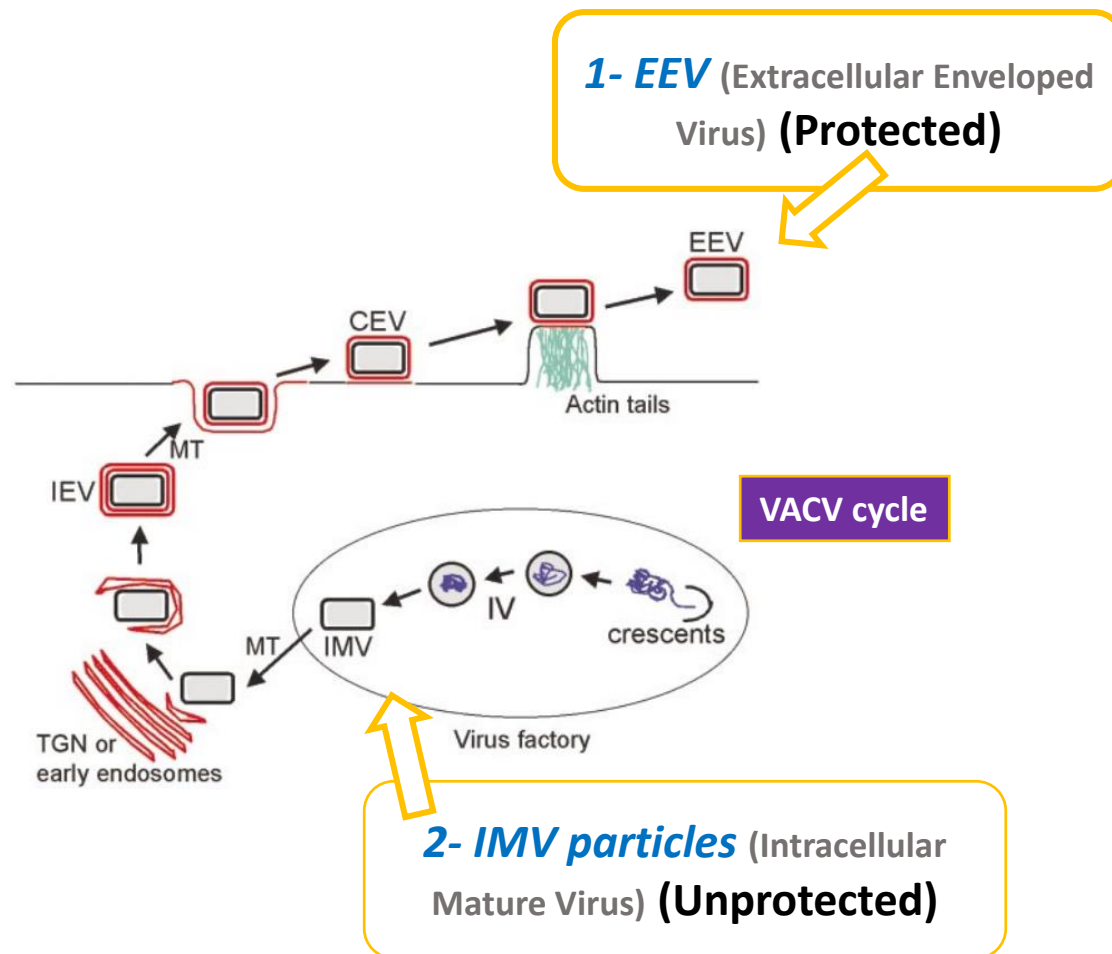
2- Genetically stable. 200kB dsDNA virus.

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.

New Vaccinia Backbone Designed for Systemic Delivery

→ Vaccinia virus has 2 main forms:



Requirements of new backbone selected and engineered by Calidi (RT strain):

High production of EEV

- ➔ To be able to be manufactured by enriching EEV particles
- ➔ Continued production of EEV after reaching tumors

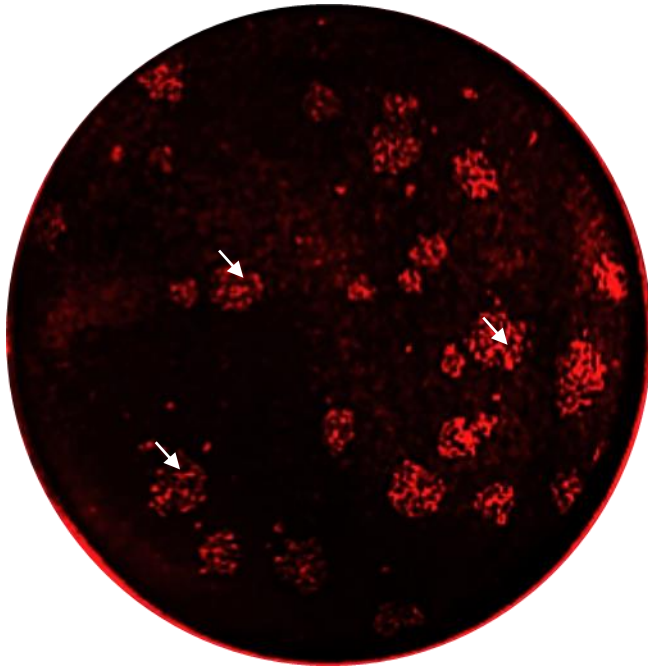
Figure adapted from: Geoffrey L Smith et al. J Gen Virol 2002 Dec;83(Pt 12)

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

Comet assay of two distinct vaccinia viruses

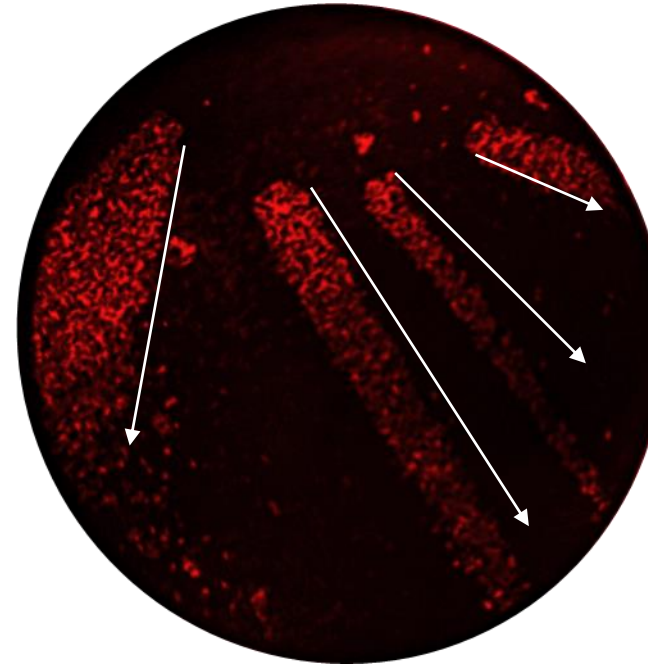
Vaccinia Viruses are genetically engineered to express TurboFP635 (red fluorescence).

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



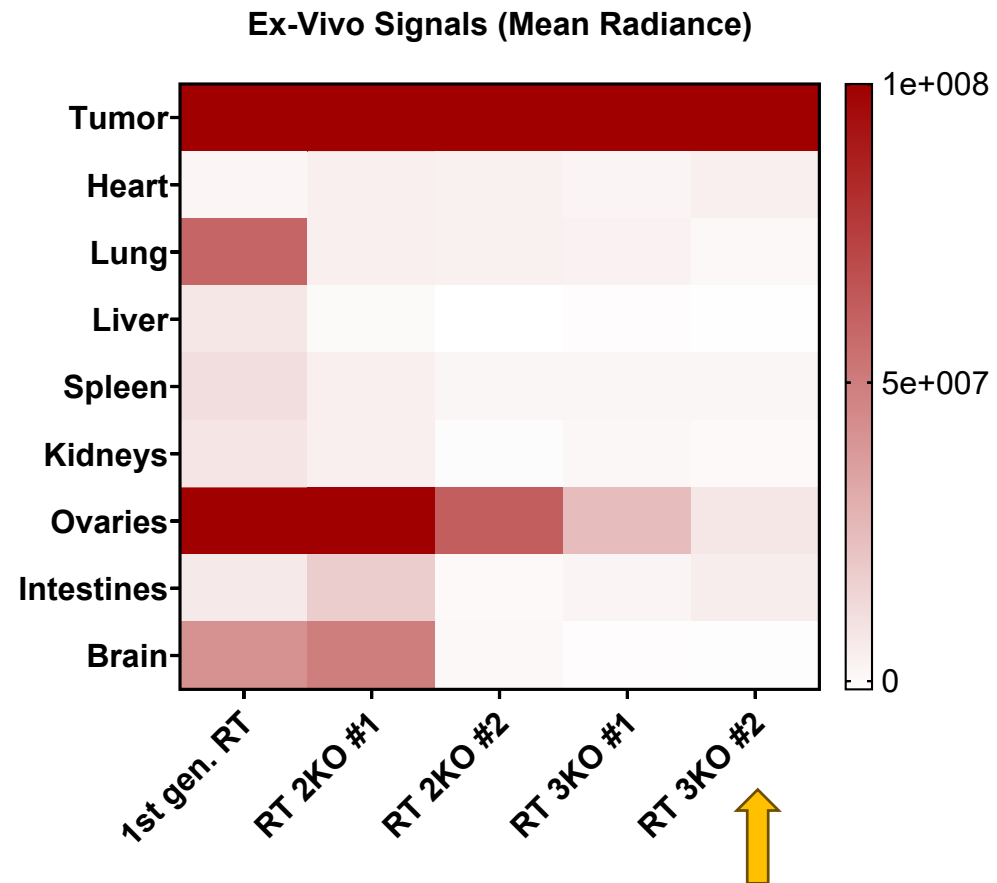
A long “tail” in a comet assay indicates that the virus can produce high levels of EEV **leading to further spread.**



Redtail (RT)
Strain

Generation of a Tumor-Selective RT (Triple Knockout, 3KO) Vaccinia Virus

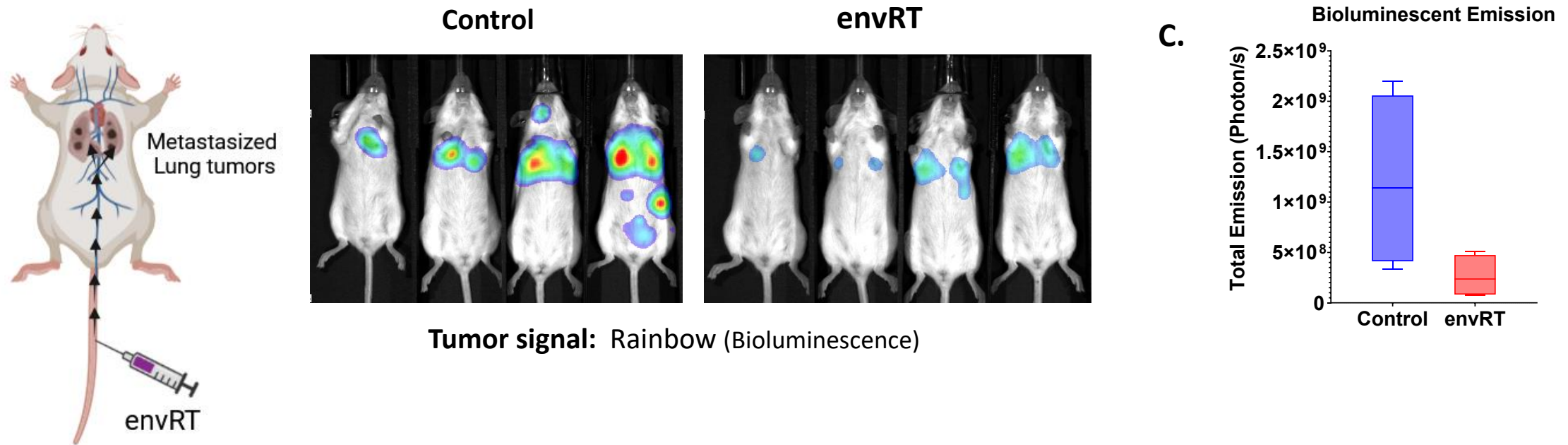
Ex-vivo imaging of major organs after administration of different engineered (KO) RT viruses (expressing TurboFP635)



- ➔ RT viruses with double KO (RT 2KO) or triple KO (RT 3KO) reduce off-tumor toxicities in the NSCLC athymic mouse xenograft model.
- ➔ RT 3KO #2 preferentially targets and amplifies in tumors and not in other major organs.

Systemic Administration of EnvRT Can Eliminate Lung Cancer And Metastasis

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

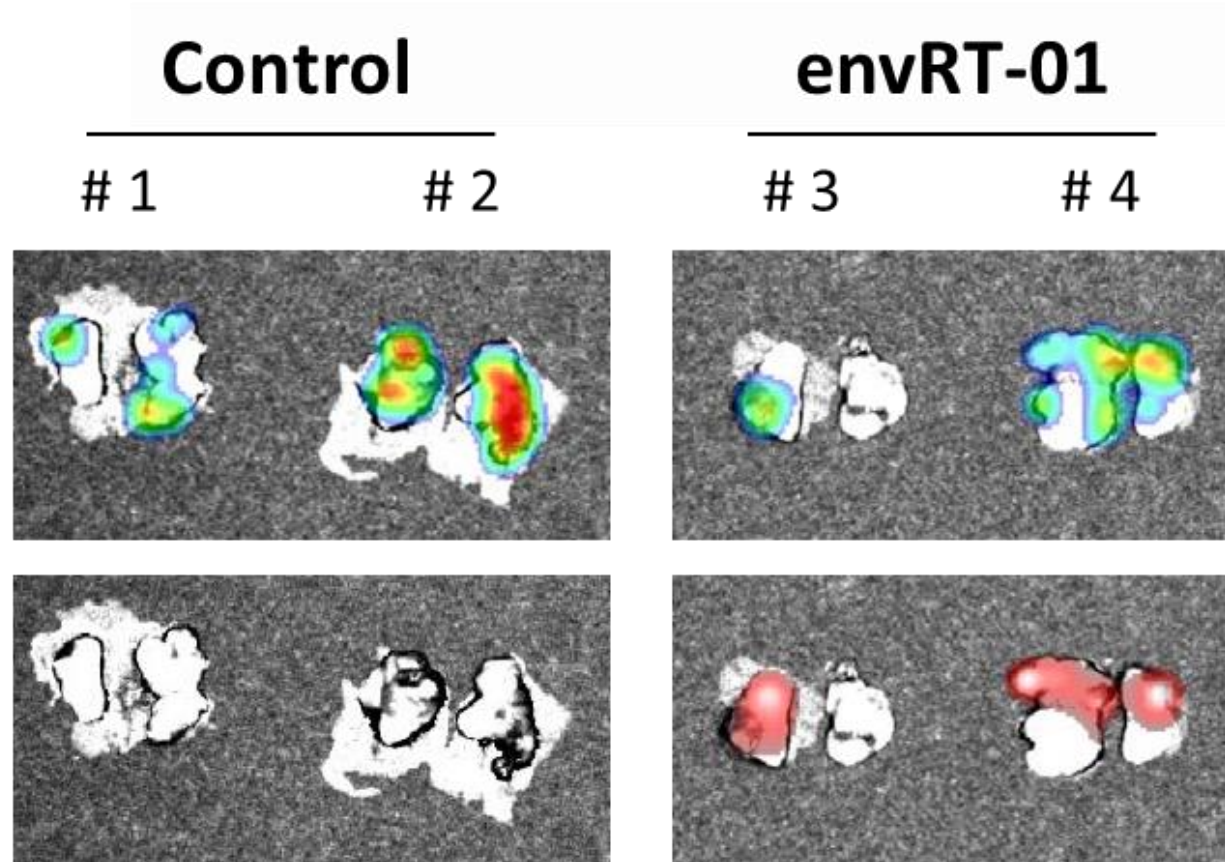


Bioluminescence picture (tumor burden) were taken 6 days after treatment

Systemic Administration of enveloped RT virus Targets Lung Cancer and Metastatic Sites

Tumor signal:
Rainbow
(Bioluminescence)

Virus location:
Red
(Fluorescence)



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

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

envRT Targets All Disseminated Tumor Sites Inducing Major Immune Modulation

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

