Oncolytic Virotherapy: Targeting Cancer Stem Cells
Cancer Stem Cells (CSCs) or Cancer Initiating Cells (CICs)

A consensus of five defining criteria has been established to affirm the existence of CICs:

- Organize self-renewing, anchorage-independent spheres
- Restriction to a small minority of the total tumor population
- Reproducible tumor phenotype
- Expression of distinctive cell surface markers, permitting consistent isolation
CSC Markers and Mechanisms of Resistance to Therapy

• Increased ATP (adenosine triphosphate)-binding cassette (ABC) transporters known as drug efflux pumps.

• Increased aldehyde dehydrogenase (ALDH) activity that can serve as a detoxification enzyme capable of metabolizing chemotherapeutics like cyclophosphamide for improved resistance.

• Increased expression levels of O⁶-methylguanine-DNA-methyltransferase (MGMT) that repairs O⁶-alkyl lesions in DNA, rendering CSCs resistant to DNA alkylating agents.

• Upregulated anti-apoptotic gene expression and constitutively active signaling pathways involved in cell survival, including PI3K/AKT and Ras pathways.

• Expression of CD133, prominin-1, is involved in regulation of MAPK and AKT signaling pathways.

• Expression of CD44, a prominent cell adhesion marker (CD44⁺CD24⁻/low); CD117, known as c-kit that binds to stem cell factor. Signaling through CD117 plays a role in cell survival, proliferation, and differentiation.

• Increased anaerobic glycolysis and defective aerobic glucose metabolism for resistance to oxygen deprivation.
Miroenvironment and the CSC Niche

- Hypoxic zones – develop when tumor cell division outpaces angiogenesis, limiting efficient oxygen exchange. In these zones, specialized oxygen-sensing transcription factors called hypoxia-inducible factors become activated and induce expression of gene products, such as notch proteins, that enhance cell survival and differentiation or chemokines that recruit endothelial progenitors.

- The perivascular region – is important for CSC development as it contains endothelial cells necessary for vascular development and increased metastatic dissemination. The perivascular niche also has a distinct extracellular matrix (EMC) protein profile favorable to CSC retention and regulation, including matrix metalloproteinases.

- Invading tumor front – is characterized by increased chemotactic migration of cells to stromal-derived factor (SDF-1/CXCL12 chemokine), which is concentrated in tumor invasive margins. This chemokine is involved in recruitment of CXCR4-expressing CSCs as well as and immunosuppressive cells.

- Immunosuppressive networks – suppressive immune cells that directly suppress antitumor immunity. They consist of:
  - tumor-associated macrophages (TAMs) and myeloid-derived suppressor (MDSCs),
  - T regulatory cells (Tregs),
  - IL-10 cytokine-producing CD8+ T cells.
Oncolytic virotherapy mechanism of action: viral replication, cell killing, virus release and spread within cancer tissue but not normal tissues.

**Oncolytic virotherapy**

**ARMED oncolytic virotherapy**
## Properties of the three best-studied family of oncolytic viruses used in clinical trials

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<thead>
<tr>
<th>Properties:</th>
<th>pros</th>
<th>cons</th>
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<tr>
<td><strong>Adenovirus</strong></td>
<td>Wide host-cell range</td>
<td>CAR expression on tumor and normal cells</td>
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<td>Large genomic capacity</td>
<td>Preexisting antiviral immunity</td>
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<td>Induction of danger signals</td>
<td>Rapid virus sequestration by Kupffer cells</td>
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<tr>
<td><strong>Vaccinia virus</strong></td>
<td>Broad-spectrum infectivity</td>
<td>Preexisting antiviral immunity</td>
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<td>Large genomic capacity</td>
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<td>Replicates in cytoplasm</td>
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<td>Ability to travel through blood</td>
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<td>Available antiviral drugs</td>
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<td></td>
<td>Initiation of danger signals</td>
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<tr>
<td><strong>Herpes Simplex virus</strong></td>
<td>Wide host-cell range (neurotropism)</td>
<td>Poor intratumoral penetration/inefficient virus replication</td>
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Limitations of Oncolytic Virotherapy

- Inefficient systemic delivery of the virus to tumors
- Inefficient replication in tumor cells and poor intratumoral spread
- Virus replication in normal cells
- Toxicity
- Immune clearance may reduce oncolytic effects
- Insufficient single agent potency due to limited understanding of the viral interaction with different elements within the context of tumor stroma

Future Goals:

- Improve clinical tolerability and efficacy
- Improve tumor selectivity with tropism-modifying strategies
- Enhance intratumoral penetration
- Improve systemic delivery for treatment of metastatic cancer (minimize virus sequestration, protect form neutralizing antibodies, increase cellular penetration)
- Induce innate and adaptive immunity
- Attack and kill cancer stem cells/cancer initiating cells
Oncolytic virotherapy is a new strategy to reduce tumor burden through selective virus replication in proliferating cells.

Oncolytic viruses belong to many families. They have undergone different modifications to enhance tumor selectivity, improve intratumoral replication, modify immune responses, enhance vascular delivery, and express antitumorigenic genes that function independently of viral replication.

Recent advances include preclinical proof of feasibility, the development of strategies to monitor virus spread detect micrometastases, and clinical trials that document tolerability and effectiveness.

Current efforts have favored intratumoral delivery, but systemic delivery is required for the treatment of metastatic disease. Strategies to increase specific tumor penetration, minimize virus sequestration in the liver and spleen, evade neutralization by serum factors, and enhance vascular penetration are under investigation.
…..and the winners are:

- viruses that lyse CSCs
- viruses that stimulate anticancer immunity
- viruses that can be delivered intravenously and eradicate metastatic dissemination
- viruses that prevent the emergence of resistant tumor variants
- viruses with low toxicity at clinically effective dose
- viruses with broad host-range spectra
thank you...,