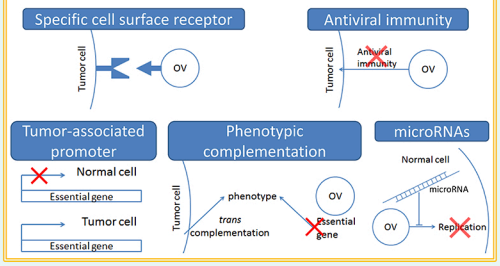
VIROTHERAPY:
Using virus for the cancer treatment

Universitat Autònoma de Barcelona
Queralt Bonet Rossinyol
Bachelor's Degree in Microbiology

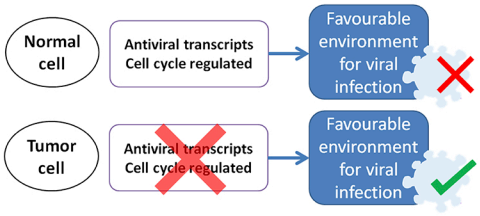
Nowadays, cancer is a matter of concern due to its large prevalence worldwide. According to WHO (World Health Organization), there are 14 million of new cases each year and this alarming amount is expected to increase. The high mortality rate is an evidence of the limitations of the current therapies, such as chemotherapy, radiotherapy or surgery. Therefore, novel therapies are needed and virotherapy is a promising one. This idea began to take hold in the 1950s, when the first trials with oncolytic viruses (OVs) where done. The results were encouraging, however, the interest diminished. At the present, the attention and trials of virotherapy are increasing.

1. MECHANISMS OF ACTION

TARGETING OVs TO CANCER CELLS[1]



SURVIVAL INTO CANCER CELL[2]



CELL-DEATH MECHANISMS

Direct	• Apoptosis • Necrosis • Viral overload
Indirect	• Destruction of tumor vessels • Amplification of specific anticancer immune responses • Armed OVs

2. TYPES OF OVs[3]

OBTAINING OVs

Rational design

❑ Using the "Hallmarks of cancer" and targeting tumor cells by phenotypic complementation or tumor-specific promoters.

Bioselection

Library of chimeric OVs → Select OVs capable of lysing cancer cells efficiently → Enrich the library → Screen this OVs to normal cells → Select candidates for development

→ The precise mechanisms may be unknown.

INDICATIONS OF OVs

❑ OVs currently in development have a **broad spectrum**, against both haematological and epithelial malignancies. Biomarkers are used to determinate if the patient is appropriate for the virotherapy.
❑ This therapy can be used after surgery, maintaining active the natural killers (NK).

3. DELIVERING OVs TO THE TUMOR[4]

ADMINISTRATION ROUTE

The aim of virotherapy is to achieve a **systemic delivering**, reaching disseminated tumors. The most promising routes are:

- Intratumoral injection
- **Intravenous injection:**

The OVs have to surpass several barriers to exceed the viremic threshold and become effective.

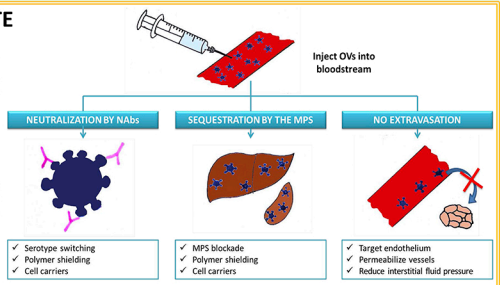


Image 1. Issues and solutions of the intravenous injection. Modified from [4]. Abbreviations used: mononuclear phagocytic system (MPS), neutralizing antibodies (NAbs).

4. PHARMACOLOGIC TRIALS[3]

T-VEC
Positive results where shown in the phase III trial in patients with metastatic malignant melanoma. Overall survival was 23.2 months.

JX-594
The obtained results in phase I trial don't seem to be satisfactory.

PROSTVAC-VF
The phase II trial in patients with metastatic castrate-resistant prostate cancer showed an 8.5 month overall survival benefit.
It has entered in phase III.

❑ OVs don't seem to present important adverse effects. However, the variability among the patients and the unpredictable immune response are an issue to predict the action of OVs.
❑ The toxicity doses are much higher than therapeutic doses.
❑ To guarantee OVs' safety, several elements must be considered, such as tropism, mutability and capacity for evolution, immunomodulatory gene products, transmissibility, prevalence of antiviral immunity in the population and availability of drugs or antiserum to eliminate unwanted or persistent infections.

Table 2. Assessment of advantages and disadvantages of virotherapy.

ADVANTAGES	DISADVANTAGES
Tumor selectivity	Not many trials to show efficacy
High safety	Transmission to a sane person*
Not important adverse effects	Uncontrolled infection*
Systemic treatment	Issues in the intravenous injection
Combined administration	Mutability, capacity for evolution*
Immune system stimulation	
Amplification of the active agent within de tumor	

*Very unlikely event

5. COMBINATED THERAPY

OVs administered with other therapeutics can produce synergic effects and enhance the efficacy. OVs can be used to sensitize cancer cells to other treatments or in resistant cells.[3]

- OVs and chemotherapy
- OVs and checkpoint inhibitors
- OVs and radiotherapy
- OVs and anti-angiogenic therapy
- OVs and monoclonal antibodies
- OVs and cytokines
- OVs and chemokines
- OVs and OVs

Rigvir®

Rigvir® is the first therapeutic based on virotherapy available for the treatment of melanoma, subcutaneous metastases of melanoma, prevention of relapse and metastases after surgery.
It was approved in Latvia (2004), Georgia (2015) and Armenia (2016).[5]

Table 1. OV used in Rigvir®.

Family	*Picornaviridae*
Genera	*Enterovirus*
Group	Enteric Cytopathic Human Orphan (ECHO)
Type	7
Strain	ssRNA +

✓ **No pathogenic**
✓ **Genetically stable**
✓ **No transmissible**
✓ **Personalized treatment**

Image 2. Vial of Rigvir® (2 mL). It contains 10^6 $TCID_{50}$ /mL of ECHO-7 and sodium chloride. From rigvir.com

TREATMENT: During 3 years or more.
EFFICACY: The regression of the tumor is observed in some patients. However, more trials are needed.
SAFETY AND TOXICITY: It seldom produces adverse effects. The most common are fever, pain in the administration zone, somnolence and diarrhea.
MECHANISM OF ACTION: Direct cell death and amplification of anticancer immune response. The target is the CD55/DAF-3 protein, which regulates the complement system by binding anchored GPI protein. In the presence of virus, complement system is not blocked and can damage the cancer cell.

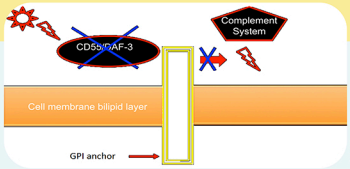


Image 3. Mechanism of action of ECHO-7.[6]

CONCLUSIONS

❖ Virotherapy provides a treatment whose specific target are the cancer cells. Although some viruses have innate tropism against tumor cells, this can be obtained by engineering.
❖ Cancer cells have inactivated antiviral responses, therefore OVs are able to survive in them.
❖ The lysis of the cells is achieved by direct cytotoxicity or stimulating the immunity system.
❖ Although being quite safe, more clinical trials are required to properly determine its effectiveness.
❖ The most promising OVs delivery is the intravenous, in this way a local treatment could be applied to a spread disease. This fact implies that the patient who has already been in contact with the virus, then develops NAbs against it.
❖ The therapy must be customized, studying each patient case individually. Moreover, there is the possibility of being used combined with other therapies acting in synergy.

Hence, virotherapy is considered a promising future treatment. Although further research on tumoral cells biology is required to find new targets where OVs could be directed, or investigate other virus strains that could act as oncolytic agents.

1. Villanueva E, Navarro P, Rovira-Rigau M, Sibilo A, Méndez R, Fillat C. Translational reprogramming in tumour cells can generate oncoselectivity in viral therapies. Nat Commun. 2017; 8:14-33 // 2. Seymour L, Fisher K. Oncolytic viruses: finally delivering. Br Journal Cancer. 2016; 114:3, 23-34. // 3. Turnbull S, West E, Scott K, Appleton E, Melcher A, Ralph C. Evidence of oncolytic virotherapy: Where have we got to and where are we going? Viruses. 2015; 7:6, 291-312. //4.Russell S, Peng K-W, Bell J. Oncolytic virotherapy. Nature Biotechnology, Nature Publishing Group. 2013; 11:5, 15-22. // 5. Donina S, Strele I, Proboka G, Auzins J, Alberts P, Jonsson B. Adapted ECHO-7 virus Rigvir immunotherapy (oncolytic virotherapy) prolongs survival in melanoma patients after surgical excision of the tumour in a retrospective study. Melanoma Res. 2015; 25:42, 1-6. // 6. Babiker H, Raiz I, Husnain M, Borad M. Oncolytic virotherapy including Rigvir and standard therapies in malignant melanoma. Oncolytic Virotherapy. 2017; 6:1, 1-8.