Systemic Antitumor Virotherapies

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

Redtail Biopharma

August 22, 2024

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Overview: Fulfilling the Promise of Systemic Virotherapies

Redtail Biopharma is a biotechnology company that is transforming cancer treatment, with innovative **systemic antitumor virotherapies**.

Our cutting-edge technology, an extracellular enveloped virotherapy (EEV) named Redtail virus (RTNova program), is **designed to survive systemic circulation targeting all tumor sites.**

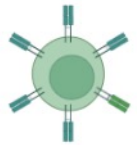
These new systemic and targeted enveloped technologies will revolutionize the treatment of advanced solid tumors.

Redtail History and Why Systemic Virotherapies?

2021	During presentations with several bio-pharma companies, we were **challenged to develop a systemic antitumor virotherapy**
5	Redtail's platform was formally introduced in February 2024 and now in **active discussion with 5 large cap global bio-pharma companies**
Platform	A systemic virotherapy platform technology with **multiple solid tumor indications**
Team	**Seasoned team with decades of experience** in oncology and virotherapy drug development

Challenges of Immunotherapies in Treating Solid Tumors

Immunotherapies

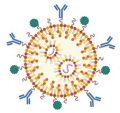


CAR-T & other Cell therapies

Cytokines

Cancer Vaccines

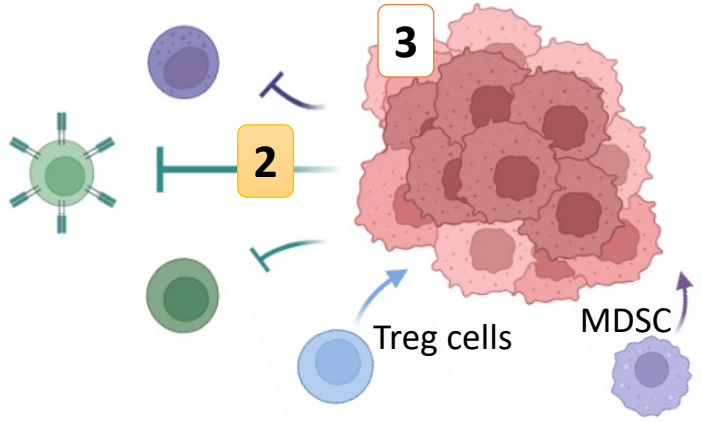
Checkpoints, other immunomodulators



Targeted nanoparticles. In Situ Car-T

1

Immunosuppressive tumor microenvironment

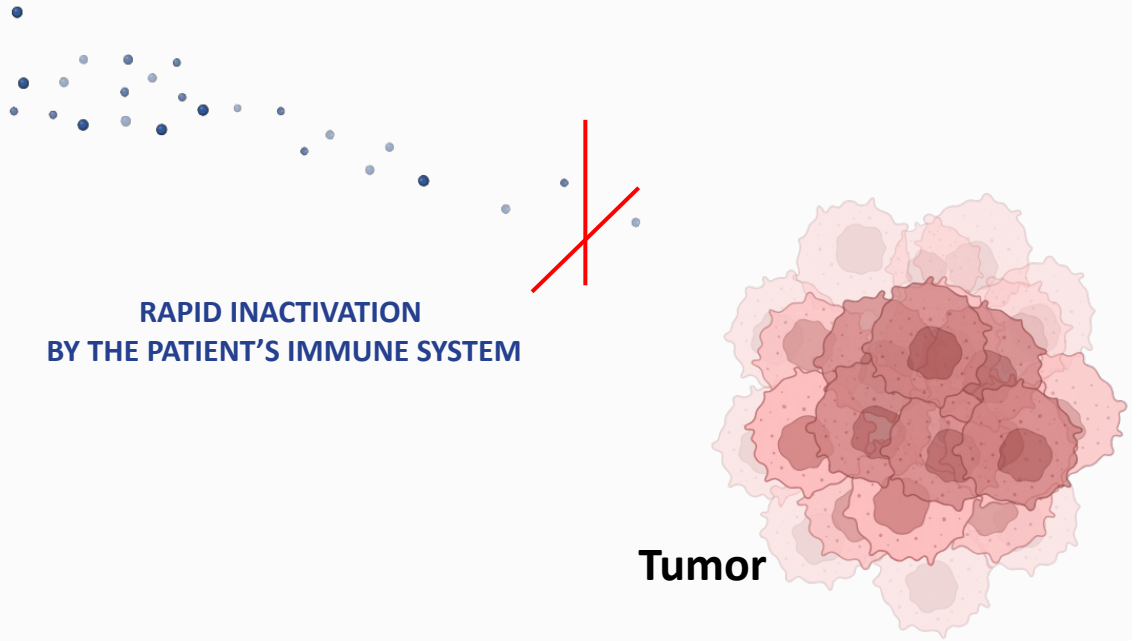


1. **Immunotherapy MOA**: relies on activated immune cells infiltrating and persisting within tumors to mount an effective response.
2. **Tumor Resistance**: Unfortunately, tumors often block this process by preventing anti-tumor immune cells from infiltrating and persisting.
3. **Challenges in Efficacy**: Most of cell therapies or other immunotherapies are ineffective to treat a wide array of solid tumors

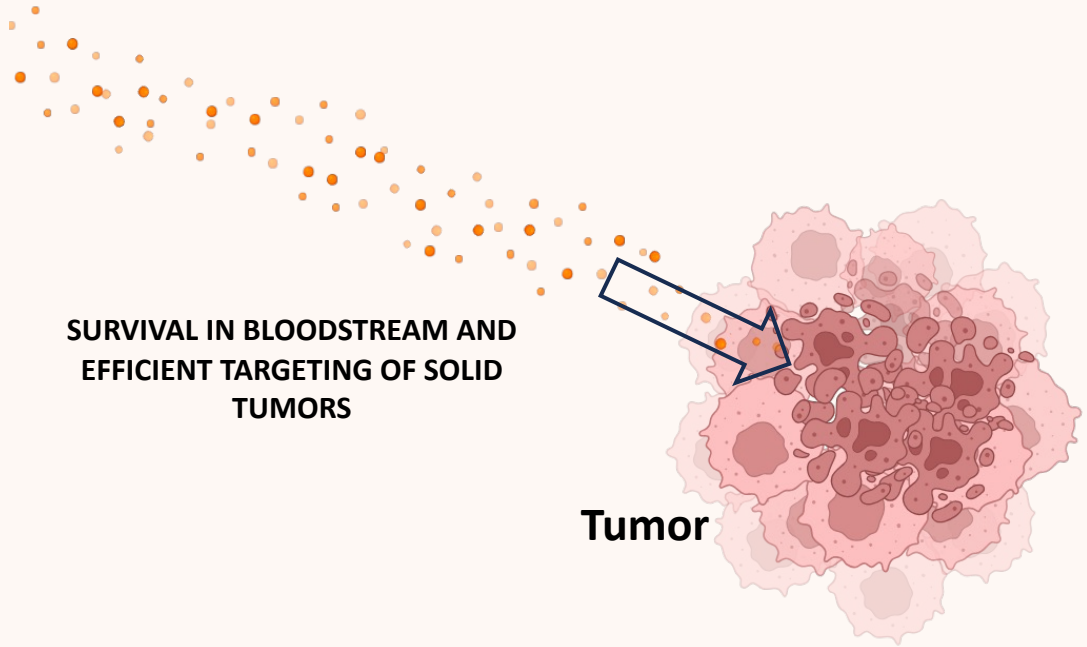
Solution: Systemic virotherapies have the potential to revolutionize immunotherapy for solid tumors

Challenges and Solutions of Systemic Antitumor Virotherapies

Clinical Challenge: Current systemic **virotherapies** are **rapidly inactivated in minutes by the immune system**, with only 0.1-5%* remaining intact, limiting the ability to reach the tumor



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



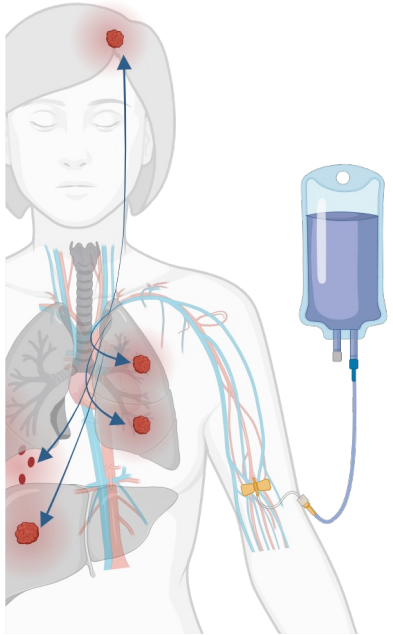
(*) depending on virus type, strain and dose. a) Nguyen DH et al Cancers. 2022 Dec; b) Evgin, L., et al., Mol Ther, 2015. 23(6) c) Martinez-Quintanilla, J et al J. Clin. Investig. 2019, 129

Mechanism of Action of RTNova Systemic Antitumor Virotherapies

I **RTNova,** an antitumor and systemic Virotherapy designed to:

- **survive** bloodstream circulation and

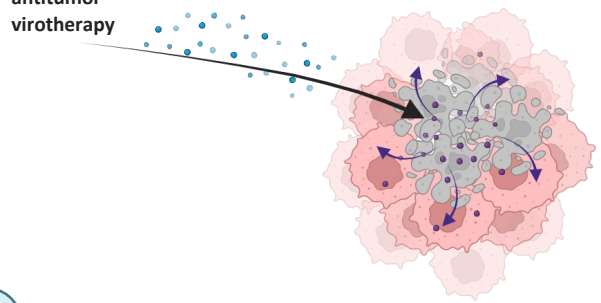
- **target all tumors** (distant metastasis)



II **Oncolysis (Antitumor Virotherapy):**

- **Direct killing** of Tumors cells

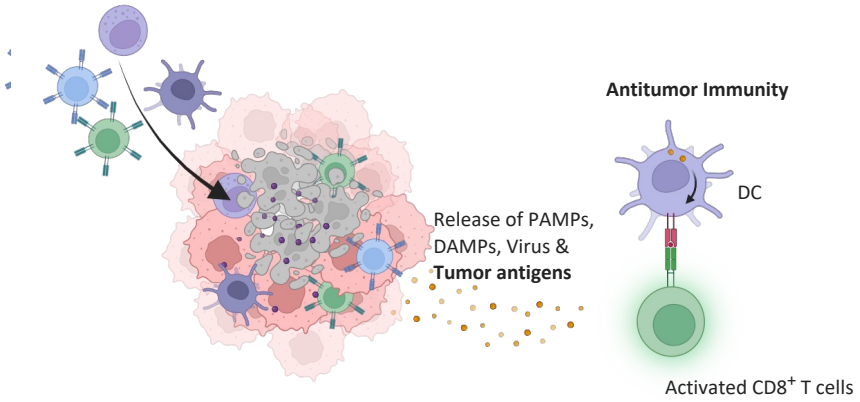
- Virus **self-amplification and spread**



III **Tumor Immune Microenviroment transformation:**

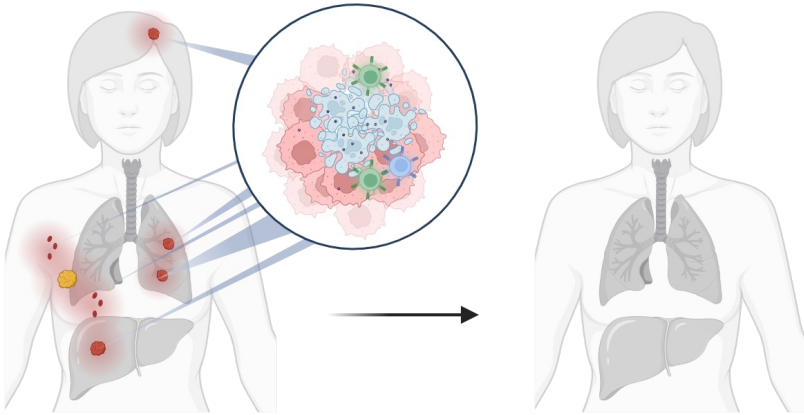
- Increase **infiltration of TILs** in all tumor sites

- Generation/Activation of **anti-tumor immunity**



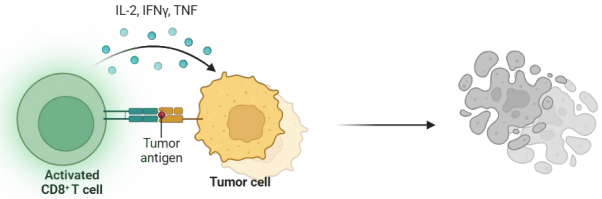
IV **Targeting all tumor sites**

✓ Selected initial indications treatment option for metastatic lung cancer (NSCLC).

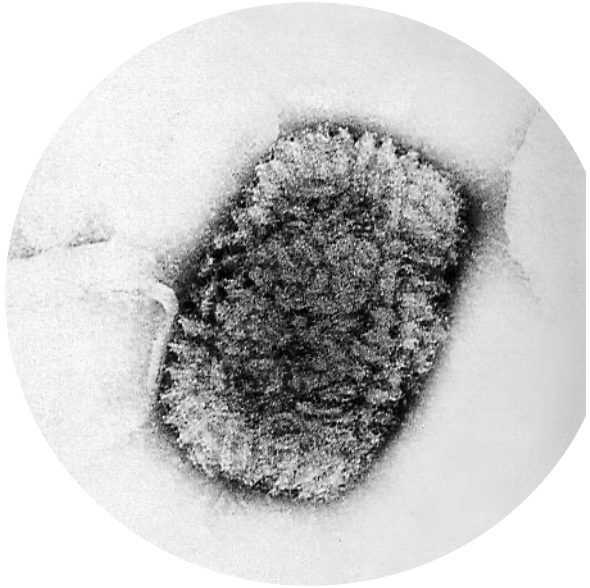


V **Antitumor immune memory:**

Elimination Future Tumor recurrence



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.

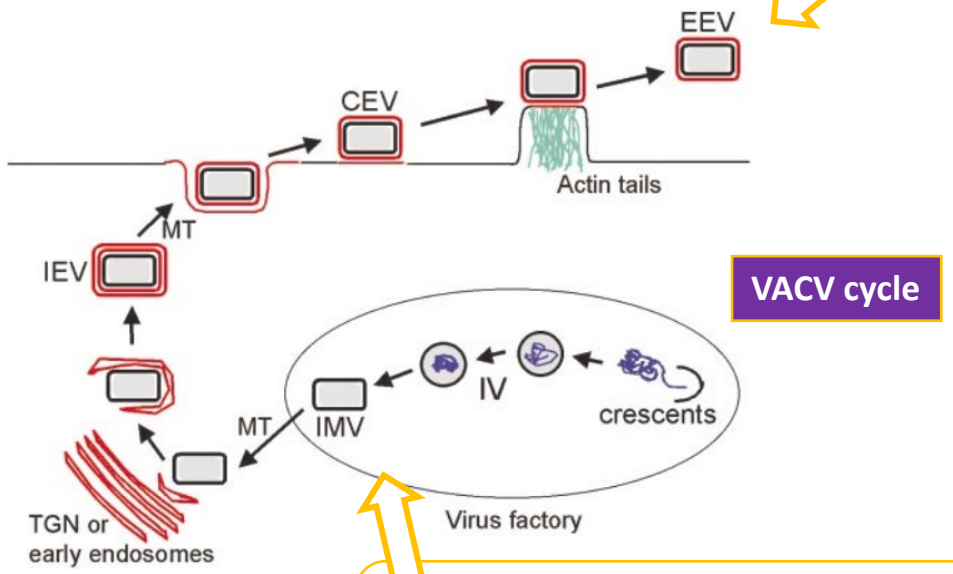
3- Large insertion capacity (25-45Kb), allowing delivery of existing therapeutic proteins into the tumor, potentiating antitumor systemic virotherapy efficacy.

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

New Vaccinia Backbone Designed for Systemic Delivery

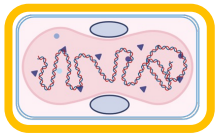
→ **Vaccinia virus has 2 main forms:**

1- EEV (Extracellular Enveloped Virus) **(Protected)**



2- IMV particles (Intracellular Mature Virus) **(Unprotected)**

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



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

High production of EEV

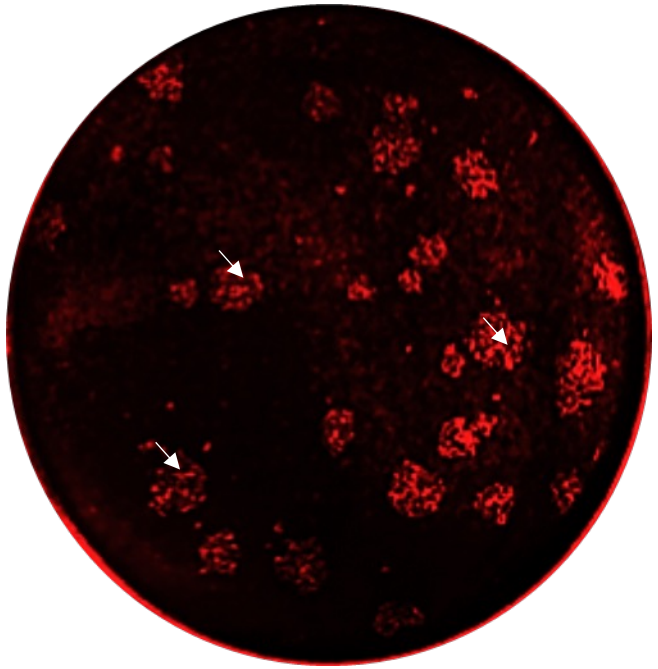
- To be able to be manufactured by enriching EEV particles
- Continued production of EEV after reaching tumors

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

Comet assay of two distinct vaccinia viruses

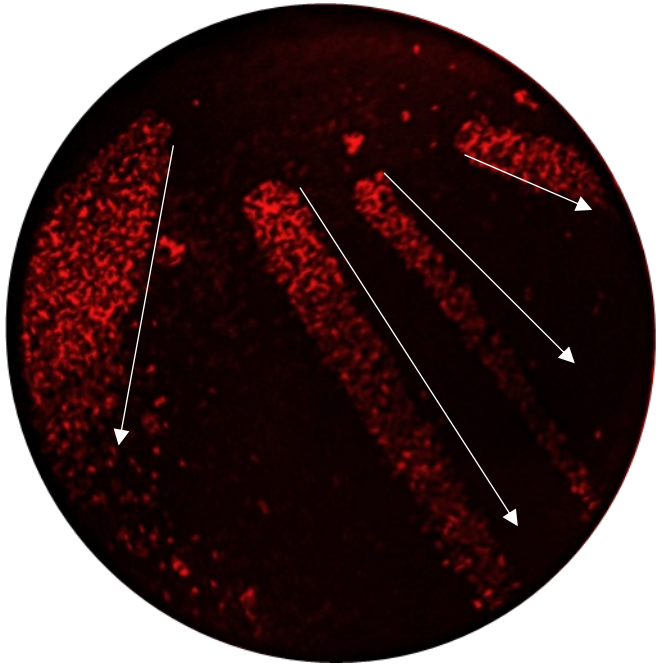
Vaccinia Viruses are genetically engineered to express TurboFP635 (red fluorescence).

Vaccinia virus strain CAL2 producing low EEV particle



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

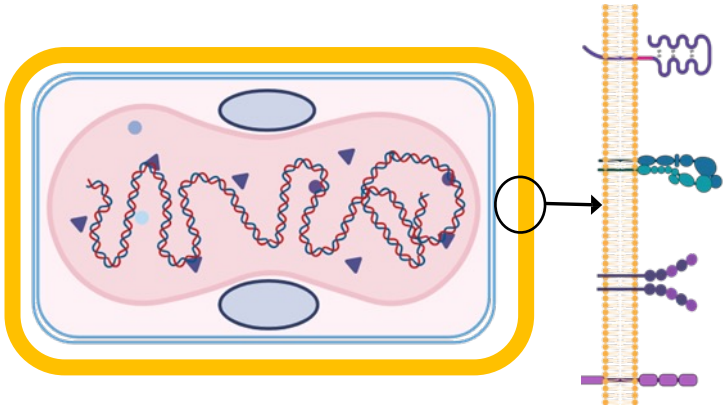
Redtail Vaccinia virus envRT-01 producing high levels of EEV particles



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

Redtail (RT) Strain

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**

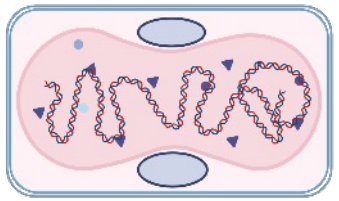
2- Does not integrate into human genome.

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

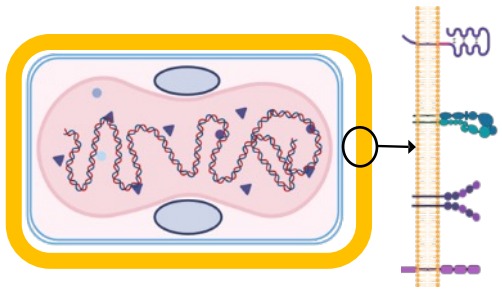
Multifunctional Human Surface Proteins Expressed in Enveloped Viral Particles

Example flow cytometry of viral particles expressing CD55 (DAF)

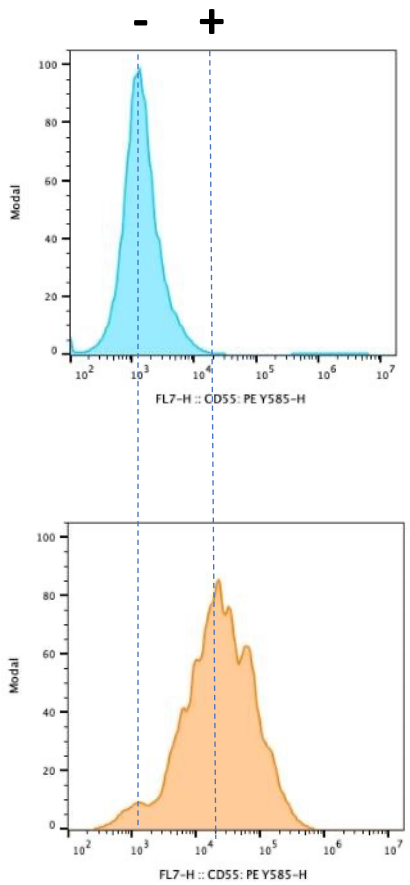
Non-enveloped



***Enveloped* virus**



envRT-01



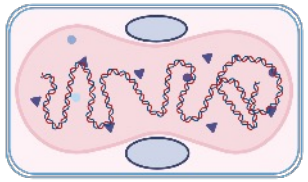
Enveloped viruses incorporate human surface proteins in their extracellular envelope. Examples:

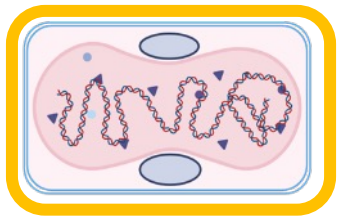
CD55 → Protection against humoral immune system

CD44/CXCR4 → Targeting/homing

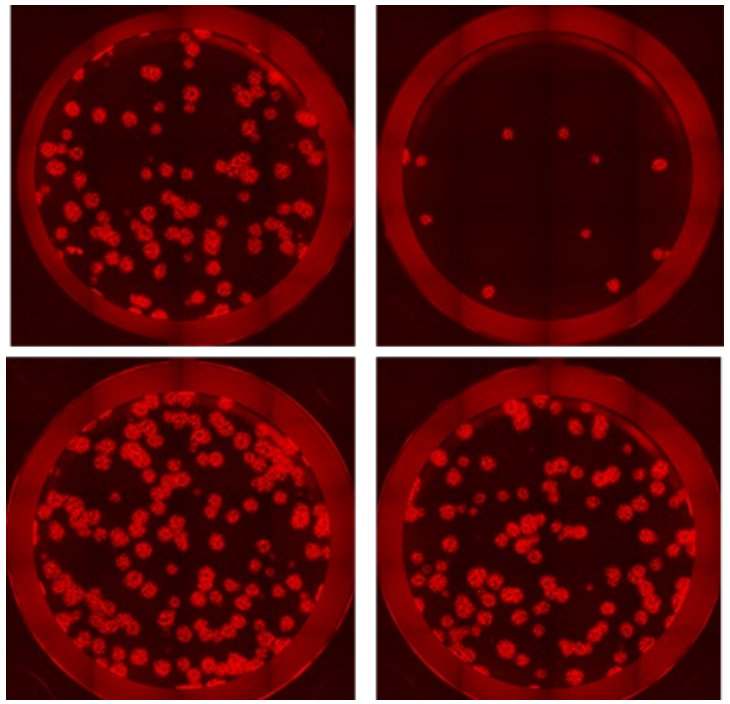
Others: non-disclosed

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 <u>extracellular enveloped viruses</u> (EEVs), was required.**
- **Human host cell line: undisclosed**
- **<u>Only enveloped virotherapies</u> can survive inactivation by human serum.**

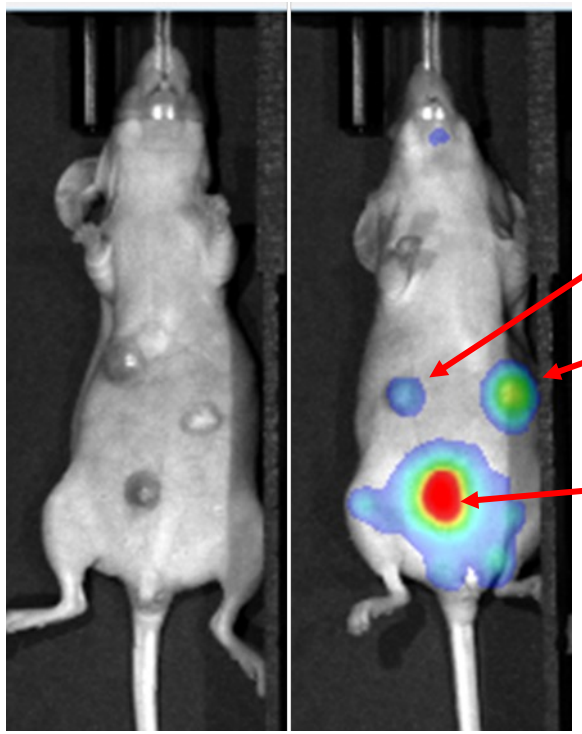
This completes a critical step to achieving systemic delivery in clinical scenarios

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

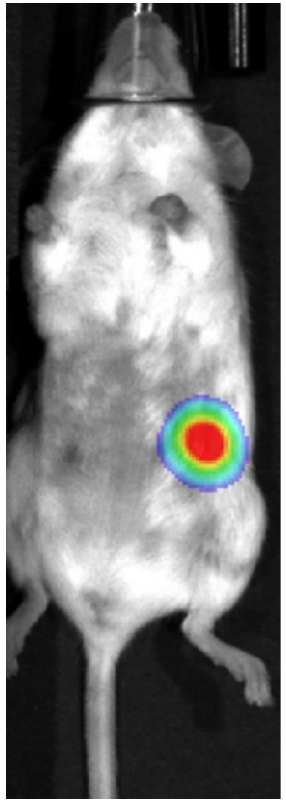


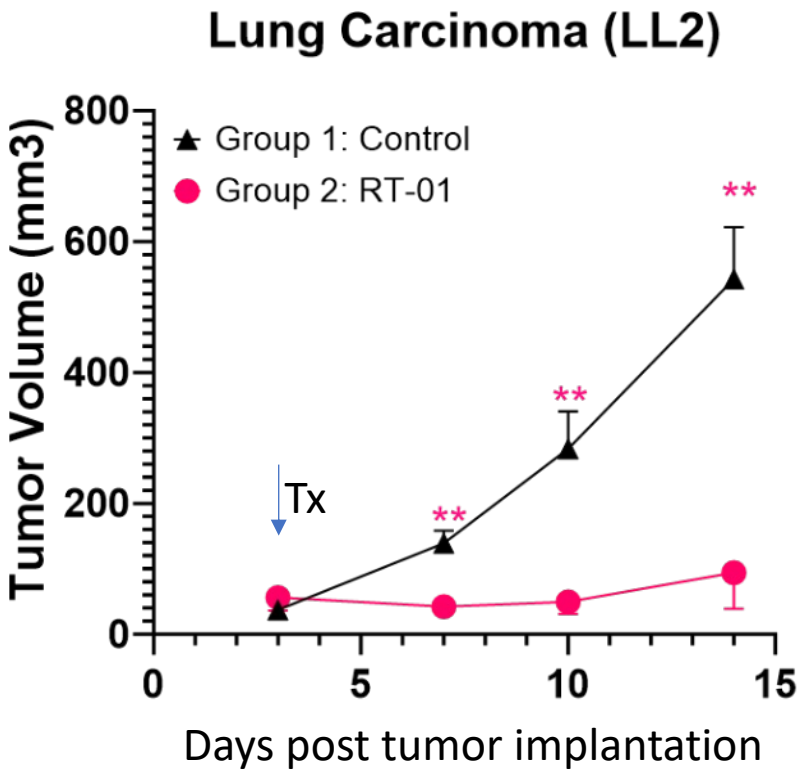
% Tumor Growth inhibition (Average n=5) day 10

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

Data indicates that targeting tumors with envRT01 enables the expression of any encoded payload within the tumor, providing an additional MOA to the therapeutic approach.

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





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

<u>Remarkable tumor selectivity.</u>

envRT-01 Virus: TurboFP635 is represented as Rainbow signal

Data indicates that targeting tumors with envRT01 enables the expression of any encoded payload within the tumor, providing an additional MOA to the therapeutic approach.

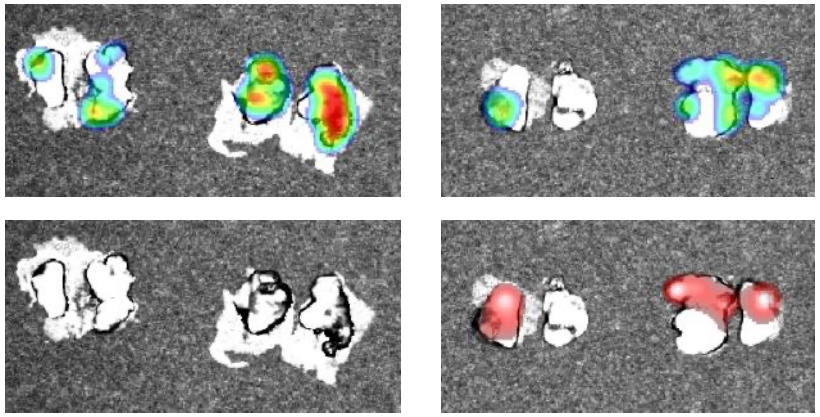
Systemic Administration of envRT-01 Targets Lung Cancer and Metastatic Sites

Tumor signal:
Rainbow
(Bioluminescence)

Virus location:
Red
(Fluorescence)

Lungs:

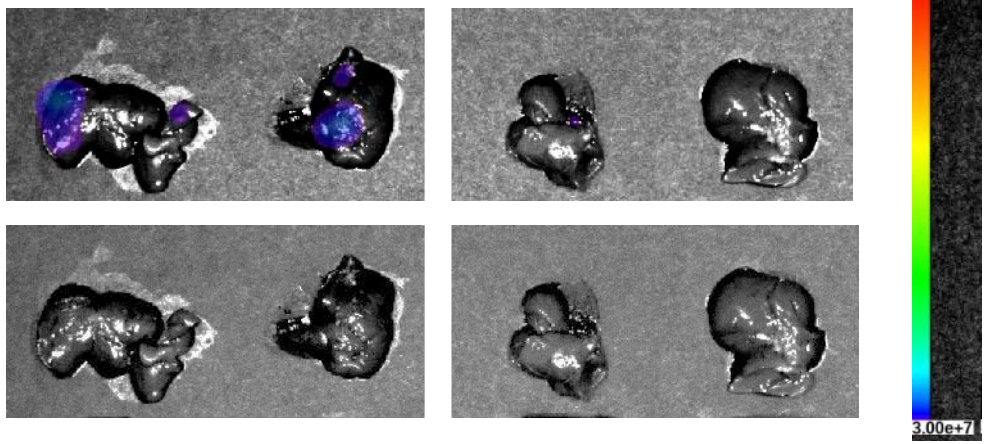
Control		envRT-01	
# 1	# 2	# 3	# 4



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

Liver:

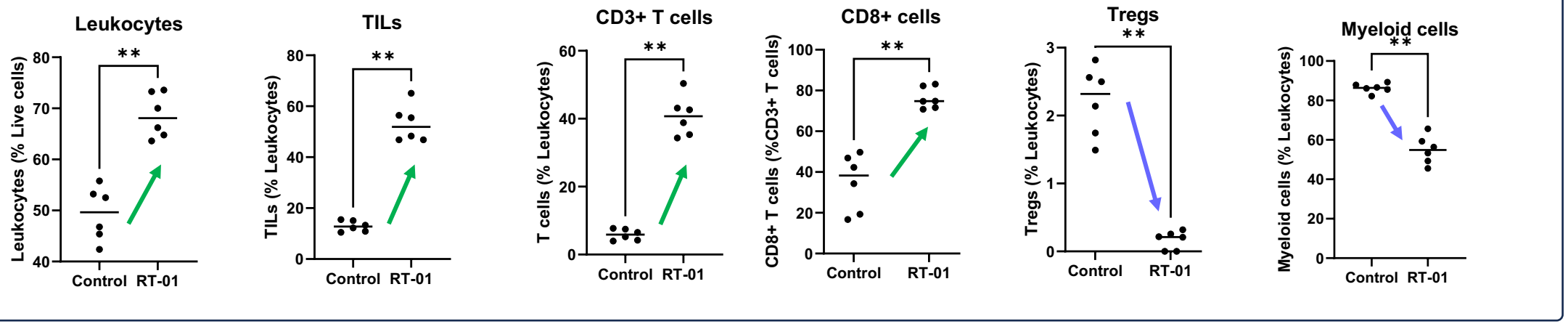
Control		envRT-01	
# 1	# 2	# 3	# 4



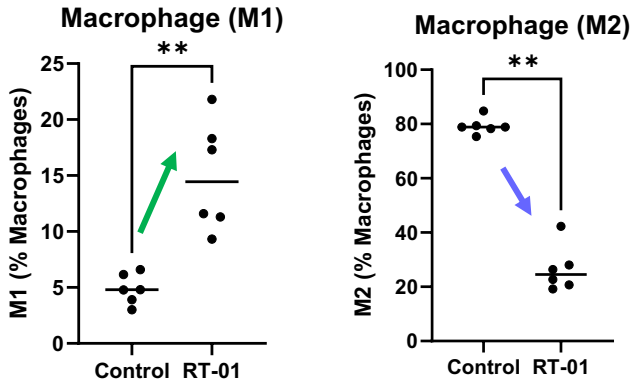
- LL2 lung cancer cells colonize liver after I.V administration.
- Animals treated with envRT-01 had lower metastatic site in Liver

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

envRT-01 Induces Major Modulation of Tumor Immune Microenvironment



Macrophage subsets

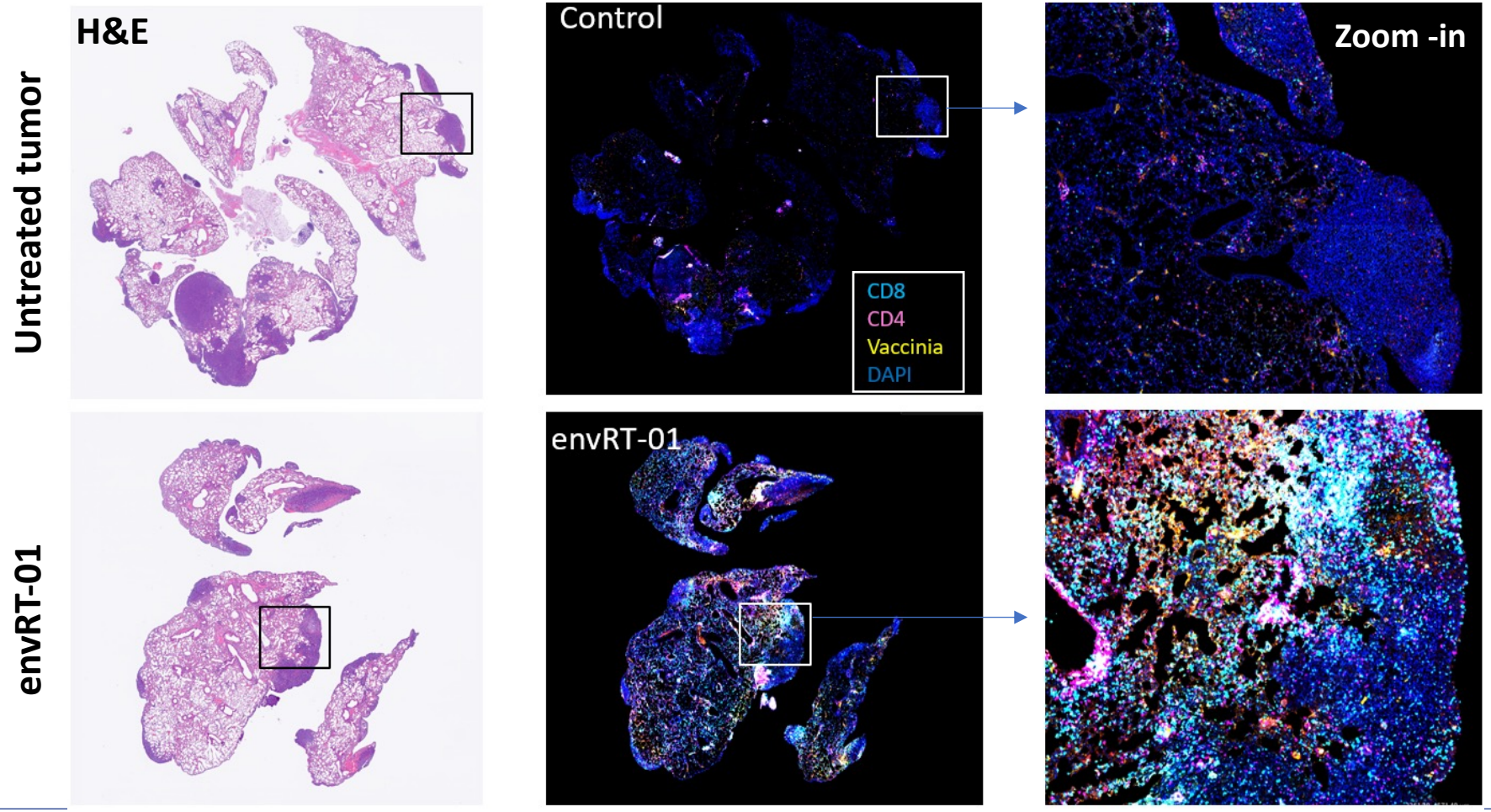


- **envRT-01 induced dramatic changes in the tumor immune microenvironment favorable for the anti-tumor response.**
  - Increased leukocyte, TILs, T cell in the tumors
  - Decreased Treg population and myeloid cells in the tumors
  - Macrophage polarization towards pro-inflammatory subtype (M1) from anti-inflammatory subtype (M2)

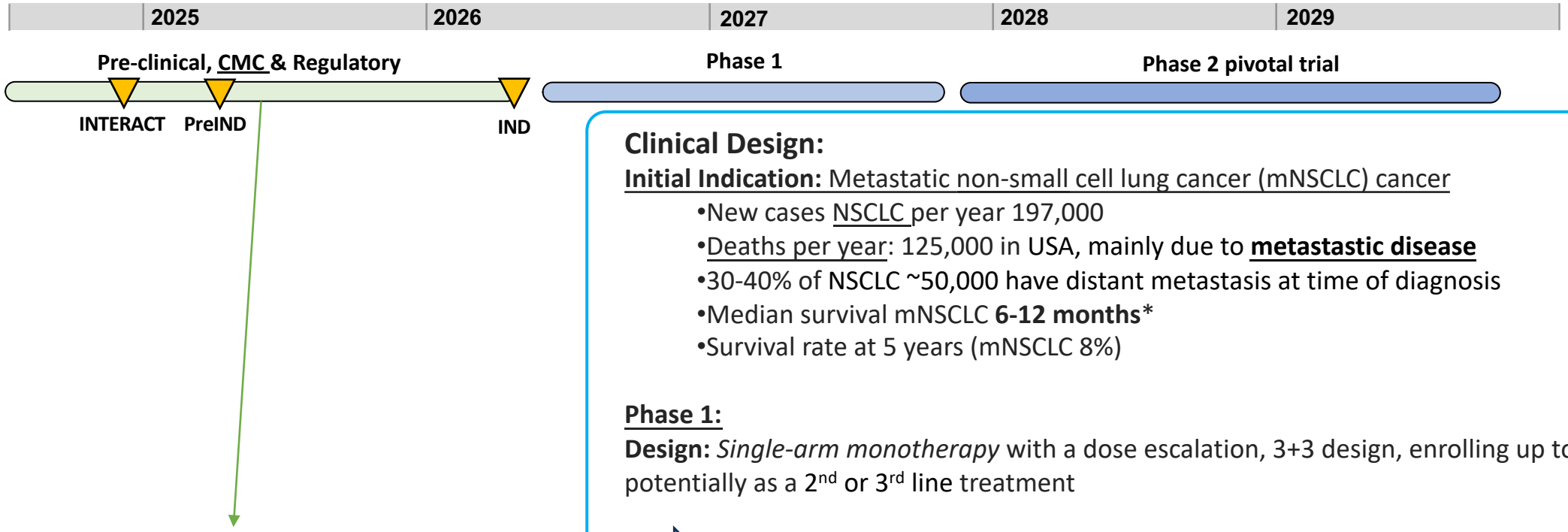
- **Confirmed in multiple tumor models**:
  - EMT6 (breast cancer), CT26 (colon cancer), LL2 (lung cancer)

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

Targeting all metastasis: Immunohistochemistry data indicates systemic envRT-01 treatment targets metastasis inducing major infiltration of immune cells in all tumor loci. (Experimental metastasis lung cancer tumors)



Clinical and Regulatory Path Lead Candidate



(for details, see next slide)

Clinical Design:

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

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

Phase 1:

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

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

Phase 2 (Pivotal)

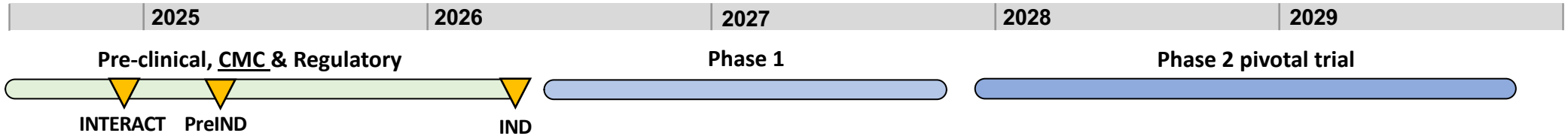
Design: Accelerated single-arm study focusing on unmet needs 2nd or 3rd line treatment, involving <100 patients The approach and number of patients, will be re-evaluated after Phase 1 Plan Approval endpoints; primary: Objective Response Rate (ORR), secondary: Duration Of Response (DOR)

- **Regulatory approval:** targeting late 2029

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

* OS may increase with new investigational treatments

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:

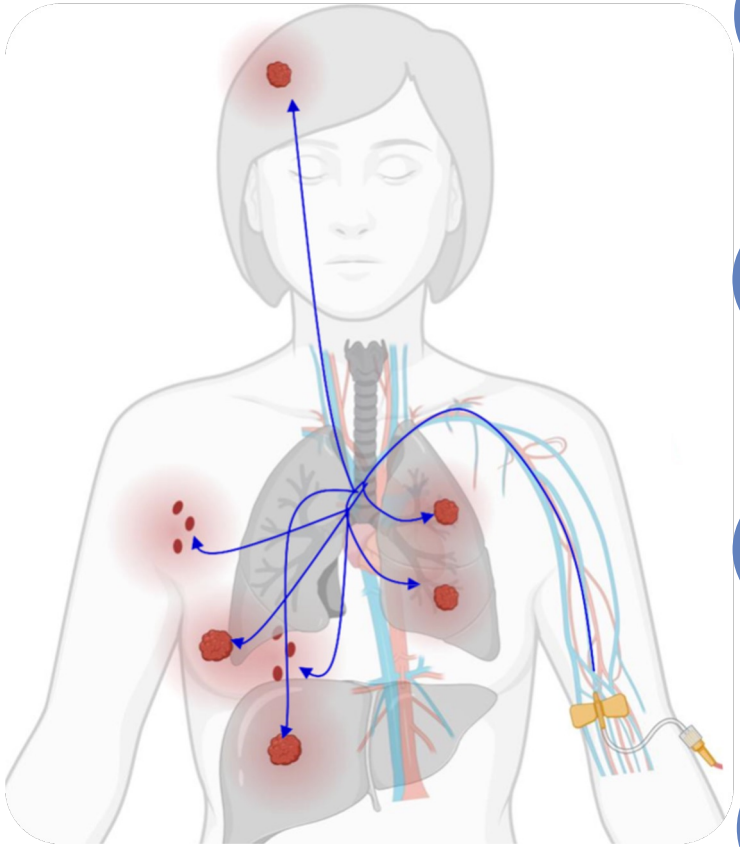
- **Final drug product (FDP**) manufacturing
- IND-enabling **toxicology** studies
- Develop the **Biomarkers Clinical program**
- Prepare **clinical sites** and **CRO**
- Open **IND**

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.**

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