Gene Therapy: Yesterday, Today and Tomorrow

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*Alone we are rare. Together we are strong.*
This webinar is being recorded.
Question and Answer Session

Submit your questions using the chat function. It can be found at the **lower left hand corner** of the window.
NORD, an independent nonprofit, is leading the fight to improve the lives of rare disease patients and families.

We do this by supporting patients and organizations, accelerating research, providing education, disseminating information and driving public policy.
What: Two days of learning, networking, innovation and more
When: October, 21-22 2019
Where: Washington, DC
Venue: Marriott Wardman Park, 2660 Woodley Rd. NW Washington, D.C. 20008

Register today:
Today’s webinar is the first webinar in an exciting five-part series on gene therapy from NORD in collaboration with the American Society for Gene and Cell Therapy (ASGCT.)

Mark your calendar for the rest of the series:

- **The Science Behind Gene Therapy** - Wednesday, September 25
  - 3:00-4:00pm EST
- **The FDA's Role in Gene Therapy** - Wednesday, October 30
- **Understanding the Gene Therapy Process and Aftercare** - Wednesday, November 20
- **Life After Gene Therapy** - Wednesday, December 18

*Dates subject to change*
Speakers

Phillip Tai, Ph.D.
Instructor, Horae Gene Therapy Center
UMass Medical School

Cenk Sumen, Ph.D.
Chief Technology Officer, Stemson Therapeutics
Adjunct Professor, NYU Tandon School of Engineering
Gene Therapy: Yesterday, Today, Tomorrow

Phillip Tai, Ph.D.
Instructor
Horae Gene Therapy Center
UMass Medical School
Each cell in our body contains inherited genetic material. This genetic material is called DNA and contains important instructions for how our bodies work.

[Diagram showing cell, chromosome, and DNA with a link to Kintalk.org for more information.]
Genes are made up of DNA, which are the blueprints to build the enzymes or proteins that perform various crucial bodily functions.

- **Gene mutations**
  - Occur as cells age, exposed to certain chemicals, or are inherited.
  - *Small* changes to DNA within and surrounding genes can have large impacts on cellular function and such as breathing, walking, and digesting food.

[Diagram showing normal and mutated genes and their resultant proteins]

[Link: https://kintalk.org/genetics-101/]

[Logos of American Society of Gene & Cell Therapy and NORD National Organization for Rare Diseases]
Once inside the cell, the agent will correct the faulty gene by:

- Reducing levels of disease-causing proteins
- Increasing production of disease-fighting proteins
- Producing new or modified proteins

What is gene therapy?

It is the introduction, removal, or change of genetic material within patient cells. This transfer of genetic material into the cells of a patient repairs a gene or compensates for the loss of a gene to treat a specific disease.

Gene therapy mechanism of action

Once inside the cell, the agent will correct the faulty gene by:

- Reducing levels of disease-causing proteins
- Increasing production of disease-fighting proteins
- Producing new or modified proteins
How does gene therapy work?

- **Gene replacement**
  - Replaces non-working mutant gene (*loss-of-function genetic disease*) with a healthy one.

- **Gene silencing**
  - Inactivates a mutated gene that becomes toxic to cells (*gain-of-function genetic disease*).

- **Gene addition**
  - Overexpression of an “foreign” gene to impact disease state.

- **Gene editing**
  - Permanent manipulation of a gene in a patient’s genome.
Delivery mechanism

Typically, genetic material is transferred into the target cell using a “vector”, which is a carrier of the gene.

The most promising vectors are derived from viruses because they have evolved to enter cells very efficiently.

All viral genes are removed and replaced by our engineered genes.

https://www.asgct.org
Once inside the cell, the gene will make functional protein or target the disease-causing faulty gene.

https://www.asgct.org
Gene Delivery Vehicles

Viral Vectors

Non-viral Vectors

RNA viruses

DNA viruses

RNA viruses

DNA viruses
History of Gene Therapy

• In 1970, the first gene therapy trial in humans was administered. involved two sisters who had a rare genetic disease called hyperargininemia. Trial to test whether the Shope papilloma virus could limit arginine levels, but failed. It was discovered that the Shope papilloma genome does not encode for arginase production.

• In 1980, a gene therapy trial on two patients with beta-thalassemia. Martin Cline tried to insert the gene needed for normal production of hemoglobin into extracted bone marrow cells of the patients’ and infused the cells back into the patients. However, the experiment failed to produce positive results.

• In December 1988, the National Institute of Health’s Recombinant DNA Advisory Committee (RAC) approved a clinical trial to introduce a foreign gene into humans. This study resulted in no growth of tumors at the injection site, and this indicated that gene transfer with engineered viruses can be used safely.
First human gene therapy for ADA via retrovirus (Sept 14, 1990)

First lentivirus against HIV (2003)

Clinical trial for X-linked ALD (2014)

CAR-T-cell therapy (2011)

Discovery of AAV8 (2002)

First adenovirus for cystic fibrosis (1993)

First AAV for CFTR (November 1995)

HVTN502 by Merck (2004)

First lentivirus against HIV (2003)

Oncoretive Herpes simplex virus for Viral therapy of cancer (2000)

Gendicin by Sibiono Gene Tech, China (2004)

Two cases of leukemia in patients receiving retroviral X-linked SCID

LUXTURNA (1st In vivo Gene Tx approved by FDA 10/22/2017)

1st ex vivo Gene Tx approved by FDA (8/30/2017)

Glybera approved by EMA (2012)

AAV to treat hemophilia B (2011)

AAV2 gene transfer to treat LCA (2008)

Gene therapy for chronic pain (2009)

Glybera approved by EMA (2012)

History of clinical viral vector gene therapies

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Trends in Gene Therapy
Gene therapy drug development:
- Starts with a specific therapeutic agent
- Skips the drug discovery phase

The promise of gene therapy
Adeno-Associated Virus (AAV)

• AAV is believed by many to be the future of gene therapy, especially following the Zolgensma approval.

• First discovered in 1960s by Bob Atchison as a contaminant in adenovirus preparations.
There are over 400 active and recruiting clinical trials for gene and cell therapy in the US. Information can be found at: https://app.emergingmed.com/asgct/home//
Why has it been difficult to develop gene therapies?

- Limited patient populations for rare disease trials
- Length of clinical trial process
  - Preclinical and clinical trials to determine safety and efficacy take a long time
- Uncertain of durability at this time
- Halts, but does not typically reverse, damage
Unique Benefits of Gene Therapy

• Unmet need: treating rare, debilitating diseases that have few to no treatment options
• Approved therapies to date have high efficacy
• Aims for single administration
• Targets the cause of disease
• Can reduce or eliminate need for other costly treatments (e.g., hemophilia and sickle cell disease)
• Potential positive effect on indirect and intangible costs (e.g., ability to work)
Gene therapy - state of the industry and future trends

Cenk Sumen, Ph.D.
Chief Technology Officer, Stemson Therapeutics
Adjunct Professor, NYU Tandon School of Engineering
Why is gene therapy so valuable?

- Efficacy
- One-time intervention
- Can potentially prevent a lifetime of expensive and/or painful treatments
Listed below are some of the major gene therapy approvals in the US and EU:

- 2016 EMA approval of Strimvelis for ADA-SCID
- 2017 FDA approval of Kymriah for certain B-cell acute lymphoblastic leukemia
- 2017 FDA approval of Yescarta for certain B-cell lymphoma
- 2017 FDA approval of Luxturna for certain Leber Congenital Amaurosis
- 2019 FDA approval of Zolgensma for Spinal Muscular Atrophy
- 2019 EMA approval of Zynteglo for beta thalassemia
Most Recent FDA Approval

- Approval of Zolgensma (AveXis/Novartis treatment) for very rare SMA Type 1 based on systemic AAV9 delivery of a working SMN1 gene to motor neurons
- Why treat children under 2 years of age? Damage accumulates and currently cannot be reversed
- This approval demonstrates a lot of promise with the AAV vector
Current Challenges for Gene Therapy Manufacturing

- Manufacturing is complex and time intensive
- Potential capacity constraints
  - Some therapies require a high dose that is difficult to mass produce.
    - For example: the dosage for Zolgensma is $10^{14}$ viral genomes per kg
    - This is more viral particles than cells in your body
• Creating a system to support families and build the necessary infrastructure to be able to provide access and care before and after therapy
• Patients should contact their health insurance provider to determine coverage and out of pocket costs. Manufacturers of gene therapies often offer patient support services to assist in navigating the process.

Patient support programs should:
• Provide dedicated, individualized support to patient families and caregivers
• Support reimbursement and financial coordination among stakeholders
Future Direction of Gene Therapy

• Ensuring access for patients globally
• Collaboration between stakeholders to make therapies affordable and accessible to patients
• Capacity scale-up for AAV manufacturing
• Gene therapy factories of the future
• Automation, AI, logistics, single use systems
• Streamlined regulatory landscape
• Other vectors and technologies for gene therapy
• Determining how many of the >5,000 genetically-based rare diseases can we treat with gene therapy
Resources for Patients and Caregivers

Clinical Trials
Clinicaltrials.gov

National Institutes of Health

Food and Drug Administration
https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

ASGCT
https://www.asgct.org/education/gene-therapy-basics

NORD
https://rarediseases.org/video-topic/research-science/#watch-39678
Question and Answer Session
Submit your questions in the chat box.

Dr. Sumen and Dr. Tai will answer them in the order in which they came in and based on relevance to the discussion.
Thank you.

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rarediseases.org