Breakthroughs in Virotherapy: Sarcomas as the Next Target

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Shedding Old Paradigms:
Developing Viruses to Treat Cancer

- Viruses destroy tissue
- Harness this destructive power for cancer therapy
When Bad Bugs Go Good

By ALICE PARK

LIKE A SEAGULL ON THE HUNT, THE VIROLOGIST TAUGHT THE DISEASE'S WORKING OF THE MIND.

Within seconds, it has pierced the cell's membrane and released its genetic material. Now, whenever the cell divides to copy itself, it also makes copies of the virus. Soon those multiplying viruses have hijacked not just that cell but also all its neighbors, turning them into one massive virus factory. When this virus runs no longer make the proteins that control it, they start, one by one, to die.

And that's exactly what Dr. Stephen Russell was hoping for. A virologist at the Mayo Clinic, Russell does everything he can to outwit and destroy these viral invaders. He arms them with detailed instructions on how to foil their plans.

In the lab like this around the world, bad bugs are undergoing the ultimate rehabilitation, being transformed from life-threatening viruses and bacteria into lifesaving therapeutic agents. Using the evolutionary cycle of the virus, Russell is harnessing and channeling these destructive powers.
DNA viruses in clinical trials

- Adeno
- HSV-1
- Vaccinia
RNA viruses in clinical trials

- Reo
- Measles
- Retro
- VSV

Classification criteria:
- Nucleic acid: RNA
- Symmetry of capsid: Icosahedral, Helical
- Naked or enveloped: Naked, Enveloped
- Genome architecture: ds, (+) ss, (+) ss, (--) ss
- Baltimore class: III, IV

Properties:
- Virion polymerase: (+), (-)
- Virion diameter (nm): 60-80, 35-40, 28-30, 60-70, 80-130, 80 x 790-14,000, 70-85 x 130-380, 90-120, 90-120, 150-300, 50-300
- Genome size (total in kb): 22-27, 7, 8, 7.2-8.4, 10, 12, 3.5-9, 16-21, 12.7, 13-16, 13.5-21, 13.6, 16-20, 10-14
2015: First Anti-Cancer Virus Approved by FDA in the US!

T-VEC (Imlygic) in Melanoma
Measles as an oncolytic agent

Efficiently infects all tumor cells tested (ovarian ca, gliomas, lymphoma, myeloma, prostate cancer, head and neck cancer, breast cancer, HCC, pancreatic cancer)

- Kills tumor cells more efficiently than normal cells
- Potent bystander effect
- Can be engineered to express additional genes

Bluming and Ziegler (1971) Lancet ii, 105-106
Phase I
Preclinical Research

Clinical Trials

Translation Requirements

Translation

Preclinical Research

Clinical Trials

Toxicology
Pharmacology

Clinical Protocol

Vector Manufacturing

Regulatory Approvals
RAC
FDA
IRB
IBC

Phase I

Phase II

Phase III

MV-CEA
Ovarian cancer
IP administration
7 dose levels

Glioma
IT administration
6 dose levels

MV-NIS

Multiple myeloma
IV administration
4 dose levels
+/- cyclophosphamide

Mesothelioma
IT administration
4 dose levels

Multiple myeloma
IV administration
4 dose levels
+/- cyclophosphamide

Ovarian cancer
IP administration
3 dose levels

PMNST
IT administration
4 dose levels

Head and neck
IT administration
3 dose levels

Ovarian cancer
IP administration
3 dose levels

Ovarian cancer
IP administration
7 dose levels

Glioma
IT administration
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CLINICAL TRANSLATION

• Vector Production
• Toxicology studies
Toxicology studies

- **Species**
  - Ifnar\(^{\text{ko}}\) CD46 Ge mice
  - Rhesus monkeys (Macaca mulatta)
  - Squirrel monkeys (Saimiri sciureus)

- **Dose**
- **Schedule of administration**
Measles Virotherapy Program at the Mayo Clinic - Safety

• Excellent safety!
  ➢ Intratumoral
  ➢ Resection cavity
  ➢ Intravenously
  ➢ Intraperitoneally
  ➢ Intrapleurally

"First, do not harm" Hippocrates 5th c BC
Treatment with Oncolytic Measles Virus

Does it work?
Complete response to measles virotherapy in ovarian cancer patients
<table>
<thead>
<tr>
<th></th>
<th>mTTP (range mo)</th>
<th>Overall Survival (range in months)</th>
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</thead>
<tbody>
<tr>
<td>MV-CEA</td>
<td>1.8 (0.7 – 52.8)</td>
<td>12.2 (1.3 – 80.1)</td>
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<tr>
<td>MV-NIS</td>
<td>2.13 (0.8 – 32.5+)</td>
<td>26.6 (1.8 – 33.9+)</td>
</tr>
<tr>
<td>MV-CEA or NIS 10^8-10^9 TCID50</td>
<td>2.7 (0.8 – 52.8)</td>
<td>28.2 (5.5 – 52.8)</td>
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</tbody>
</table>

Expected survival: 6-12 months; Markman et al, 2004; Wagner et al, 2007; Dizon et al, 2012

**Prior chemotherapy regimens for recurrent disease (N)**

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<th>Mean</th>
<th>Min.</th>
<th>Max.</th>
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<tbody>
<tr>
<td>MV-CEA</td>
<td>3.1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>MV-NIS</td>
<td>4.3</td>
<td>1</td>
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Intravenous Administration of MV-NIS in Multiple Myeloma

- Systemic delivery
  - Development of novel FDA approved viral production methodology

Pt SE: s/p stem cell transplant x 2, Rev/Dex, CyBorD

Lambda FLC (mg/dL)

<table>
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<tr>
<th>Dates</th>
<th>Lambda FLC (mg/dL)</th>
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<tr>
<td>9/14/11</td>
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<tr>
<td>11/22/13</td>
<td>9</td>
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BM (Negative)

PET/CT (Improvement)

MV-NIS (10^11)
Treatment with Oncolytic Measles Virus

How it works?
Measles Vaccine strains replicate in brain tumors
MV treatment elicits antitumor immune response in ovarian cancer
MEASLES VIRUS and VSV: ACTIVITY IN SARCOMAS

Osteosarcoma

Soft tissue sarcoma

Malignant peripheral nerve sheath tumor
MEASLES AGAINST MPNST

Deyle et al, 2015
Viruses have significant activity against bone sarcomas
Clinical Gene Transfer/Virotherapy Program at the Mayo Clinic

- Tumor types: melanoma, renal cell carcinoma, sarcoma, colorectal cancer, breast cancer, ovarian cancer, pancreatic cancer, GBM, hepatocellular carcinoma, lymphoma, multiple myeloma, prostate cancer, head and neck cancer, mesothelioma
- Sarcoma focus
  - Trial of measles virus in MPNST opening in 2016!
  - Trial of T-VEC for soft tissue sarcoma in planning stages
You want your virus when?