International Society for Biological Therapy of Cancer
2008 Oncology Biologics Development Primer

Oncolytic Viruses: Reovirus
REOLYSIN® - mode of action

- REOLYSIN contains the reovirus, a naturally occurring, replication competent oncolytic virus
  - Not a gene therapy agent so no interaction with GTA (UK)
  - Not recombinant so no interaction with NIH DNA RAC (US)
- Asymptomatic in humans (does not cause disease)
- Replicates in Ras-activated cancer cells resulting in cell death
Two methods of tumor killing

Reovirus replicates in Ras-activated cancer cells, causing virus-mediated cell death

Tumour antigens generated by viral oncolysis may educate the immune system to recognize and kill tumour cells
• Fully replication-competent
• Replication is exclusively cytoplasmic
• Proof of viral replication in tumors following systemic delivery
• Mammalian permissive therefore effective modeling in murine and non-human primate models

Picture courtesy of Scott Wadler, Cornell University
Preclinical toxicology – unique challenges

- Reovirus replicates in target cells
- Non-tumor bearing animals will not have the ability to replicate the virus
  - Input virus could be significantly less than virus amplified in tumor tissue
  - Animals bearing tumors with actively replicating virus experience prolonged virus exposure
  - Various chemotherapeutic agents can increase progeny virus production
  - Lytic release of tumor associated antigens cannot be modeled in non-tumor bearing animals
Tumor regression and viral amplification

A. REOLYSIN Induced Local and Remote Tumor Regression in Breast Cancer Xenografts

- RIGHT FLANK LIVE VIRUS
- LEFT FLANK LIVE VIRUS
- RIGHT FLANK INACTIVE VIRUS
- LEFT FLANK INACTIVE VIRUS

B. Viral Amplification in Xenograft

- Left (injected) flank
- Right (uninjected) flank
- Blood

Days post-injection (Into left flank)

Days post-injection
Clinical Development Strategy
&
Appropriate Toxicology Modeling
Clinical development strategy

From local to systemic, monotherapy to combination

• Local or regional administration using REOLYSIN as a monotherapy

• Systemic administration using REOLYSIN as a monotherapy

• Combination therapy using REOLYSIN locally, regionally or systemically with radiation or chemotherapy
Preclinical toxicology - changing route of administration increases commitment to toxicology

Thirteen GLP safety studies – consistent results

Three routes of administration
  • SubQ, intracerebral, and intravenous

Three animal species
  • Rat, canine, primate

Single and multiple dose studies
  • 28-day infusion studies completed in 3 species

No product-related severe adverse events or dose-limiting toxicities in immune competent animals
Why start with local administration?

Although local administration is not as clinically relevant as systemic treatment, there are advantages:

- Considered “safer” than repeat systemic administration
- Proof of concept – could assure virus delivery to tumor
  - Activity could be measured by local response, systemic response, and superficial lesions can easily be biopsied pre and post treatment
- Requires less virus than systemic administration

If the above criteria were met (i.e. safe, demonstration of tumor regression, and improved manufacturing) then move to systemic administration
Results – Phase I intratumoral

- Dose escalation from $1 \times 10^7$ to $1 \times 10^{10}$ TCID$_{50}$ given a single or multiple injections
  - No anaphylaxis seen in multiple injection cohorts
- No severe adverse events noted, no DLTs, MTD not reached
- Viral activity detected in 11 of 18 patients (>30% 2-D tumor regression)
- Evidence of field effects noted in several patients
- Results mostly mirror preclinical results
- During this period improvements to manufacturing were implemented, with resulting increases in yield from 4% to 40%
Preclinical Toxicology & Intravenous Delivery
Repeat IV studies

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose in TCID$_{50}$</th>
<th>Frequency</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spraque-Dawley Rats</td>
<td>2.1 x 10$^6$</td>
<td>Once daily for 28 days</td>
<td>No compound-related effects produced on any of the parameters assessed in this study.</td>
</tr>
<tr>
<td></td>
<td>2.1 x 10$^7$</td>
<td></td>
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<tr>
<td></td>
<td>2.1 x 10$^8$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beagle Dog</td>
<td>7.1 x 10$^7$</td>
<td>Once daily for 28 days</td>
<td>No compound-related effects produced on any of the parameters assessed in this study.</td>
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<tr>
<td></td>
<td>7.1 x 10$^8$</td>
<td></td>
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<tr>
<td></td>
<td>7.1 x 10$^9$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primate</td>
<td>5.0 x 10$^7$</td>
<td>Once daily for 28 days</td>
<td>Dosing and recovery phases completed. No observed morbidity or mortality. EKGs conducted on day one and during week two demonstrated no abnormalities.</td>
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<tr>
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<td>5.0 x 10$^8$</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5.0 x 10$^9$</td>
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Systemic administration studies

Phase I systemic administration study at the Royal Marsden Hospital and St. George’s Hospital, UK

- Intravenous administration in patients with advanced or metastatic solid tumors refractory to standard therapy
- Examined dose frequency, dose escalation, retreatment (4 week cycle), and a treatment arm at the MTD
- Enrolment from May ’04 – Nov ’06

Phase I systemic administration study at the Montefiore Medical Center, US

- Intravenous administration in patients with advanced or metastatic solid tumors refractory to standard therapy
- Examined dose escalation
- Enrolment from Nov ’05 – Oct ’06
UK dose escalation – Phase I component

- Study designed to look at effect of increasing frequency and dose
- Allowed multiple administrations (4 week cycle)
- Expansion at top dose to better measure efficacy
US dose escalation – Phase I

- Study designed to look at increasing dose only
- Single cycle only (until sufficient data generated from UK study)
- No expansion at top dose

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top Dose</td>
<td>Top Dose (x 3)</td>
</tr>
<tr>
<td>Top Dose</td>
<td></td>
</tr>
<tr>
<td>Dose C</td>
<td></td>
</tr>
<tr>
<td>Dose B</td>
<td></td>
</tr>
<tr>
<td>Dose A</td>
<td></td>
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Different jurisdictional issues

- **MHRA**
  - Pro – early allowance to look at repeat administration and multiple cycles
  - Con – concern with shed required first cohorts to be treated in hospital in negative pressure rooms resulting in slow accrual and added cost

- **FDA**
  - Pro – realistic view of the risk posed by shed of a naturally occurring virus allowed patients to be treated in out-patient care resulting in rapid enrolment
  - Pro - allowed early interaction with the Agency
  - Con – initial concerns with risk of repeat administration required first cohorts to receive single administration only

- By concurrently running the studies, it was believed that the transition into Phase II studies in multiple jurisdictions would be expedited
## REOLYSIN clinical overview - systemic monotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Tumour Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I systemic administration (UK)</td>
<td>Late-stage or advanced cancer patients who have failed all other therapies. (N=33)</td>
<td>Responses noted in several tumor types</td>
</tr>
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<td>- Colorectal cancer 2 patients: Stable Disease at 3 and 6 months; CEA tumor marker reduction of 27% and 60%</td>
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<td></td>
<td>- Metastatic prostate cancer one patient: Stable disease at 4 months 50% decrease in PSA. Biopsy lymph node – EM: Viral replication. Pathology - Necrosis</td>
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<td>- Metastatic bladder cancer one patient: Stable disease at 4 months. Minor tumor response (24% tumor reduction) in metastatic lesion (lymph node); patient later reported as disease free post surgery (pPR).</td>
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<td>- Pancreatic cancer one patient: Stable disease at 4 months.</td>
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<td>- NSC Lung Cancer one patient: Stable Disease at 4 months.</td>
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<tr>
<td>Phase I systemic administration (US)</td>
<td>Late-stage or advanced cancer patients who have failed all other therapies. (N=18)</td>
<td>44% showed stable disease or better</td>
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<td>One partial response in progressive breast cancer</td>
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REOLYSIN clinical overview – Phase II program

Monotherapy Phase II Program
Program status – ongoing

- **US**: recurrent sarcoma metastatic to lung (ongoing)
  - Trial has met initial criteria to proceed to full enrolment
  - One patient stable for >6 months
- **NCI**: melanoma and ovarian cancer
  - Trials received FDA approval, enrolment to begin Q1 2008

These studies employ the recommended dose from the UK study (ie 5 injections/week on a 4 week cycle)

Phase II monotherapy program is currently exclusively conducted in the US
REOLYSIN clinical overview – Phase I/II program

Phase I/II Drug Combination Program
Program status - ongoing

Combination:
UK: Phase II low dose radiation including head/neck (ongoing)
Combinations with cytotoxics (dose escalation ongoing)
  - Gemcitabine
  - Docetaxel
  - Carboplatin/paclitaxel
REOLYSIN + cyclophosphamide (MHRA approval received)
Imaging, tumor markers and histopathology

- Phase I program suggested that conventional imaging (CT) was inadequate to measure responses caused by REOLYSIN
  - Demonstrable tumor marker responses by CEA, PSA, and CA199 without 2D changes in CT
  - Histopathologic response in post-treatment biopsies and surgical specimens without 2D changes in CT
Example - PSA response – patient JB

JB PSA profile

PSA ng/ml

0 20 40 60 80 100 120

date

#1 #2 ← Treatment cycles
CT Scan – patient JB

Pre-treatment

Post 2 cycles of REOLYSIN®

Contrast: 90MLS VISI 320
Gantry: 0°
FoV: 380 mm
Time: 1000 ms
Slice: 7 mm
Pos: 284
FFS

F: SOFT
160 mA
120 kV
Image no: 46
Image 46 of 62
20/09/2005, 12:30:09
Metastatic prostate patient’s histology – patient JB

Original bx- shows prostate cancer mod differentiated

PSA stain post REO bx- shows biopsy positive For PSA i.e. confirms this is prostate cancer in the node

JB Biopsy

necrosis

tumour

Post REO bx

Necrotic tumour

Post-REO bx
In response to imaging concerns the Company introduced the use of PET/CT into Phase II programs. Introduction of this imaging modality is already bearing fruit:

- Phase II sarcoma study has demonstrated that a patient with 6 month SD (CT RECIST) has metabolically inert disease by PET and study has moved to full enrolment (enrolment ongoing)
REOLYSIN: lessons and issues

- Key strategic decisions
- Impact of regulatory interactions
- Financial considerations: projected costs vs. reality
- Lessons learned
Oncolytic Viruses: Reovirus