Viral Mediated Gene Therapy and Genetically Modified Therapeutics: *Occupational Safe Drug Handling in a Health-System Pharmacy*

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Objectives

1. Define the current FDA-approved clinical therapies requiring biosafety precautions in a healthcare setting.
2. List the key guidelines that should be consulted when developing institutional gene therapy policy and procedure.
3. Describe requirements within the upcoming hazardous drug handling guidelines that apply to viral vectors.

Disclosures

- Licensing agreement for gene therapy handling
  - Sarepta Therapeutics
  - Prevail Therapeutics

Nationwide Children's Hospital

- 527 bed free-standing pediatric institution in Columbus, Ohio
- More than 1.4 million patient visits annually

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Abigail Wexner Research Institute

- More than 1000 clinical research projects
- Center for Gene Therapy
- Viral Vector Core / Clinical Manufacturing Facility
  - Recombinant AAV

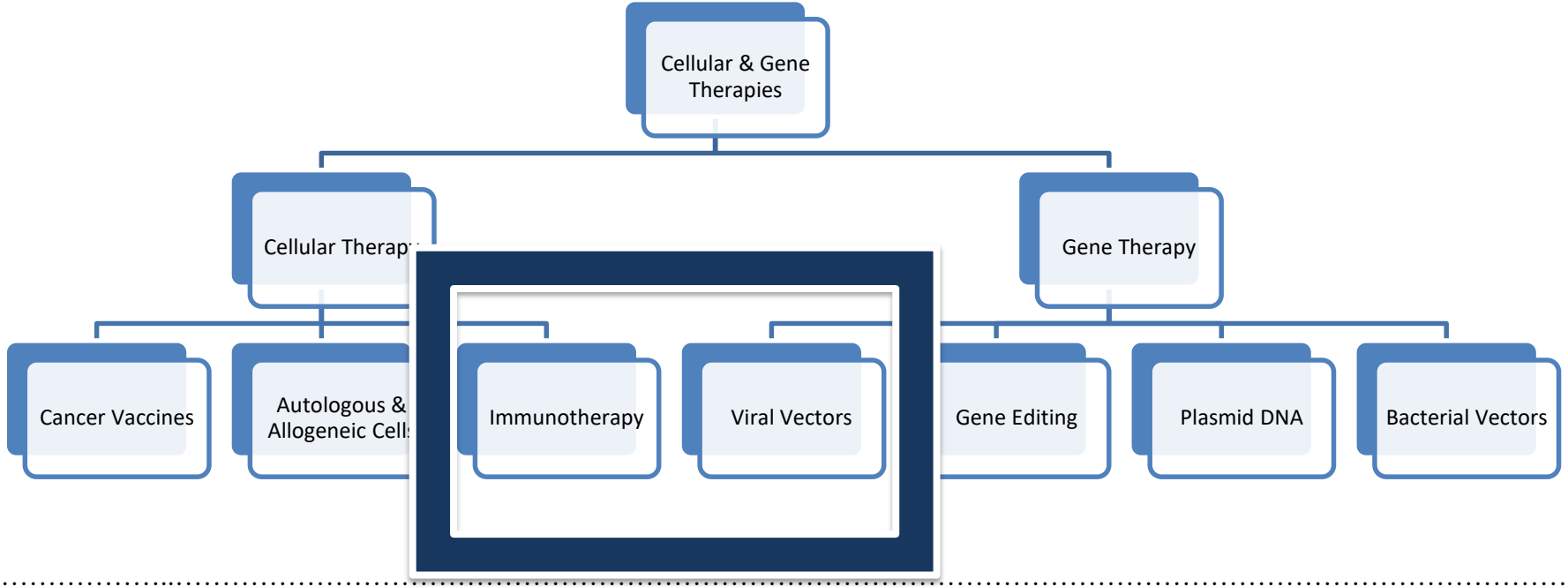
Research Pharmacy at NCH

- First clinical gene therapy trials in 2006
- Over 185 infusions to date
  - Cellular therapy
  - Immunotherapy
  - Viral vector therapy
- AAV, HSV, VSV, measles, etc.

New Era of “Drugs”

- Unknown in many pharmacy and healthcare settings
- Some estimate 40 gene therapy approvals by 2022

FDA Approved Gene Therapies



Commercial Products

Immunotherapy

- Imlygic® (talimogene laherparepvec)

Viral Vector Gene Therapy

- Luxturna® (voretigene neparvovec)
- Zolgensma® (onasemnogene abeparvovec)

Transitioning to Clinical Care

Gene Replacement Therapy: A Primer for the Health-system Pharmacist

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Michael Storey, PharmD[4], and Jill Blind, PharmD[4]

Abstract

Purpose: Comprehensive review of gene replacement therapy with guidance and expert o
for pharmacists. Summary: There are currently ~2600 gene therapy clinical trials wor
istration (FDA)-approved gene therapy products available in the United States. Gene thera
other drugs; however, there is a lack of guidance from the National Institutes of Health (NIH
and Prevention (CDC), World Health Organization (WHO), and professional associat
application. Although the NIH stratifies the backbone biologicals of viral vectors in gene t
information regarding minimization of exposure and reduction of risk exists. In the ab
institutions develop their own policies and procedures, which often differ and are often o
opinion on the role of pharmacists in institutional preparedness, as well as gene therapy ha
infrastructural model for gene replacement therapy handling is described, including requisite
operating procedure development. Personnel, patient, and caregiver education and trainin
macists have a key role in the proper handling and general management of gene replace
establishing infrastructure, and developing adequate policies and protocols, particularly in th
the handling and transport of gene replacement therapies.

Keywords
gene therapy, hospital pharmacy services, biosafety

Introduction

Gene therapy offers a novel approach to treating rare and some-
times life-threatening genetic diseases and may require new
responsibilities for pharmacy practice.[1] The American Society
of Gene and Cell Therapy (ASGCT) defines gene therapy as
the introduction or removal of genetic material or modificatio
of gene expression to alter the biological function of an indi-
vidual's genetic code with the objective of achieving a thera-
peutic benefit.[2] These approaches include replacing a
nonfunctional gene with a functioning healthy gene, inactivat-
ing a disease-causing gene, or introducing a new or modified
gene into the body. Mechanisms of gene therapy can include
gene replacement therapy, in which a fully functioning gene is
introduced to replace a mutated gene; gene addition for com-
plex cancerous and infectious diseases, in which a new gene is
introduced into the body to help fight a disease; gene inhibition
or "knockdown" to inactivate a mutated gene that is overpro-
ducing its product by targeting RNA; and gene editing that
permits targeted changes to a gene sequence.[3,4] Although there
are many types of gene therapy, this review will provide gui-
dance related to safe handling and administration of gene
replacement therapy, a form of gene therapy designed
specifically to provide o
a gene. Transfer of genet
plished through nonvira
delivery systems.[2] Alth
approaches use similar v
this modality will not be

Gene Replacemen

Gene therapies using vira
genetic gene both ex viv
consists of direct delivery
the option of systemic de

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Viral-mediated gene therapy and genetically modified therapeutics: A primer on biosafety handling for the health-system pharmacist

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Purpose. The guidance documents applicable to the manipulation of viral vectors in a health-system pharmacy are reviewed to provide recommendations for occupational safe drug handling.

Summary. Biosafety handling principles should be drawn from 2 guidance documents essential in the manipulation of biological material: *Biosafety in Microbiological and Biomedical Laboratories, 5th Edition*, and the National Institute of Health's *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*. Incorporating the biosafety guidance of these 2 documents into the pharmaceutical standards of *United States Pharmacopeia* chapter 800, "Hazardous Drugs—Handling in Healthcare Settings," will assist in the establishment of viral gene therapy handling guidelines in a health-system pharmacy.

Conclusion. Novel gene therapies and genetically modified therapeutic products will expose health-system pharmacists to classes of medications with unique biological handling requirements. Occupational safety data on the handling of these medications will be limited. The health-system pharmacy will need to rely on published biosafety recommendations to evaluate the infectious and genotoxic risks of these products while determining the necessary containment strategies to ensure safe work practice.

Keywords: biosafety, gene therapy, viral vector

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In December 2017, the United States Food and Drug Administration (FDA) granted approval of a novel gene therapy product for market in the United States. Clinical trials of voretigene neparvovec-rzyl, an adeno-associated viral vector therapy for patients with a biallelic *RPE65* mutation-associated retinal dystrophy, demonstrated significant improvement of functional vision over placebo.[1,2] This gene therapy approval came on the heels of 2 other genetically modified autologous T-cell-based immunotherapy authorizations for hematologic malignancies.[3,4] Tisagenlecleucel was shown to provide a durable remission in pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia,[4] while treatment with a cabtagene ciloleucel demonstrated 52% overall survival rate at 18 mont in patients with relapsed or refracto large B-cell lymphoma.[3] These tw targeted therapies have a high potent to treat or cure a variety of inherited d orders. Under the European Medicin Agency, these products are known advanced therapy medicinal products a class of biopharmaceutical age that covers gene therapy, somatic-c therapy, and tissue-engineered pro ucts.[4] In the United States, FDA includ human gene-editing technology, li CRISPR-Cas9 (i.e., clustered regula interspaced short palindromic repe and CRISPR-associated protein 9), a the oncolytic viral therapy of talimoge

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- Need for Policy Development
  - EAHP published handling guidelines in the 2007
- Two recent publications on gene therapy and viral vector handling

Recommendations for Policy Development

- Biosafety Requirements
  - CDC: *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*
  - *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*
- Local requirements
- United States Pharmacopeia General Chapters 797 (USP<797>) & 800 (USP<800>)

What is USP<800>?

- Chapter 800 from the United States Pharmacopeia
  - *Hazardous Drugs--Handling in the Healthcare Setting*
- Expands the definition of ‘hazardous drug’ and extends handling considerations outside of pharmacy
- Focuses on occupational safety of healthcare workers that handle hazardous drugs

USP<800> & Gene Therapy

- Biohazard precautions are a new consideration
- Package inserts of commercial products contain safe handling recommendations
  - Imlygic®: Use limited for immunocompromised and pregnant staff
  - Zolgensma®: 30 day contact precautions
- Most gene therapy still in investigational state

Recommended Handling

- Compounding environment
- PPE
- Training
- Spills & Cleaning
- Disposal & Waste
- Medical Surveillance

Table 1. Biosafety Handling Guidelines for a Health-System Pharmacy[a]

Item	Recommendation
Hazardous drug list	Recommend the addition of all gene therapy products to the hazardous drug lessen the restrictions.[17]
Storage	Access should be limited to those trained on biosafety handling procedures. transmission risk to the community or agricultural commodities. Recomme bol in required colors of fluorescent orange or orange-red for all gene ther BSL containment level; contact information for responsible party; procedu on storage units and at the entrance of any room when the agent is prese
Training	Standard operating procedures must be adopted prior to initial work with ge able for each agent and include actions in the event of an exposure. Effec cover all aspects of handling the agents. The health system must conside ment for appropriate response in the event of an exposure.
Medical surveillance	Medical surveillance should be provided to any individual that regularly hand of serum samples. Commercial vaccines should be made available to pro exposed. Personnel of reproductive capacity must confirm in writing that t individuals should be encouraged to self-identify.
Engineering controls	Primary engineering controls for sterile hazardous drug compounding as out biological compounding within a health system pharmacy.[17]

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Clinical Care Considerations

- Identify key experts within the institution
- Review available literature to develop safe & compliant policy
- Educate & train staff on biosafety handling

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