Ask the Experts: Key Considerations in Using Viral Vector Gene Therapies

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View faculty bios at www.ashpadvantagemedia.com/genetherapy/experts

Webinar Information
Visit www.ashpadvantagemedia.com/genetherapy/experts to find
- Webinar registration link
- Group viewing information and technical requirements

On-Demand Activity
Recording of live webinar
Available after May 1, 2019
Ask the Experts: Key Considerations in Using Viral Vector Gene Therapies

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Disclosures

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- Michael Storey, Pharm.D., M.S., BCPS
  - AveXis, Inc.: advisory board

Products that have not received FDA approval will be discussed during this presentation.
Ask the Experts: Key Considerations in Using Viral Vector Gene Therapies

Learning Objectives

At the conclusion of this activity, participants should be able to

• Review issues related to the preparation and safe handling of viral vector gene therapies
• Examine administrative considerations related to introducing viral vector gene therapies into a health system

Nationwide Children’s Hospital Center for Gene Therapy

• 11 principal investigators from bench to bedside
• 9,000 sq ft cGMP clinical manufacturing facility
• 12 open gene replacement therapy clinical trials
• Focus on neurology and neuromuscular diseases

Cellular and Gene Therapy Is Coming

We anticipate that by 2020 we will be receiving more than 200 INDs per year, building upon our total of more than 800 active cell-based or directly administered gene therapy INDs currently on file with the FDA. And by 2025, we predict that the FDA will be approving 10 to 20 cell and gene therapy products a year...

Scott Gottlieb, MD, Commissioner of FDA
Peter Marks, MD, PhD, Director of FDA’s CBER
January 15, 2019


Gene Expression: From DNA to Protein

[Diagram showing the gene expression process from DNA to protein]

IND = investigational new drug
CBER = Center for Biologics Evaluation and Research
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Types of Gene Therapy

• Cellular gene therapy
• Regulators of gene expression
  – Antisense oligonucleotides
  – Double-stranded RNA
• Gene replacement therapy (GRT)
• CRISPR-Cas9

RNA = ribonucleic acid
CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats
**Gene Replacement Therapy**

**Viral Vector Gene Therapy**
Useful for treating monogenic disease

**FDA-Approved Products**
voretigene neaparovovec-rzyl

Transgene   Viral Capsid


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**CRISPR-Associated Protein 9 (CRISPR-Cas9)**

**Clustered Regularly Interspaced Short Palindromic Repeats**
“Gene Editing”

Enable modification of the cell's genome at specific sites

Preclinical and early clinical trials
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Cleveland Clinic Investigational Drug Service (IDS) Pharmacy

• >400 clinical trials, 12 FTEs
• USP-compliant clean room with dedicated negative pressure investigational drug room
• 7 open gene therapy trials

Biosafety Level 1 (BSL1)

• Work practices
  – Standard
    • Hand washing
    • Do not pipette by mouth
    • Proper sharps disposal
    • PPE as needed
    • Minimize aerosols
    • Decontaminate surfaces
    • Worker training

• Room requirements
  – Door to restrict access
  – Biohazard sign
  – Cleanable surfaces (no carpet)
  – Hand-washing sink available

PPE = personal protective equipment

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Biosafety Level 2 (BSL2)

- Work practices
  - All for BSL1 plus
  - Demonstrate proficiency
  - Follow written procedures
  - Decontaminate equipment
  - Remove PPE before leaving room
  - Conduct procedures generating aerosols in BSC
  - Personnel provided medical surveillance as appropriate
  - Report and evaluate all incidents of exposure

- Room requirements
  - All for BSL1 plus
  - Self-closing and lockable doors
  - Consider negative airflow into room if new facility
  - BSCs certified at least annually
  - Eyewash station available
  - Method for decontaminating waste available

BSC = biological safety cabinet


Biosafety Level 3 (BSL3)

- Work practices
  - All for BSL1 and BSL2 plus
  - All work must be done in a BSC – no open bench work
  - Solid front gowns worn
  - PPE discarded in biomedical waste or decontaminated before laundering
  - Demonstrate proficiency

- Room requirements
  - Work done in class 2 or 3 BSC
  - Room has 2-door access
  - Hands-free handwashing sink
  - Negative airflow and no recirculation to other areas of the building
  - Room must be capable of being sealed for decontamination

Biosafety Level 4 (BSL4)

- As the highest level of biological safety, a BSL4 lab is used for work with highly dangerous microbes
- Infections caused by these types of microbes are frequently fatal, and treatment and vaccines are not available
- Two examples of such microbes are Ebola and Marburg viruses
- Personnel are required to change clothing before entering and shower upon exiting the BSL4 lab
- Materials must be decontaminated before exiting
- Personnel must wear appropriate PPE as for BSL3, as well as a full body, air-supplied, positive pressure suit
- A class III BSC must be used


## Determinant of Biosafety Level

<table>
<thead>
<tr>
<th>Vector</th>
<th>Vector Replication Ability</th>
<th>Suggested Biosafety Level</th>
<th>Safety Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Deficient</td>
<td>Level 2</td>
<td>Can provoke inflammatory response</td>
</tr>
<tr>
<td>Retrovirus</td>
<td>Deficient</td>
<td>Level 2</td>
<td>Insertional mutagenesis</td>
</tr>
<tr>
<td>Vaccinia virus</td>
<td>Competent</td>
<td>Level 2 with level 3 practices</td>
<td>Can infect weakly; vaccines are available</td>
</tr>
<tr>
<td>Fowlpox, canarypox</td>
<td>Competent</td>
<td>Level 1</td>
<td>Do not infect humans</td>
</tr>
<tr>
<td>Adeno-associated virus</td>
<td>Deficient</td>
<td>Level 1</td>
<td>Could infect if “helper viruses” are present; possible mutational concern</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Deficient</td>
<td>Level 2</td>
<td>Unknown effect on latent viruses in patients</td>
</tr>
</tbody>
</table>

### Determinant of Biosafety Level (cont.)

<table>
<thead>
<tr>
<th>Vector</th>
<th>Vector Replication Ability</th>
<th>Suggested Biosafety Level</th>
<th>Safety Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonviable</td>
<td>None</td>
<td>Level 1</td>
<td>None</td>
</tr>
<tr>
<td>Nonviral systems (naked DNA, plasmids, RNA transfer)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Deficient</td>
<td>Level 2 with level 3 practices</td>
<td>Very low risk (but not zero) of converting to replication competent</td>
</tr>
<tr>
<td>Lentivirus (HIV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial</td>
<td>Competent</td>
<td>Level 1 or 2</td>
<td>Refer to risk group</td>
</tr>
<tr>
<td>Yeast</td>
<td>Competent</td>
<td>Level 1 or 2</td>
<td>Refer to risk group</td>
</tr>
</tbody>
</table>


### Biosafety Decision Tree

- **Gene transfer product**
  - **Nonviable rDNA (plasmids, liposomes)**
    - **BSL1**
    - **Consider the risk group of the organism; usually BSL2**
  - **Viable Bacteria, yeasts viruses**
    - **Replication competent**
      - **Infected human cells?**
        - **Yes**
          - **Consider the risk group of the organism; may be able to decrease level of containment**
        - **No**
          - **BSL1**
    - **Replication deficient**
      - **Infected human cells?**
        - **Yes**
          - **BSL1**
        - **No**
          - **BSL1**

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Standard Operating Procedures (SOPs)

- Receipt and storage
- Preparation
- Dispensing
- Disposal

Receipt and Storage

- Managed by the experts
- PPE
- Secure
- Temperature monitor
- Segregate
- Limit access

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Preparation

• Assess biosafety level
• Biological safety device
• Decontaminate, deactivate, disinfect
• Documentation


Dispensing

• Collaborate with IT
• Implement compounding technology
• Compounding worksheet
• Transport
• Drug accountability in clinical trials

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Disposal

- Regulations and guidelines
  - U.S. Environmental Protection Agency (EPA)
  - ASHP guidelines
- Licensure
- Legislation
- Research policy


Pharmacist Role - Operational

- Pharmacists have a key role
  - Identify risk level
  - Establish infrastructure
  - Develop policies and procedures
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Pharmacist Role – SOPs

• Standardize gene therapy
  – SOPs that are therapy specific
• Consider appointing a pharmacist to assume responsibility for gene therapies

Pharmacist Role - Education

• Training and education
  – Fill education gaps resulting from additional and changing roles and responsibilities
• Caregiver education
  – Educate patients and caregivers about administration issues, waste handling
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Administrative Challenges

- Clinically complex
- High-cost, one-time
- Payer complications
  - Site of care
  - Pharmacy vs. medical benefit
  - Patients living beyond normal referral area
- Analyzing financial impact on organization
- Operational difficulties

Senior Leadership Engagement

- Engage senior leadership early and often
- Novel therapies often represent a considerable budget variance (or planned increase)
- Senior leadership team is able to be supportive of processes to provide patients with access
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Our High-Cost Therapy Structure

• Separate work into clinical and financial teams
  – Shared organizer(s), but otherwise separate team membership
  – Minimizes waste of time by team members
  – Mitigates potential conflicts of interest
  – Facilitates confidential and compliant discussions

Teamwork Across Disciplines

**Clinical Team**

- Include physicians, nurses, pharmacists, clinical therapies
- Focus on providing the highest level of care to patients
- Discuss patient care issues, staff education, REMS requirements
- Collaborate on research and quality projects
- Develop clinical SOPs

**Finance Team**

- Include representatives from service-line administration, pharmacy administration, revenue cycle, payer relations, legal services
- Model finances of therapies
- Decide pharmacy vs. medical benefit
- Create closed-loop billing processes
- Establish terms of engagement with payers

REMS = risk evaluation and mitigation strategy
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Advice on Financial Analysis

• Pharmacy and finance should collaborate
• Develop population volume and payee mix
• Include reimbursement per payer class
• Account for WAC/340b mix as applicable
• Inpatient vs. outpatient administration
• Price is usually unavailable before FDA approval
• Analyze multiple scenarios

WAC = wholesale acquisition cost

Population-Specific Payer Mix

• Payer mix may vary significantly clinic to clinic
• Helps to identify variance that may impact your organization financially
• Helps you make prudent, informed financial decisions
• Run reports on payer mix of patient population by clinic or ICD-10 code
Estimating Volume - Example

• Duchenne muscular dystrophy
  – Always in boys
  – Incidence: 1:5000 boys; 1:10,000 births
    • Use incidence if treating at birth or at young ages, use prevalence if treating older patients
  – Birth rate in state: 140,000
    • Will all patients in our state come to us? No – 60%
    • Will patients from out of state come to us? Yes – additional area with 100,000 live births
  – Does a therapy work in all patients?
    • Phenotypical/severity differences? No – all patients have severe disease
    • Targeting specific genetic mutation? No – benefits all patients with disease

Annual Volume = [(140,000 x 50%) + 100,000]/10,000 = 17 new patients per year
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Prior Authorization Pitfalls

• Authorizing wrong benefit
• Authorizing the incorrect payer (primary vs. secondary)
• Authorization contrary to medical policy
• Using the incorrect HCPCS code

HCPCS = Healthcare Common Procedure Coding System

Operational Challenges

• Facilities
  – Multiple biological safety cabinets?
  – Dedicated space?
• Staff
  – Which staff will do this?
  – Does it fit into normal workflow?
• Training
  – Safe handling
  – Liquid nitrogen and ultra-low freezers
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Key Takeaways

- Gene therapy will likely be a significant part of treatment for genetic diseases in the near future
- Operational planning is necessary to be sure your organization is capable of providing gene therapy
  - Organizational capacity
  - Appropriate facilities
  - Staff training
- Gene therapies have large price tags, requiring significant financial planning and forecasting

Which of these practice changes will you consider making? (Select all that apply.)

a. Educate colleagues about gene therapies in the pipeline
b. Be a champion to ensure safe handling of gene therapies to protect myself, other staff, and patients and their caregivers
c. Develop policies and procedures related to handling gene therapies
d. Train staff to handle gene therapies in a controlled environment
e. Involve clinical and administrative representatives in evaluating the capacity of my organization to provide gene therapies in the future
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Q&A

• Submit your questions using the question tool in GoToWebinar