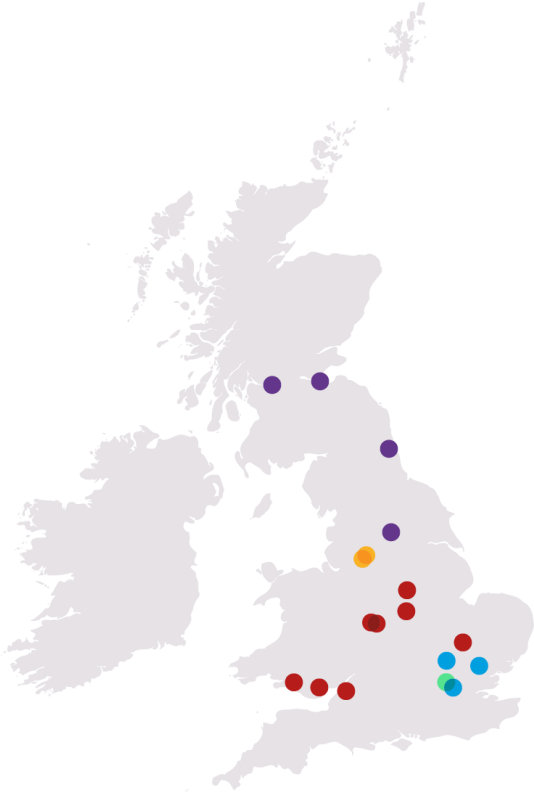
Advanced Therapy Treatment Centres

LONDON ADVANCED THERAPIES

Gene Therapy for the eye

Jack Hickmott,
Research Associate, Imperial College London

Chaired by Sarah Hanson
Senior Paediatric Research Nurse, Leeds General Infirmary



Funded by

INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by

CATAPULT Cell and Gene Therapy

Who are LAT and the ATTCs?

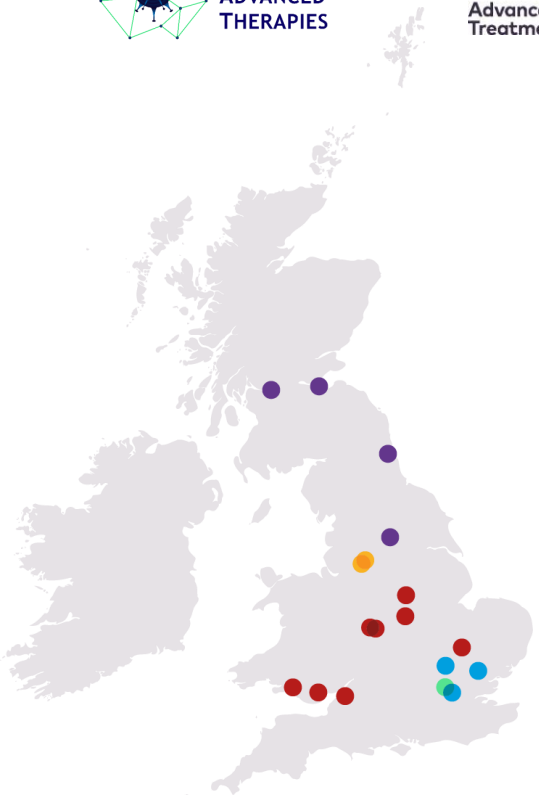
The ATTC (Advanced Therapy Treatment Centre) network is funded by Innovate UK and the Industrial Strategy Challenge Fund

London Advanced Therapies (LAT) is funded by Research England

The centres are working together, along with the Cell and Gene Therapy Catapult to specifically look at the training requirements for the current workforce and what needs to be put in place for them to be ready to deliver the treatments that are currently being developed.

This series of webinars is designed to help increase the awareness of advanced therapies and their impact in the clinic

Find out more at https://www.theattcnetwork.co.uk/



Coordinated by

Imperial College London

Gene Therapy for the Eye

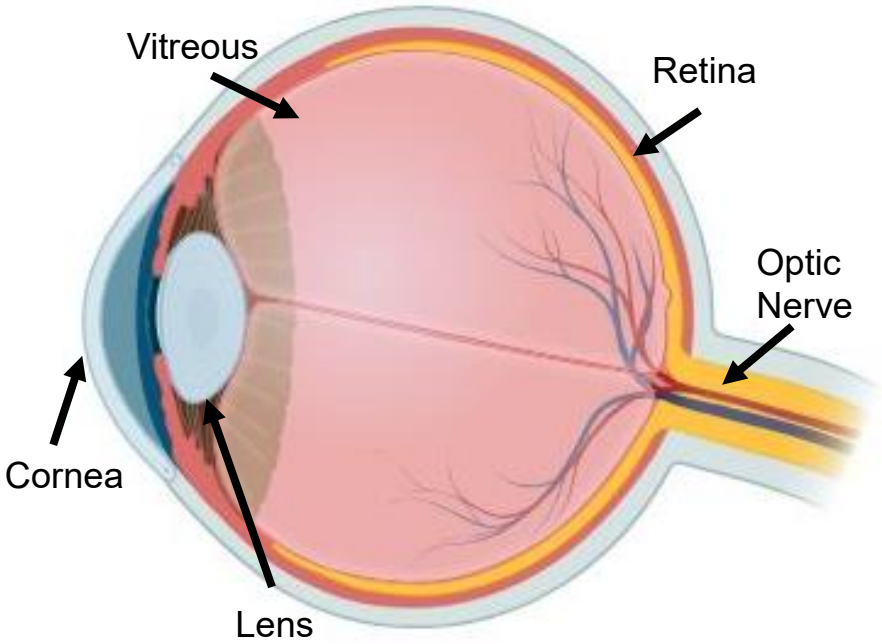
Using Viruses, Bacteria, and Algae to Treat Blindness

Jack W Hickmott, PhD

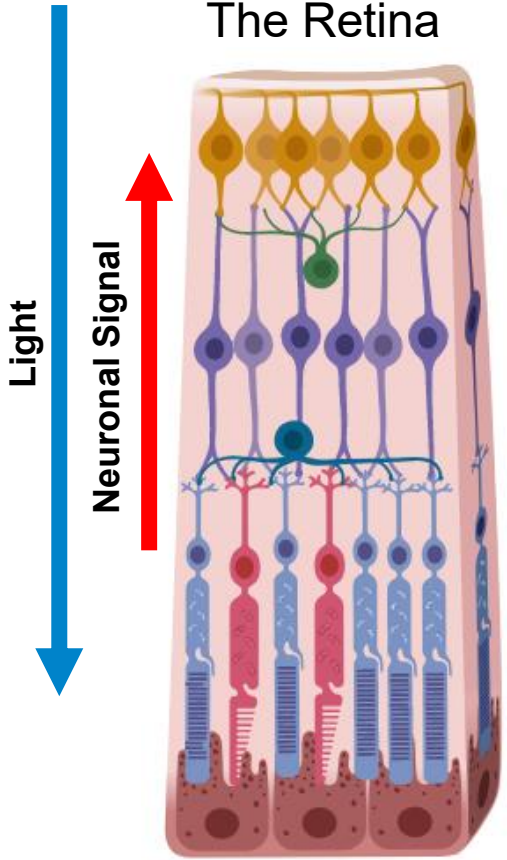
22nd June 2021

Anatomy of the Eye

The human eye

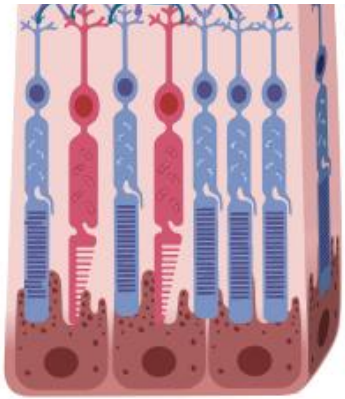


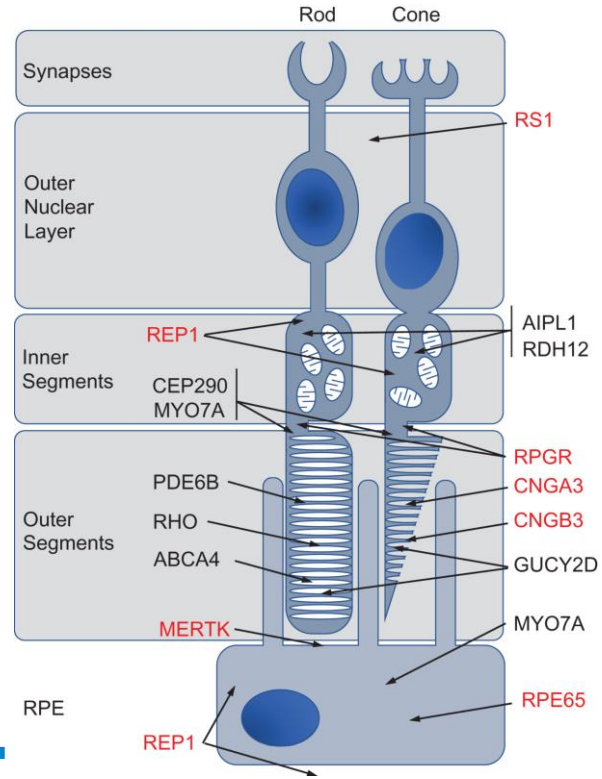
The Retina



Images adapted from biorender.com

Numerous Eye Disorders of the Photoreceptors Alone





CEP290 – Leber Congenital Amaurosis Type 10

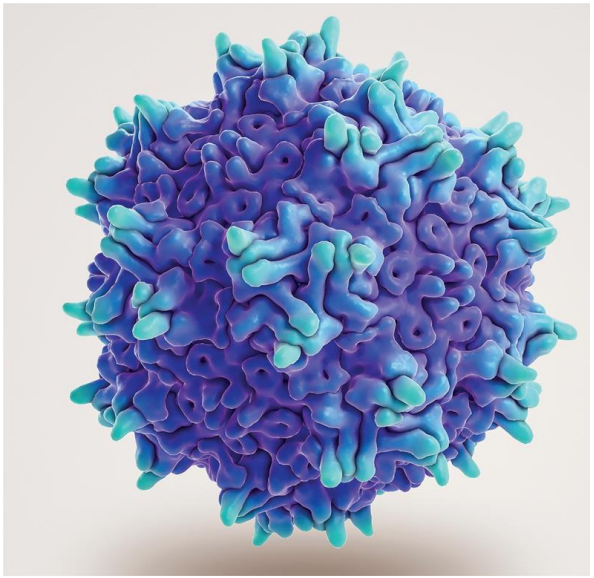
REP1 – Retinitis Pigmentosa

RPE65 –Leber Congenital Amaurosis Type 2

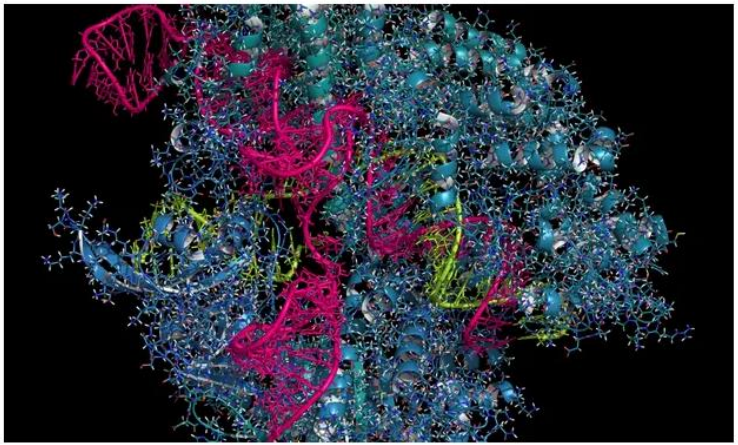
Images from: Biorender.com & Kumaran, N., et al, 2018, Br Med Bull

Using Viruses, Bacteria, and Algae to Treat Blindness

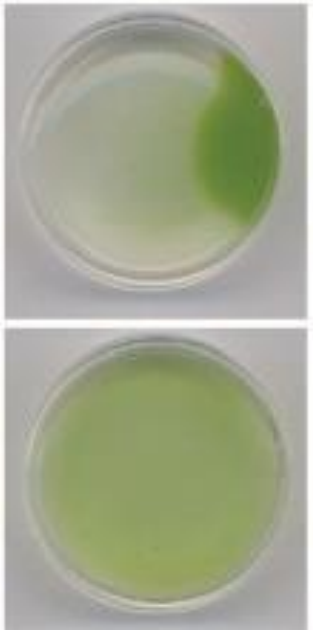
Adeno Associated Virus



CRISPR-Cas9



Channelrhodopsin



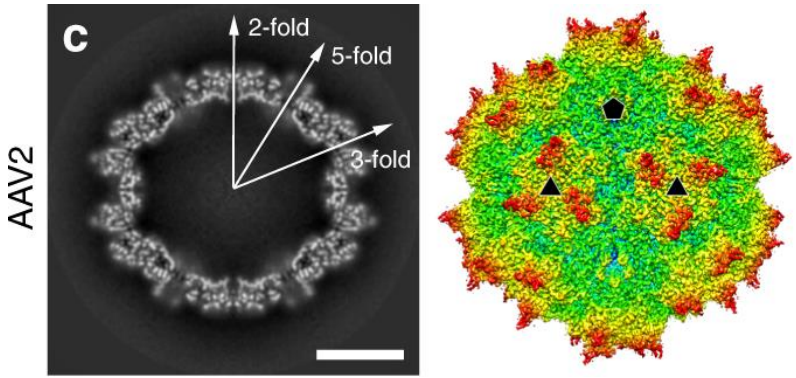
Images adapted from: https://science.sciencemag.org/content/366/6469/1090.1, https://www.theguardian.com/, and Hegemann & Nagel 2013, EMBO Mol Med

Clinical Case 1: 15 Year Old Patient

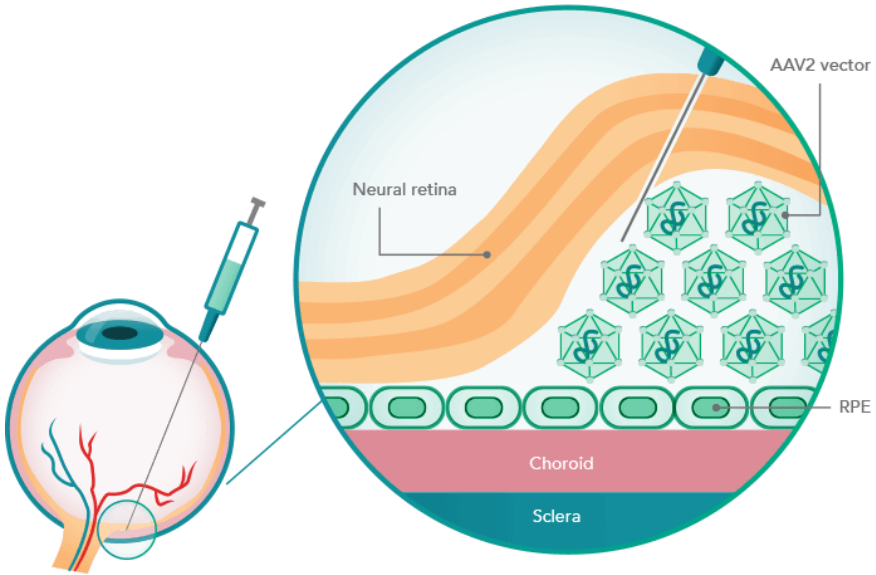
- Diagnosed as an infant with Leber Congenital Amaurosis Type 2
- Confirmed mutations in *RPE65*
- Patient has night blindness
- Declining visual acuity during the day
- No small molecule drugs to prevent further vision loss
- What can be done for the patient?

Need a Way to Replace RPE65 in the Eye

AAV2 – The favourite vector for the eye



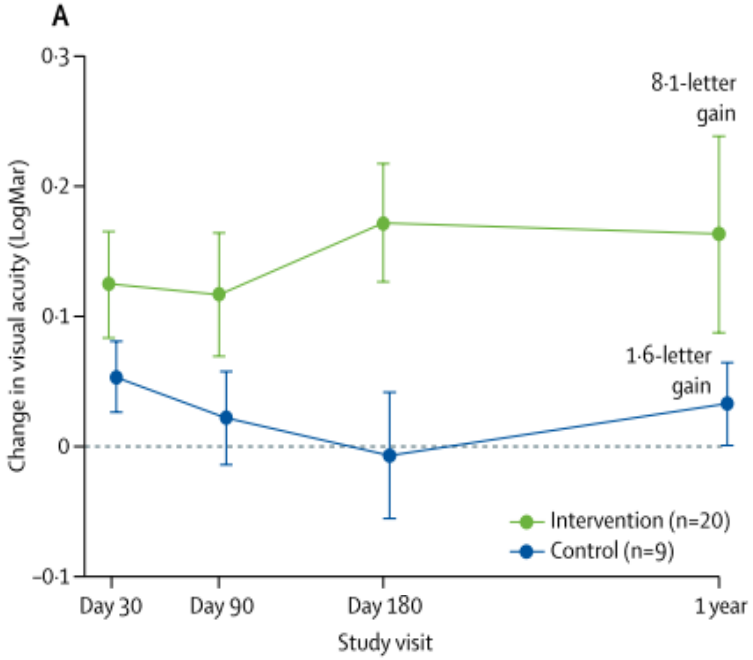
Subretinal Delivery



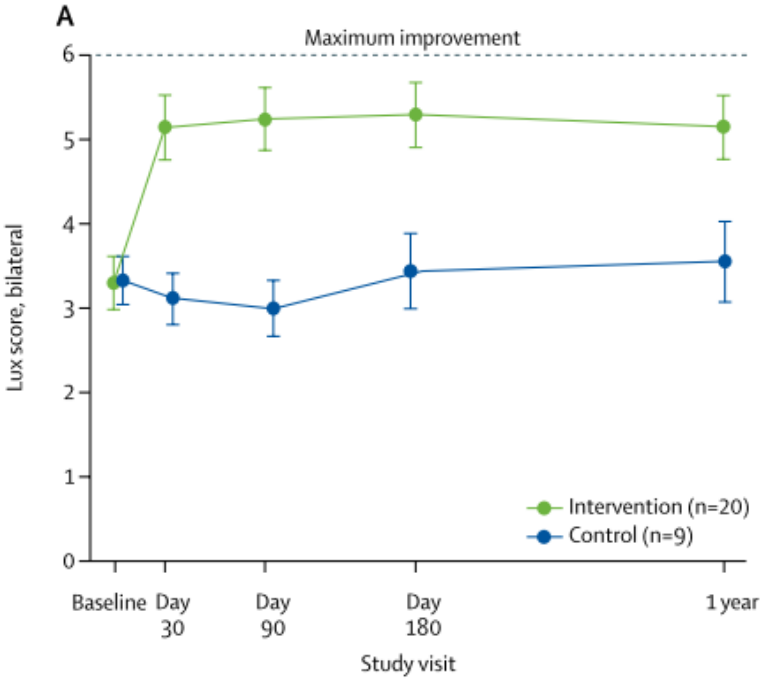
Images from: Zhang, R. (2019), & https://luxturnahcp.com/how-LUXTURNA-works/mechanism-of-action/

RPE65 Gene Therapy (Luxturna) Makes Clear Improvements

BCVA Visual Acuity Test



Multi-Luminance Mobility Test



Images from Russell et al (2017)

Luxturna is Leading the Way for AAV Gene Therapy

NEWS

Home | Coronavirus | Brexit | UK | World | Business | Politics | Tech | Science | Health | Family & Education

Health

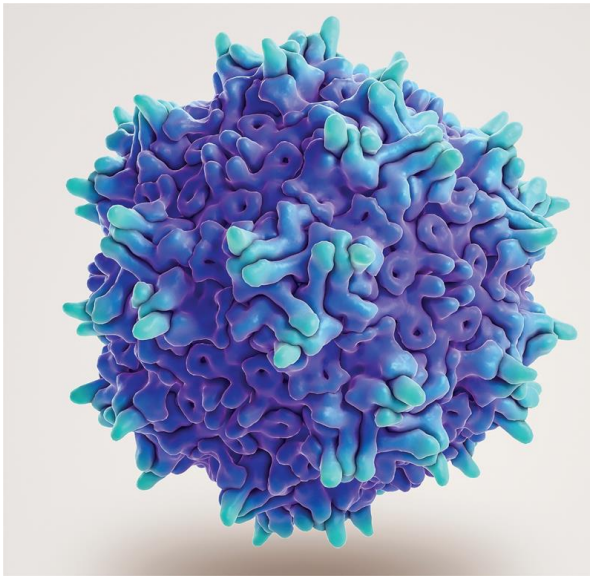
Gene therapy: 'Now I can see my own face again'

By Fergus Walsh
Medical editor

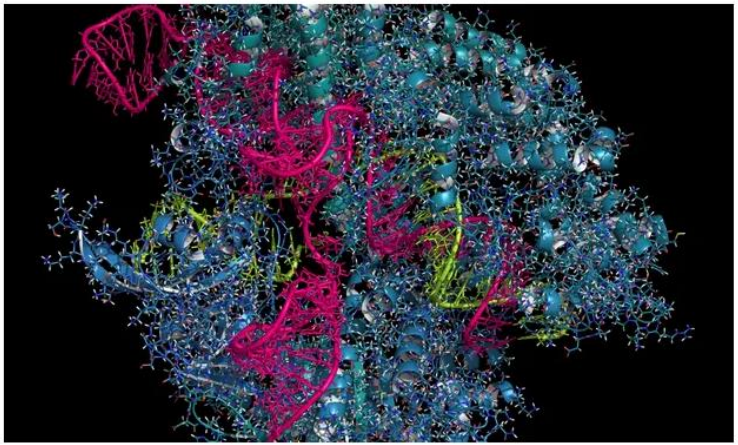
29 April

Using Viruses, Bacteria, and Algae to Treat Blindness

Adeno Associated Virus



CRISPR-Cas9



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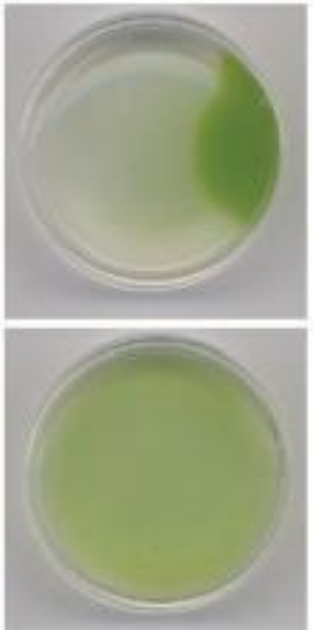
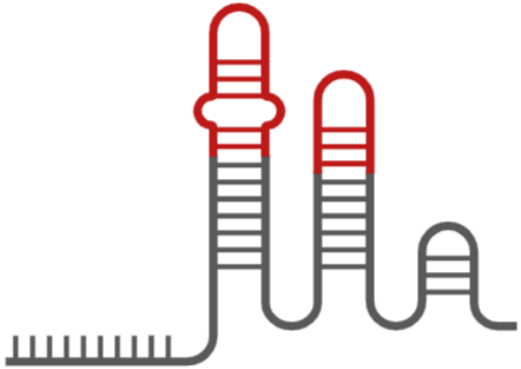


Images adapted from: https://science.sciencemag.org/content/366/6469/1090.1, https://www.theguardian.com/, and Hegemann & Nagel 2013, EMBO Mol Med

Clinical Case 2: 43 Year Old Patient

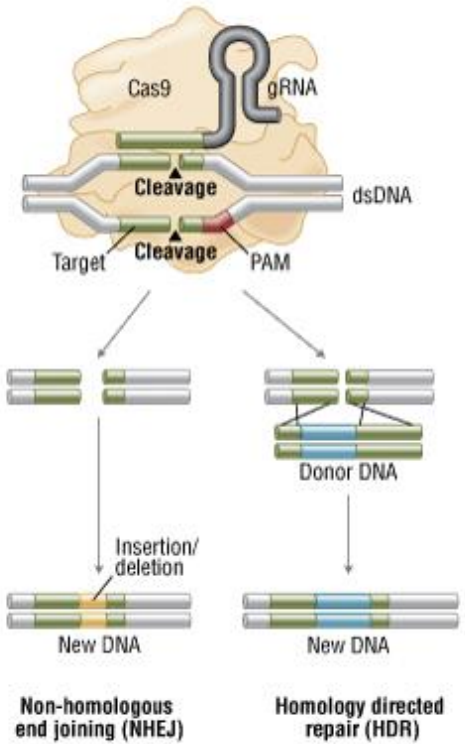
- Visual impairment from infancy
- Diagnosed with Leber Congenital Amaurosis Type 10
- Caused by mutations to *CEP290* gene, too big to fit into AAV
- No peripheral vision, no visual autonomy
- No interventions to improve vision
- Need a different approach for these patients

CRISPR-Cas9: Bacterial Immune System for Gene Editing



Guide RNA – locates a specific spot in the genome and base pairs with it

Cas9 – Binds to a guide and cuts DNA



Images from: Biorender.com and NEB.com. For more on gene editing: Advanced Therapies Education Webinar by Kyriel Pineault

Solution – Use AAV to Deliver CRISPR-Cas9

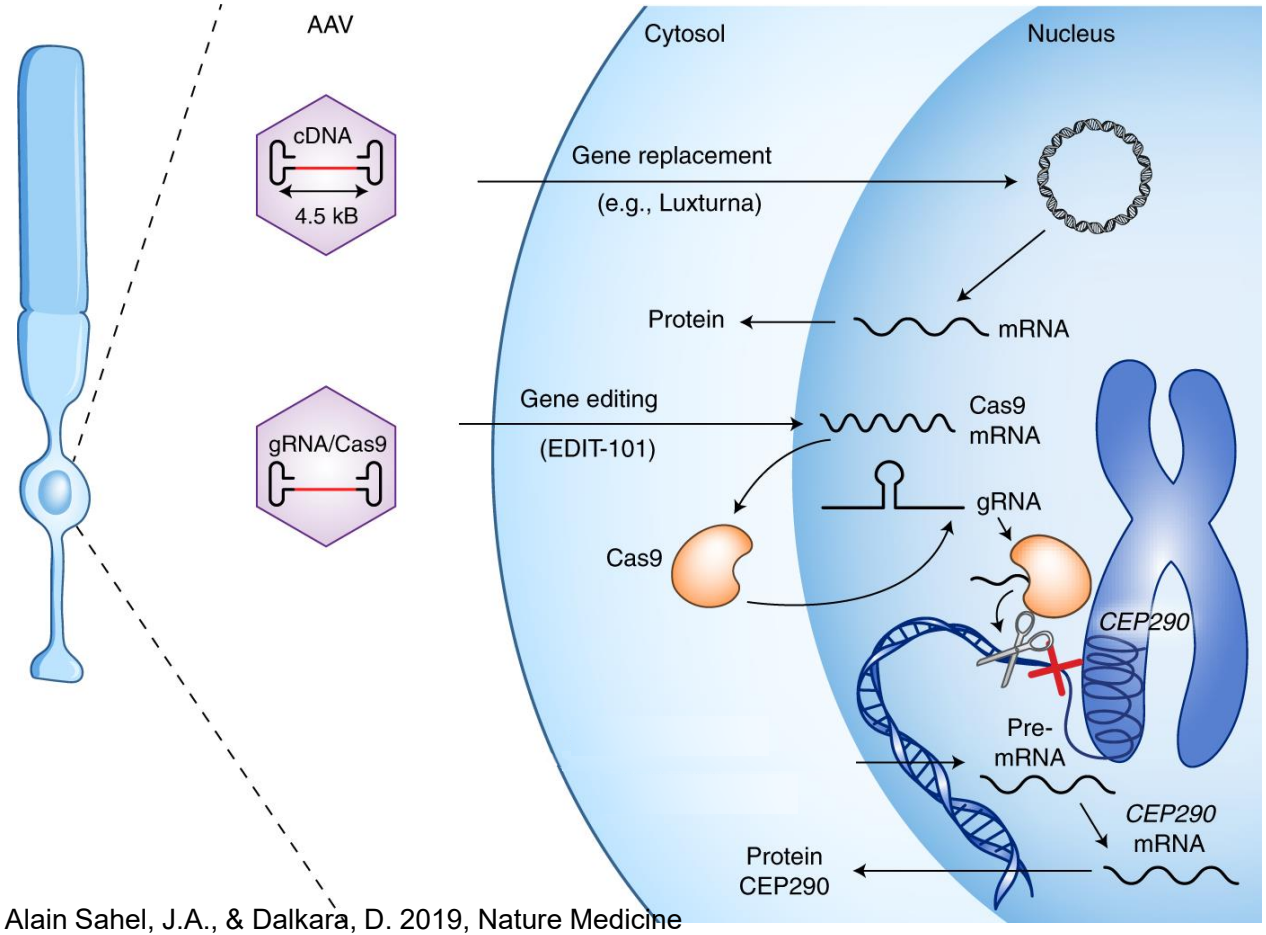
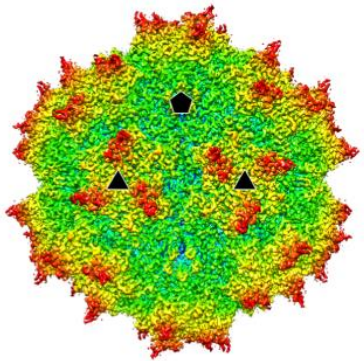


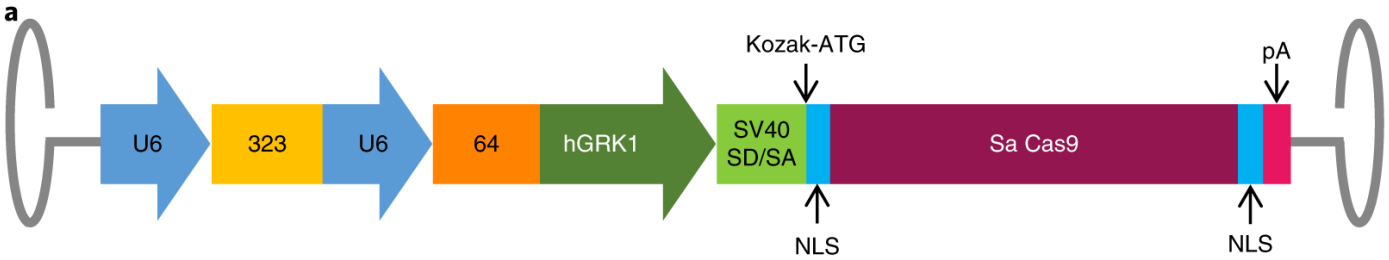
Image adapted from: José Alain Sahel, J.A., & Dalkara, D. 2019, Nature Medicine

First time CRISPR-Cas9 Injected Into Patients: BRILLIANCE Clinical Trial (NCT03872479)

AAV



Gene Editing Strategy



Images adapted from: Zhang, R., et al, 2019 and Maeder, M.L., et al, 2019, Nature Medicine

BRILLIANCE leads the way for gene editing in humans

TREATMENTS

Blind Patients Hope Landmark Gene-Editing Experiment Will Restore Their Vision

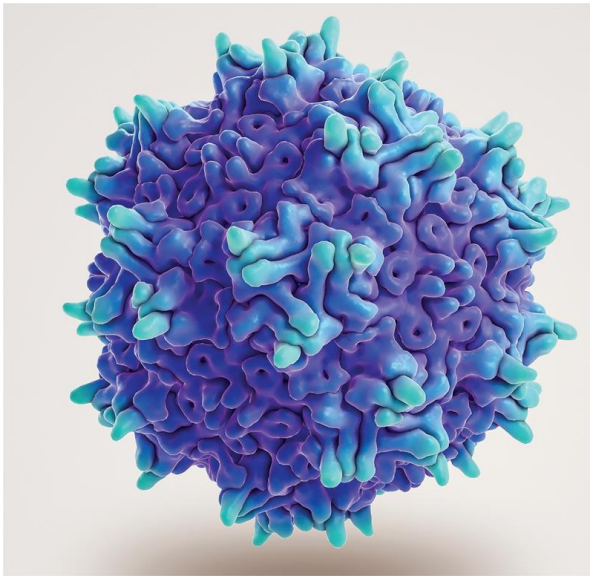
May 10, 2021 · 5:00 AM ET
Heard on Morning Edition

"It's hard to put into words," Kalberer said. "You hope for it. You do the best you can. But to even have the possibility — it's a gift."

Headline from NPR: May 10, 2021

Using Viruses, Bacteria, and Algae to Treat Blindness

Adeno Associated Virus



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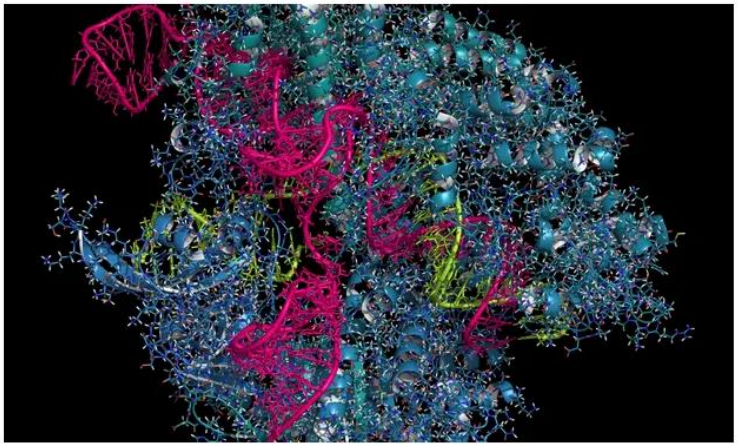

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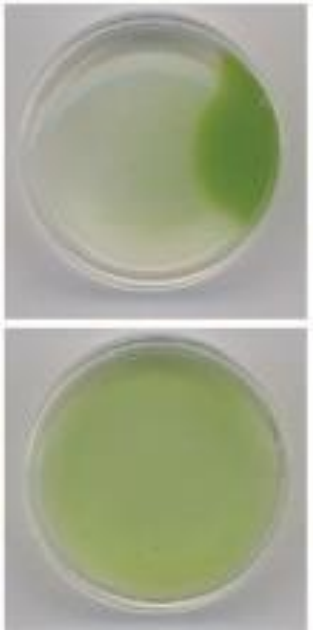


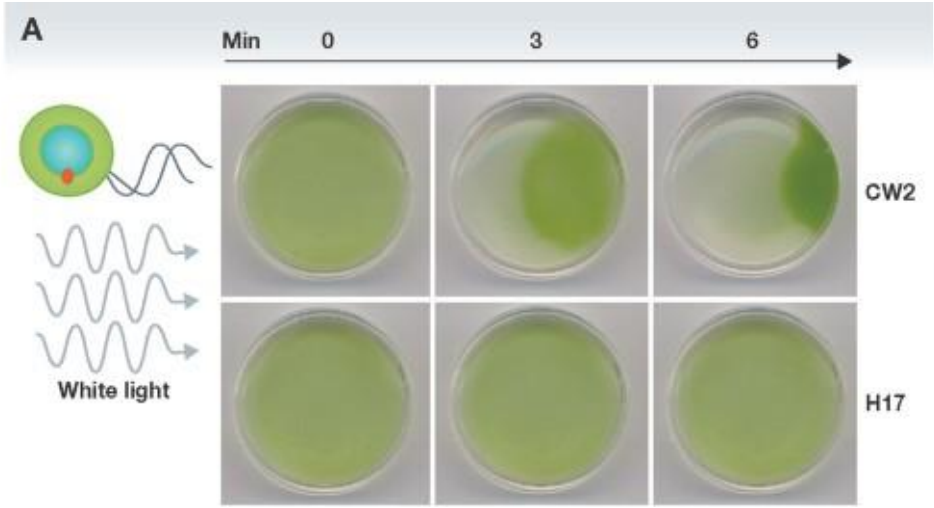
Images adapted from: https://science.sciencemag.org/content/366/6469/1090.1, https://www.theguardian.com/, and Hegemann & Nagel 2013, EMBO Mol Med

Clinical Case 3: 58 Year Old Patient

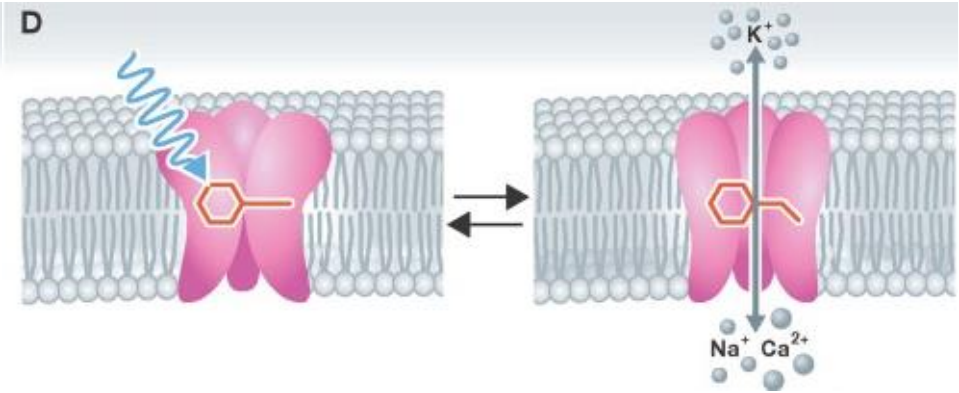
- Diagnosed at 18 with Retinitis Pigmentosa
- Life long decline in vision
- Light perception only
- Has a complex disease - Over 70 known genes
- Photoreceptors damaged, dead, and can not be replaced

Need a Way to Restore Photodetection

Algae respond to light



Channelrhodopsin mediates this response



Images adapted from: Hegemann & Nagel 2013, EMBO Mol Med

Combine Gene Therapy With a Device to Restore Vision

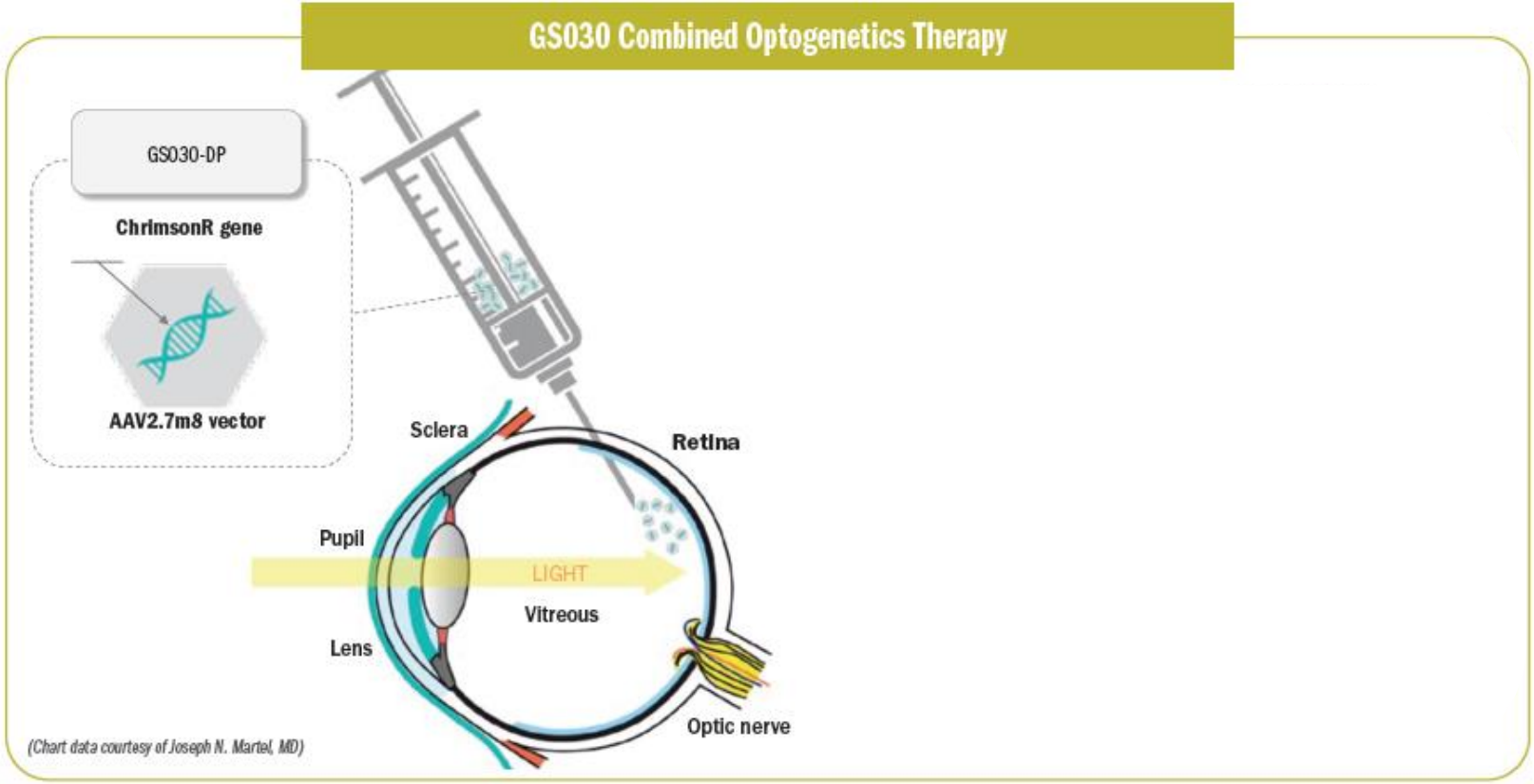


Image from: https://www.modernretina.com/

PIONEER Clinical Trial (NCT03326336)

Without device

With device

Images adapted from: Sahel, J.-A., et al 2021, Nature Medicine

PIONEER is Leading the Way, but There is a Way to go

MATTER

Scientists Partially Restored a Blind Man's Sight With New Gene Therapy

Using a technique called optogenetics, researchers added light-sensitive proteins to the man's retina, giving him a blurry view of objects.

Health

Algae proteins partially restore man's sight

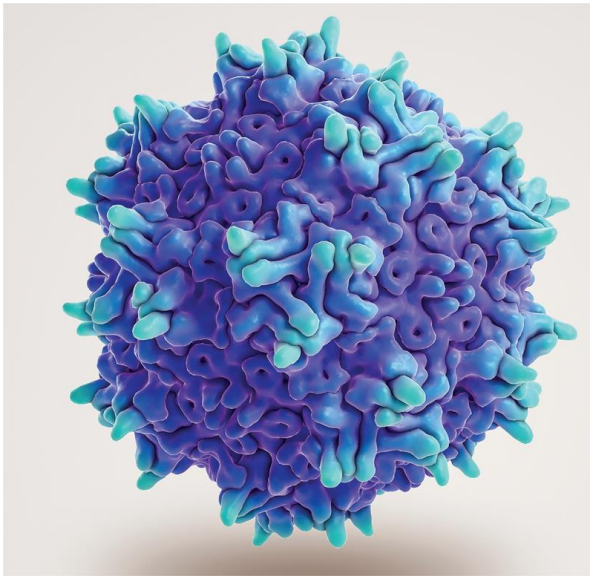
By James Gallagher
Health and science correspondent

24 May

Headline from: the New York Times & BBC May 24, 2021

Using Viruses, Bacteria, and Algae to Treat Blindness

Adeno Associated Virus



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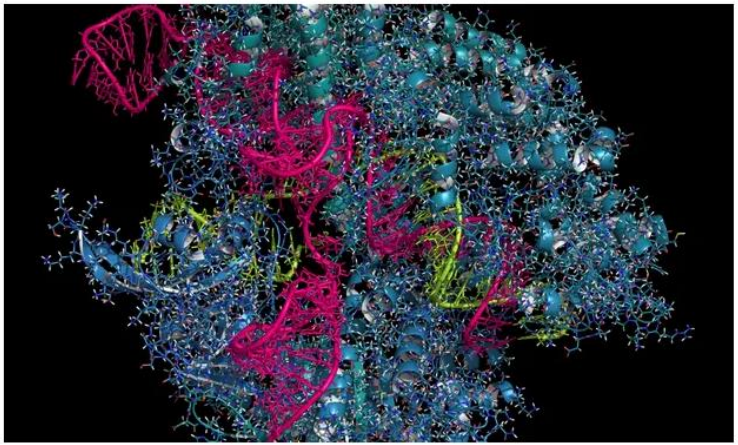

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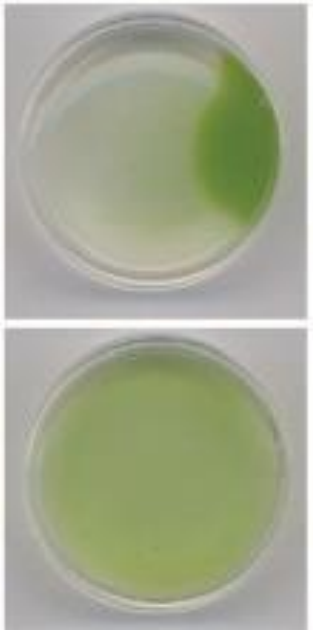

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Thank You!

- **Q&A**

- Please add any question you have into the Q&A box
- Please fill in feedback survey, your input is really valuable to us
- Look out for our new series of webinars starting in September