The Road to Ocular Gene Therapy: Lessons from the Past

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The Road to Ocular Gene Therapy: Lessons from the Past

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UMASS Medical School

Eyes to the Past Conference
October 29, 2019

Khanna Lab
The ultimate application of molecular biology would be . . . . . when polynucleotide sequences can be grafted by chemical procedures onto a virus DNA....
Gene Therapy for Human Genetic Disease?

Proposals for genetic manipulation in humans raise difficult scientific and ethical problems.

Theodore Friedmann and Richard Roblin

Schematic Model of Genetic Disease

Some aspects of a hypothetical human genetic disease in which an enzyme is defective are shown in Fig. 1. The consequences of a gene mutation which renders enzyme $E_3$ defective could be (i) failure to synthesize required compounds $D$ and $F$; (ii) accumulation of abnormally high concentrations of compound $C$ and its further metabolites by other biochemical pathways; (iii) failure to regulate properly the activity of enzyme $E_1$, because of loss of the normal feedback inhibitor, compound $F$; and (iv) failure of a regu-
The Good News
1990

Michael Blaese, French Anderson and colleagues: 1990

1st approved gene therapy for severe combined immune deficiency

1995

Dr. Terence Flotte, 1995

First use of recombinant AAV in humans in Cystic Fibrosis clinical trials
The setback
Jesse Gelsinger, an 18 year old with a relatively mild form of the nitrogen metabolism disorder ornithine transcarbamylase (OT) deficiency, is the first person to die on a gene therapy trial because of vector associated toxicity.
The Return
Novel adeno-associated viruses from rhesus monkeys as vectors for human gene therapy

Guang-Ping Gao, Mauricio R. Alvira, Lili Wang, Roberto Calcedo, Julie Johnston, and James M. Wilson*
First Ocular Gene Therapy Drug

2001
Proof of concept in dogs

2008
1st clinical trial

2017
FDA approved drug

2017
First Treated Patient

First Ocular Gene Therapy Drug

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Proof of concept in dogs

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First Treated Patient

First Ocular Gene Therapy Drug
The present
Gene Therapy

**Gene augmentation therapy**
- **Cell with faulty gene**
- **Introduce functioning gene**
- **Cell functioning normally**

**Gene-specific targeted therapy**
- **Cell in a disease condition**
- **Introduce therapeutic/suicide gene**
- **Cell death**
- **Cell functioning normally**

**Genome editing or correction therapy**
- **Cell with faulty gene**
- **Introduce genome editing system**
- **Cell functioning normally**
Ocular gene therapy

- X-linked retinoschisis
- Optic neuropathies
- Achromatopsia
- LCA
- X-linked RP
The road ahead
Genetic Testing and
Natural History

Mapped and Identified Retinal Disease Genes 1980 - 2019
Delivery route and vehicles

- Intravitreal delivery
- Subretinal delivery

Techniques for Vector delivery
Delivering large genes

Modeling ocular diseases
AOTC:
Advanced Ocular Therapeutics Center
Advanced Ocular Therapeutics Center (AOTC):
Dr. Shlomit Schaal, Director

Clinical research:
Dr. Johanna Seddon, Director

Translational Research:
Dr. Haijiang Lin, Director

Basic Mechanisms and Preclinical Research:
Dr. Hemant Khanna, Director

Ocular Research Services:
Dr. Claudio Punzo, Director

Age-related Macular Degeneration
Retinitis Pigmentosa
Diabetic Retinopathy
Leber congenital amaurosis
Stargardt Disease
Glaucoma
Usher Syndrome
Retinal ciliopathies
Other ocular conditions
The Team, to date

- Dr. Terence Flotte
- Dr. Guangping Gao
- Dr. Anastasia Khvorova
- Dr. Michael Volkert
- Dr. Neil Aronin
- Dr. Miguel Sena-Esteves
- Dr. Heather Gray-Edwards
- Dr. Robert Kotin
Mission

• Innovative therapeutic paradigms
• Clinical trials site
• State of the art research services
• Train and recruit exceptional talent