

Medical Biotechnology 2026'

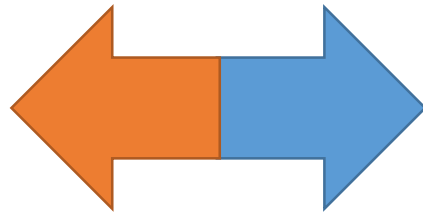
Biological therapies

**Treatment of malignant tumors with
oncolytic viruses**

Olasz Katalin

2026.04.16

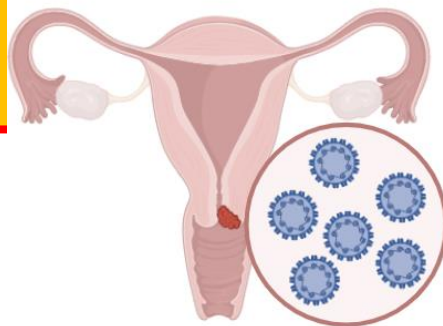
Oncogenic viruses



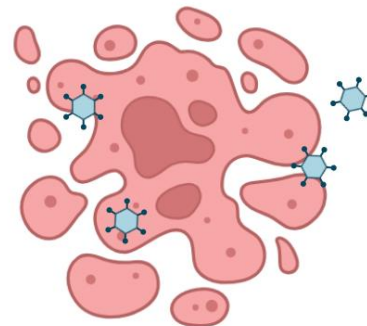
Oncolytic virus

Viruses that can **induce tumor formation**

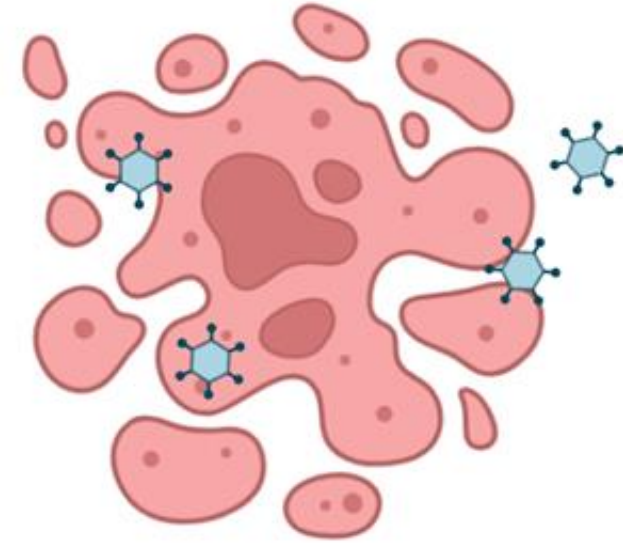
- Two main groups:
 - **RNA tumor viruses** (e.g., Retroviridae)
 - **DNA tumor viruses**
- Examples of oncogenic DNA viruses:
 - Poxviruses
 - Papillomaviruses
 - Herpesviruses
 - Polyomaviruses



- Viruses that **selectively infect and destroy cancer cells**
- **Do not harm normal healthy cells**
- Can be:
 - ✓ **Naturally occurring**, or
 - ✓ **Genetically engineered**
- Basis of **oncolytic virotherapy**
- Promising approach in cancer treatment over the **past two decades**



History of viral oncolysis



1904 – First clinical observation

- George Dock reported remission of myeloid leukemia
- Occurred after **influenza virus infection**

Early experimental evidence

- Levaditi and Nicolau demonstrated that **vaccinia virus inhibits tumor growth**
- Proven in **mice and rats**

1950s–1960s – Early clinical trials

- Multiple viruses tested
- Selected for ability to **replicate in tumor cells**
- Conducted after **tissue culture adaptation**

Difficulties of oncolytic virus therapies

Advantages

- ✓ Can be administered **intravenously**
- ✓ Potentially effective against **metastatic cancers**
- ✓ Useful where conventional therapies are **less effective**

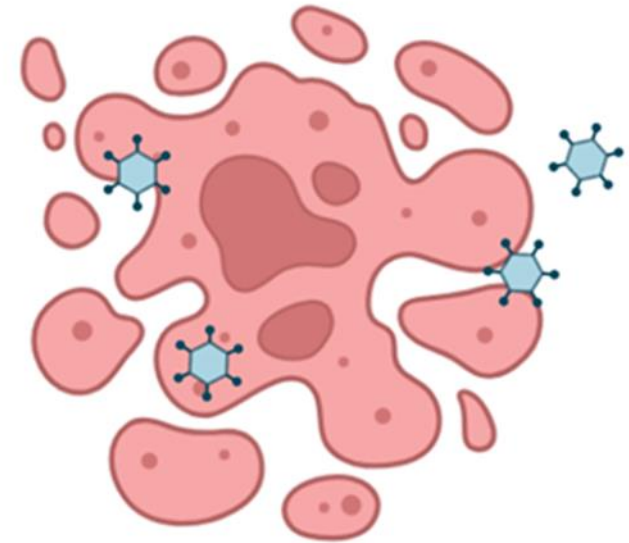
Challenges

- ✓ **Rapid immune clearance**
 - Neutralized by **antibodies**
- ✓ **Removal from bloodstream**
 - Cleared by liver cells (e.g., **Kupffer cells**)
- ✓ **Reduced therapeutic efficiency**
 - Virus may not reach tumor in sufficient amounts

Immunotherapy with oncolytic viruses

Mechanism of action:

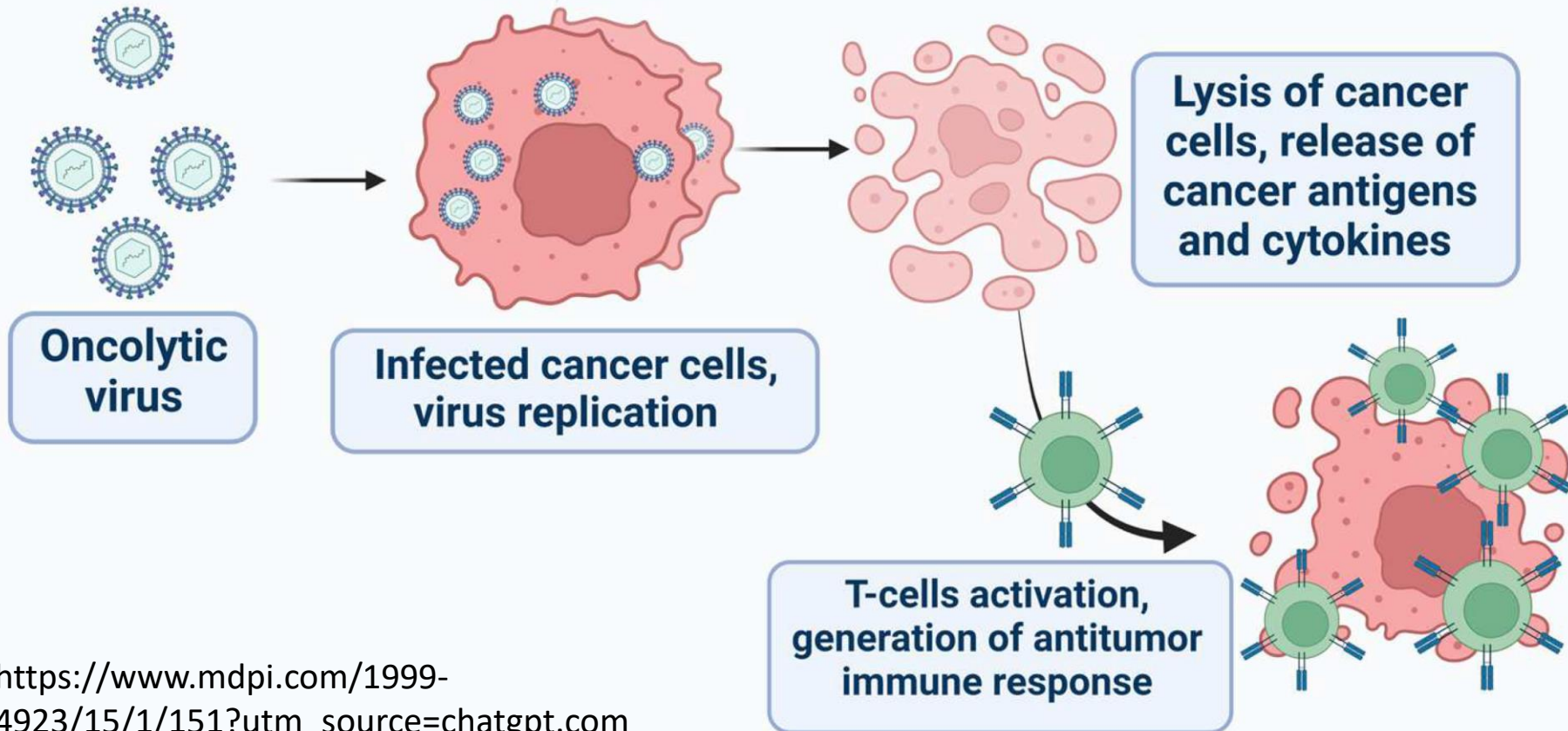
- Selectively **infect and lyse cancer cells**
- Provide **direct tumor destruction**
- Can be **genetically modified** to:
 - Deliver **anticancer genes** (e.g., *p53*)
 - Enhance therapeutic effect



Types of oncolytic viruses:

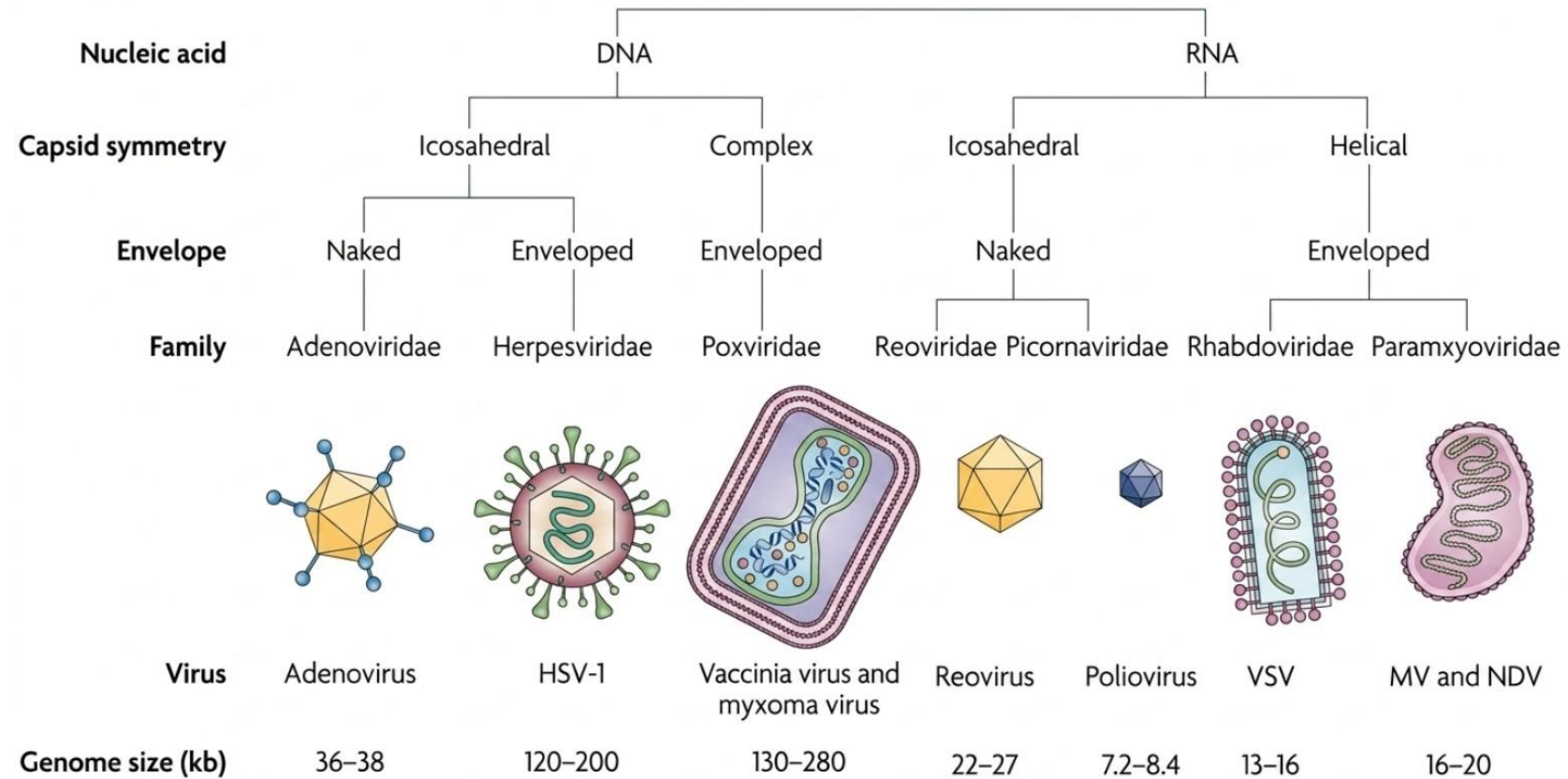
1. **Engineered viruses** (most common): Designed for **tumor selectivity**
2. **Naturally occurring viruses**: Parvoviruses, Seneca Valley virus (SVV), Myxoma virus, Reovirus, Newcastle disease virus (NDV)

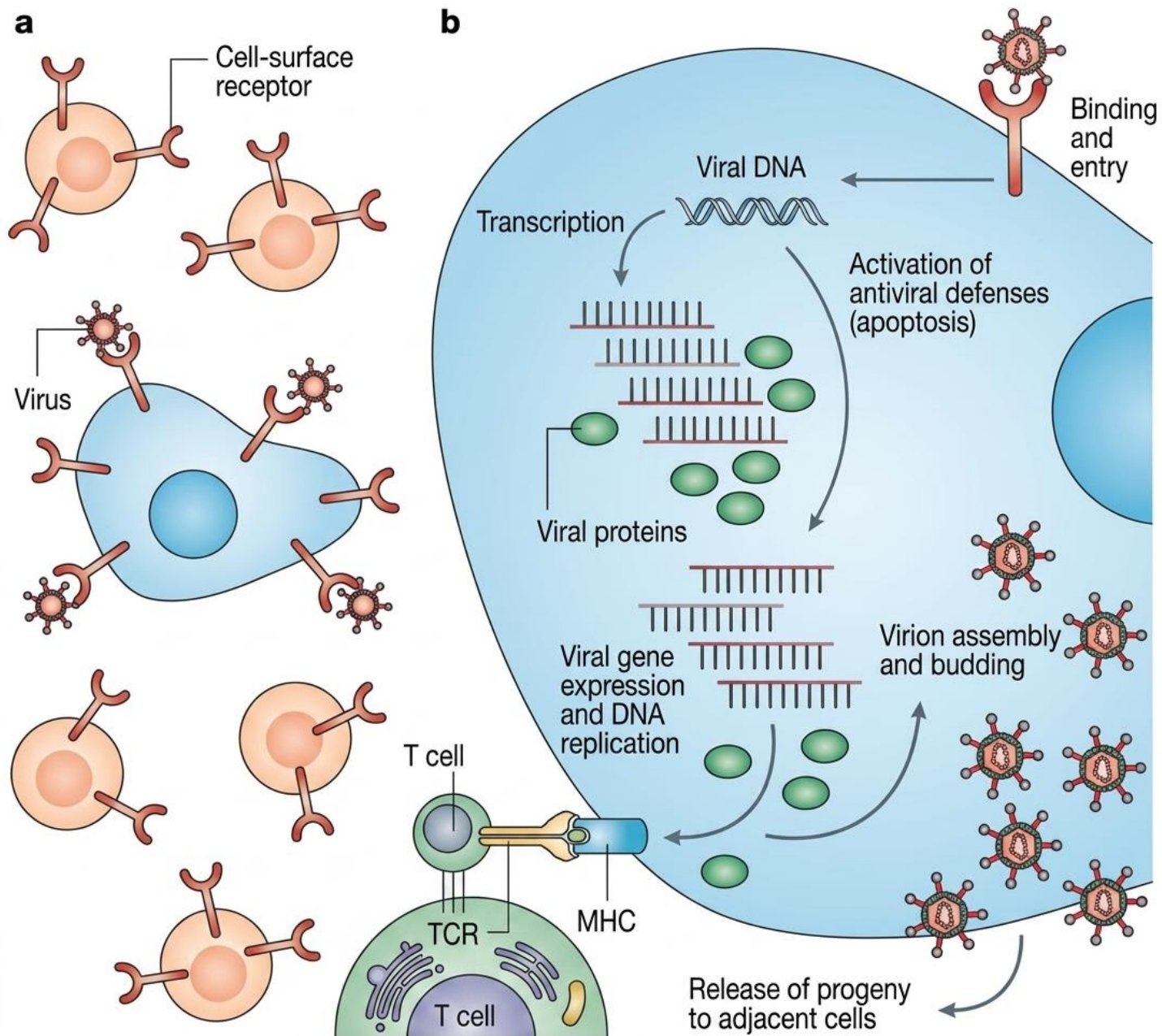
Mechanisms of oncolytic virus action to cancer cells



Major Oncolytic Virus Platforms in Cancer Therapy

- **Multiple viral platforms are used** in oncolytic virotherapy
- **Each virus differs** in: genome type (**DNA** vs **RNA**) structure (enveloped vs non-enveloped) clinical application
- Key examples:
 - ✓ Herpes simplex virus (HSV) → clinically approved (T-VEC)
 - ✓ Adenovirus → widely used, easy to engineer
 - ✓ Measles virus → promising vaccine-based approach
 - ✓ Reovirus, NDV, VSV → natural tumor selectivity





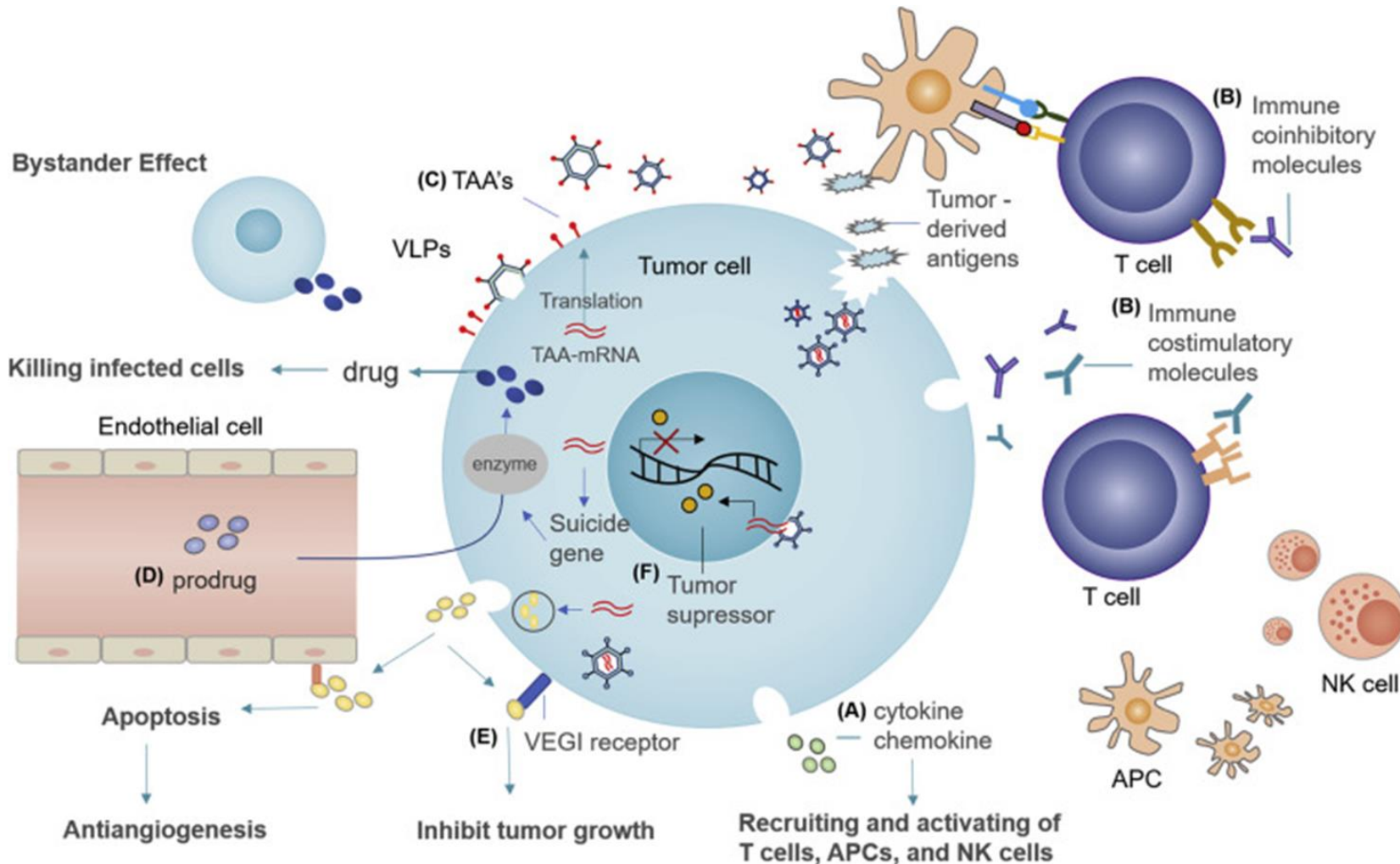
a) Virus binding and targeting

- Oncolytic viruses bind to **specific cell-surface receptors**
- Cancer cells often **overexpress these receptors**, making them more susceptible
- This allows **selective infection of tumor cells**

b) Viral replication and immune activation

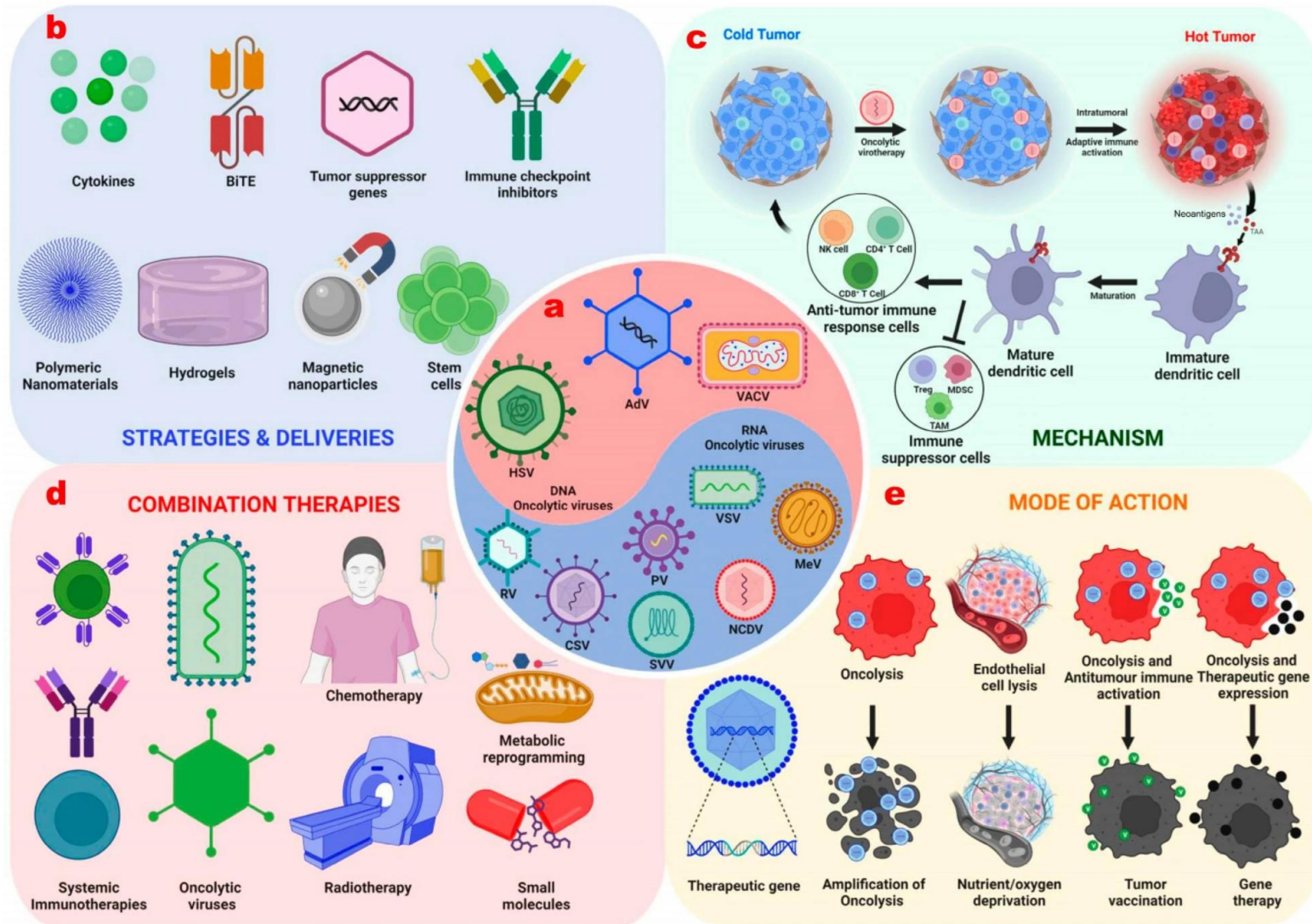
- **Entry and gene expression**
- Viral genes are **transcribed and translated** into viral proteins
- **Selective replication**
 - In **cancer cells**: Viral replication is **efficient**
 - In **normal cells**: **Antiviral defenses** (e.g., apoptosis) limit replication
- **Virion assembly and spread**: New viral particles are assembled : They are released to infect **adjacent tumor cells**
- **Immune system activation**

Anti-tumor mechanisms of oncolytic virus therapy - beyond simple tumor cell lysis



- Direct tumor cell killing
- Bystander effect
- Prodrug activation (gene-directed therapy)
- Anti-angiogenic effect
- Immune system activation
- Modulation of immune signals
- Viral gene expression and antigen production

Enhancing cancer therapy: the integration of oncolytic virus therapy with diverse treatments

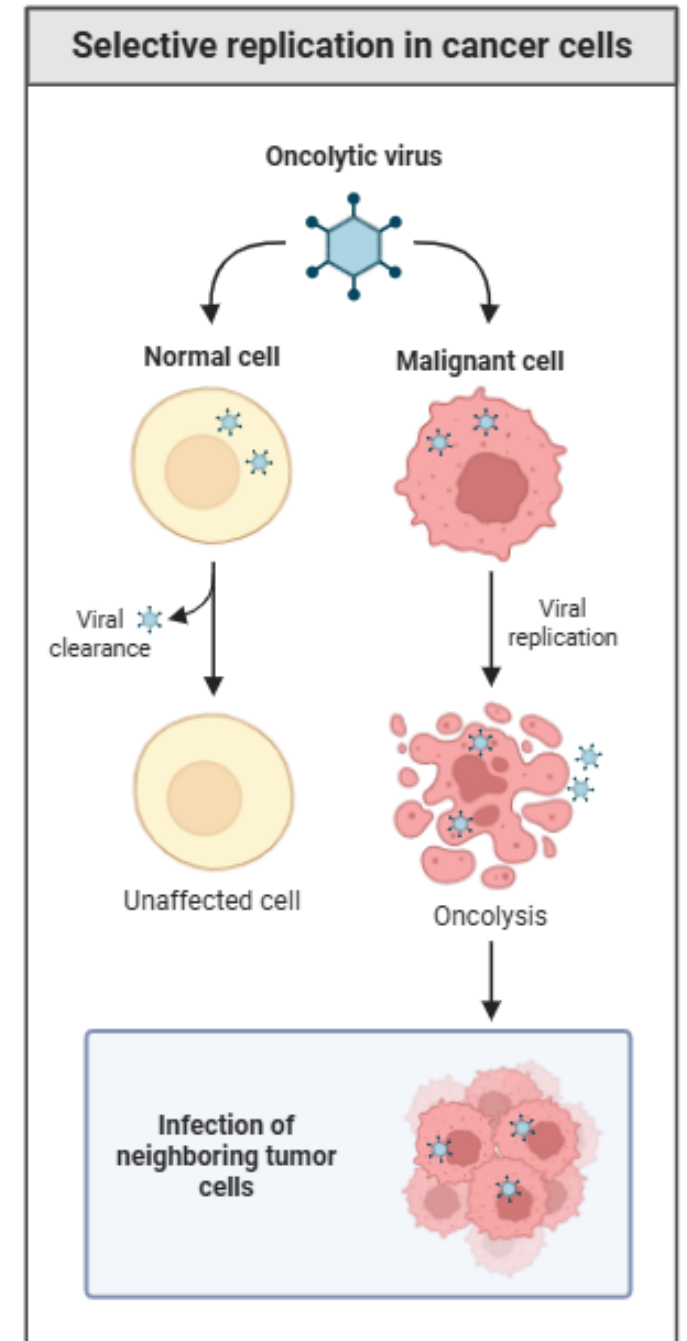
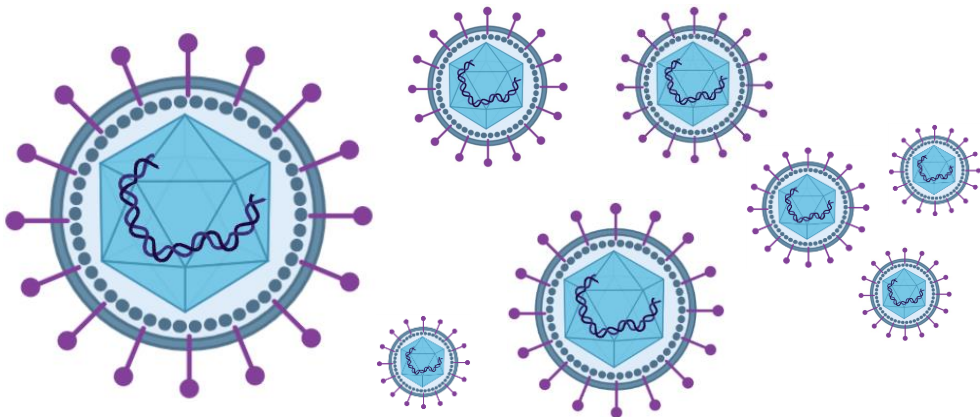


- DNA and RNA viruses serve as tools for **genetic manipulation**, enabling the creation of Ovs
- Various approaches **facilitate OVs reaching tumors**
- The **OVs transform immunologically “Cold” tumors into “Hot” tumors** through oncolysis and immunological anti-tumor activities
- The **combination of OVs with traditional therapies.**
- Genetically engineered OVs cause damage to tumor cells through various means.

Optimizing oncolytic viruses

Key requirements:

- **Not pathogenic**, but can infect human cells
- **Low toxicity** to normal tissues
- **Genetically modifiable**
 - ✓ Allows insertion of **therapeutic genes**
 - ✓ Enables monitoring of **viral spread**



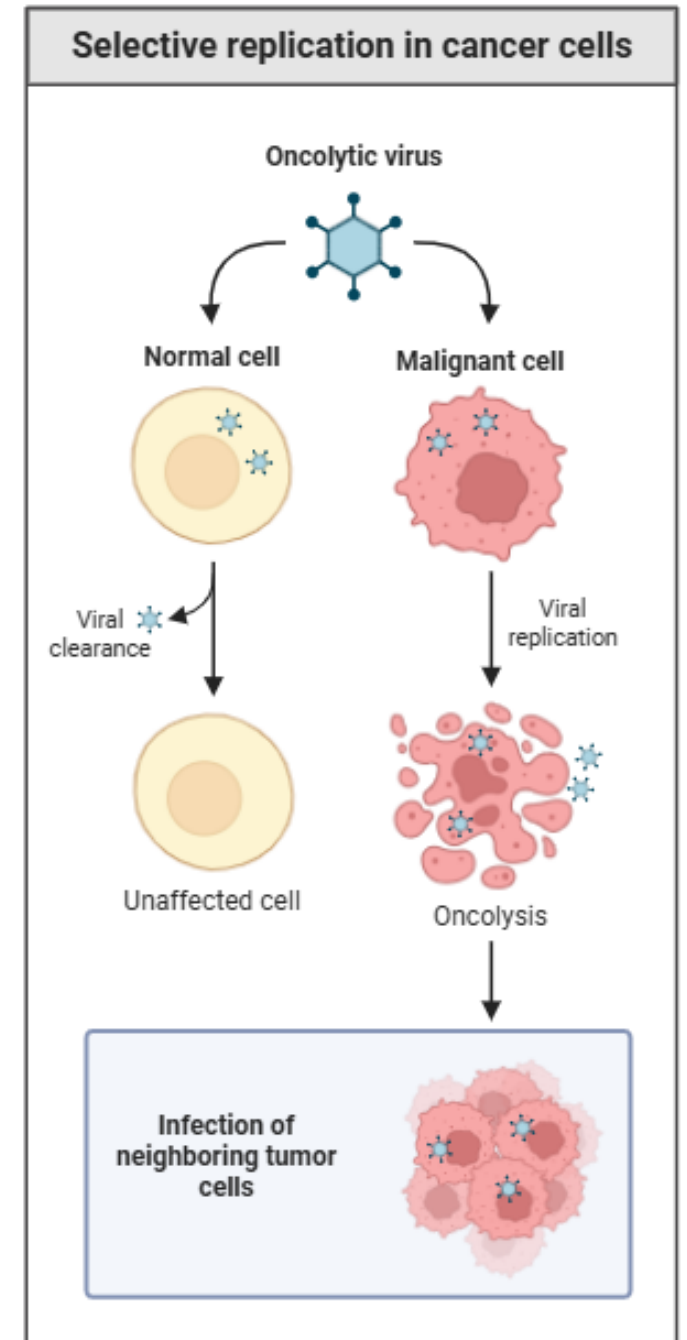
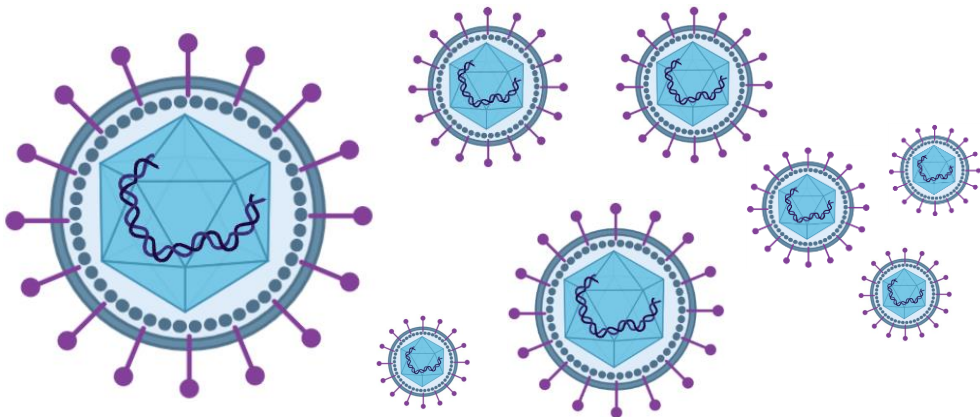
Optimizing oncolytic viruses

Key features:

- ✓ Rapid replication
- ✓ Efficient cell lysis
- ✓ Fast spread between tumor cells
- ✓ **Clinical requirement:**
Can be administered **systemically**

Advantages:

- ✓ Amplifies therapeutic effect
- ✓ Spreads faster than immune response
- ✓ Enables **cell-to-cell transmission**
- ✓ Limits **systemic exposure**



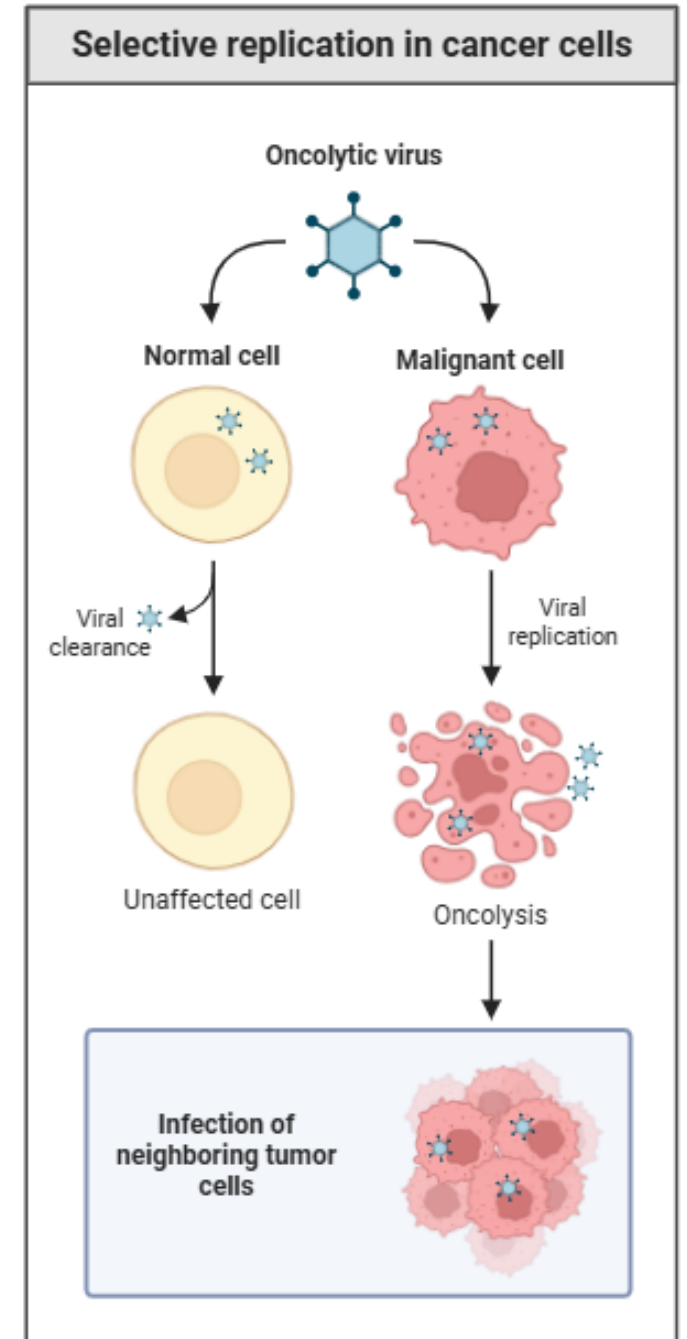
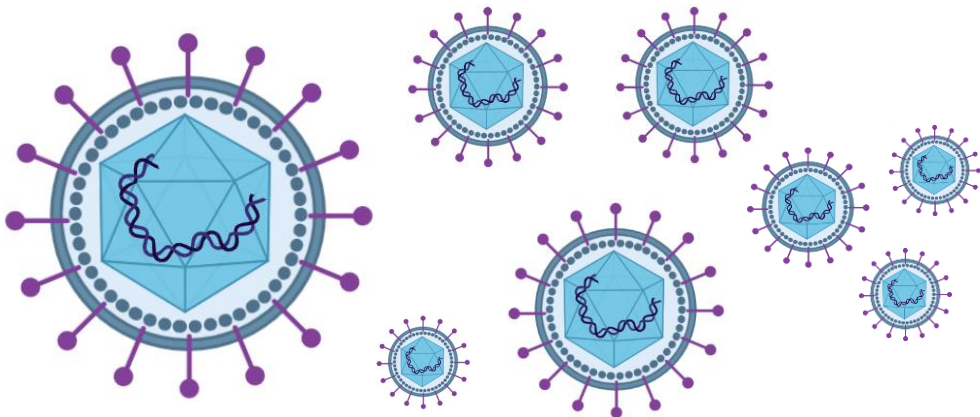
Optimizing oncolytic viruses

Immune function

- ✓ Acts as a **potent adjuvant**
- ✓ Can function as an **anticancer vaccine**
- ✓ Induces **long-term anti-tumor immunity**
- ✓ Helps control **metastases**

Safety

- ✓ Does **not integrate into host genome**
- ✓ Minimizes risk of **genetic recombination**
- ✓ Replicates preferentially in tumor cells



Clinical Status of Oncolytic Virus Therapy

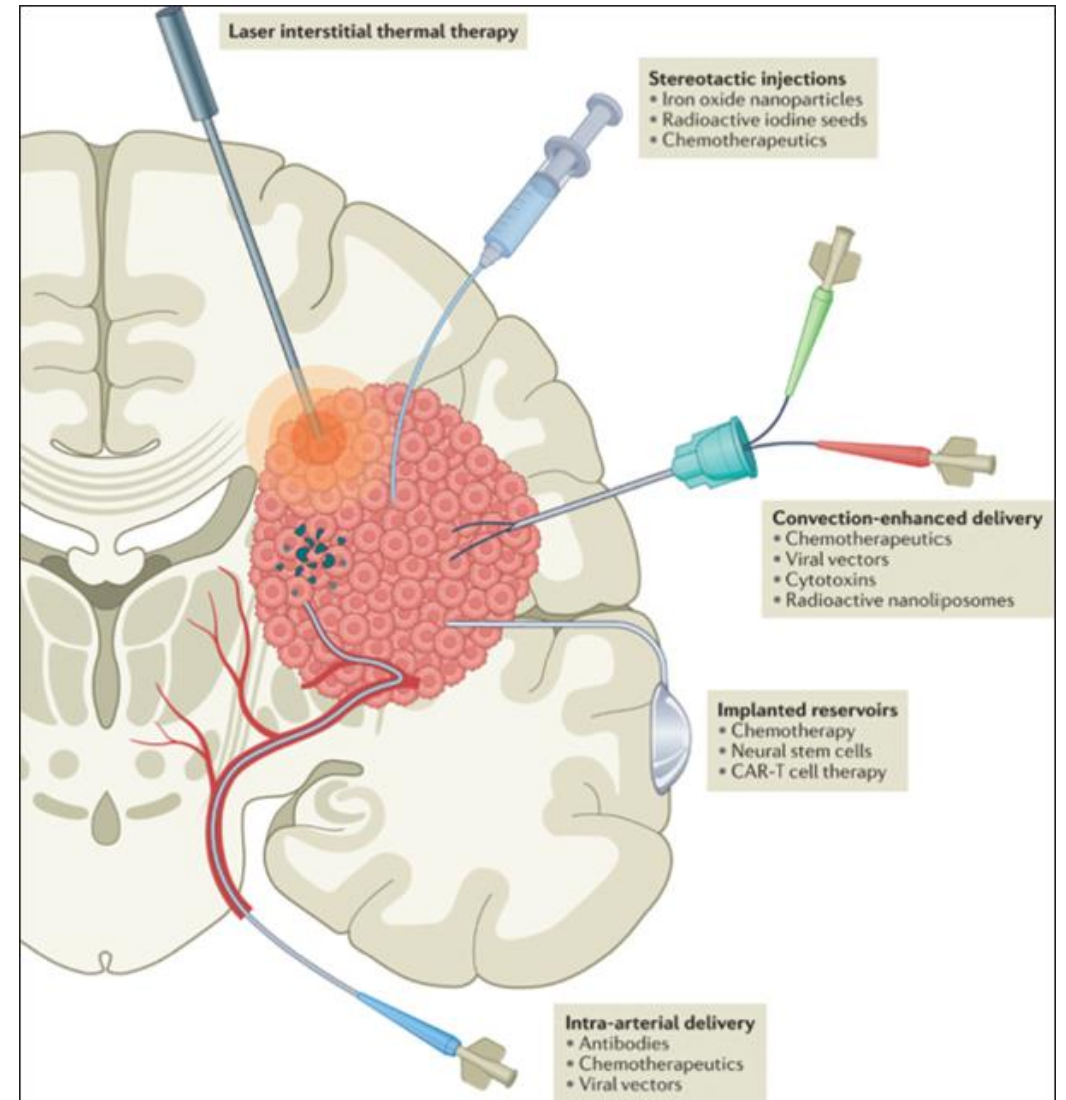
- Approved therapy: T-VEC (Imlygic)
- Modified HSV-1
- Approved for melanoma (FDA & EMA)
- Injected directly into tumors
- Causes tumor lysis + immune activation

The screenshot displays the Imlygic website header with navigation links: "IMLYGIC® Is Different", "IMLYGIC® Results" (underlined), "Treatment With IMLYGIC®", and "Resources and Support". The main content area features the text "IMLYGIC® RESULTS" and "IMLYGIC® takes the fight to advanced melanoma tumors". Below this is a photograph of a skin lesion with a blue circle around it and a blue arrow pointing to it. To the right is a circular graphic with two blue hexagons containing yellow squares. At the bottom, a white box contains the text "IMLYGIC® HAS RESULTS THAT LAST FOR 6 MONTHS OR LONGER¹".

<https://www.imlygic.com/efficacy-clinical-trial-results>

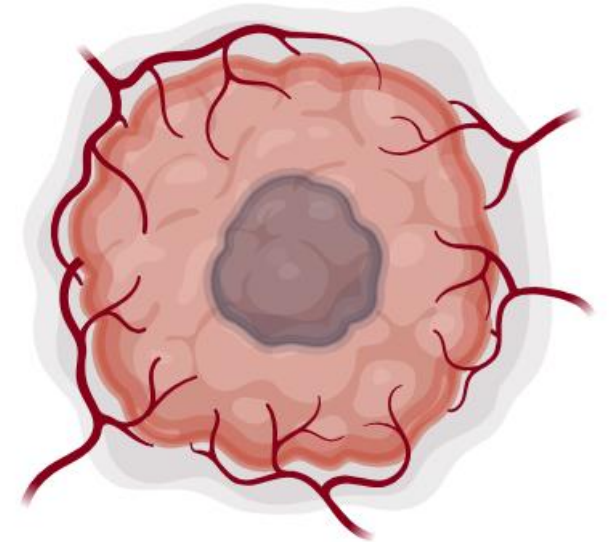
Clinical Status of Oncolytic Virus Therapy

- **Delytact** was approved by the **Japan's Ministry of Health, Labour and Welfare (MHLW)** which granted conditional approval to Daiichi Sankyo's (Japan) oncolytic virotherapy Delytact for the treatment of malignant glioma on 11 June 2021.



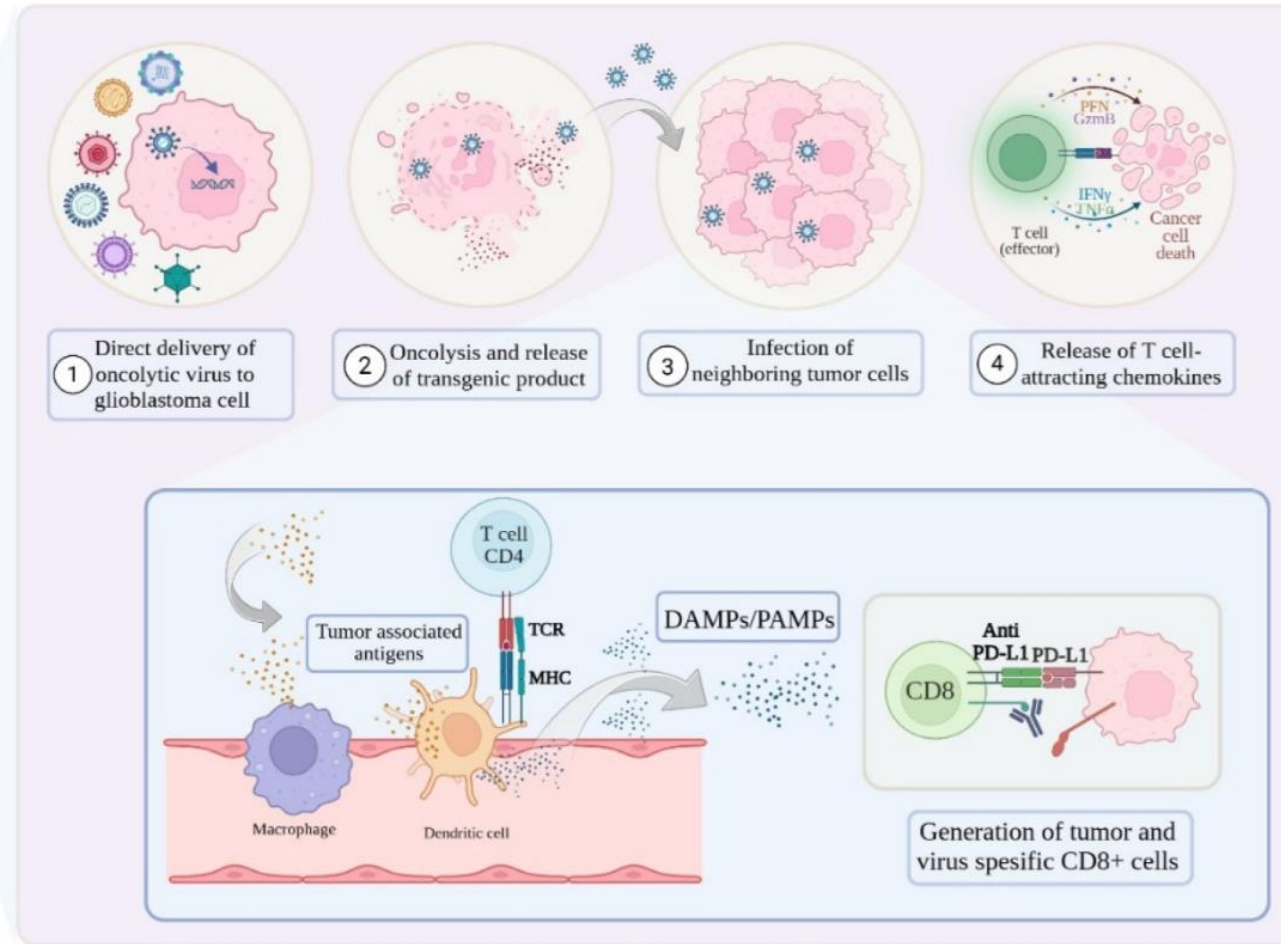
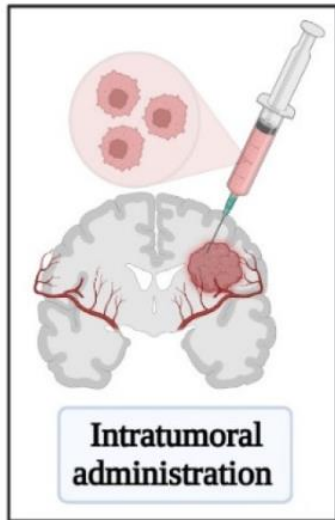
Oncolytic Virotherapy in Glioma Treatment

- Glioblastoma is one of the **most aggressive brain tumors**, with **poor prognosis**. Therefore, **novel approaches** such as oncolytic virotherapy are being actively investigated.
- **Limited effectiveness of:** surgery, radiotherapy, chemotherapy
- **Advantages of Oncolytic Viruses in Glioma**
 - ✓ Selective infection of **tumor cells**
 - ✓ Ability to **cross or bypass BBB**
 - ✓ Induce **tumor cell lysis**
 - ✓ Activate **anti-tumor immunity**
 - ✓ Can be **genetically engineered**



Oncolytic Virotherapy in Glioma Treatment

ONCOLYTIC VIROTHERAPY



Virus-Based Oncolytic Viruses

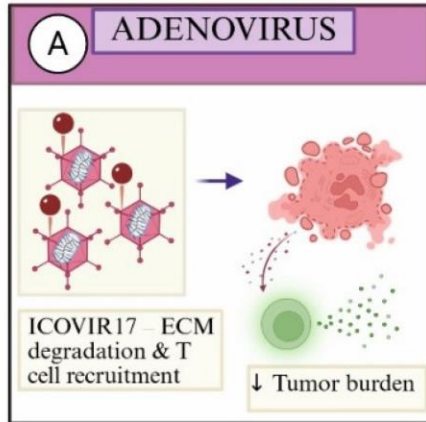


Alomari, O: Oncolytic Therapies for Glioblastoma: Advances, Challenges, and Future Perspectives. *Cancers* **2025**, *17*, 2550.
<https://doi.org/10.3390/cancers17152550>

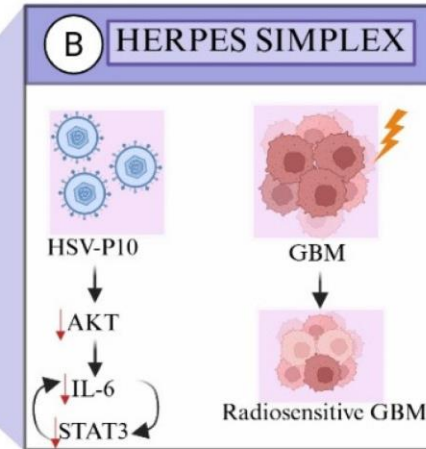
Oncolytic Virotherapy in Glioma Treatment

Mechanistic Overview of Oncolytic Viruses in GBM: A Comparative In Vivo Approach

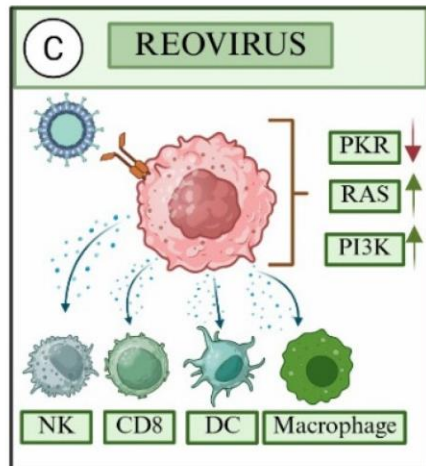
Adenovirus promotes extracellular matrix degradation and T-cell recruitment



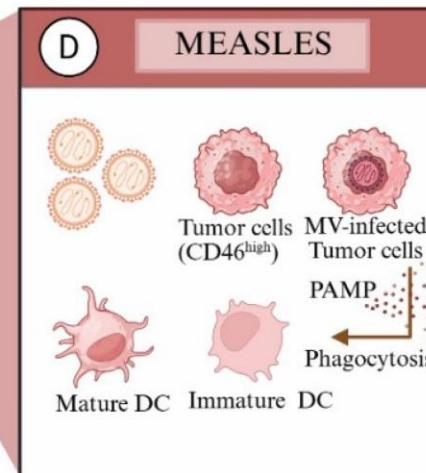
Herpes simplex virus downregulates the AKT/IL-6/STAT3 pathway, sensitizing GBM cells to radiotherapy.



Reovirus selectively replicates in RAS-activated tumor cells by suppressing PKR, activating NK cells, CD8+ T cells, macrophages, and dendritic cells.



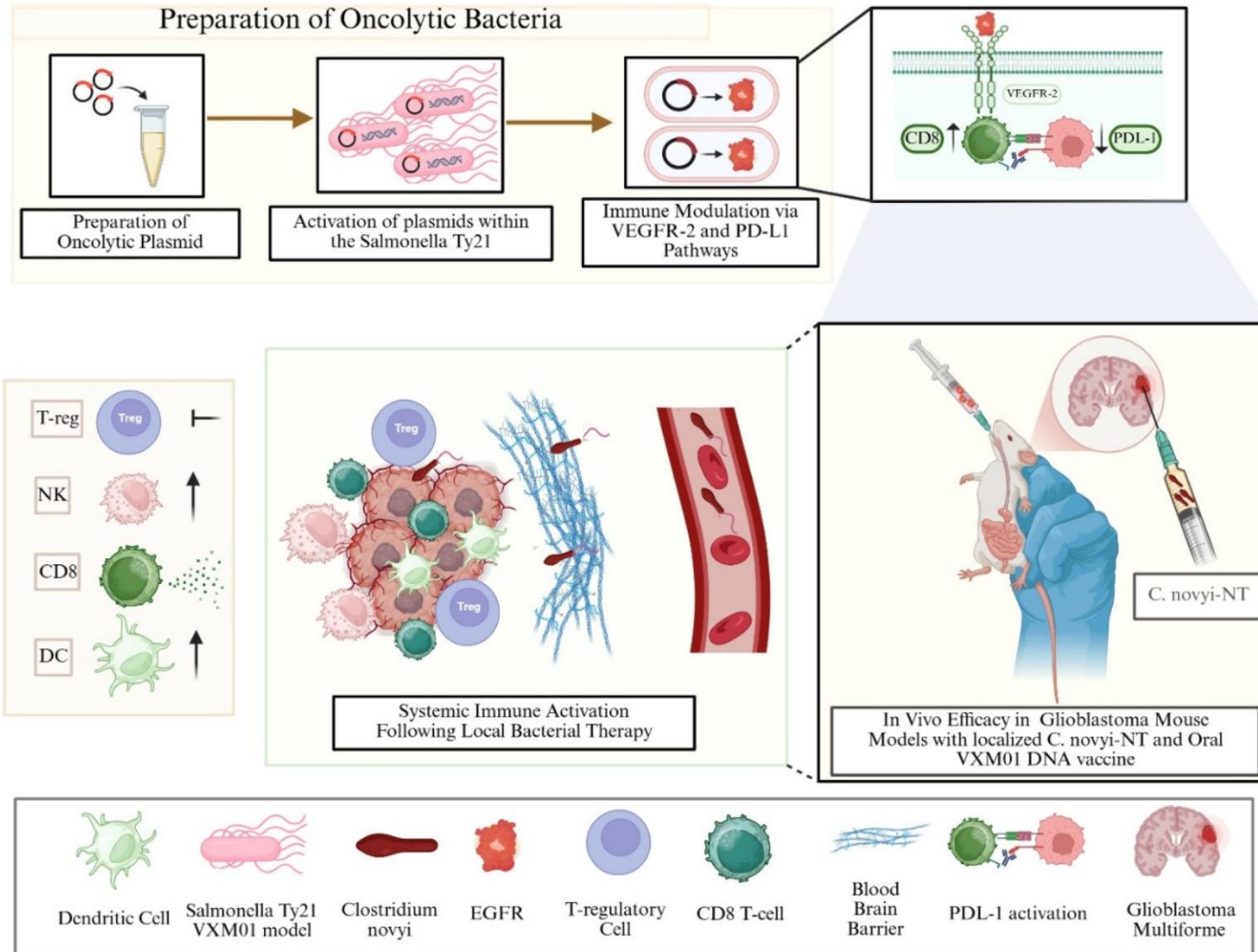
Measles virus infects CD46-high tumor cells, releasing PAMPs and enhancing phagocytosis by dendritic cells.



Intratumoral or systemic viral delivery in GBM mouse models

Non-Viral Oncolytic Strategies

Oncolytic Bacteria for Treatment-Resistant Glioblastoma



Oral **Salmonella**-based VEGFR-2 DNA vaccine, enhances CD8⁺ T-cell responses and reduces PD-L1 expression.

Locally injected ***Clostridium novyi-NT*** germinates in hypoxic tumor cores, inducing direct oncolysis and immune activation

Limitations of Oncolytic Virus Therapy

- **Immune neutralization**

- Viruses are inactivated by **neutralizing antibodies**

- **Rapid clearance**

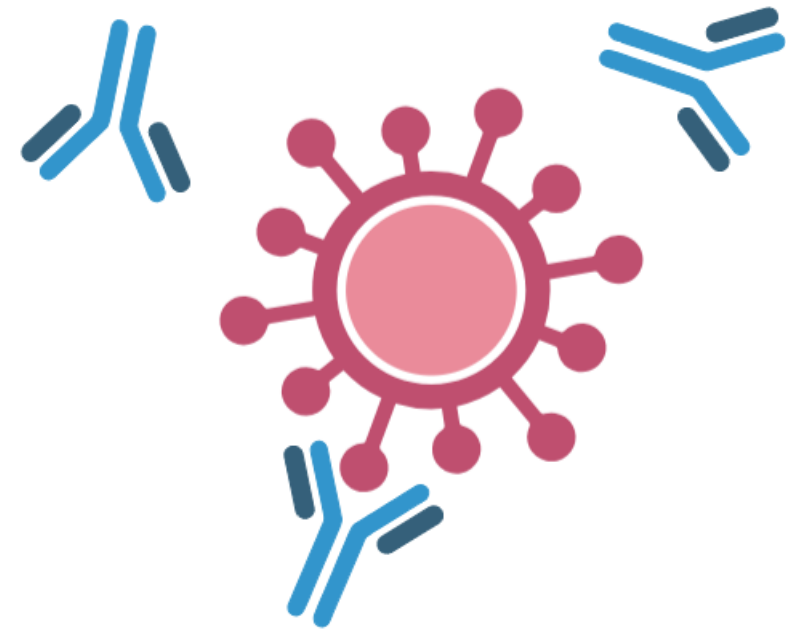
- Removed from bloodstream by **liver (Kupffer cells)**

- **Reduced delivery efficiency**

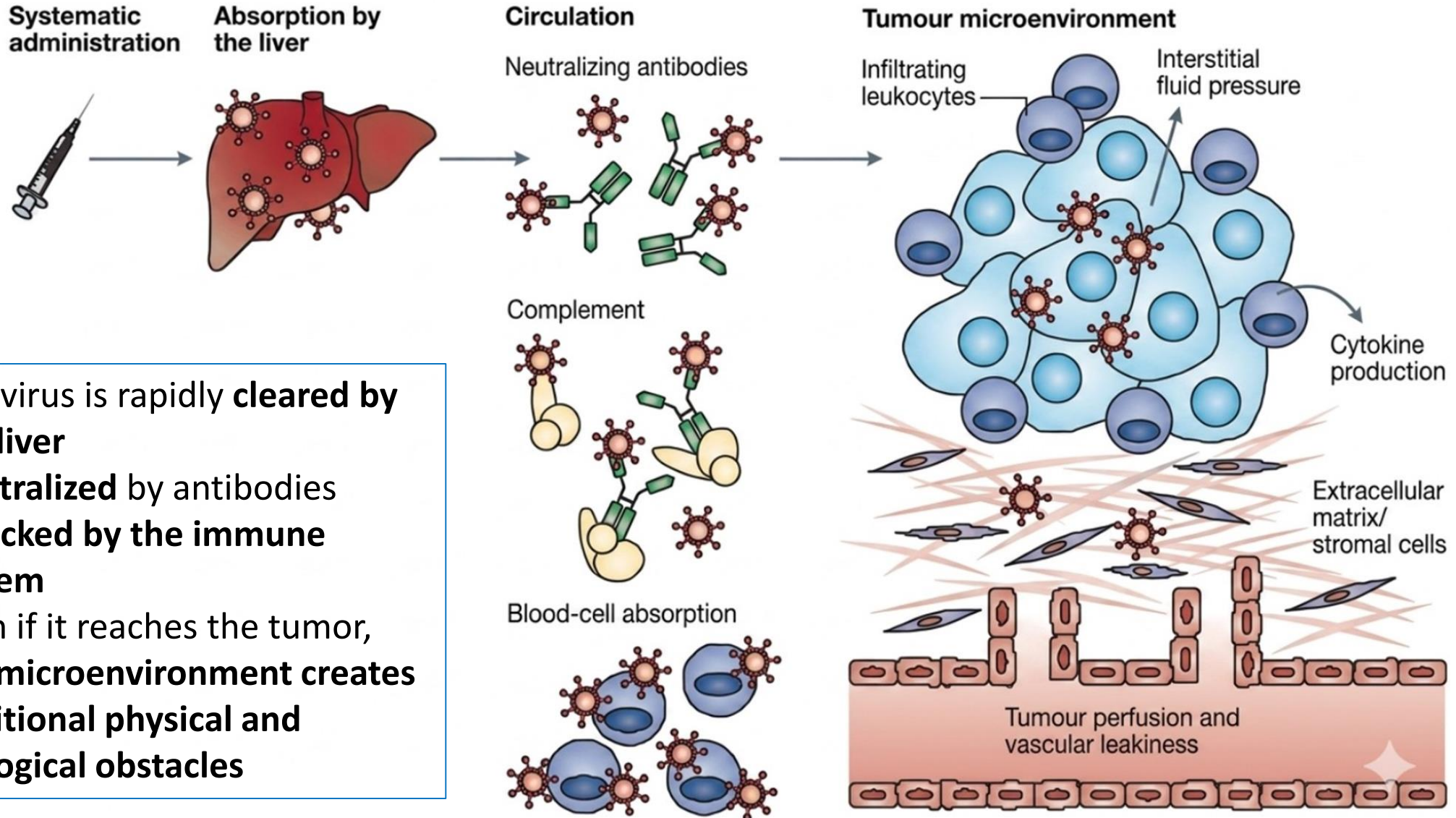
- Limited amount of virus reaches the tumor

- **Clinical implication**

- Systemic administration is challenging
- May reduce overall therapeutic effectiveness



Limitations of Oncolytic Virus Therapy



- The virus is rapidly **cleared by the liver**
- **Neutralized** by antibodies
- **Attacked by the immune system**
- Even if it reaches the tumor, the **microenvironment creates additional physical and biological obstacles**

<https://create.kahoot.it/details/oncolytic-viruses-from-bench-to-bedside/d5076b2c-74d6-41d7-b528-0940f6a1f003?drawer=>