

# First Use of a Novel Gene Transfer Agent in a Single Subject Protocol: Role of the RAC

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# Overview

- What types of single subject gene transfer protocols register with OBA
- How often is a novel gene transfer agent used first in a single subject protocol
- What issues do these protocols raise
  - Unique challenges in informed consent
  - For the field generally
- What is the best role for the RAC in review of these protocols

# Single Subject Protocols

- Exemptions to reviewed protocol design
- Involve judgments about the suitability of gene transfer for an individual patient based on their unique clinical circumstances
- Usually time sensitive

# Single Subject Protocols

## Same Disease

- Redosing beyond what is specified in protocol based on response
- Failure to meet inclusion criteria:
  - Glioblastoma trial: subject failed to have resection as primary therapy
  - Cytotoxic T cells for prophylaxis and therapy of adenoviral infection post stem cell transplant: subject develops adenoviral pneumonia and respiratory failure after transplant and too ill to meet eligibility criteria
  - Lung cancer vaccine: expanded access protocol for subjects who do not meet inclusion criteria, e.g. progression of disease, alternative chemotherapy regimen, above the age for entry

# Single Subject Protocols

## Different Disease

- Vector containing an intact p53 gene that is being used in a trial for squamous cell cancer of the head and neck is used in a single subject with Li-Fraumeni disease in which a defective p53 is the underlying gene defect
- Autologous tumor cells transduced with a gene containing GM-CSF that is being used in a trial breast cancer is used for a single subject with advanced pancreatic cancer
- Vector containing VEGF gene that is being use in a trial for diabetic neuropathy is used for a single subject with autoimmune neuropathy

# Single Subject Protocols: New Product

## Leiomyosarcoma – TGF- $\beta$ 2 antisense/GM-CSF

- Vector brought together two transgenes previously used separately
- Subject did not receive the gene transfer and passed away due to disease
- Vector not since used in OBA registered clinical trial

## Lung Cancer – EBV specific CTLs Expressing HER2/neu Chimeric receptors

- New target receptor for EBV specific CTLs
- Subject received gene modified cells but passed away shortly thereafter of complications from disease
- Vector not since used in OBA registered clinical trial

# Single Subject Protocols: New Product

- Hereditary Inclusion Body Myositis
  - Liposomal encapsulated plasmid containing a novel transgene - GNE gene, a bifunctional enzyme of the sialic acid biosynthetic pathway
  - RAC recommended public review
  - PI requested permission to proceed prior to the RAC meeting due to the patient's clinical condition
  - NIH gave PI permission to proceed with first dose in August 2008 and protocol discussed at the September 2008 RAC meeting

# Single Subject Protocols: New Product

- Subject received intramuscular injections followed by intravenous injections over a period of two years. Data published in 2010 after four intramuscular injections:
  - Significant durable improvement in locoregional skeletal muscle function was observed in the injected left extensor carpi radialis longus in correlation with GNE transgene upregulation and local induction of sialic acid without significant toxicity
  - Proof of principle for manufacturing of 'clinical grade' GNE gene Lipoplex, and clinical safety and activity are demonstrated.

# Single Subject Protocols: New Product

## ➤ Pancreatic Cancer

- Liposomal plasmid containing a novel bifunctional shRNAPDX1 (pbi-shPDX1). Pancreatic and duodenal homeobox-1 (PDX-1) is a transcription factor that plays a role in regulating embryonic pancreas development as well as insulin expression and islet cell maintenance but is also an oncogene that is overexpressed in pancreatic cancer
- Subject with stage IV pancreatic cancer
- No data yet received on clinical outcome

# Are Single Subject Protocols Research or Treatment?

- Use of unapproved experimental agent with limited or no efficacy record to support its characterization as treatment
- Primary goal is to ameliorate disease in patients with no other treatment options
- Patient's interest in experimental treatment often takes precedence over ability to generate generalizable knowledge
- Limited data likely to be generated from  $n=1$

# Are Single Subject Protocols Research or Treatment?

- NIH Guidelines define human gene transfer research as the transfer of recombinant DNA or DNA or RNA derived by recombinant DNA into one or more individuals
- Therefore, such protocols require registration with OBA and RAC review

# Single Subject Protocols

- What circumstances might lead an investigator to enter the clinic first with a compassionate use
  - Final approvals for full protocol are pending but expected in a short time?
  - Extremely rare disease?
- What data can be expected from such protocols?
- Is there a risk that a serious adverse event could derail development of this agent?
  - Are the ethical implications of taking that risk for a single patient if it potentially sets back a promising approach for multiple patients?

# Single Subject Protocols

- How is selection of the subjects made for an individual protocol?
- How does one address informed consent and therapeutic misconception?
- How can the RAC contribute to this process?