Critical Path: OCTGT Perspective

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Overview

- Types of Products
- OCTGT Program
- Critical Path Challenges
- Critical Path Successes
- Ongoing Critical Path Initiatives
- Future Critical Path Issues

Types of Products

- Cell therapies
- Gene therapies
- Tissues and tissue-based products
- Xenotransplantation
- Tumor vaccines
- Anti-idiotypic antibodies
- Combination products
- Devices used with cells

Review/Research Structure

Designed to identify and solve challenges

- Review team
  - Regulatory project manager
  - Product reviewer
  - Clinical reviewer
  - Pharm-tox reviewer
  - Statistician
- Critically evaluates product development programs and identifies challenges for specific products and across product areas

Review/Research Structure

Designed to identify and solve challenges

- Research – key fields and programs
  - Virology (retrovirus, adeno, herpes)
  - Immunology (host-vector interactions, transplant rejection)
  - Tumor biology (safety and potency assays)
  - Developmental biology (control pathways in animal models, stem cell biology)
  - Novel medical technology (Microarray, Proteomics, Flow Cytometry)

Critical Path Challenges

- Product safety
  - Vector Safety (toxicity, host interactions, transgene safety)
  - Screening for adventitious agents and understanding infectivity
  - Controlling growth of cells
  - Controlling cellular differentiation
  - Product/Recipient interactions
- Product characterization – correlate with efficacy
  - Potency
  - Identity
- Assay development - Reference materials

Critical Path Challenges

- Preclinical development
  - New animal models
  - Link to clinical outcomes
  - Refine/Reduce preclinical studies
- Efficacy
  - Clinical trial design
  - Biomarkers – surrogate endpoints
- Others?

Regulatory Accomplishments with Critical Path Contributions

- Evaluation of gene therapy adverse events to reduce future risks
- BRMAC re: Development of islet cell transplantation, cord blood, cardiovascular use of stem cells, ooplasm transfer
- Finalization of 3 HCT/P rules
- Outreach/international activities in all product classes (harmonization, guidances)
- Major research on GT, xenotransplantation and tumor vaccine safety, stem cell characterization, CT products and assays

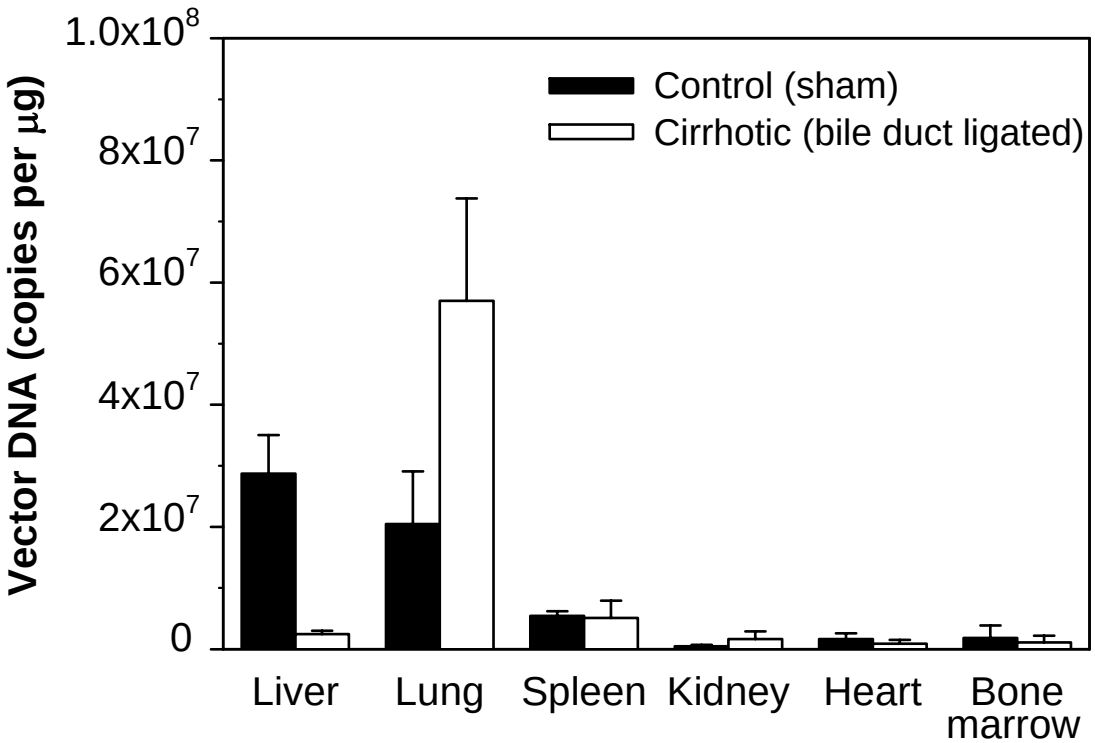
Vector Safety
– Adenoviral Toxicity

- Issue:
  - Respiratory Distress Syndrome, Death
  - 1999: Gene therapy trial in patients with hereditary liver disease. One patient died; symptoms were not predicted by pre-clinical animal models.
- Actions:
  - OCTGT developed animal model showing that adenovirus may cause lung damage in the setting of liver disease

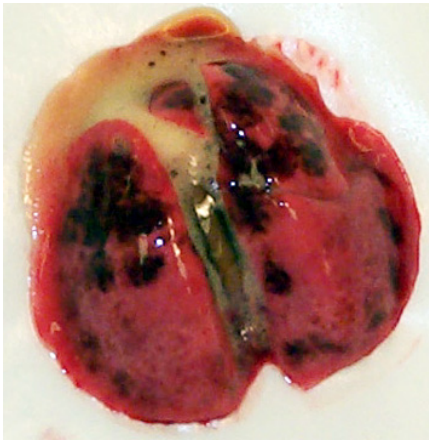
Adenovirus biodistribution and safety:

Action: Research to determine if liver disease increases the risks of adenovirus gene therapy

Physical biodistribution – quantitative PCR



Pulmonary hemorrhage and edema in a cirrhotic rat given adenovirus vector i.v.



Outcome: ***recommend caution when using adenovirus vectors in patients with severe liver disease***

Gene Therapy Product Safety – The X-SCID Trial

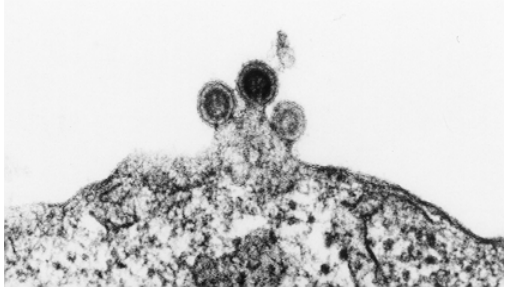
- Issue:
  - Vector-linked leukemia developed in two patients after receiving promising gene therapy
- Actions:
  - Identified risk factors
  - Put similar protocols on hold
  - Identified testing and risk management tools
  - Two advisory meetings to discuss publicly
- **Outcomes:**
  - ***International cooperation***
  - ***Clinical trials resumed with improved safety monitoring and revised informed consent***

Product Safety
– Public Health

- Issue:
  - Product suspected of being contaminated with HIV and HCV – trial was stopped
- Action
  - CBER labs analyzed the product and ruled out the presence of viruses
- **Outcome**
  - ***Study continued***

Retrovirus
- Risk in Xenotransplantation

- Issue:
  - CBER and others have shown that pigs express an endogenous retrovirus capable of infecting human cells.
- Actions:
  - CBER analyzed the safety impact
  - Put all porcine INDs on hold

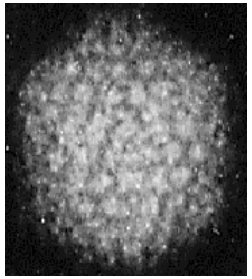


- **Outcomes:**
  - ***OCTGT advised sponsors how to detect PERV in the product and patient samples***
  - ***Clinical trials proceeded with improved safety monitoring and revised informed consent***

Reference Materials

Issue: Needed to assure sensitivity, precision of testing methods

Complete: Available from ATCC



Retroviral reference material

- RCR assay sensitivity

Adenovirus reference material

- Allows precise titers:
  - Viral particle
  - Infectious titer
- Comparison of safety across ad vector trials

Ongoing

External RNA Controls Consortium

- Spike-in controls for RT-PCR and micro-array

AAV reference material

Reference Materials

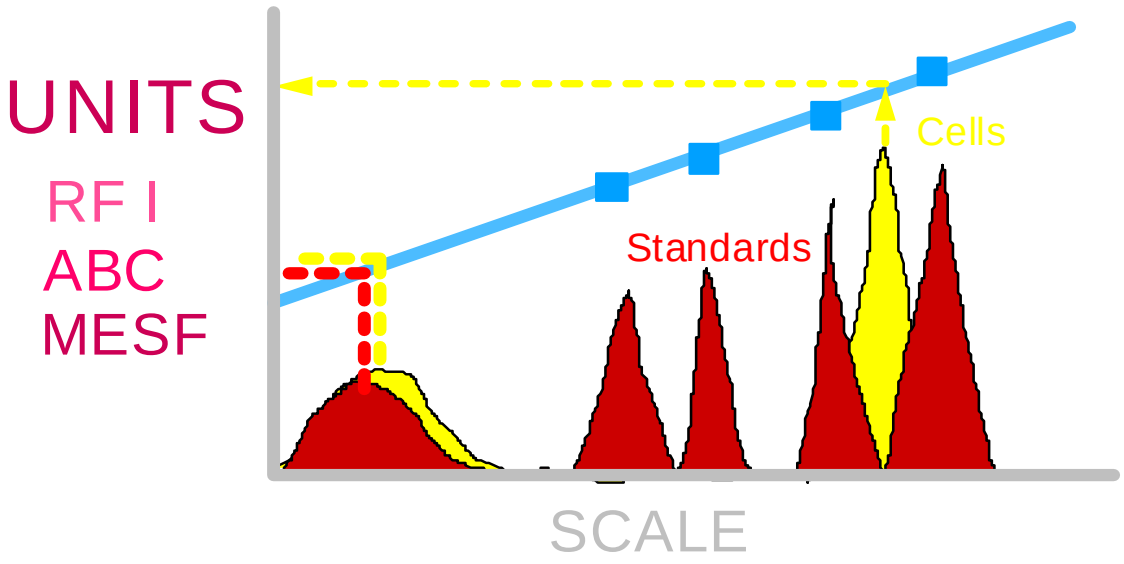
Fluorescence Technology

- Flow Cytometry and Microarrays Needs Standards
- Federal Standardization Initiative: NIST FDA CDC
- Standard Fluorescein Solution Developed
- Standard Microbeads Developed

NIST Microbead Standard

Reference Materials
Fluorescence Technology

- FDA Fluorescence Working Group Formed
- Guidelines for Fluoresence Calibration Created
- Need National Laboratory for Fluorescence Intensity Calibration standards Development



Cells Run with Calibration Standard

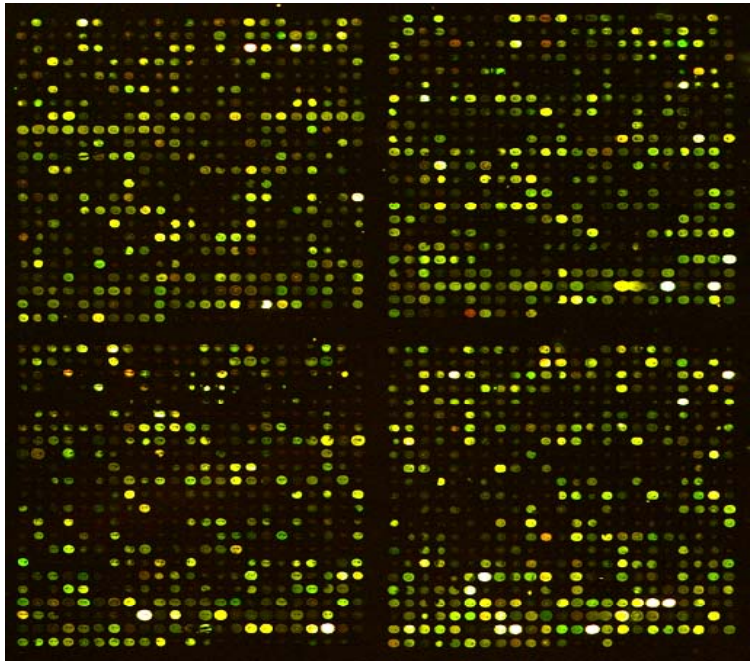
Outcome: *Improved product safety. Savings due to sensitive, consistent testing*

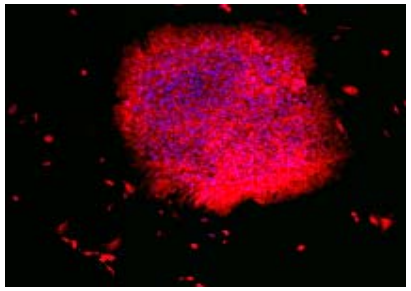
Stem Cells
- Safety and Effectiveness

- Issue:
  - Pluripotent stem cells can form a variety of tissues and cell types
  - Safety concerns include
    - Risk of unregulated growth
    - Contamination of infectious agents
    - Immunogenicity
    - Role of in vivo environment
  - Need for novel technology for characterization

Quality Assessment of Stem Cells

Actions: Research to identify gene expression markers of stem cell state





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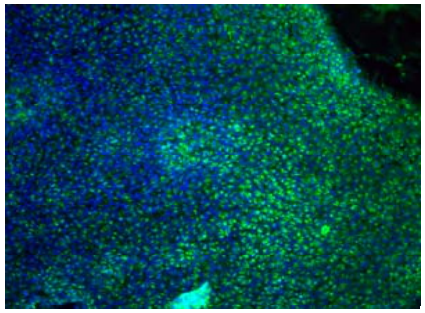

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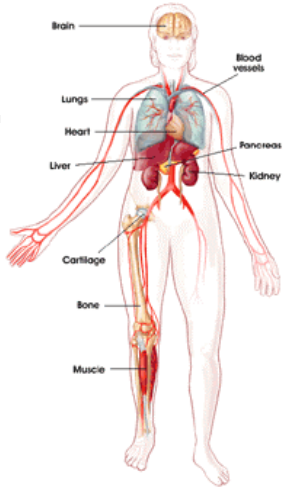
Outcome: ***CBER/NIH/Industry scientists developed a method to identify and characterize 92 common "stemness" genes in 6 stem cell lines***

Critical Path Challenges for Cell-based Products

Cell Product

Safe, effective cell therapy



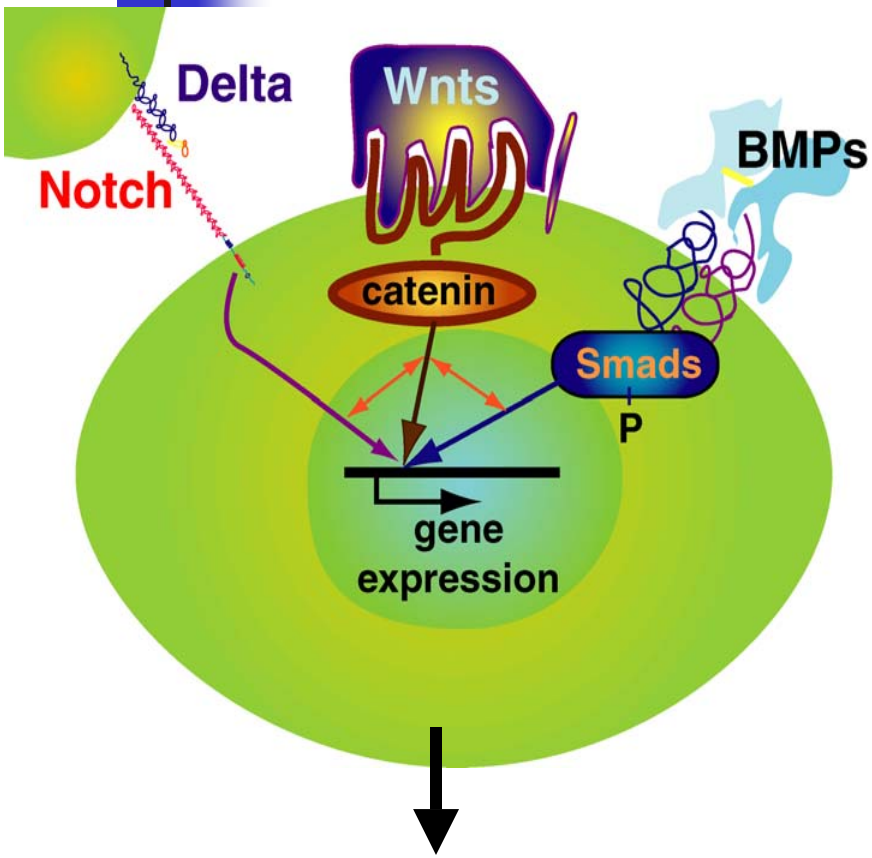
Bad outcome: tumor

- Cell fate is controlled by cell-cell interactions carried out by signaling pathways.
- These pathways are critical to the safety and effectiveness of cell therapy products.

Cell Therapies: Characterization

- Issue: Key questions for safety and effectiveness
  - What are the critical characteristics to measure?
    - Proteins?..... 40,000/cell
    - Secreted molecules?..... 5,000/cell
    - Microenvironment?..... many features
  - Can't measure everything!
  - How do you identify what really matters?

Signal Pathways Control Cell Product Quality



Cell fate

- **Crucial in cell differentiation**
- **Crucial in repair and regeneration**
- **Predict cell product behavior**
- **Dysregulated pathways cause cancer**
- **Affect safety and effectiveness of cell products**

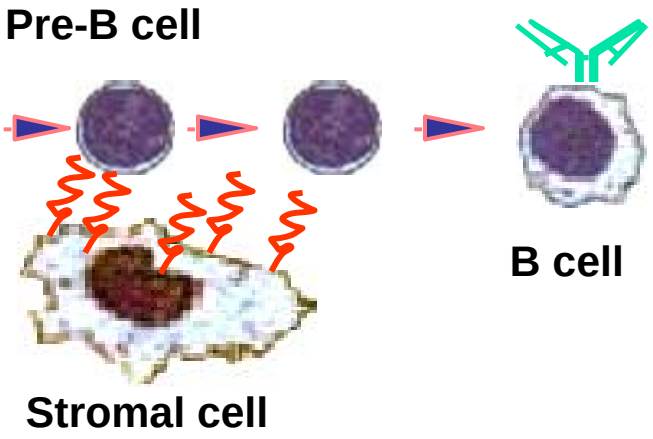
• Signaling pathways conserved in all animals
• Work in model organisms: cheap, fast

Identify key controls of cell and tissue formation

Action: Develop genetic screens and tissue culture systems to identify crucial controls

Normal signaling

Disrupted signaling

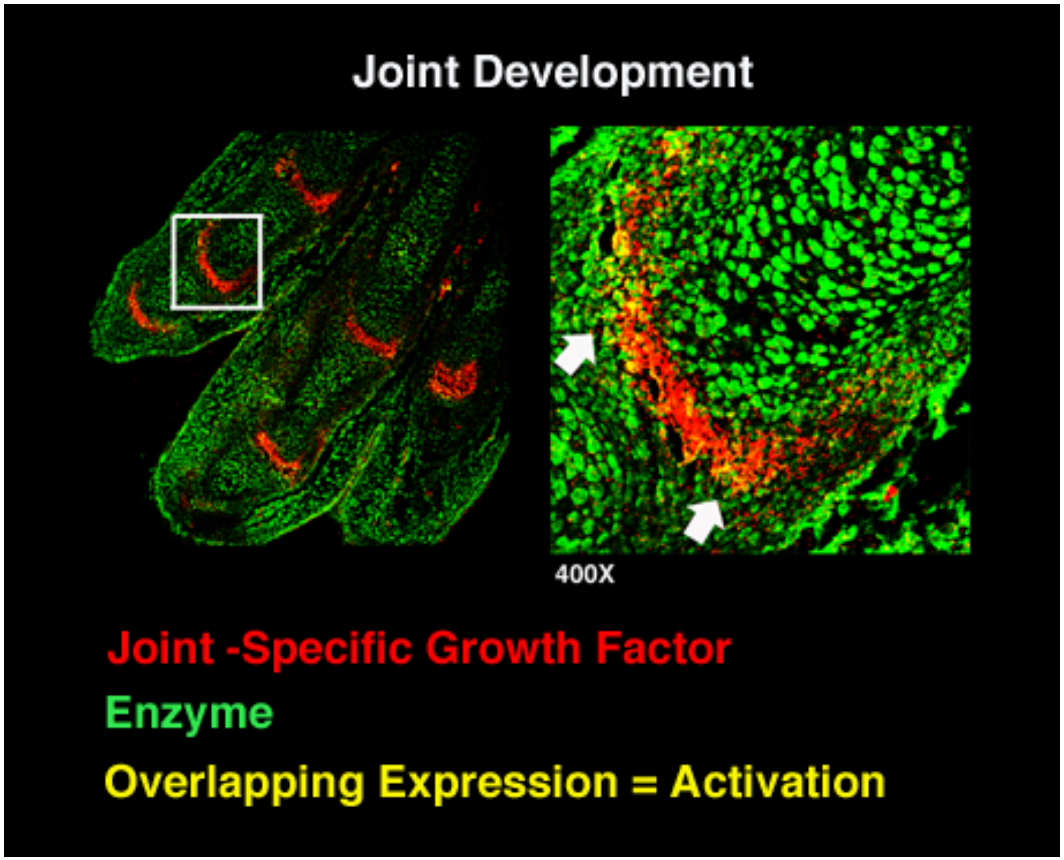


Stromal cell signals control normal differentiation

Potential Outcome: ***screening methods identify characteristics predictive of safe effective cellular products***

Challenges in Developing Safe and Effective Tissue Engineered Products

Actions: Identify product features that affect formation of anatomic boundaries



Example:

Expression of growth factors and the enzymes that activate them overlaps only at anatomic boundaries–*spatial patterns matter!*

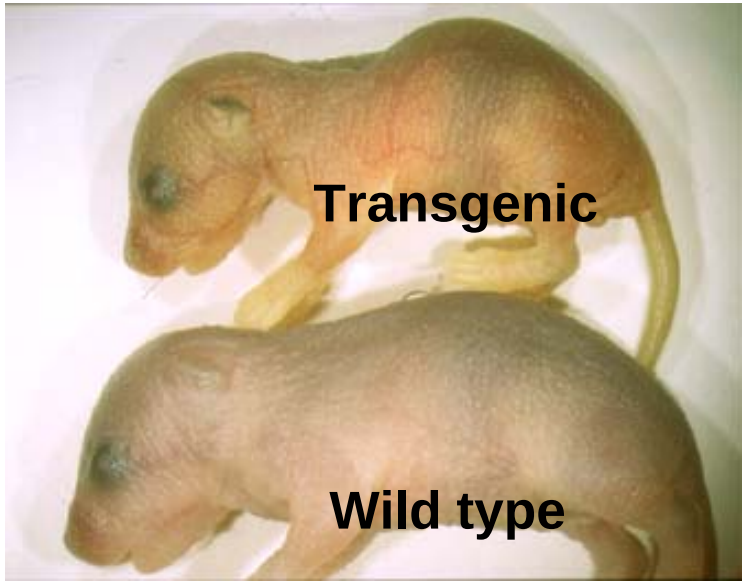
Potential Outcome:

Product characterization may need to address spatial patterns of gene expression

Identify Crucial Signaling Pathways in Organ Development

Action: Test specific *in vivo* gene functions that promote or disrupt normal organ development

Transfer of genetically modified mouse cells into a blastocyst



Example: Notch2 is required for hepatocyte development

Potential Outcome: *Definitive specifications for cell therapy and tissue engineered products*

Cell-based products: Critical Path challenges

- Research goal
  - Simple, most predictive tests for cell-based products
- Potential Outcome
  - Efficient product development
  - Minimize testing costs
  - Safe, effective products to market

Ongoing Critical Path Contributions

- Identification of critical control pathways in cell differentiation and proliferation
- Importance of cellular microenvironment
- Assessment of product safety and efficacy

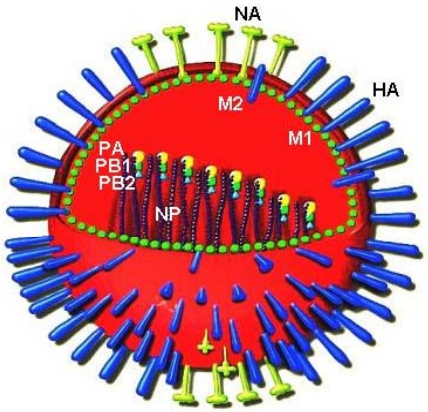
- Understanding product/host interactions

Vector-Host Interactions

- Issue:
  - Achievement of sustained therapeutic effect can require repeat administrations
  - Reality - Reduced effectiveness
  - Cause - Immune response to vector or transgene

Vector-host interactions

Actions: Research to identify markers of immune responses that alter outcome of repeat administration



Immunize with plasmid or viral vector

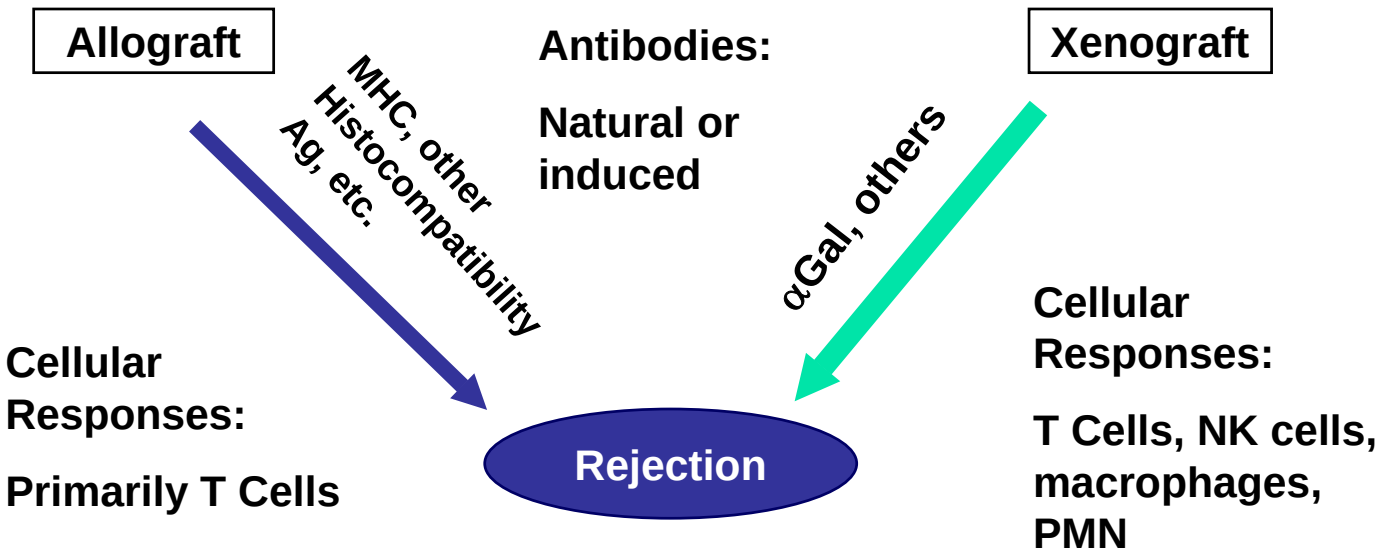
Challenge with matched or divergent strain

Potential Outcomes:

- ***Immune response markers that predict blocking by preexisting immunity***
- ***Effective gene therapy vectors***

Issue: Transplantation Rejection

Action: Research to identify cellular markers involved in protecting xeno- and allogeneic cells from rejection



Potential Outcome:

- ***Methods and biomarkers to assess potential for engraftment and susceptibility to rejection***
- ***Access to novel and alternative sources of replacement cells, tissues, organs***

Future Challenges

- What are the scientific barriers to taking promising products/ideas forward?
- How can we use/leverage your and our expertise to address the challenges?
- What guidance, standards, assays for safety and efficacy would be useful?
- What should we be doing to prepare for the next generation of products?
  - Where do we see future needs for scientific support?

OCTGT welcomes your input

Cell and Gene Therapy Session

Tissues and Tissue Engineering

Statistics, Risk Management and Clinical Trial Design