ONCOLYTIC VIRUSES AS TARGETED THERAPY FOR PANCREATIC DUCTAL ADENOCARCINOMA

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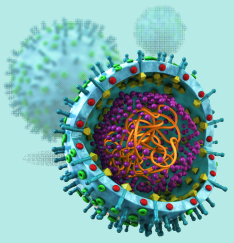


OBJECTIVES

- To discuss the therapeutic potential of **Oncolytic Viruses (OVs)** to overcome the limitations of current therapies against **Pancreatic Ductal Adenocarcinoma (PDAC)**.
- To provide a global vision of the state-of-the-art of virotherapy against PDAC.
- To illustrate a paradigmatic case of rationally engineered OV against PDAC from a critical outlook.

METHODOLOGY

This **Bibliographic Review** is based on recent high impact journals, clinical trials, patents and official websites, to provide a critical vision of the state-of-the-art of OVs against PDAC. Some experts were contacted (special mention to **R. Alemany** (VCN Biosciences), **A. Baker** (Cardiff University), **S. Borrós** (Sagetis Biotec)) to enrich the research with first-hand information.

PDAC: A CHALLENGE FOR MEDICINE

Pancreatic cancer is predicted to be the second deadliest cancer malignancy within the next decade in western world. **Pancreatic Ductal Adenocarcinoma (PDAC)** is the major subtype of pancreatic cancer. The median survival is about **6 months** and the 5-year survival rate is lower than **5%**. The tumour is characterised by a **rapid progression**, **invasiveness** and **metastasis**.

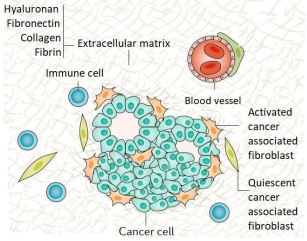


Figure 1: PDAC microenvironment. It encloses a fibrotic stroma consisting of cellular and non-cellular compounds. *Adapted from [1].*

Physical barrier

The dense, fibrotic and hardly penetrable desmoplastic stroma (**Fig. 1**) accounts about 80% of total tumour mass. It impedes **drug extravasation**, increases **vessel compression** and **hypovascularity** and creates an **inhospitable environment for immune cells**.

Immune evasion

PDAC tumour microenvironment (TME) (**Fig. 1**) consists of **immune suppressor cells** that inactivate T-cell anti-tumour responses. Other causes for immune evasion are: a **defective tumour antigen presentation**, overexpression of **immunosuppressive factors**, **low levels of tumour infiltrating T-lymphocytes**, **T-cell evasion** and **tolerance**.

Chemoresistance

Only 5-10% of patients respond to first-line chemotherapy with Gemcitabine. Resistance occurs due to **deregulated pathways**, increased **Epithelial-to-mesenchymal transition** (EMT), **drug dependent alterations** and **innate resistance**.

The reasons for PDAC to be one of the most difficult-to-treat cancers are: the aggressive pathobiological features, the heterogeneity, the difficult early detection, the few reported bio-markers, the difficult surgical resection.

ONCOLYTIC VIRUSES

Rigvir (2004, Latvia) → Oncorine (2005, China) → T-VEC (2015, US, EU)

Oncolytic viruses are genetically engineered viruses to selectively infect and replicate in cancer cells, provoking their lysis and triggering anti-tumour immunity (**Fig. 2**). **Desirable** features are: **low pathogenicity, large and non-integrative genome, efficient replication and easily modifiable capsid**.

Table 1. Therapeutic effectiveness of Oncolytic Viruses for PDAC.

Treatment	Gem	Gem + Nab-P	VCN-01	Reolysin	ONYX-015	HF10	TNFerade
			Gem + Nab-P	Gem	Gem	Gem	Gem
n	430	431	10	29	21	9	187
DCR (%)	NA	NA	100	82.76	47.62	77.78	82.50
ORR (%)	7	23	40	3.45	19.05	33.33	8.20
PFS (months)	3.7	5.5	9.9	3.4	6	6.3	6.8
OS (months)	6.7	8.5	11	10.2	7.5	NA	10

Gem: Gemcitabine; Nab-P: Nab-Paclitaxel; n: number of enrolled patients; DCR: Disease Control Rate; ORR: Overall Response Rate; PFS: Progression Free Survival; OS: Overall Survival; NA: Not available. *Results from ClinicalTrials.gov.*

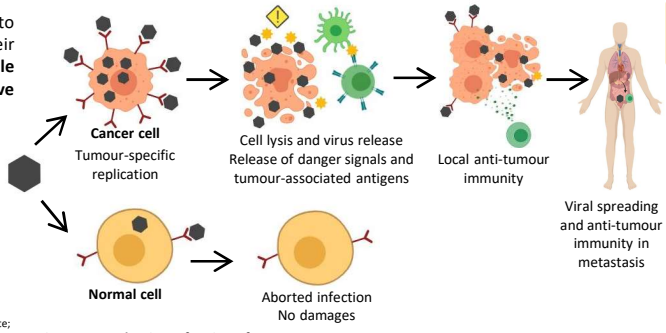


Figure 2: Mechanism of action of OVs.

3. VIRAL ENGINEERING to overcome OVs limitations

Internalization selectivity

Capsid proteins engineering to target specific ligands of PDAC

Replication selectivity

Gene deletion, tumour-specific promoters, tumour-specific miRNAs.

Transgene expression

Immunomodulators (chemokines, cytokines, check-point inhibitors), suicide genes, tumour-associated antigens, antibodies, Bispecific T-cell engagers, matrix degradation enzymes.

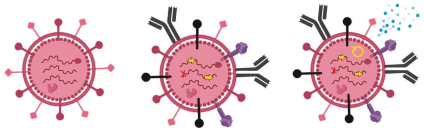
1. ADVANTAGES

OVs advantages in comparison to current treatments render them attractive candidates to overcome the challenging barriers of PDAC.

- Ability to counteract the **immunosuppressive TME**.
- **Self-amplification** and **spread**, killing **metastasis** and **uninfected cells**.
- **Immunogenicity**: T-cell recruitment + activation + infiltration.
- **Defective antiviral machinery** in PDAC cells enhances viral persistence.
- **Synergy** with other treatments (immune/chemotherapies).
- Viral capsid engineering increases targeting and reduces toxicity.
- **Antigen agnostic** approach.

2. LIMITATIONS

- Lack of relevant **animal models** (Viral species-specificity)
- **Tropism**: viruses are not natural tumour selective.
- Antiviral response + Acquired **immunity** (antibodies).
- **Systemic administration** is hindered.
- Lack of validated **biomarkers** of OVs.
- Tumour **recurrence**: not all cells will be killed.
- Costly vector **production** and **manufacturing**.
- Horizontal **transmission**.



1st generation: Natural tumour selectivity or laboratory passages

2nd generation: Tumour targeting by capsid engineering + Selective replication by genomic edition

3rd generation: Capsid engineering + Genomic edition + Transgene expression

VCN-01: A RATIONAL DESIGN

VCN-01 (VCN Biosciences, Barcelona) is an OV rationally engineered to overcome virotherapy limitations. Preliminary data from a Phase I clinical trial of **VCN-01 plus gemcitabine/nab-paclitaxel** reported the best results among the published clinical outcomes for other OVs for PDAC (**Table 1**). They also prove VCN-01 efficiency and modest improvement compared to chemotherapy alone.

Selective Internalization

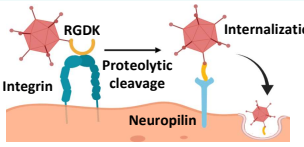


Figure 3: Integrin-mediated internalization of VCN-01. KKTK → RGDK substitution within the capsid protein decreases liver transduction and increases PDAC cells internalization. *Adapted from [2].*

Selective Replication

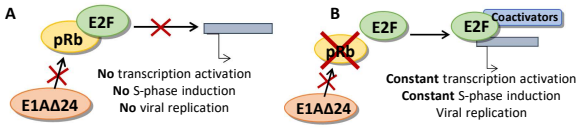


Figure 4: VCN-01 selective replication due to gene deletion. Deletion in the pRb-binding domain of E1A gene (Δ24) prevents viral replication in healthy cells while maintains it in tumour. In normal cells (A), transcription factor E2F is restrained by retinoblastoma protein (pRb), but when E1A binds to pRb, E2F releases and induces viral replication. In cancer cells (B), mutations in pRb impede E2F restraint, promoting cell proliferation. *Adapted from [3].*

Transgene expression

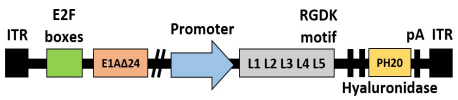


Figure 5. Genomic scheme of VCN-01 oncolytic virus. Hyaluronidase expression promotes viral tumour penetration by breaking down the hyaluronan of the extracellular matrix. ITR: Inverted Terminal Repeat; E2F boxes: E2F-binding sites; L: Late genes; pA: Polyadenylation site. *Ceded by R. Alemany.*

CONCLUSIONS AND FUTURE PERSPECTIVES

- **Oncolytic Viruses** are a hopeful strategy to overcome the challenging barriers of PDAC by **modifying the TME**, **counteracting the immunosuppression** and **synergizing with chemotherapeutics**.
- Early phase clinical results proved **OVs efficiency** but not significant improvement in patient survival. Thus, larger trials are required. Moreover, ongoing clinical trials will provide **information that cannot currently be obtained in pre-clinic studies**.
- Further research should be focused on exploiting **viral engineering** and **naturally tumour selective virus**.
- Virotherapy is not the ultimate cure for PDAC but an approach to consider in combination therapies.

RELEVANT REFERENCES

1. **Kobayashi, H., Enomoto, A., Woods, S., Burt, A., Takahashi, M. and Worthley, D. (2019).** Cancer-associated fibroblasts in gastrointestinal cancer. ***Nature Reviews Gastroenterology & Hepatology***, 16(5), pp.282-295.
2. **Rodriguez, A., Gimenez, M., Rojas, J., Moreno, R., Bazan, M., Cascallo, M. and Alemany, R. (2014).** Safety and Efficacy of VCN-01, an Oncolytic Adenovirus Combining Fiber HSG-Binding Domain Replacement with RGD and Hyaluronidase Expression. ***Clinical Cancer Research***, 21(6), pp.1406-1418.
3. **Baker, A., Aguirre, C., Halldén, G. and Parker, A. (2018).** Designer Oncolytic Adenovirus: Coming of Age. ***Cancers***, 10(6), p.201.
4. **Nattress, C. and Halldén, G. (2018).** Advances in oncolytic adenovirus therapy for pancreatic cancer. ***Cancer Letters***, 434, pp.56-68.
5. **Bommareddy, P., Shettigar, M. and Kaufman, H. (2018).** Integrating oncolytic viruses in combination cancer immunotherapy. ***Nature Reviews Immunology***, 18(8), pp.498-513.
6. **Neoptolemos, J., Kleeff, J., Michl, P., Costello, E., Greenhalf, W. and Palmer, D. (2018).** Therapeutic developments in pancreatic cancer: current and future perspectives. ***Nature Reviews Gastroenterology & Hepatology***, 15(6), pp.333-348.