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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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Horae Gene Therapy Center

UMASS Medical School

Eyes to the Past Conference

October 29, 2019

Khanna
Lab

1963

Joshua Lederberg



MAN and his FUTURE
Edited by GORDON WOLSTENHOLME
Copyright © 1963 Ciba Foundation

Biological Future of Man

JOSHUA LEDERBERG

DARWIN's theory set off the historic debate on man's past. Today, with a new biology we mirror his future. Poetry may speak more bravely than Science. However, Policy must rely on Science for an accurate vision of the bounds of human evolution.

The ultimate application of molecular biology would be when polynucleotide sequences can be grafted by chemical procedures onto a virus DNA....



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1972

Excitement and Caution

3 March 1972, Volume 175, Number 4025

SCIENCE

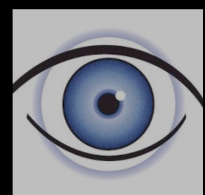
Gene Therapy for Human Genetic Disease?

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-



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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



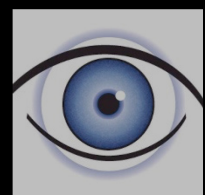
1999



The screenshot shows the top portion of a Washington Post article. At the top left, there are navigation links: HOME, INDEX, SEARCH, and ARCHIVES, next to the 'wp' logo. Below this is the website address 'washingtonpost.com'. A horizontal menu contains categories: NEWS, STYLE, SPORTS, CLASSIFIEDS, and MARKETPLACE. A second row of links includes: PRINT EDITION, TOP NEWS, WORLD, NATION, POLITICS, METRO, BUSINESS & TECH, HEALTH, OPINION, and WEATHER. The main headline reads 'Teen Dies Undergoing Experimental Gene Therapy'. Below the headline, it says 'By Rick Weiss and Deborah Nelson' and 'Washington Post Staff Writers'. At the bottom of the article header, it states 'Wednesday, September 29, 1999; Page A01'. On the left side, there is a 'Related Items' button and a 'Print Edition' link.



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



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The Return



2002

Dr. James Wilson

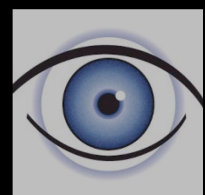


Dr. GaungpingGgao



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*



First Ocular Gene Therapy Drug

2001
Proof of concept in
dogs



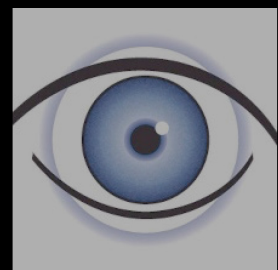
2008
1st clinical trial



2017
FDA approved drug



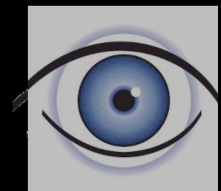
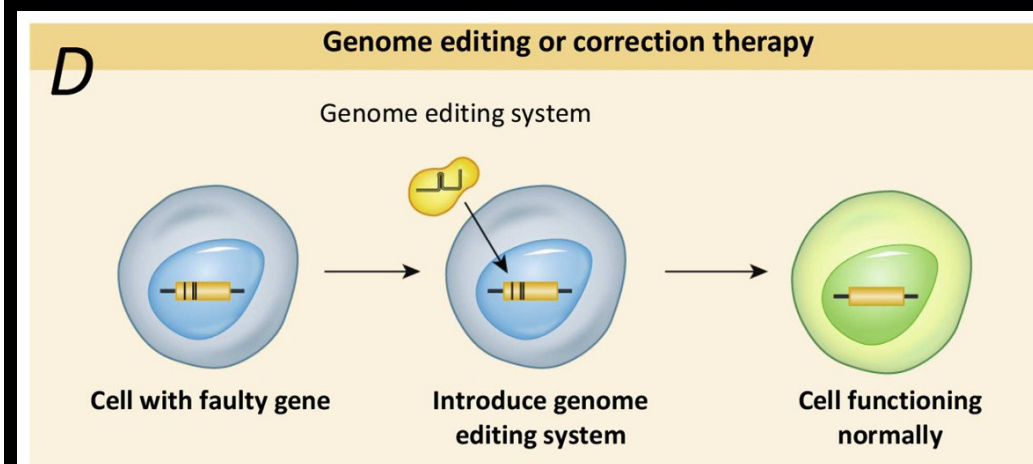
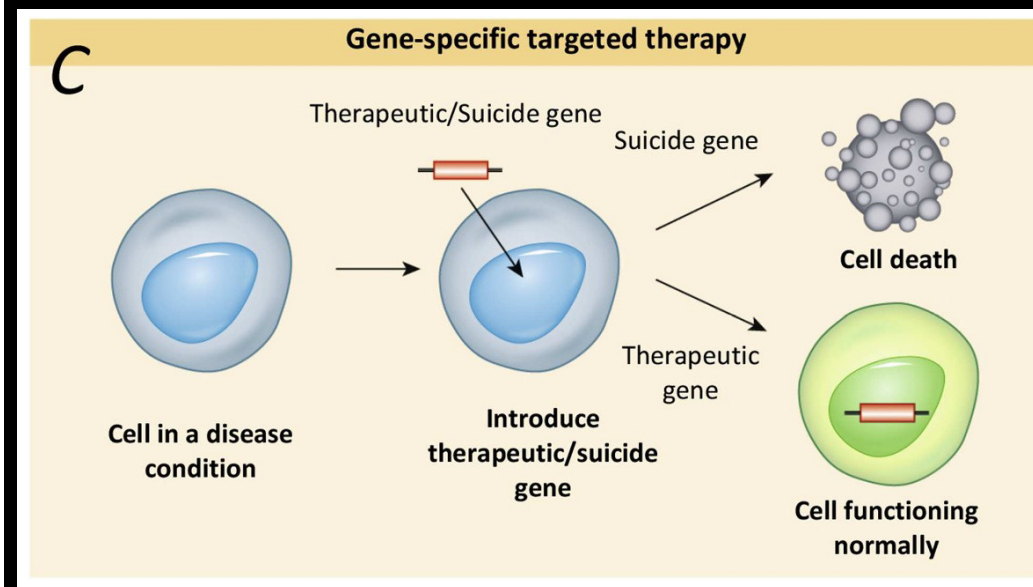
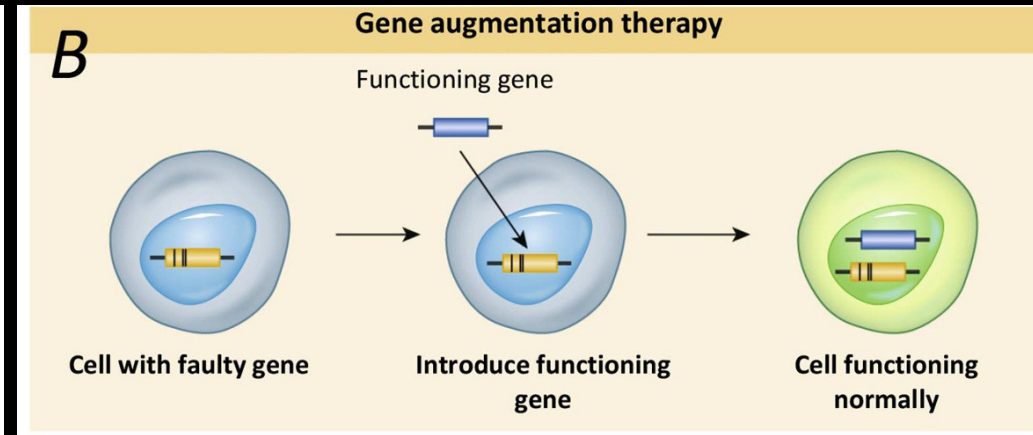
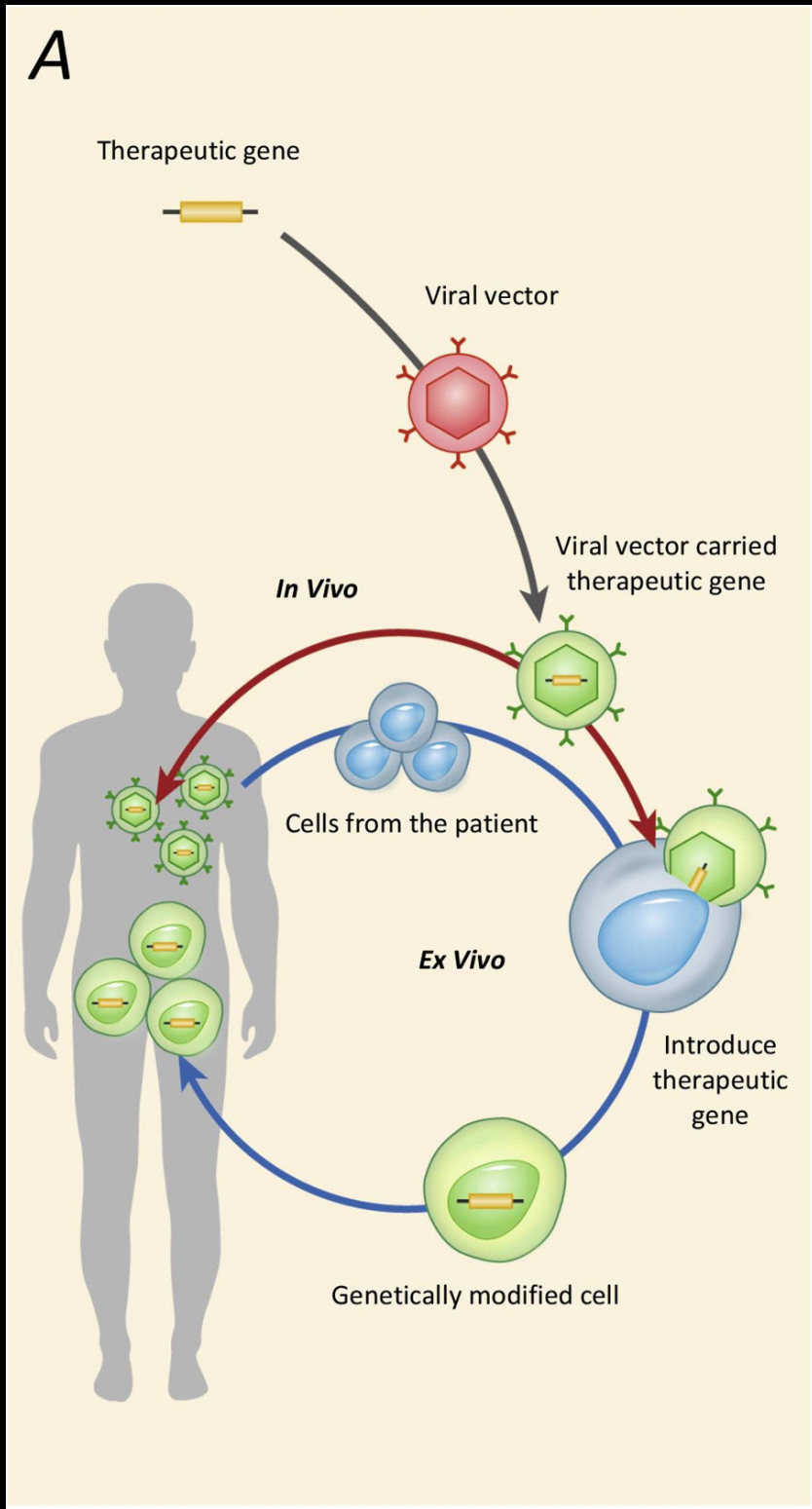
2017
First Treated Patient



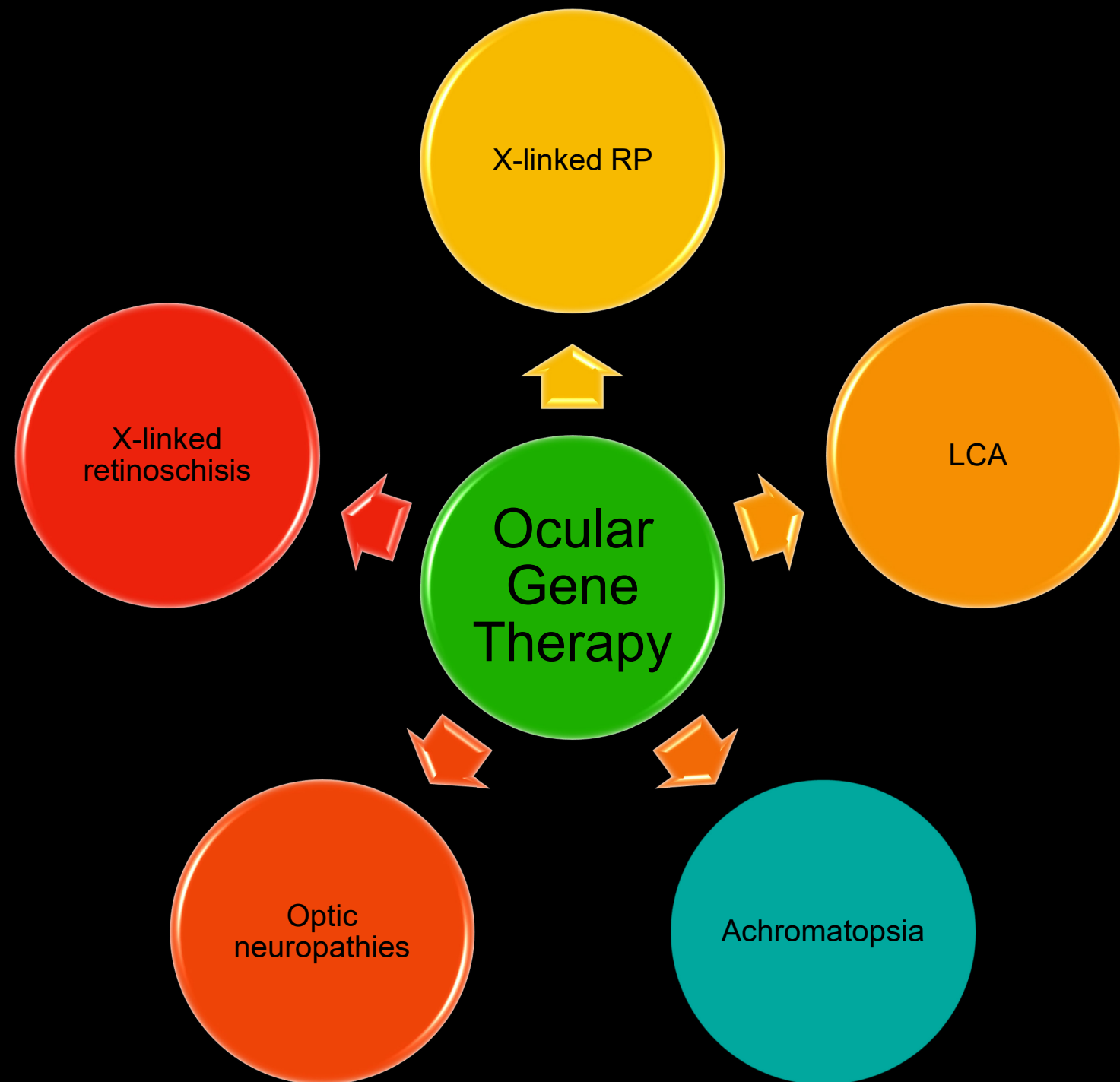
The present



Gene Therapy



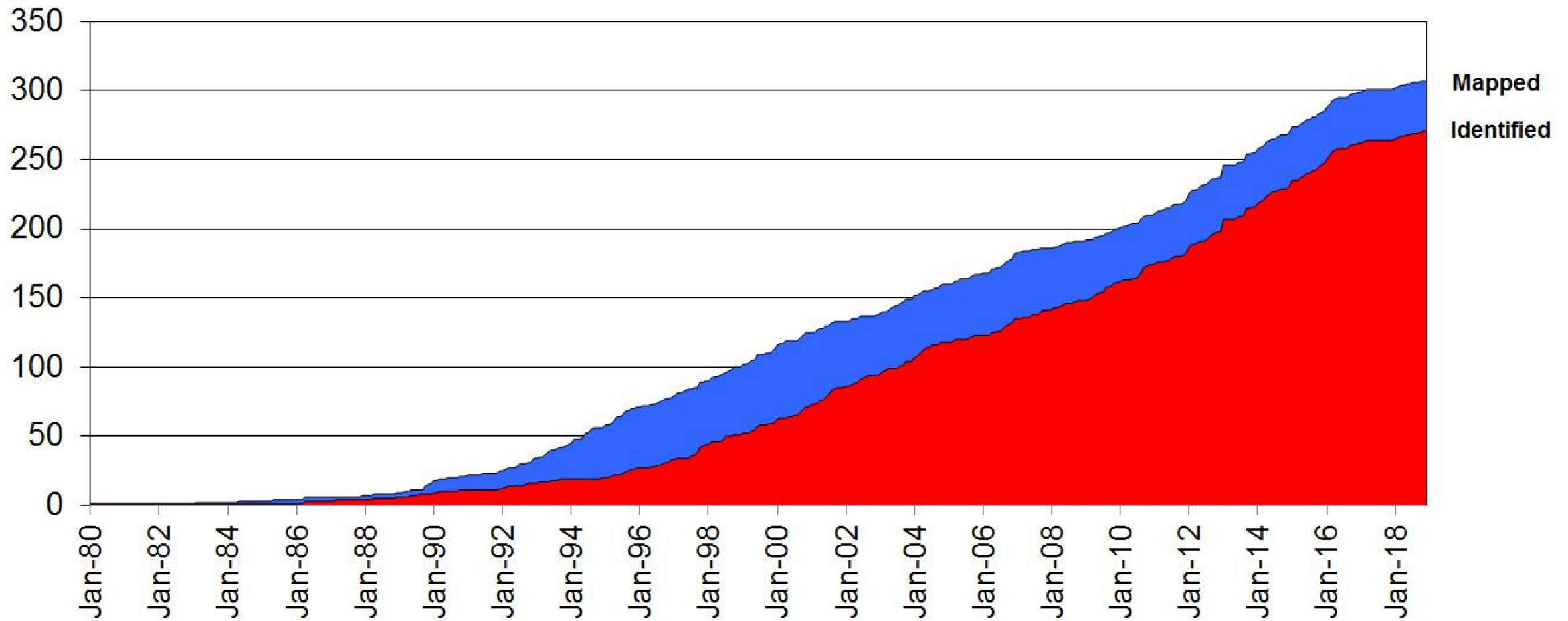
Ocular gene therapy



The road ahead



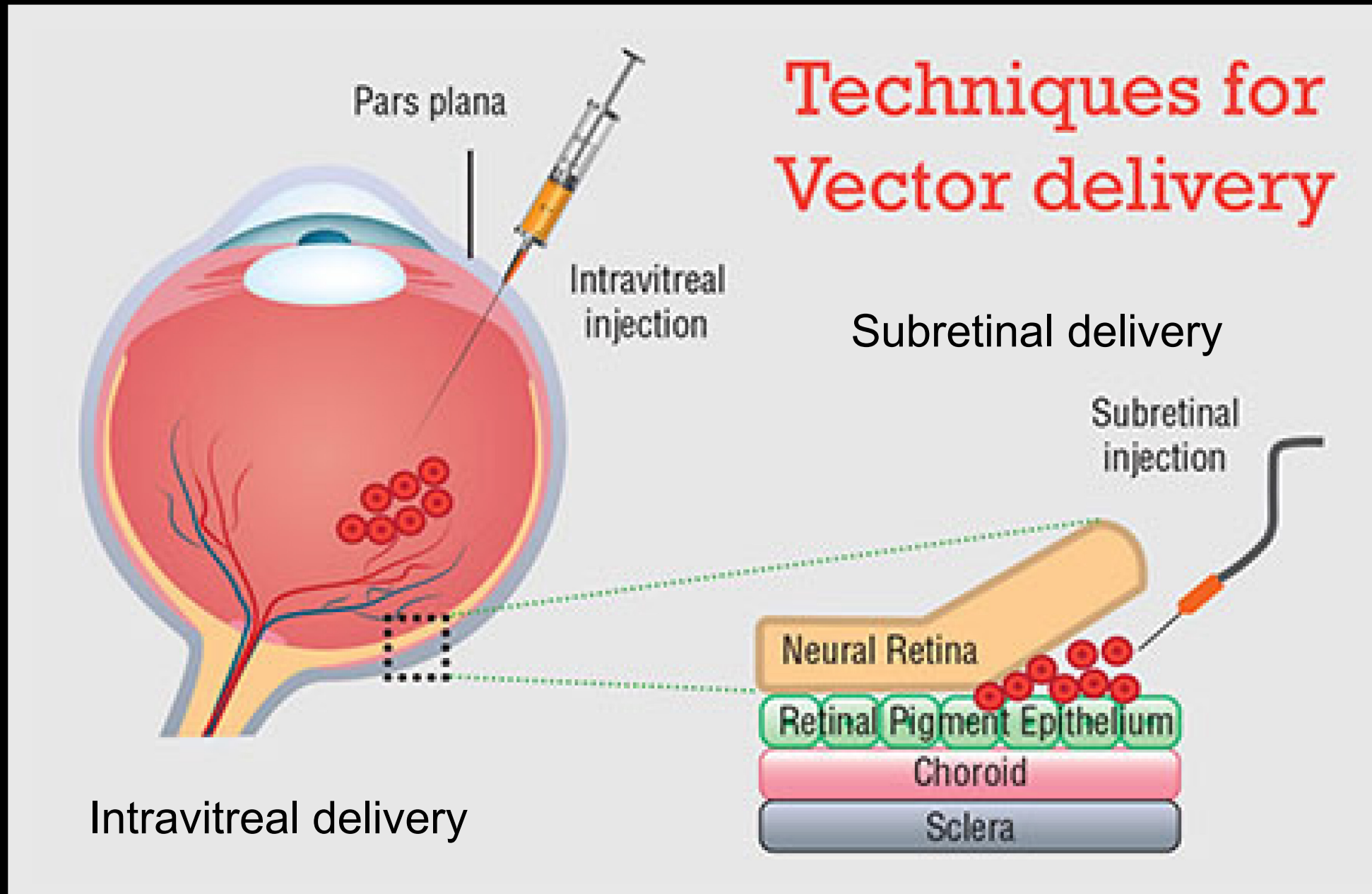
Genetic Testing and Natural History



Mapped and Identified Retinal Disease Genes 1980 - 2019

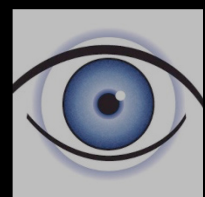


Delivery route and vehicles

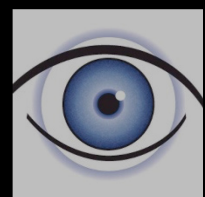


Delivering large genes

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



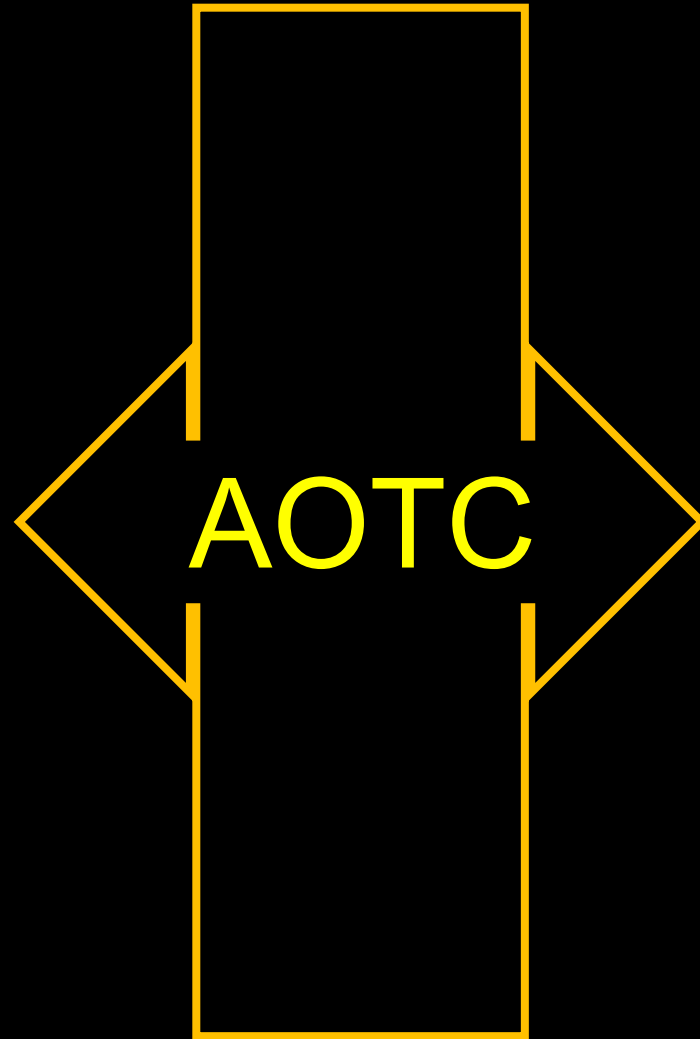
The Team, to date



Dr. Terence Flotte



Dr. Guangping Gao



Dr. Neil Aronin



Dr. Heather Gray-Edwards



Dr. Anastasia Khvorova



Dr. Michael Volkert



Dr. Miguel Sena-Esteves



Dr. Robert Kotin



Mission

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

