Enhancing Anti-tumour Immunity with Oncolytic Viruses

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JENNEREX BIOThERAPEUTICS INC
Cancer complexity slows quest for cure

“the focus should shift from hunting for individual genes that cause certain cancers, to disrupting broader biological pathways that support cancer growth”


Oncolytic Viruses

• *Thrive* on Malignantly Activated Signaling Pathways
• Attack Cancers in Multiple Ways
Oncolytic Viruses: Multiple Mechanisms of Action

- Tumour cell infection and virus-induced destruction
- Vascular collapse
- Virus-induced immune reaction against tumour cells and antigens

Infection in and around tumour endothelial cells leads to vascular collapse

Infection of tumour cells leads to induction of innate and adaptive immune responses, leading to destruction of infected and uninfected tumour cells

Tumour cell infection and virus-induced destruction

Vascular collapse
TUMOUR EVOLUTION

- Healthy Cell
- Cancer Cell
- Malignant Tumour
- Disruption of Apoptotic Pathways
- Metabolic Deregulation
- Genetic Mutations
- White Blood Cells Immune Surveillance
- Immune Escape
- Unrestricted Growth
- Deregulated Angiogenesis
The Same Biological Processes that Control Cell Growth and Death also Control the Ability of Individual Cells to Fight Virus Infections!
Normal Cells Fight Virus Infections

Healthy Cell

- Interferons
- Stop cell growth 
  & division
- Induce cell death
- Suppress Metabolism
- Alert the immune system
- Stop blood vessel formation

Cancer Cell

Cancer Driver Mutations are OV Driver Mutations!

The biological processes underlying anti-viral defense are incompatible with efficient tumour evolution
ONCOLYTIC VIRUSES: THERAPEUTICS FOR SYSTEMIC DISEASE
Oncolytic Virus Activity in Mouse Models

2 weeks following intravenous tumour cell injection (CT26)

IV Administer OncolyticVirus (GFP) and wait 24 hours
IV delivery of Pexa-Vec: biopsy-proven cancer-specific targeting in Cancer Patients

Colon cancer glandular structures = infected (IHC+) & evolving necrotic tumor tissue

Breitbach et al, 2011
Oncolytic Viruses: Clinical Activity Following Locoregional Therapy

Pexa-Vec

David Kirn

Caroline Breitbach
Tumor Responses Following Direct Vaccinia Virus Therapy

HCC Metastasis Response with Single Agent Pexa-Vec IT
Tumor Responses Following Pexa-Vec Therapy

[Images of medical scans showing tumor responses before and after therapy]
Complete Response in HCC Patient over 24 Months

Baseline  Day 5  Week 26  Week 38
ANTI-TUMOUR IMMUNITY GENERATED BY ONCOLYTIC VIRUS THERAPY

AN “IN SITU” VACCINE APPROACH
Immunology and OV therapy

T cell based Immunity leading to long term immune surveillance:
An *in Situ* Vaccine that attacks *the tumour mutanome*... humoral and cellular responses

Mice reject Colon Tumours!
Long-term Survivor Disease-Free after Pexa-Vec Therapy

*Phase I Clinical Trial Metastatic Melanoma: Evidence of Anti-tumour Immunity*

32 year-old woman:
- Refractory, widespread met
- Complete tumor regressions:
  - Injected
  - Distant dermal, chest (surg)
- Disease-free 3.5+ years

*Intratumoral recombinant GM-CSF-encoding virus as gene therapy in patients with cutaneous melanoma*

Michael J. Mastrangelo,¹ Henry C. Maguire Jr.,¹ Laurence C. Eisenlohr,² Carol E. Laughlin,² Claude E. Monken,¹ Peter A. McCue,³ Albert J. Kovatch,³ and Edmund C. Lattime¹,²
A. IT of vaccinia leads to complete regression of injected tumours
B. Regression of uninjected tumours was observed at day 60, suggestive of an anti-tumour immune response
Tumor biopsy of HCC patient ~1.5 years post Pexa-Vec treatment

Tumor cells

Lymphocytic infiltrate
How can we make OV therapy stimulate effective anti-tumour immunity consistently and robustly?

Immune Checkpoint Inhibitors
- Encoded within the virus genome (anti-CTLA4)
- Combination therapy e.g. Anti-PDL1

Immune Modulators
- Low Dose Cyclophosphamide
- HDAC inhibitors

Oncolytic Vaccines
- Program OV to express a tumour antigen
Oncolytic Vaccines: Designer Immune Responses Against Tumours

- Use a Virus as both an Oncolytic and a Tumour Vaccine
- The Benefit of both viral oncolysis and potent anti-tumour immune responses
- Have Oncolytic Virus Encode and Express a Relevant Tumour Antigen

Dave Stojdl
Children’s Hospital of Eastern Ontario

Jonathon Bramson    Yonghon Wan    Brian Lichty
Michael G. DeGroote Institute McMaster University

Byram Bridle
University of Guelph
Emerging evidence that vaccination schedules comprising more than one delivery method against the same antigen are best positioned to overcome the therapeutic immunity threshold and adequately harness the immune system.”  Aurisicchio and Ciliberto, Cancers, Sept. 2011

Maraba “Oncolytic Vaccine”

Virus-TAA PRIME + Maraba virus-TAA BOOST = Anti-tumour IMMUNE RESPONSE & robust debulking by ONCOLYSIS

Virus-TAA PRIME

Time 0

Maraba virus-TAA BOOST

Day 14

Day 18

TAA = Tumour Associated Antigen
Enhancing Therapeutic Immune Responses

B16 Melanoma tumours are only transiently responsive to OV activity
Oncolytic Vaccines as Immune Boosters


.png
Oncolytic Vaccines as Immune Boosters

Tumour-bearing vs Tumour-free

~3 fold greater

Increased TILs

~80 fold increase

Antigen Spreading

mGP100 response

p<0.001, 1-way ANOVA

~3 fold greater

~80 fold increase

mGP100
## Translating Oncolytic Vaccines to Humans

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>MAGE A3 expression</th>
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<tbody>
<tr>
<td>Head and neck&lt;sup&gt;1,2&lt;/sup&gt; – squamous</td>
<td>36-51%</td>
</tr>
<tr>
<td>Esophagus&lt;sup&gt;3&lt;/sup&gt; - squamous</td>
<td>91%</td>
</tr>
<tr>
<td>NSCLC&lt;sup&gt;4&lt;/sup&gt;</td>
<td>39-46%</td>
</tr>
<tr>
<td>Breast&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>37-50%</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>50%</td>
</tr>
<tr>
<td>Cholangiocarcinoma&lt;sup&gt;8&lt;/sup&gt;</td>
<td>27%</td>
</tr>
<tr>
<td>Hepatocellular carcinoma&lt;sup&gt;9&lt;/sup&gt;</td>
<td>47%</td>
</tr>
<tr>
<td>Colorectal&lt;sup&gt;10&lt;/sup&gt;</td>
<td>66-81%</td>
</tr>
<tr>
<td>Endometrial&lt;sup&gt;11&lt;/sup&gt;</td>
<td>25%</td>
</tr>
<tr>
<td>GIST&lt;sup&gt;12&lt;/sup&gt;</td>
<td>23%</td>
</tr>
<tr>
<td>TCC bladder&lt;sup&gt;13&lt;/sup&gt;</td>
<td>53-59%</td>
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Toxicity and Immunogenicity Study of Maraba:MAGE A3 Oncolytic Vaccine in Cynomolgus Macaques

Andrea McCart         Dave Stojdl       Brian Lichty
Immune analysis – T-Cell responses against MAGE A3

Peak Responses - Top Ten

- Andy
- Charley
- Magnum
- Isabella
- Thelma
- Danno
- Marilyn
- Cameron
- Starsky
- Lucy

Peak Responses - Bottom Ten

- Whoop!
- Louise
- Murdoch
- Angelina
- Colombo
- Helen
- Face
- Drew
- Sandra
- Alley

Legend:
- Pool 1-10
- Pool 11-20
- Pool 21-30
- Pool 31-40
- Pool 41-50
- Pool 51-60
- Pool 71-80
- Pool 81-87
Potency of Immune Boosting

- Ad prime: Maraba boost achieves 2-13% T cell responses in Macaques against a weakly immunogenic tumour antigen
- State of the art HIV vaccines achieve approximately 0.5% T cell responses in macaques and humans
- GSK MAGE A3 vaccine in phase III studies induces barely detectable T cell responses… but has shown clinical benefit

*Graph from A.J. Bett et al. / Vaccine 28 (2010) 7881–7889*
Planned Clinical Trial
Oncolytic Viral-MAGE A3 vaccine

Arm One
- MG1 Maraba-MageA3 alone
- Dose finding, safety, immune response

Arm Two
- Ad-MageA3 alone
- Safety and immune response

Arm Three
- Ad-MAGE A3 prime plus MG1 Maraba-MageA3 boost
- Dose finding, safety, immune response
Oncolytic Viruses: Multi-Modality Therapeutics

- Cytolytic
- Self-amplifying dose
- Gene delivery vehicles
- Systemic targeting
- Vascular Targeting
- Inflammation
- Innate & adaptive effectors
- Sensitizing agent
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