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Engineering Viruses to Kill Cancer: How Oncolytic Virotherapy Combines Tumor Lysis With Immune Activation

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A newly published review synthesizing the engineering, mechanisms, and clinical translation of oncolytic viruses (OVs) highlights how a once-niche concept has matured into a recognized pillar of cancer immunotherapy [1, 2] . Oncolytic viruses are native or genetically modified viruses that preferentially infect and replicate inside malignant cells, destroying them directly while triggering a broader anti-tumor immune response [2, 3] . Only a handful of OVs have won regulatory approval worldwide, but dozens of engineered candidates are in clinical trials, often paired with immune checkpoint inhibitors [1, 2] .

Two Mechanisms in One Therapy: Lysis and In Situ Vaccination

Oncolytic viruses attack tumors on two fronts [2, 3] . First, they exploit the signaling defects that cancer cells accumulate -- most notably impaired interferon antiviral responses -- to replicate selectively in tumor tissue, eventually bursting (lysing) the infected cell and releasing new viral particles that spread to neighboring tumor cells.

Second, and arguably more important clinically, tumor-cell death caused by viral infection is immunogenic . Dying cells release tumor-associated antigens, neoantigens, and danger signals (damage-associated molecular patterns), which recruit and activate dendritic cells, cytotoxic CD8 + T cells, and natural killer cells [1, 2] . In effect, the tumor becomes its own personalized vaccine , converting an immunologically "cold" microenvironment -- one with few infiltrating T cells -- into an inflamed, "hot" one that is more responsive to immunotherapy [1, 2] .

Engineering Strategies: Safety, Selectivity, and Armed Payloads

Natural viruses are rarely ideal cancer drugs, so developers reprogram them along three axes [2, 4] :

* Selectivity by deletion. Deleting viral genes that normally let the virus survive in healthy cells -- such as the neurovirulence gene ICP34.5 in herpes simplex virus 1 (HSV-1) -- restricts productive replication to cancer cells that compensate for the missing function [3, 4] .

* Selectivity by control elements. Placing essential viral genes under tumor-specific promoters (for example, the telomerase reverse transcriptase promoter) or adding microRNA target sites that silence the virus in normal tissue such as the liver keeps replication confined to malignant cells [4] .

* Arming with transgenes. Next-generation OVs carry payloads that amplify the immune response locally: cytokines such as GM-CSF, checkpoint-blocking antibodies , T-cell engagers, or enzymes that degrade the dense extracellular matrix of fibrotic tumors

[1, 2, 4] . Delivering these molecules inside the tumor limits the systemic toxicity seen with intravenous dosing.

Clinical Translation: Approved Agents and Combination Therapy

| Agent | | Viral Backbone | | Key Engineering | | Setting |

| Talimogene laherparepvec (T-VEC) | | HSV-1 | | ICP34.5 deletion; GM-CSF transgene | | First FDA-approved OV; advanced melanoma [5] |

| Teserpaturev (G47Delta) | | HSV-1 | | Triple-mutated, multi-gene deletion | | Approved in Japan; glioblastoma [6] |

| H101 | | Adenovirus | | E1B-region deletion | | Approved in China; head and neck cancer [2] |

Because oncolytic viruses draw T cells into tumors and raise PD-L1 expression, combining them with immune checkpoint inhibitors has become a central clinical strategy for patients who do not respond to checkpoint blockade alone [1, 2, 5] .

Remaining Bottlenecks

Several obstacles keep OVs from broader use [1, 2] . Intravenously delivered viruses are cleared by neutralizing antibodies, complement, and liver sequestration before they reach distant tumors, which is why most approved products are injected directly into lesions. Dense tumor stroma limits viral spread, and manufacturing clinical-grade, replication-competent viruses at scale is complex and costly. Active research directions include carrying viruses inside stem cells or immune cells as "Trojan horses," using CRISPR and advanced reverse genetics for more precise genome design, and developing biomarkers to select patients whose tumors are permissive to infection [1, 2] .

References & Primary Sources

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