2019-10-29

The Road to Ocular Gene Therapy: Lessons from the Past

Hemant Khanna  
*University of Massachusetts Medical School*

Let us know how access to this document benefits you.  
Follow this and additional works at: [https://escholarship.umassmed.edu/eyes-to-the-past-presentations](https://escholarship.umassmed.edu/eyes-to-the-past-presentations)

Part of the [Eye Diseases Commons](https://escholarship.umassmed.edu/eye-diseases), [Health Sciences and Medical Librarianship Commons](https://escholarship.umassmed.edu/health-sciences-and-medical-librarianship), [History of Science, Technology, and Medicine Commons](https://escholarship.umassmed.edu/history-of-science-technology-and-medicine), [Medical Education Commons](https://escholarship.umassmed.edu/medical-education), [Medical Humanities Commons](https://escholarship.umassmed.edu/medical-humanities), and the [Ophthalmology Commons](https://escholarship.umassmed.edu/ophthalmology)

Recommended Citation  
Khanna H. (2019). The Road to Ocular Gene Therapy: Lessons from the Past. Eyes to the Past Reception Presentations. [https://doi.org/10.13028/d22g-n975](https://doi.org/10.13028/d22g-n975). Retrieved from [https://escholarship.umassmed.edu/eyes-to-the-past-presentations/1](https://escholarship.umassmed.edu/eyes-to-the-past-presentations/1)

This material is brought to you by eScholarship@UMassChan. It has been accepted for inclusion in Eyes to the Past Reception Presentations by an authorized administrator of eScholarship@UMassChan. For more information, please contact Lisa.Palmer@umassmed.edu.
The Road to Ocular Gene Therapy: Lessons from the Past

Hemant Khanna, PhD
Associate Professor
Department of Ophthalmology & Visual Sciences
Horae Gene Therapy Center
UMASS Medical School

Eyes to the Past Conference
October 29, 2019
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 regul-
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
2002

Dr. James Wilson  Dr. GaungpingGgao

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*
You can simply impress your audience and add a unique zing and appeal to your Presentations.

2001 Proof of concept in dogs
2008 1st clinical trial
2017 FDA approved drug
2017 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 RP

X-linked retinoschisis

Optic neuropathies

Achromatopsia

LCA
The road ahead
Genetic Testing and Natural History

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

- Intravitreal delivery
- Subretinal delivery
Delivering large genes

Modeling ocular diseases
AOTC: Advanced Ocular Therapeutics Center
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