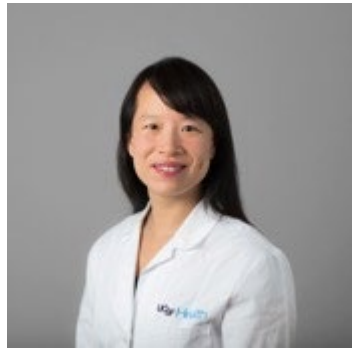
MODERATED SESSION

Prevent Blindness
Focus on Eye Health National Summit

Aging Eye and Vision



Session Moderator:
Yvonne Ou, MD
University of California, San Francisco

Bruce R. Ksander, PhD
Massachusetts Eye and Ear
Harvard Medical School

Anand Swaroop, PhD
National Eye Institute, National Institutes of Health

Mass General Brigham
Mass Eye and Ear

Turning Back Time:
Breakthrough research in reversing glaucoma and age-related vision loss

Bruce R. Ksander, Ph.D.

Glaucoma

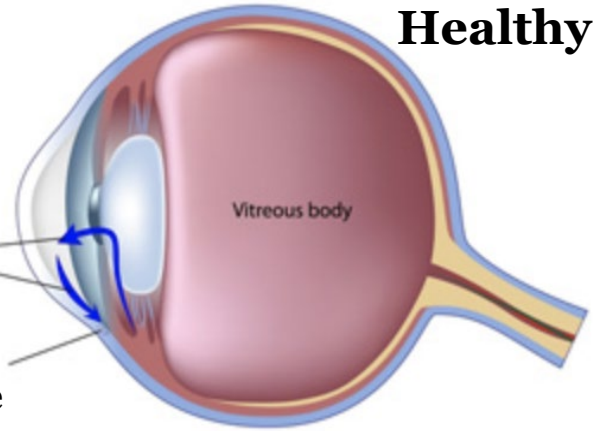
- Chronic neurodegenerative disease causing irreversible blindness
- A leading cause of blindness in the world (**>75 million people worldwide**)
- Multiple forms of glaucoma (open angle, closed angle, secondary glaucoma)

All share a common endpoint: **death of Retinal Ganglion Cells (RGCs)**

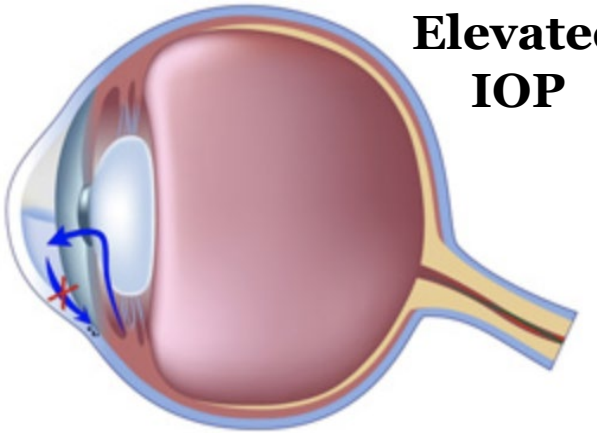
Elevated Intraocular Pressure (IOP)

A significant risk factor for glaucoma

Healthy

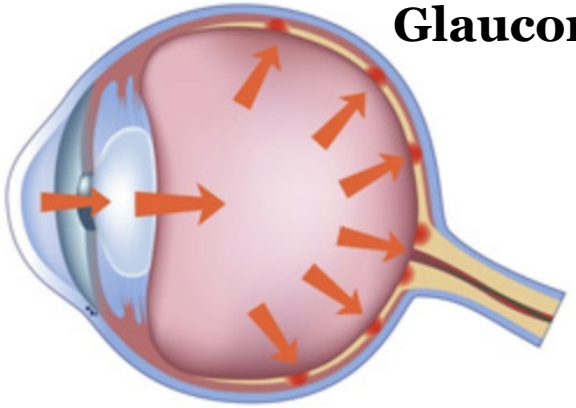


Elevated IOP



Drainage canal becomes blocked and leads build up of AqH and increased IOP

Glaucoma



The increased IOP causes damage to the optic nerve and RGCs

Only treatment for glaucoma
Lowering IOP through surgical and pharmacological approaches.

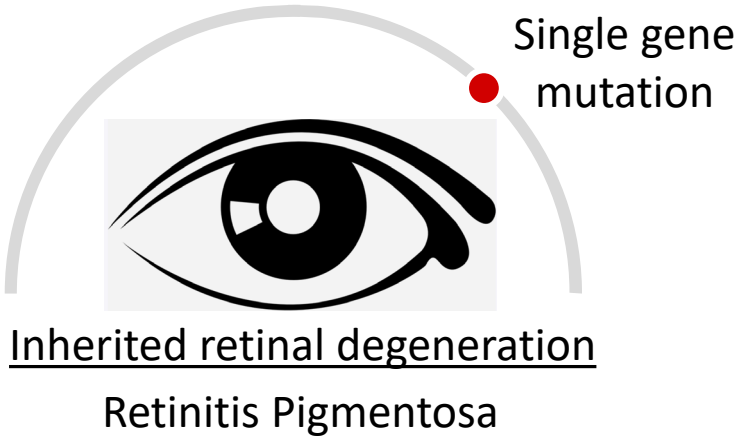
→

Lowering IOP **<u>does not</u>** halt progression of disease

→

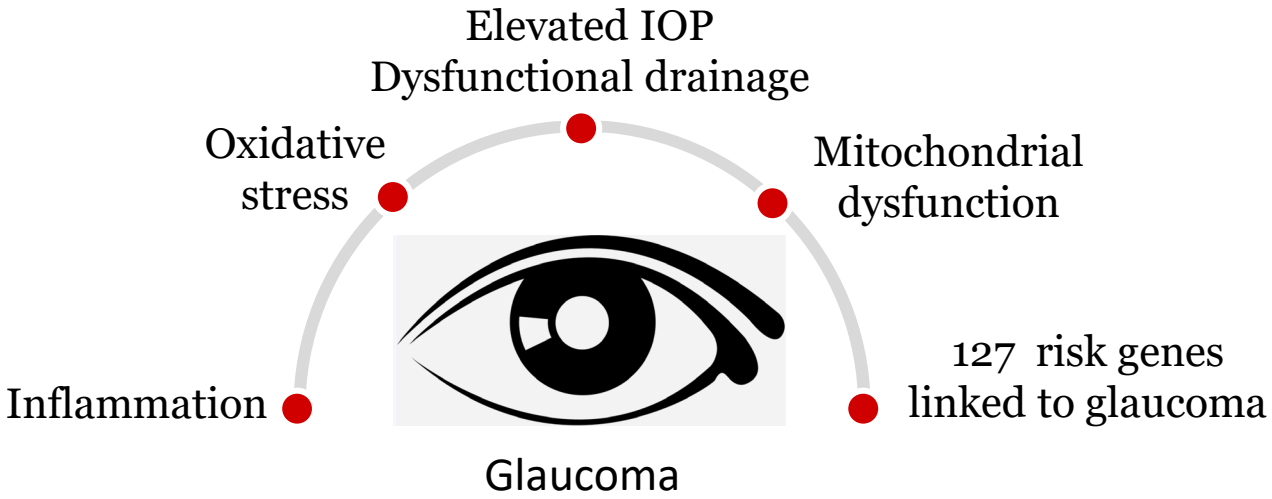
IOP-independent therapies are needed for the treatment of glaucoma

Glaucoma is a multifactorial disease



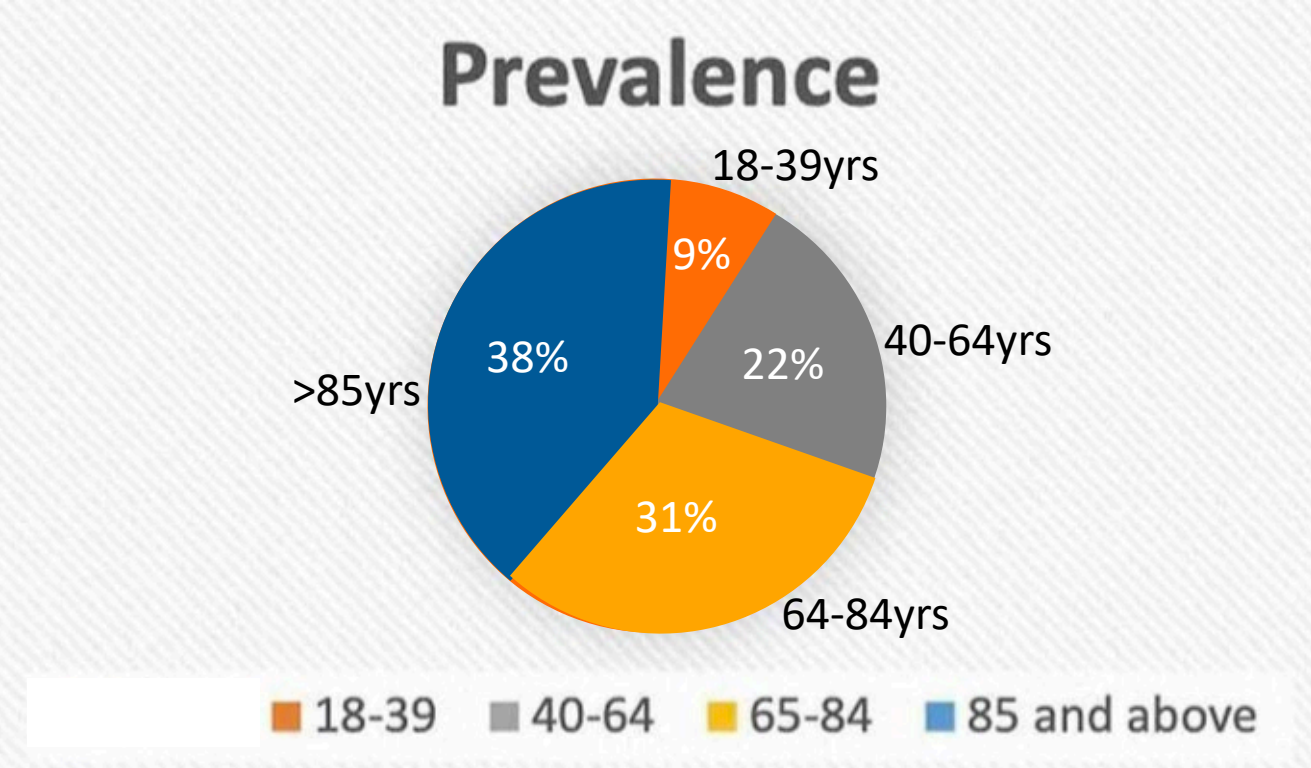
Correct the gene mutation

Prevent disease



How do we treat a multifactorial disease ?

Age is the **single most significant** risk factor for developing neurodegenerative diseases such as glaucoma



Allison K, Patel D, Alabi O (2020) Epidemiology of Glaucoma: The Past, Present, and Predictions for the Future. Cureus 12(11): e11686.

One of the root-causes of glaucoma is aging

How can we target aging?

Developed a treatment for glaucoma that reverses the age of retinal neurons (RGCs)

What is aging?

- Slow gradual decline of tissue and organ function over time

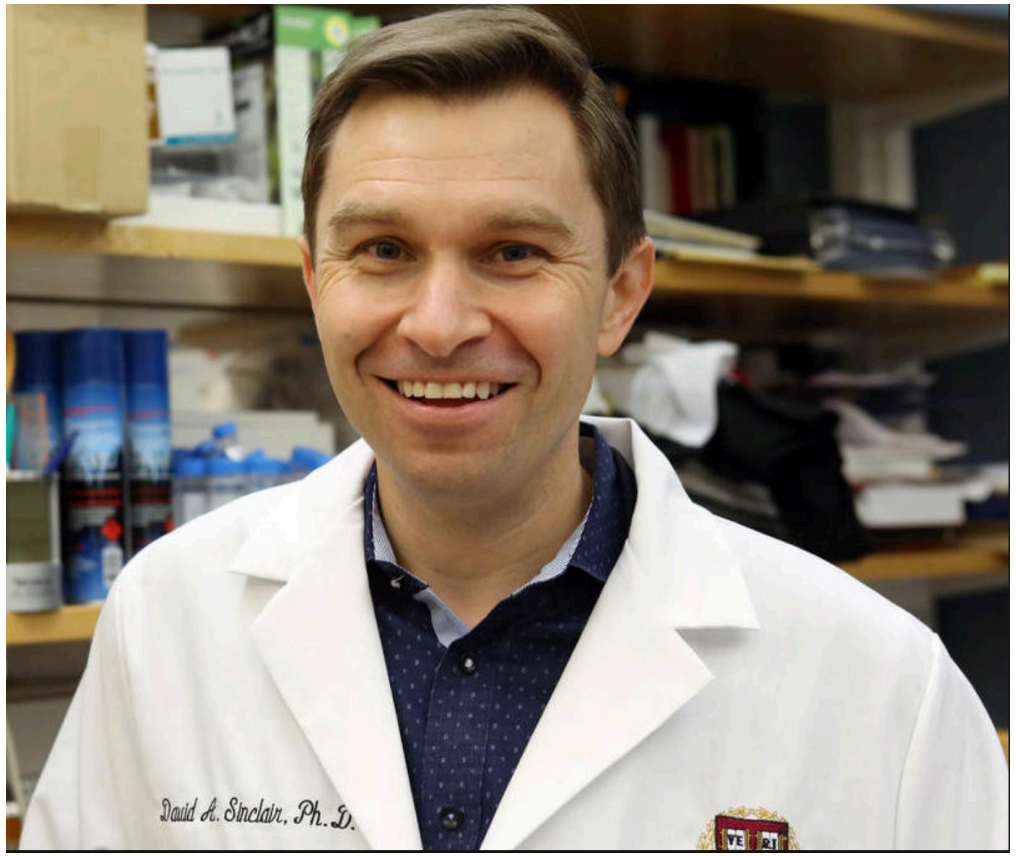
Widely believed that aging moves in one direction only and cannot be reversed

- Research has shown this is not the case

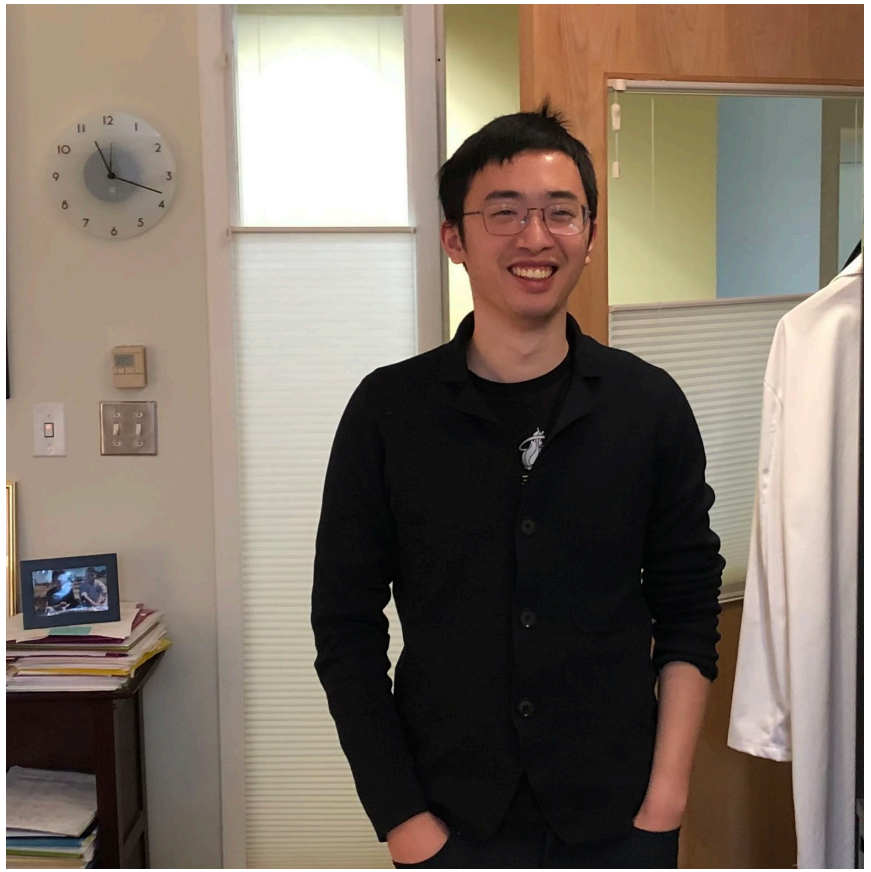
Department of Genetics, Harvard Medical School

Paul F. Glen Center for the Biology of Aging

David Sinclair, Ph.D.
Professor

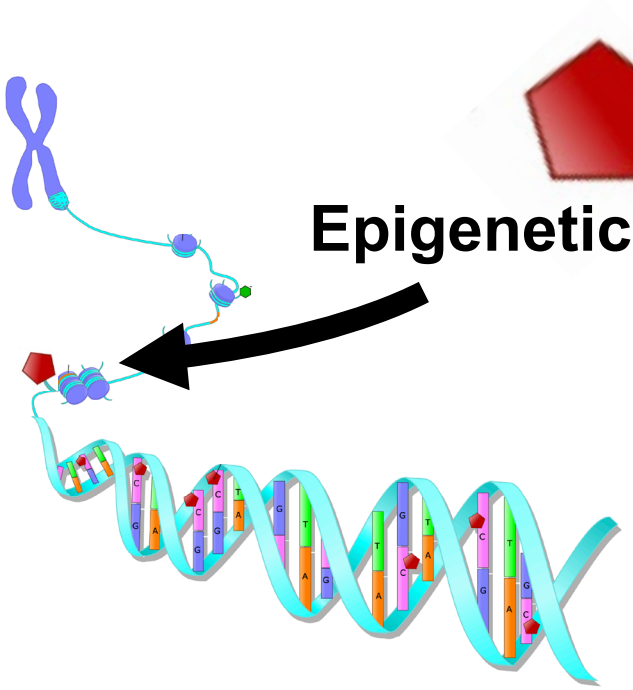


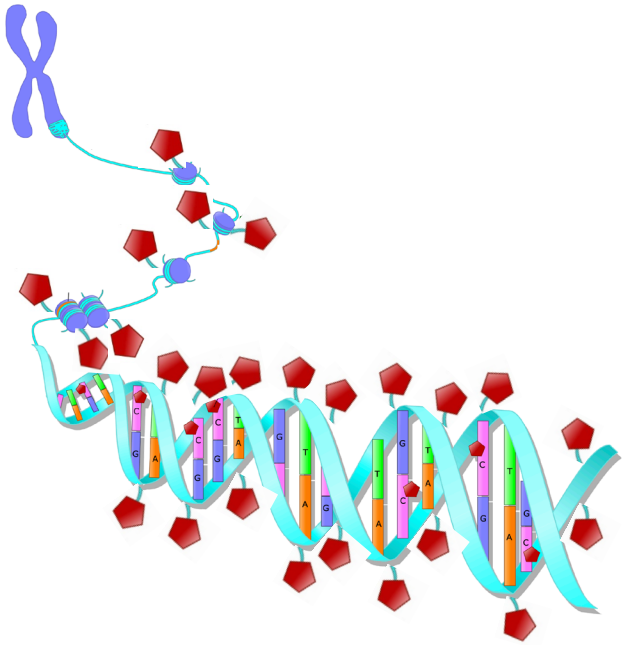
Yuancheng Lu
Graduate Student



Epigenetic “marks” on your DNA drive the aging process

As you age, “Epigenetic Marks” accumulate on DNA

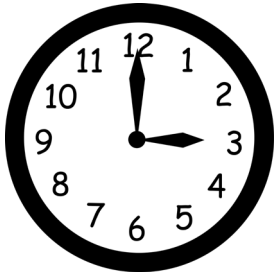




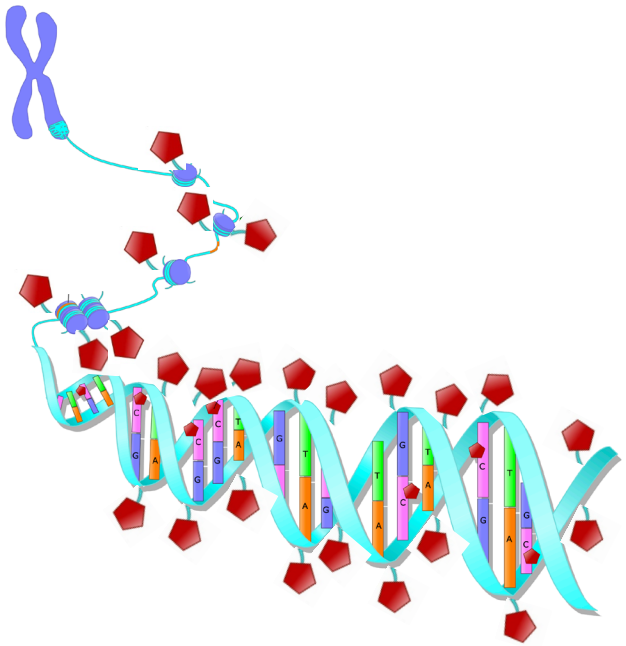
1-year-old DNA

80-year-old DNA

This is a biomarker of aging
Called the *epigenetic clock*



Epigenetic marks are not merely “markers” of aging

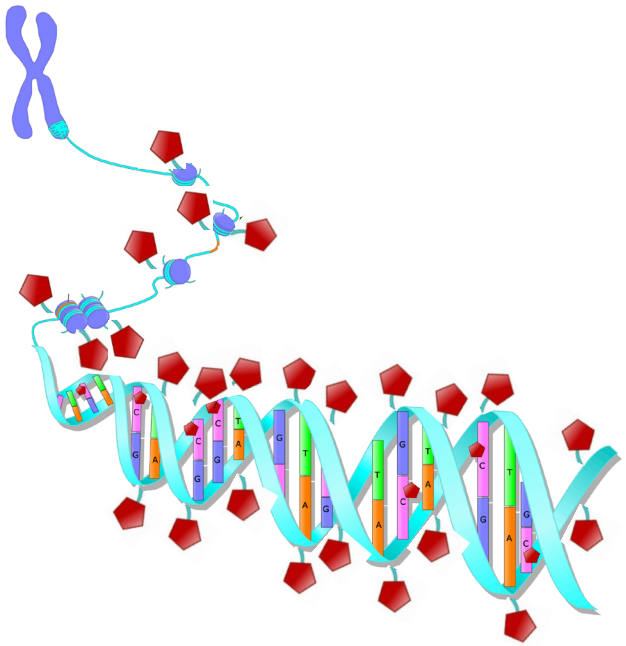


80-year-old DNA

Accumulating markers ***cause aging*** by changing how the cell functions.

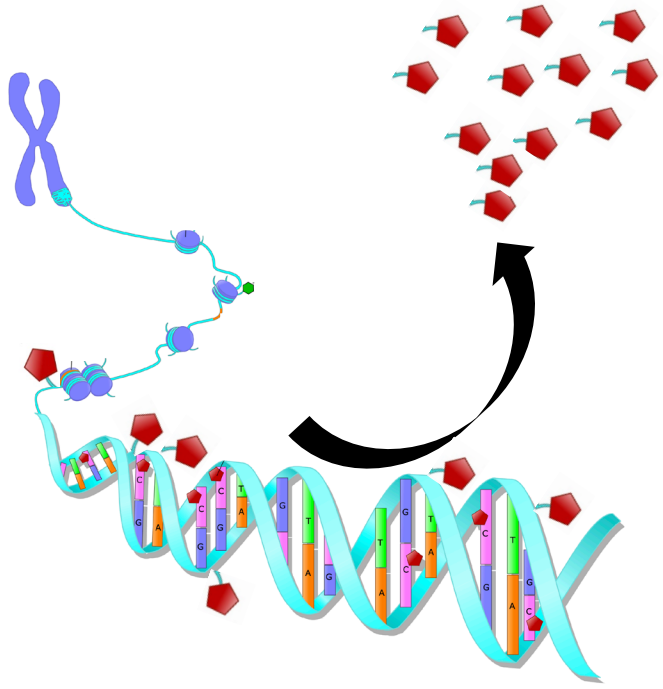
Can you reverse aging by removing these epigenetic markers?

Epigenetic reprogramming reverses the clock by removing the epigenetic markers

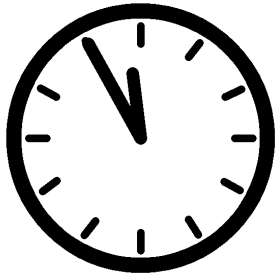


80-year-old DNA

Epigenetic reprogramming



Epigenetic Marks

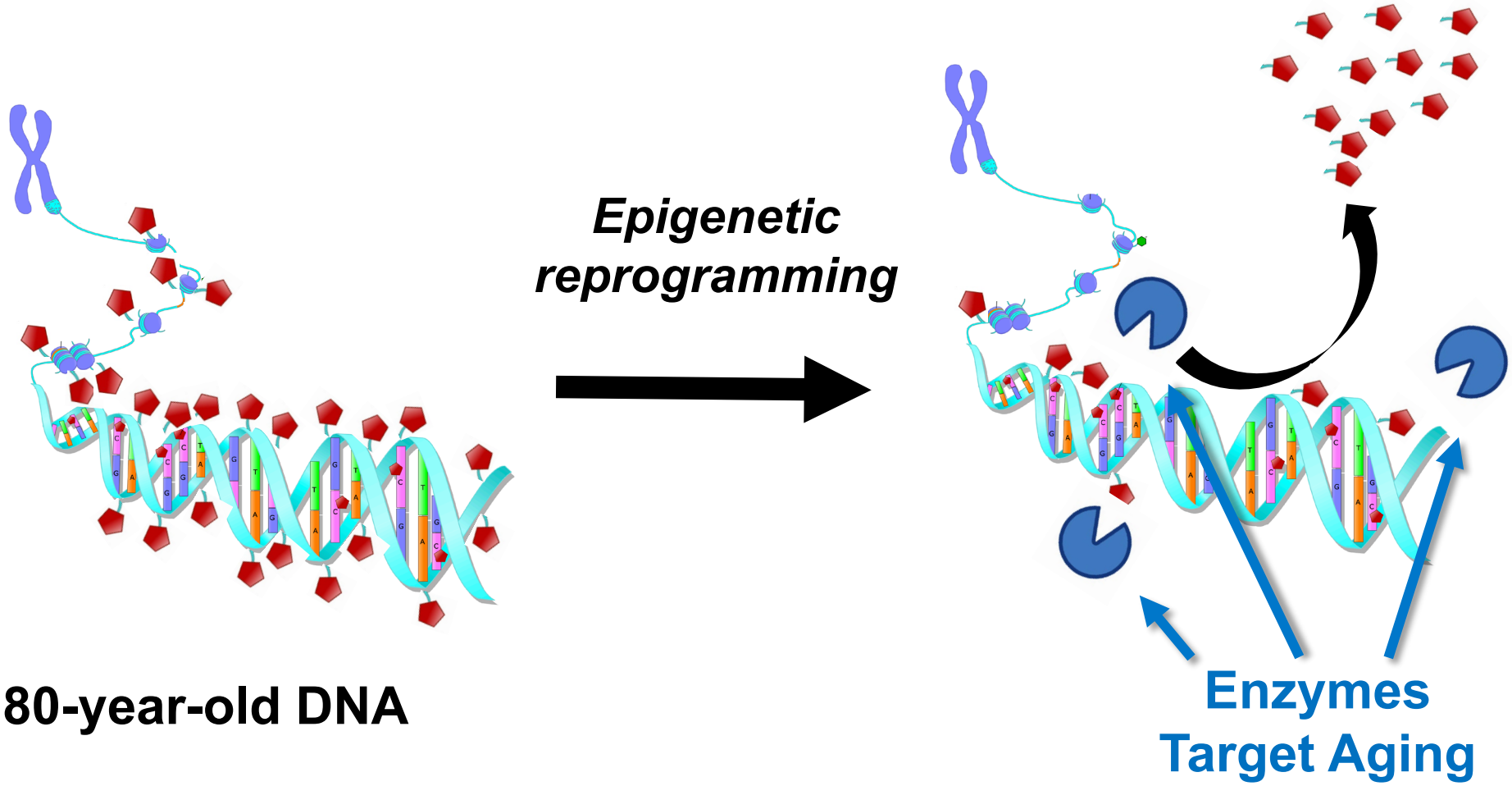


Reserves the epigenetic clock "younger"

80-year-old DNA functions like 40-year-old DNA

Cells regain youthful functions

Epigenetic reprogramming reverses the clock by removing the epigenetic markers

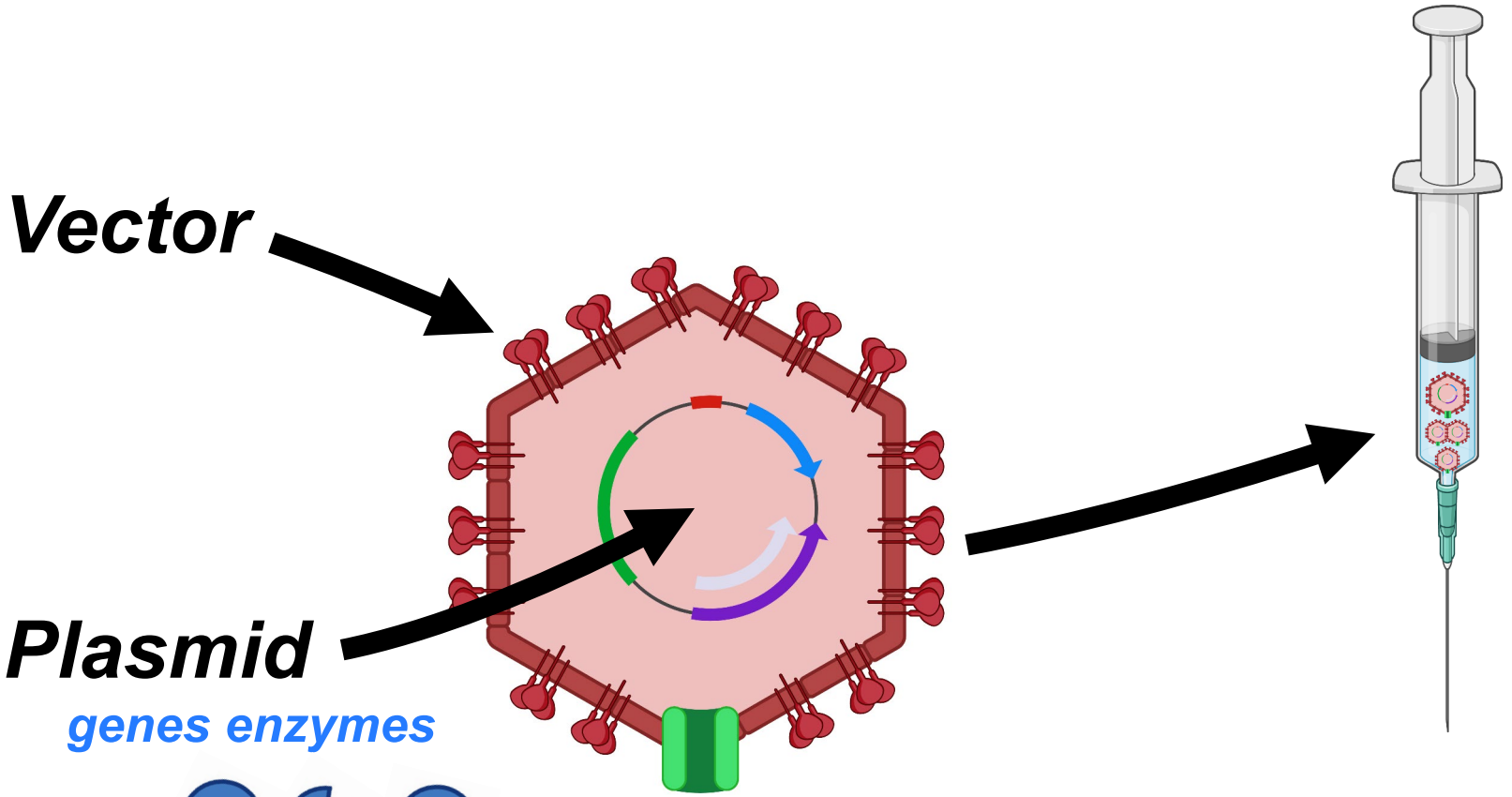


80-year-old DNA

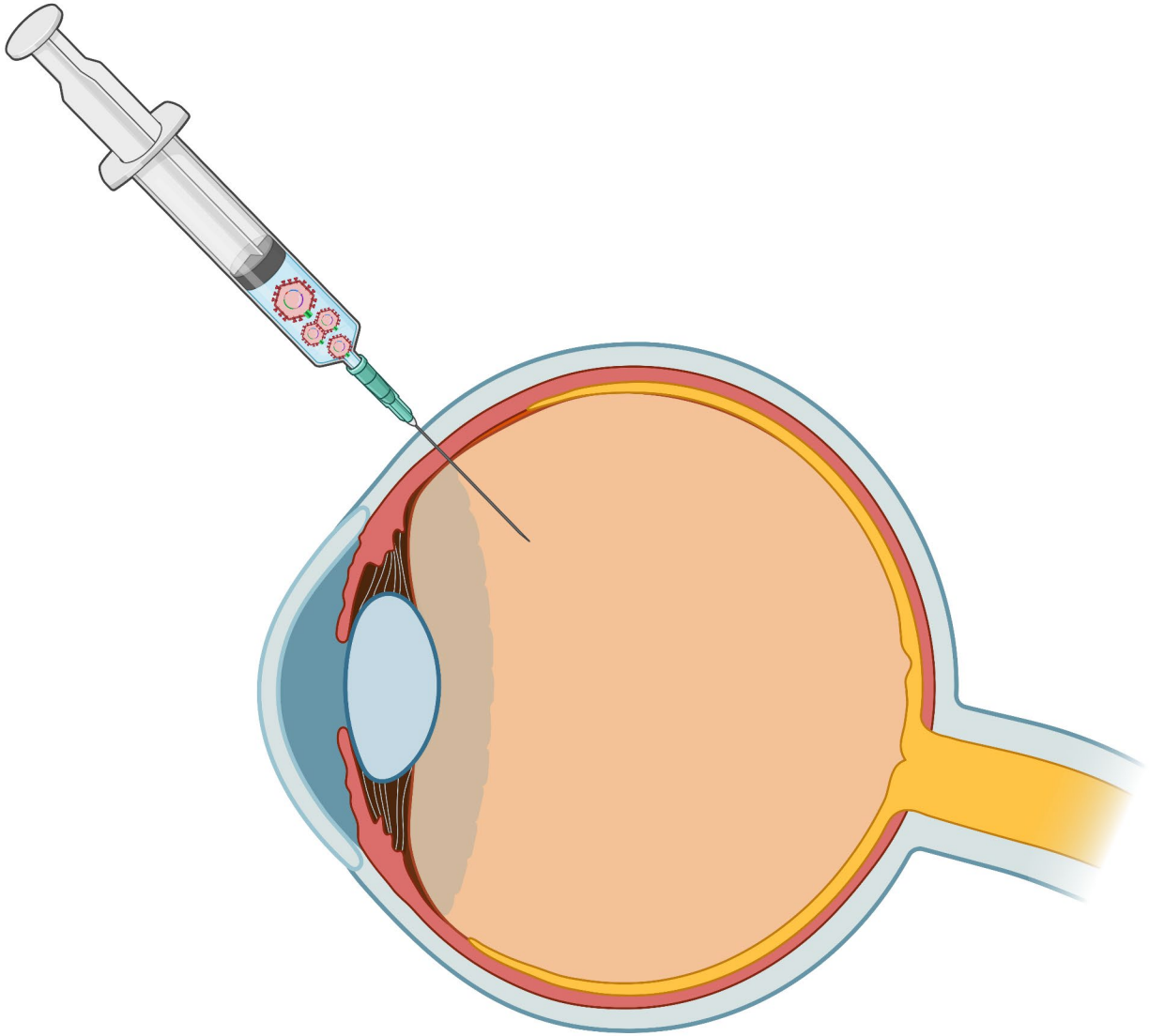
Target Multifactorial Diseases

How can epigenetic reprogramming” be used as a treatment for glaucoma?

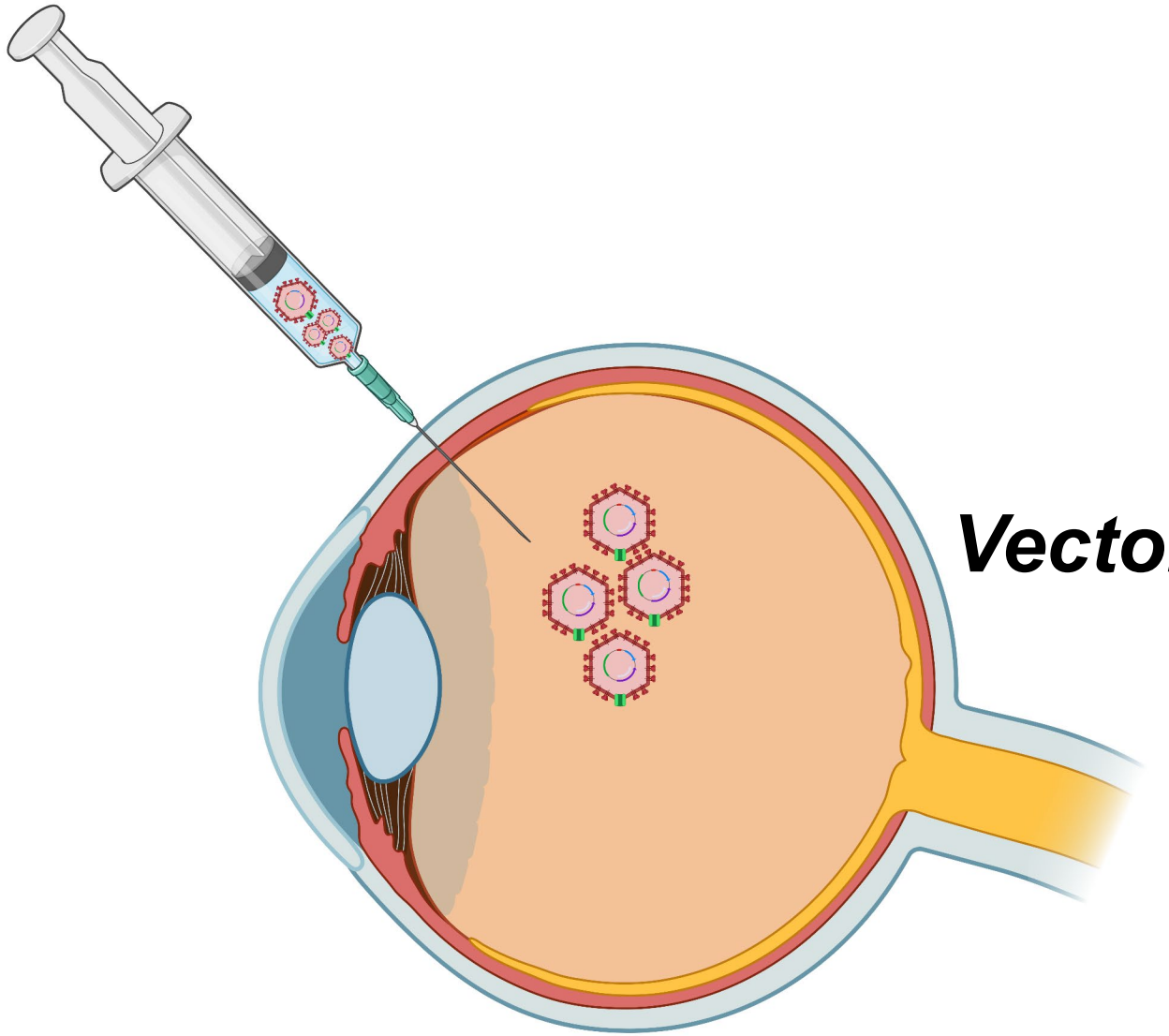
Gene therapy to trigger epigenetic reprogramming



Gene therapy to trigger epigenetic reprogramming

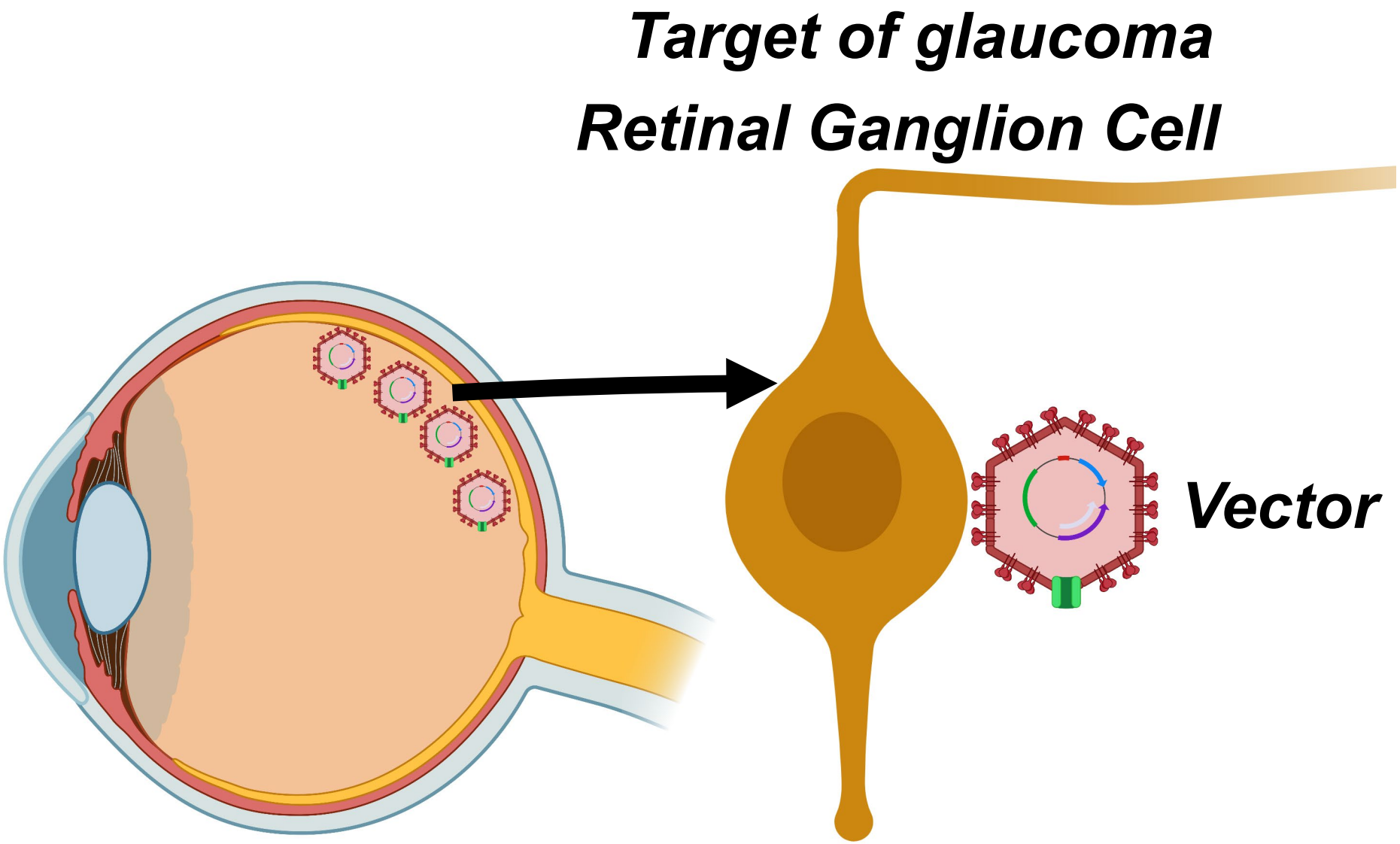


Gene therapy to trigger epigenetic reprogramming

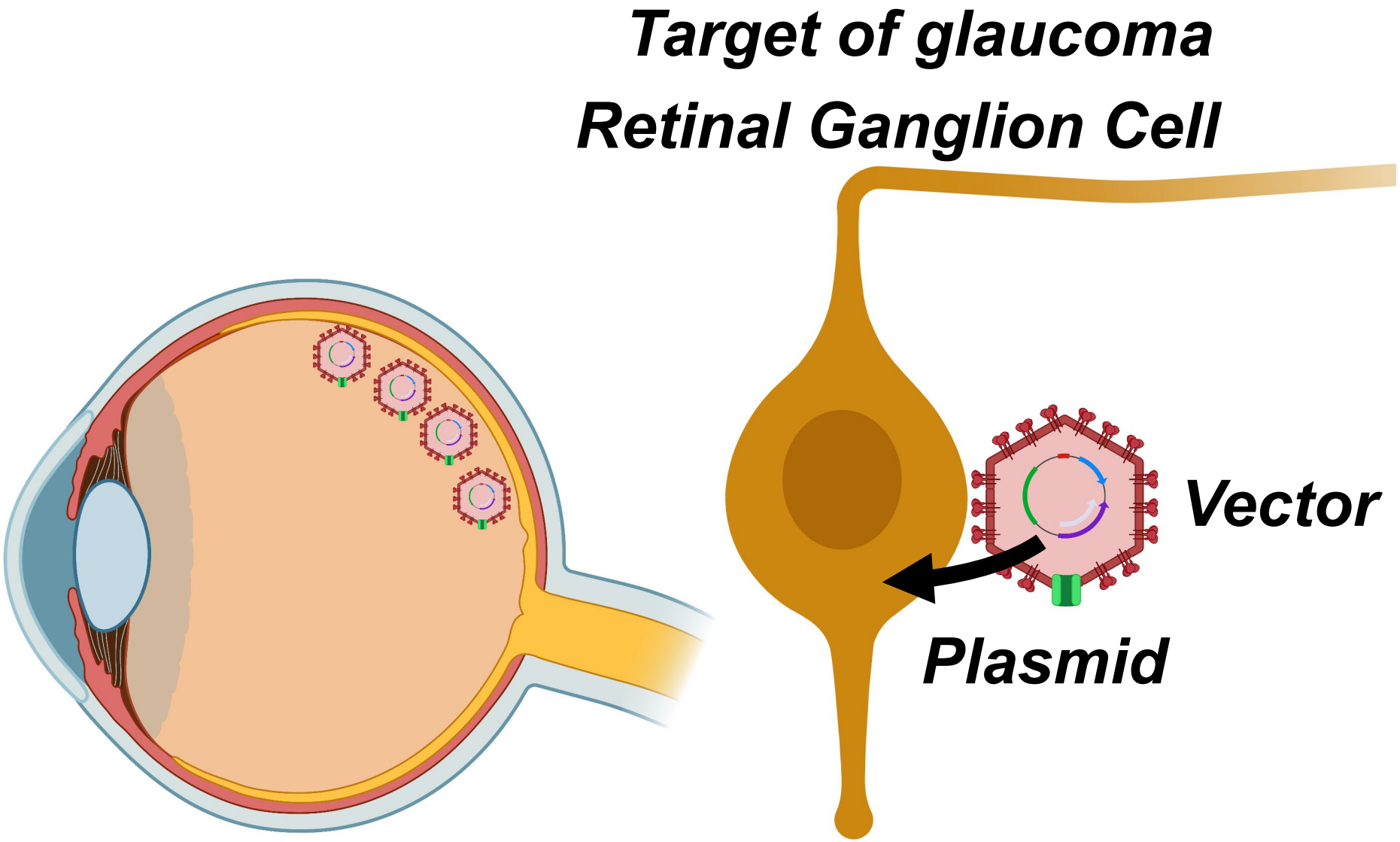


Vector + Plasmid

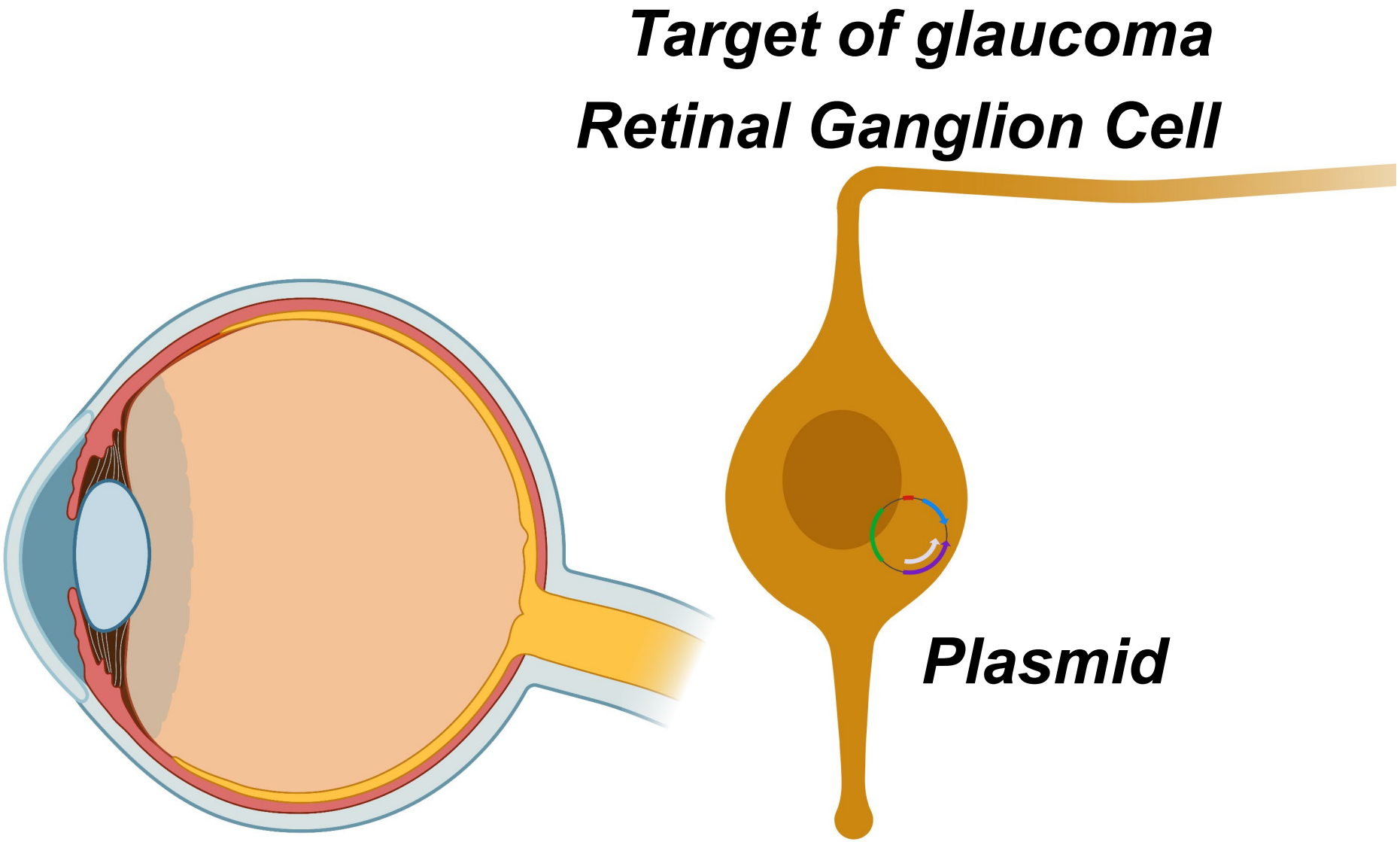
Gene therapy to trigger epigenetic reprogramming



Gene therapy to trigger epigenetic reprogramming



Gene therapy to trigger epigenetic reprogramming



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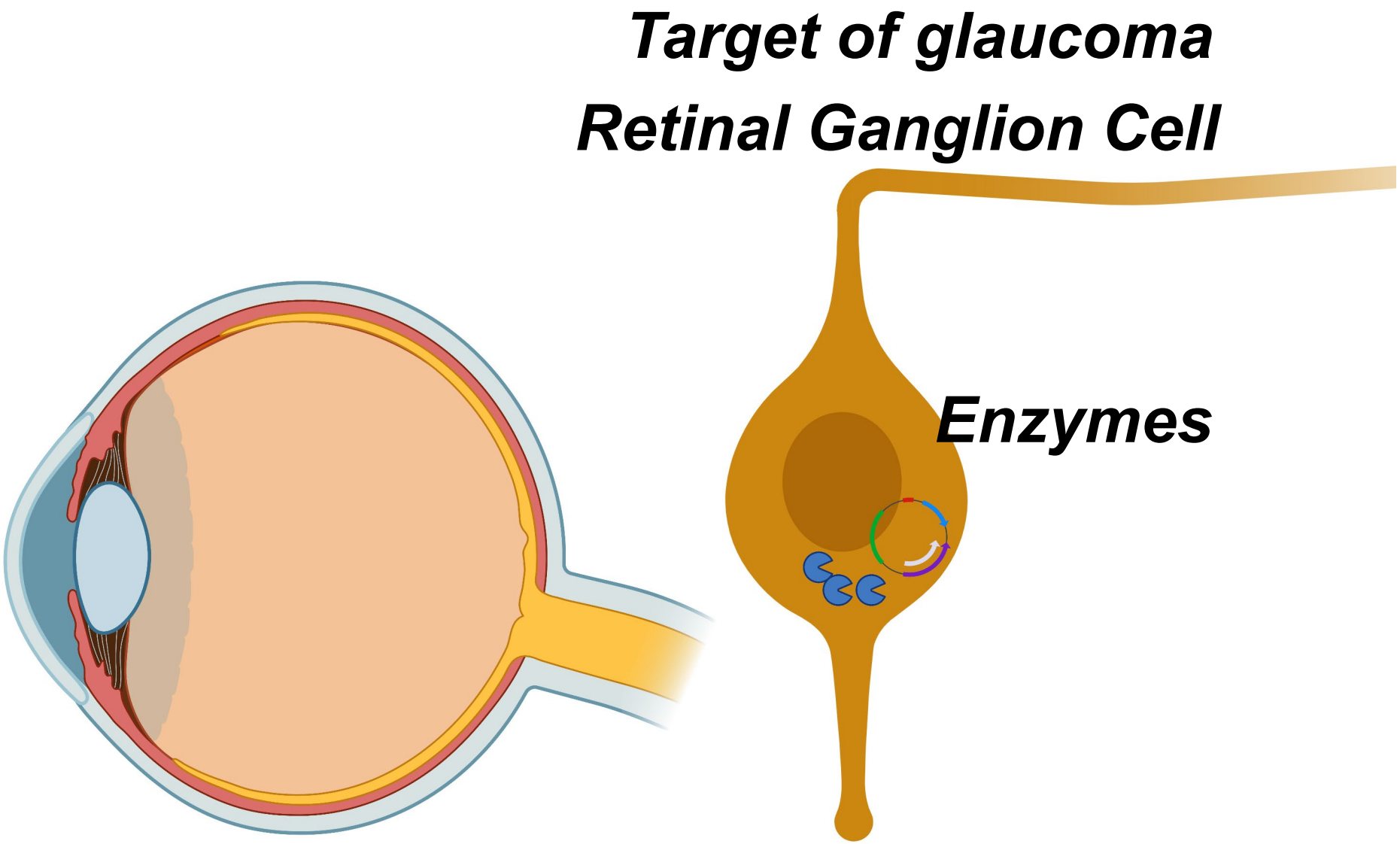
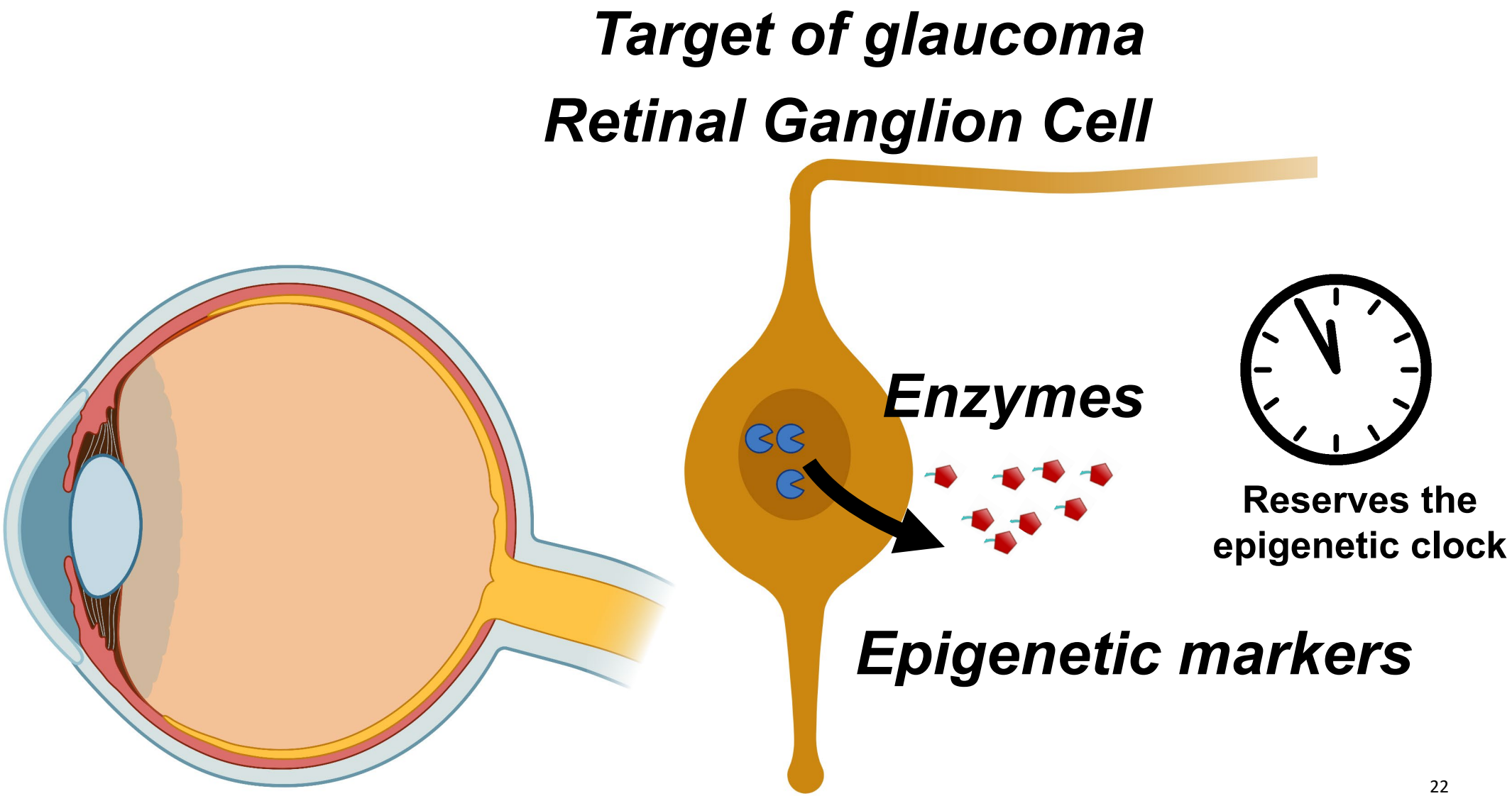
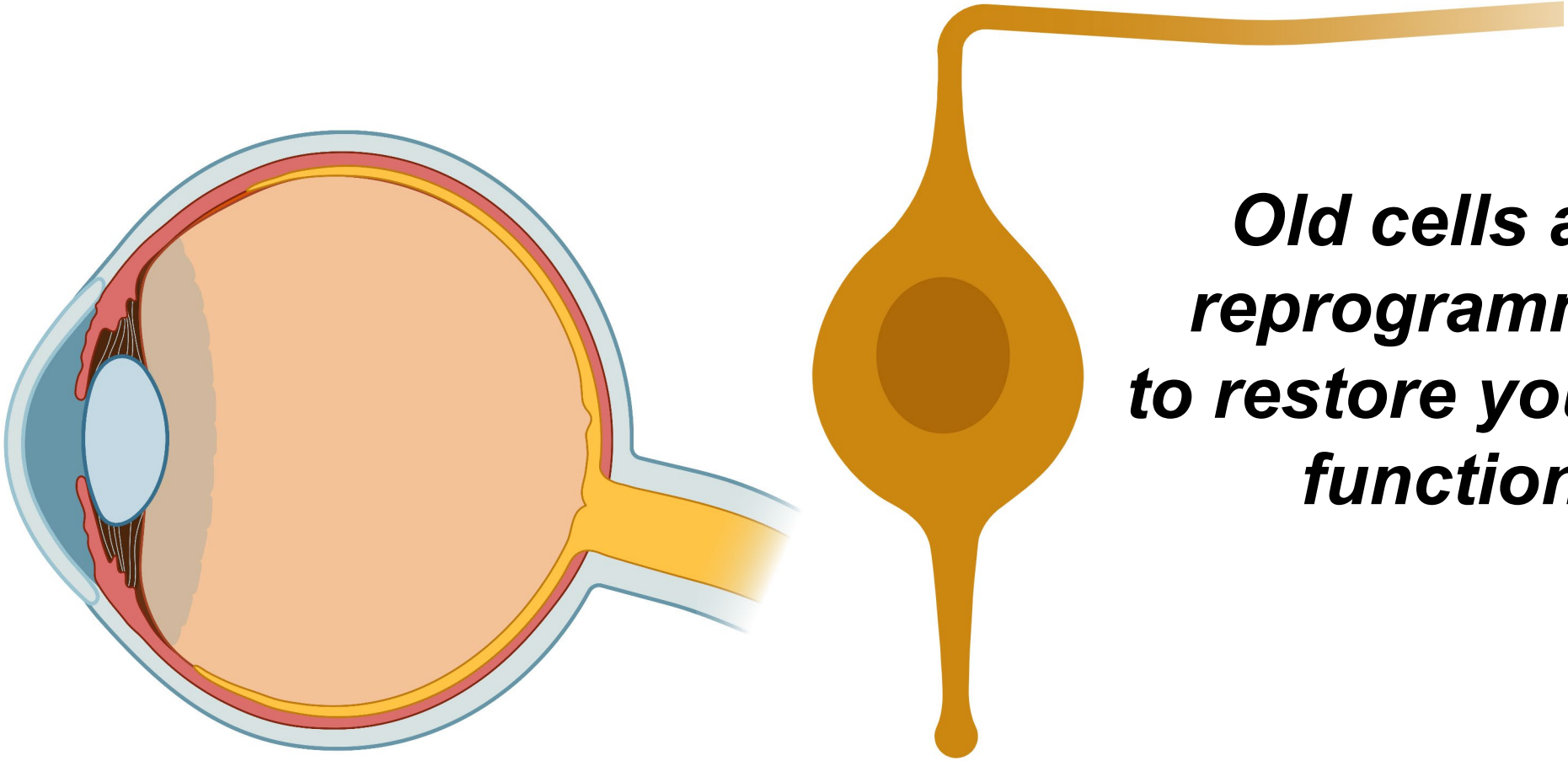


Gene therapy to trigger epigenetic reprogramming



Gene therapy to trigger epigenetic reprogramming

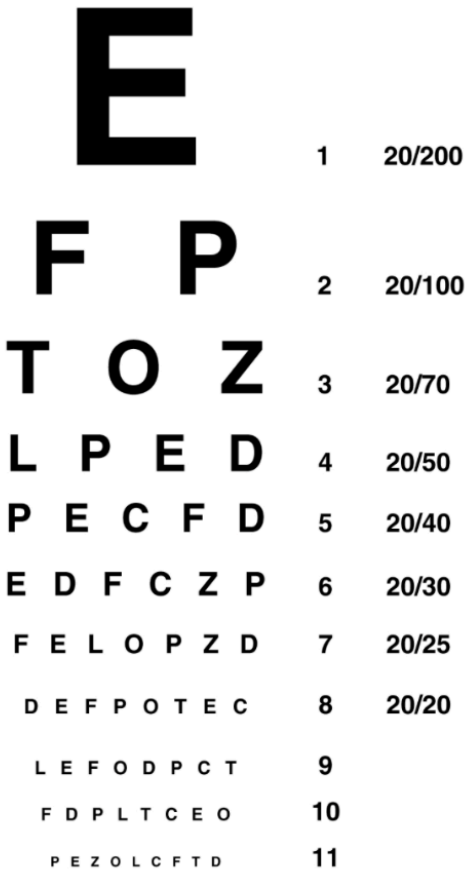


Old cells are reprogrammed to restore youthful function

Using this new type of gene therapy, we restored vision in mice lost due to glaucoma

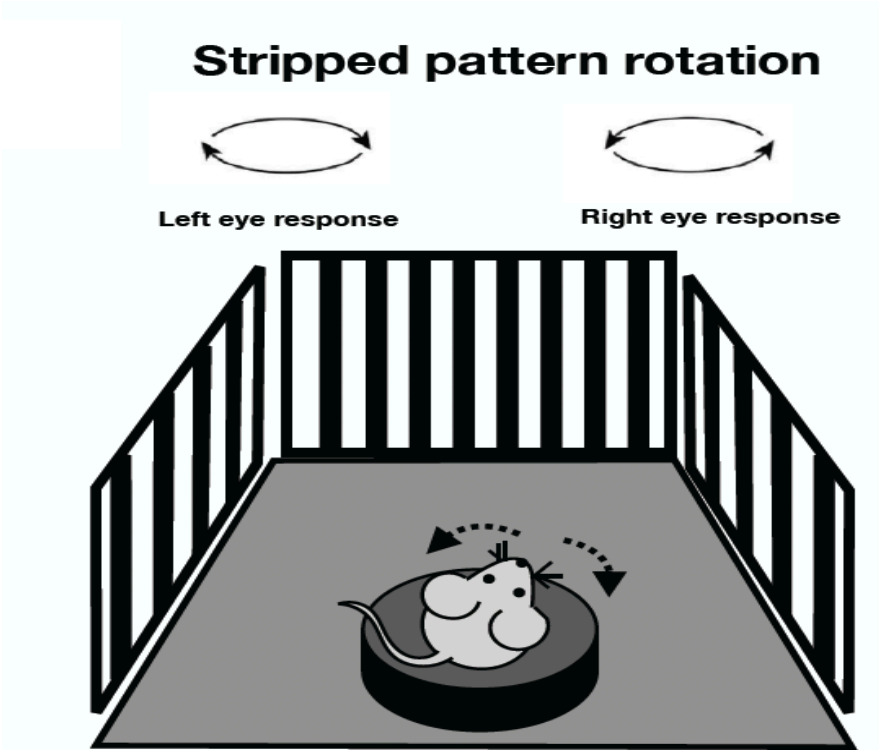
Measuring Visual Acuity in Mice

Snellen visual acuity eye chart



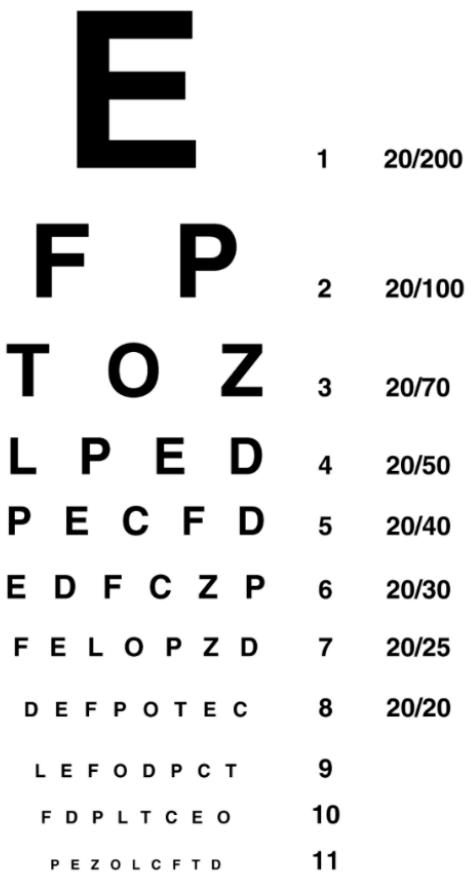
Low visual acuity

High visual acuity



Measuring Visual Acuity in Mice

Snellen visual acuity eye chart



Low visual acuity

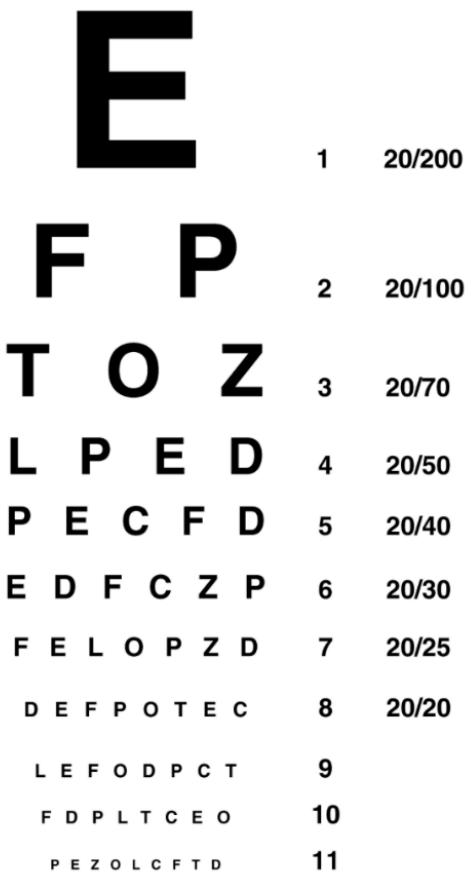
High visual acuity

Normal vision

Loss of vision

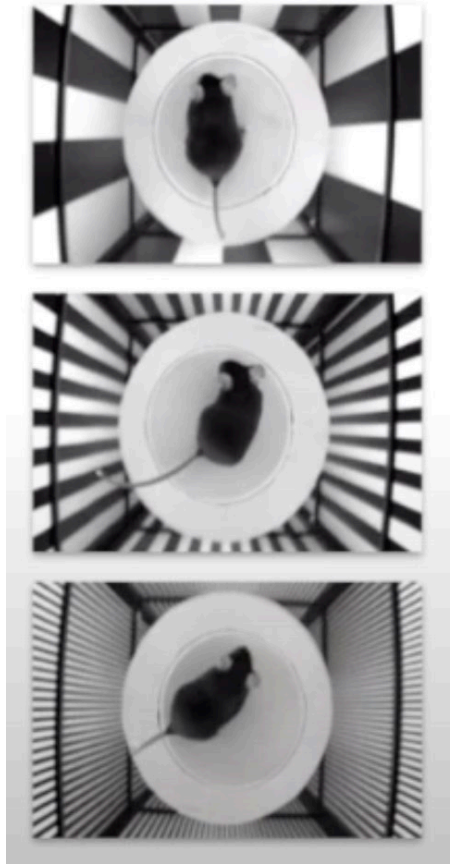
Measuring Visual Acuity in Mice

Snellen visual acuity eye chart



Low visual acuity

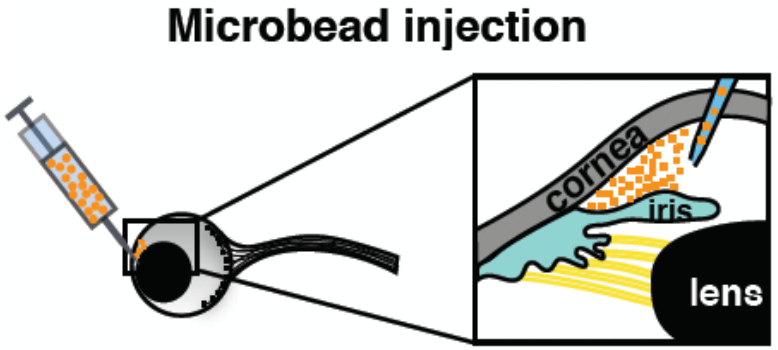
High visual acuity

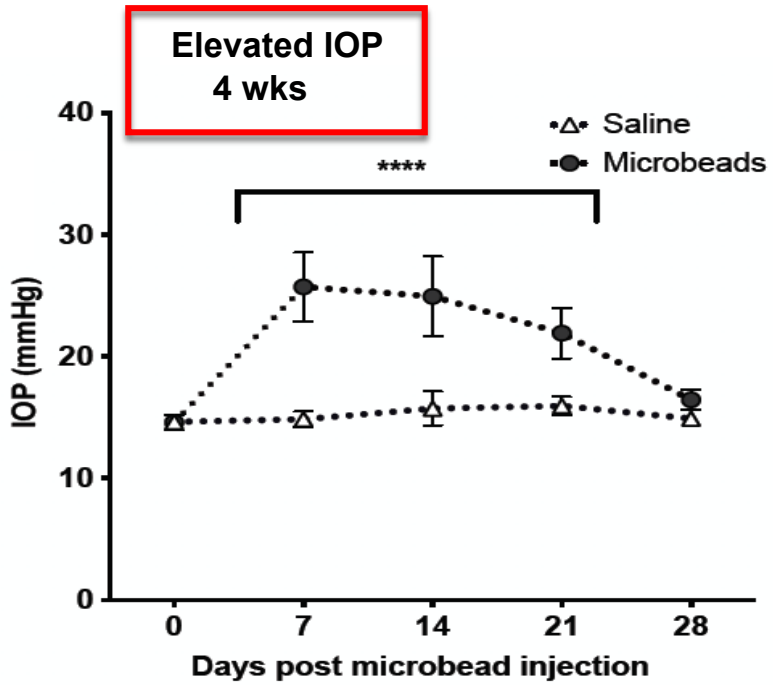


Low visual acuity

High visual acuity

Inducible mouse model of glaucoma





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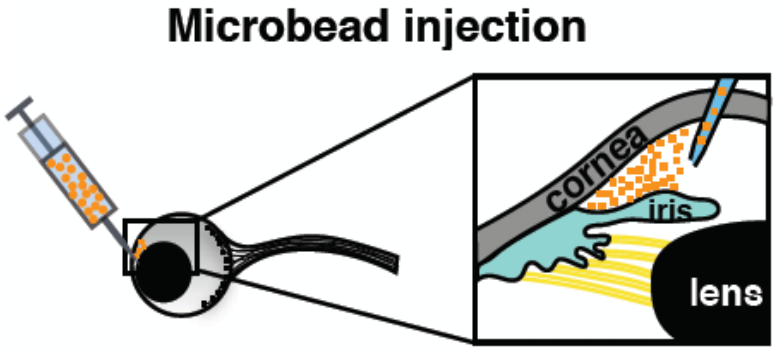
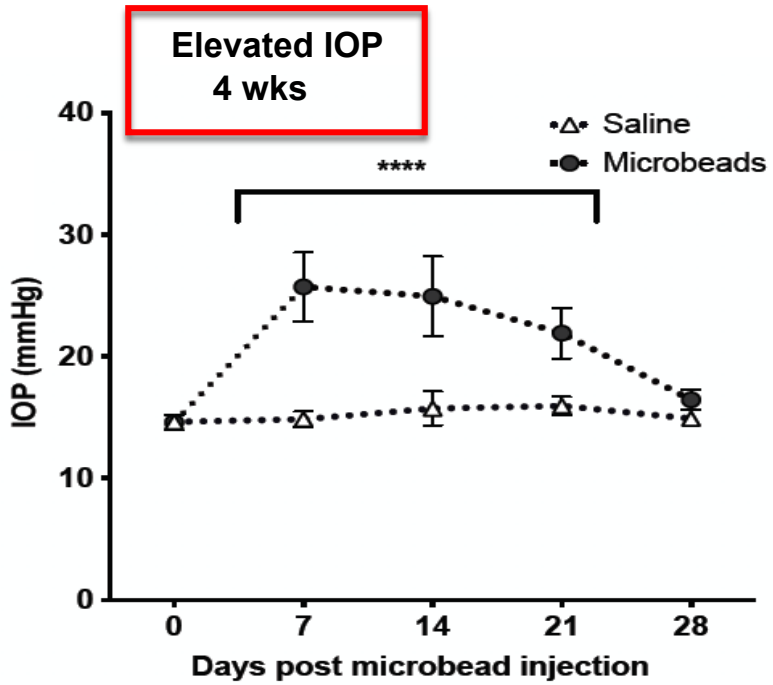
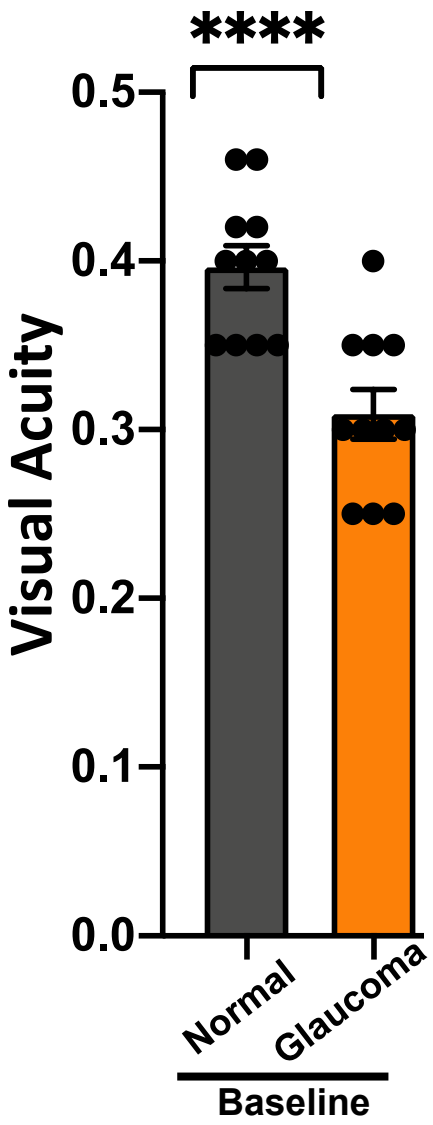
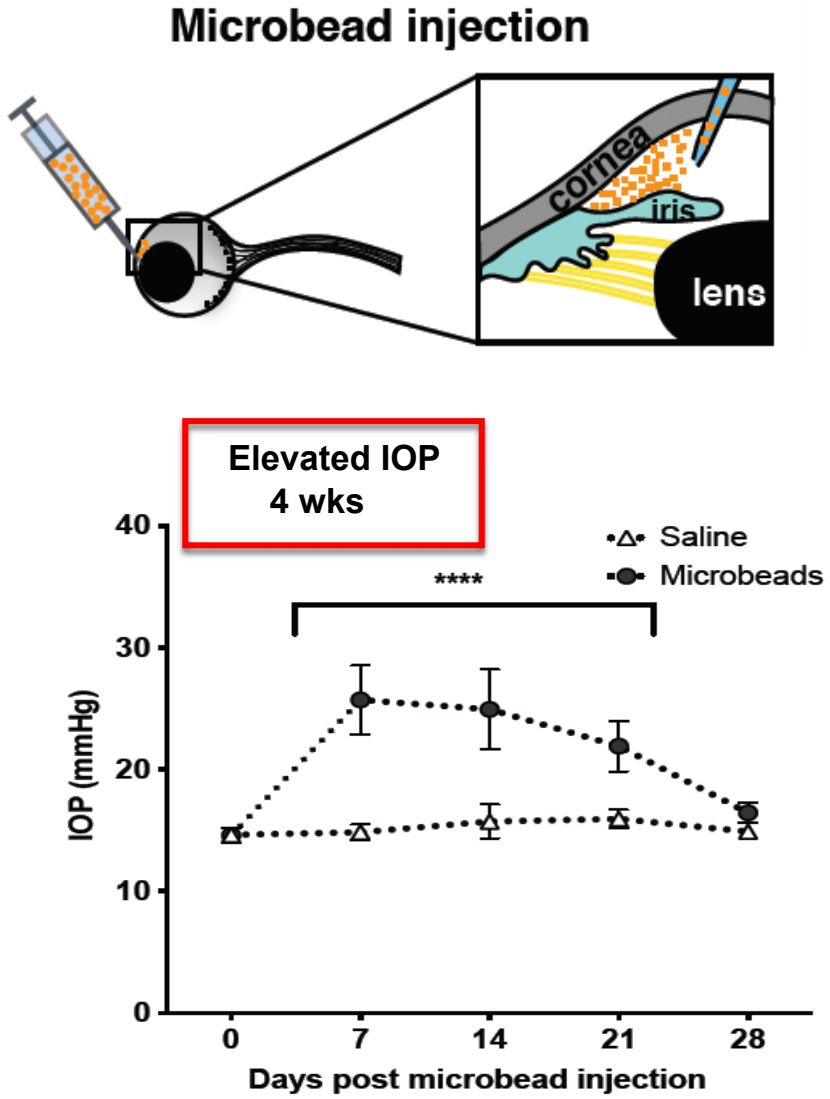
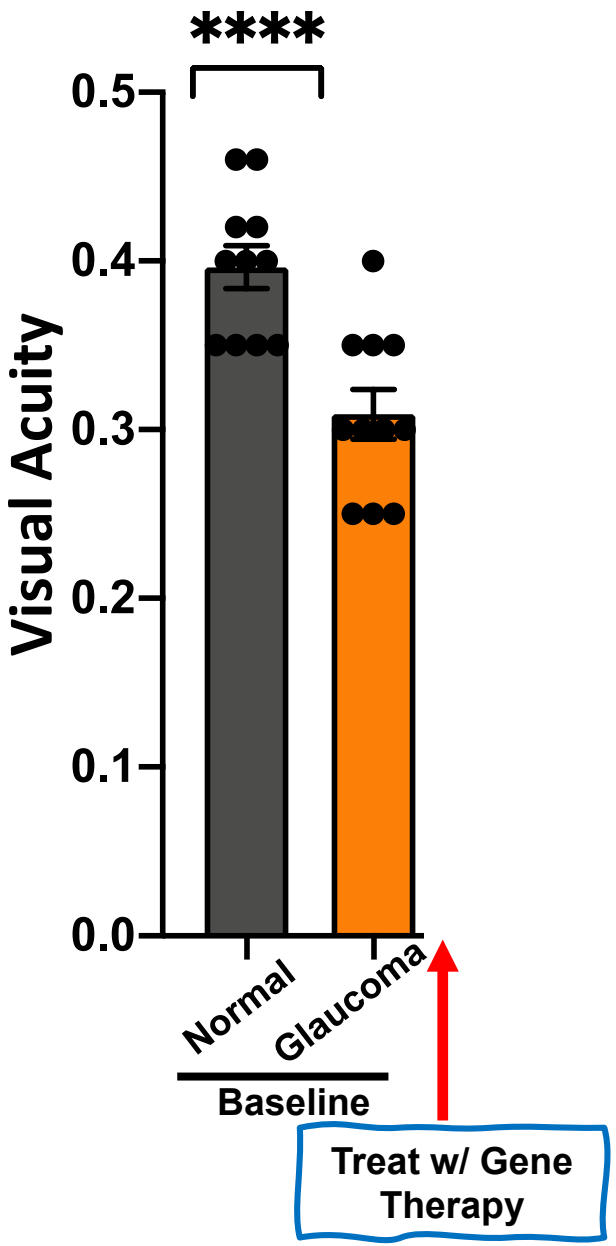






Inducible mouse model of glaucoma





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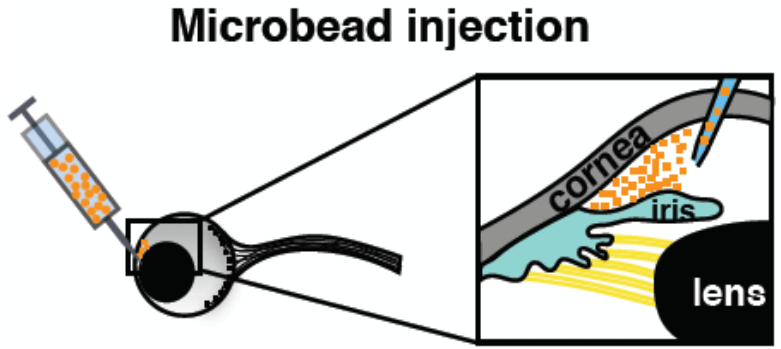
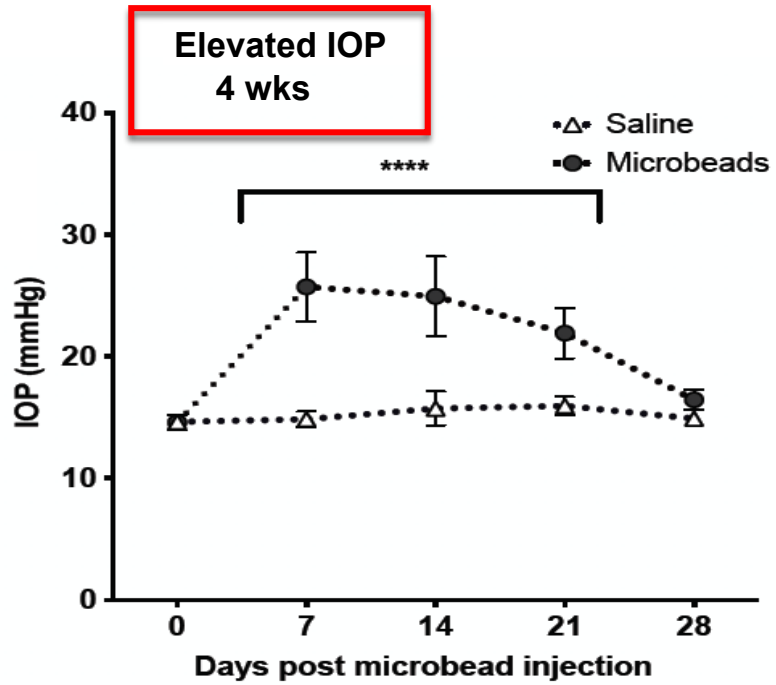
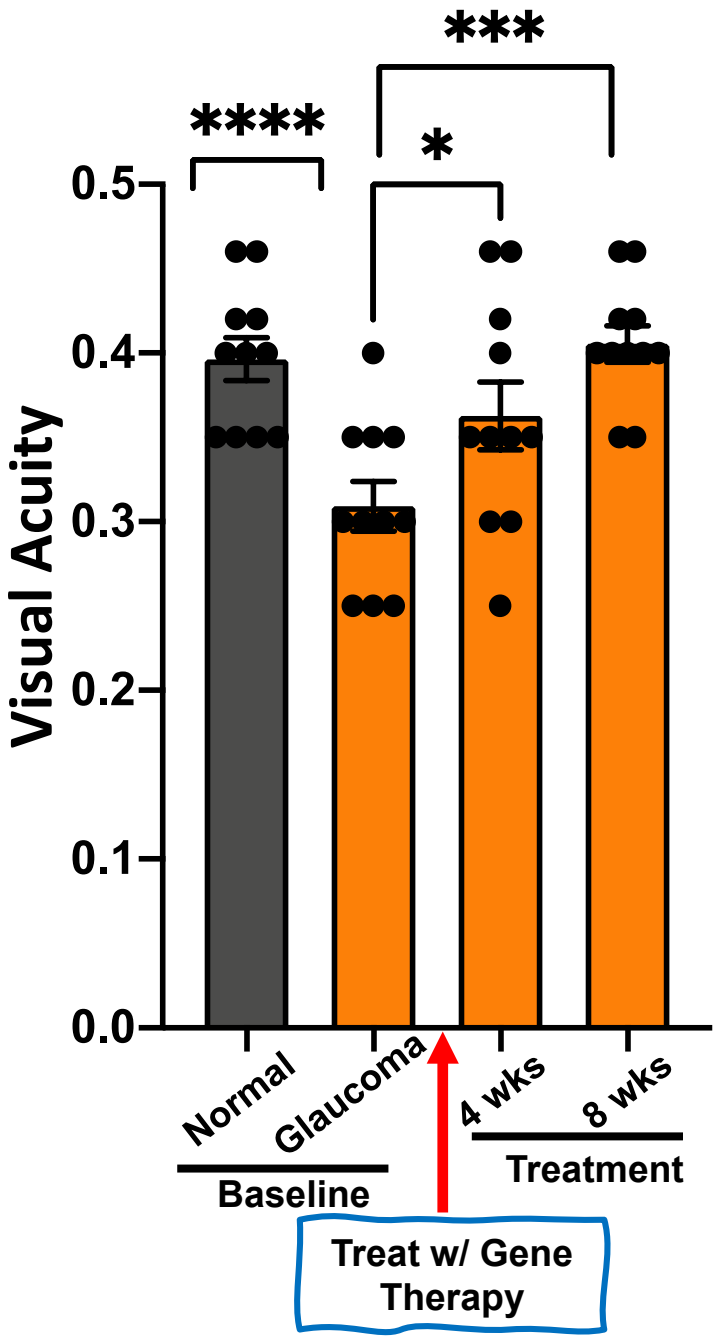






Conclusions / future implications

- ✓ **Demonstrated that we can reverse age and restore function in mouse retina**
- ✓ **Proof-of-principal experiments / pre-clinical experiments**
- ➢ **Working hard to translate this approach to the clinic**
  - Safety testing
  - Efficacy in human cells “ex vivo”
- ➢ **Implications for treating other age-related diseases in the eye**
  - Age-related macular degeneration (AMD)
- ➢ **Age-related diseases in general**
  - Alzheimer’s
  - Cardiovascular disease
  - Diabetes

Prevent Blindness

Focus on Eye Health
National Summit

Our Changing Vision

Focus on Eye Health Summit:
Our Changing Vision

NIH
National Eye Institute

Prevent Blindness
Focus on Eye Health National Summit

Epigenetic Regulation of Retinal Aging

Anand Swaroop, PhD
Senior Investigator & Chief,
Neurobiology, Neurodegeneration & Repair Laboratory

RESEARCH IN VISION REPAIR AND HEALTH

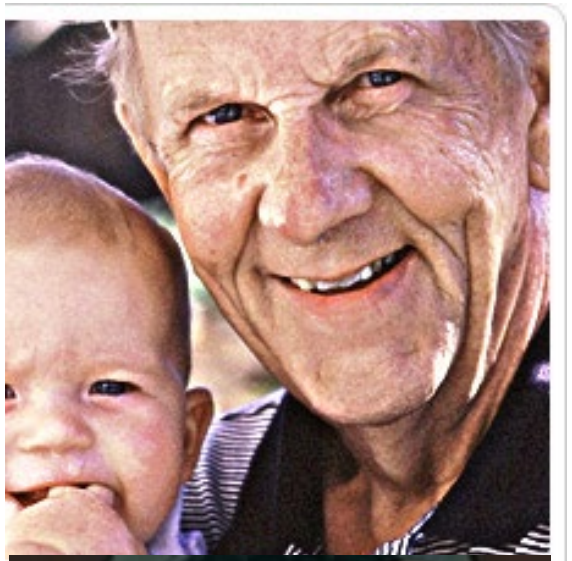
AGING: Perfect or Not

"Aged to Perfection"

Last November researchers at the Harvard Medical School and the National Institute on Aging made headlines when they reported that a substance found in red wine, known as resveratrol, offsets the bad effects of a high-calorie diet in mice and slows their aging process.

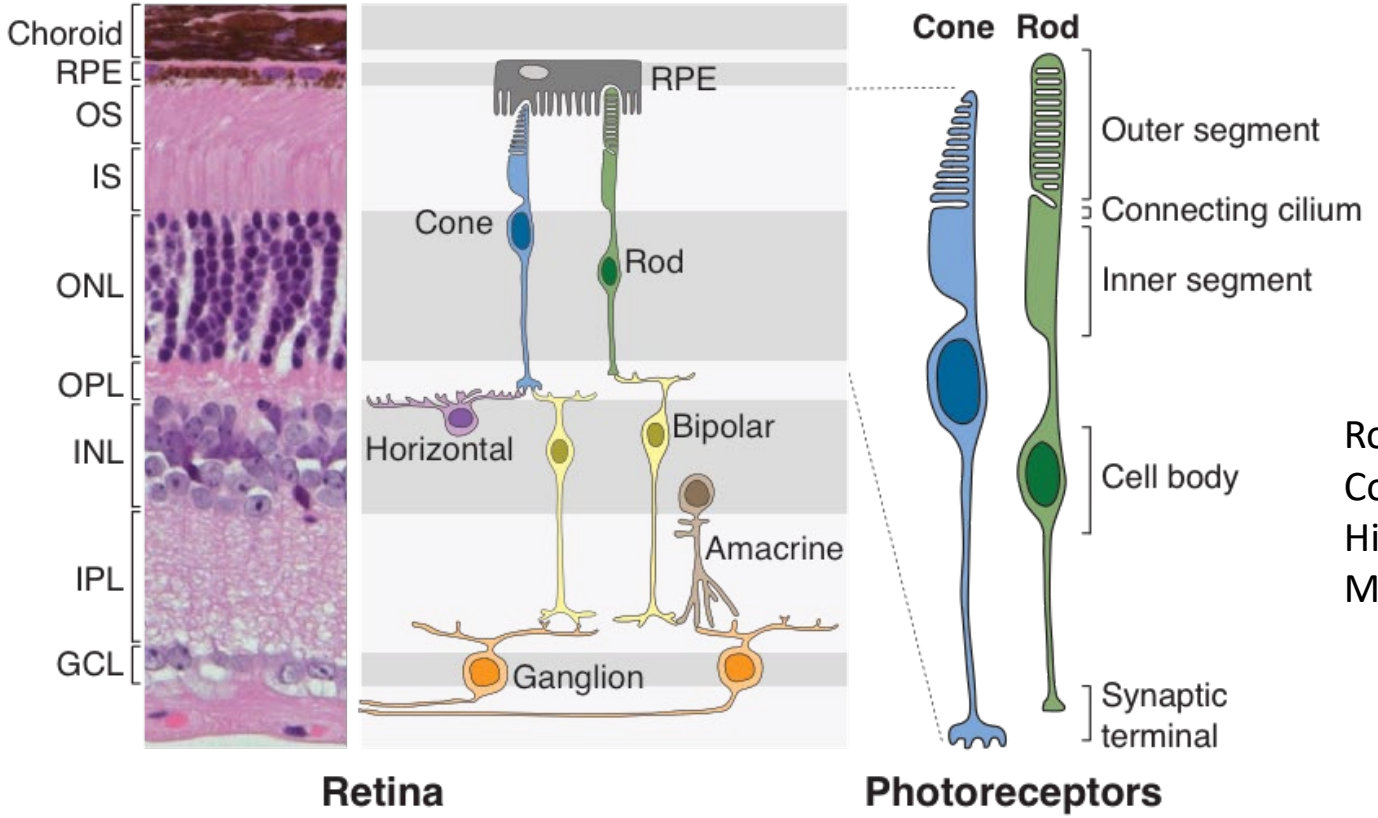
Following the symposium, the Alliance will showcase many fine red wines at its annual "Aged to Perfection" wine tasting event. The wine tasting and auction will take place from 6:00–8:00 p.m. two blocks from the symposium at The Presidio Officers' Club, 50 Moraga Ave., San Francisco, CA 94129. To purchase tickets to this event, or for more information, please contact Colleen Browne at (202) 293-2856.

or click here to register online



- Progressive functional decline
- Reduced adaptive response to stress
- Increased susceptibility to disease

The Retina and The Photoreceptors

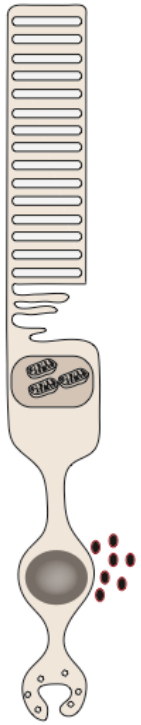


Rods – dim light vision, 95%
Cones – day light vision, color, 5%
High energy demands
Mitochondria-rich

Dysfunction or death of photoreceptors is a major cause of (currently) incurable vision impairment

Yang et al. *Prog Retin Eye Res* 2015

Aging of the Retina/Rod Photoreceptors



- Rate of peripheral rod loss is highest between 2nd and 4th decades (~50%)
- Central rods have a slower progressive loss, 30% are lost by the 9th decade. Cone density does not change
- Rod changes with aging in both humans and mice
- Rod loss precedes cones, in normal aging and AMD
- Rods are primary drivers of aging-related synaptic remodeling

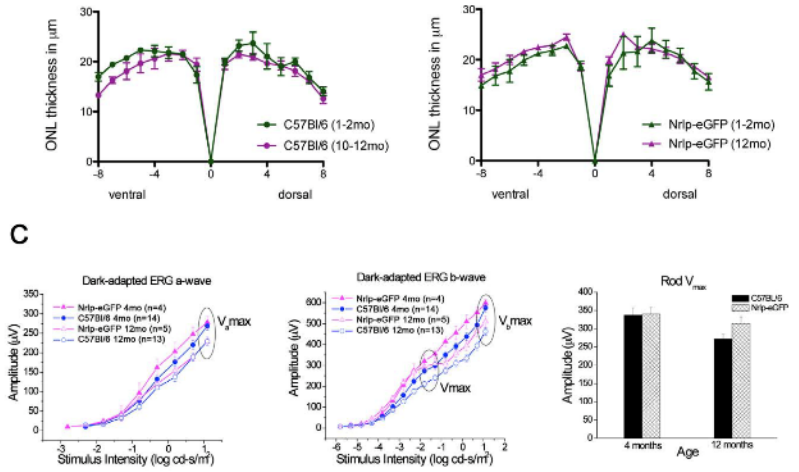


Figure 1. Comparison of young and old C57Bl/6 and Nrlp-eGFP retinas. (A) Representative 10 µm plastic sections of central retina from

FREE

Biochemistry and Molecular Biology | August 2002

Microarray Analysis of Gene Expression in the Aging Human Retina

Shigeo Yoshida; Beverly M. Yashar; Suja Hiriyanna; Anand Swaroop

+ Author Affiliations

Investigative Ophthalmology & Visual Science August 2002, Vol.43, 2554-2560. doi:https://doi.org/

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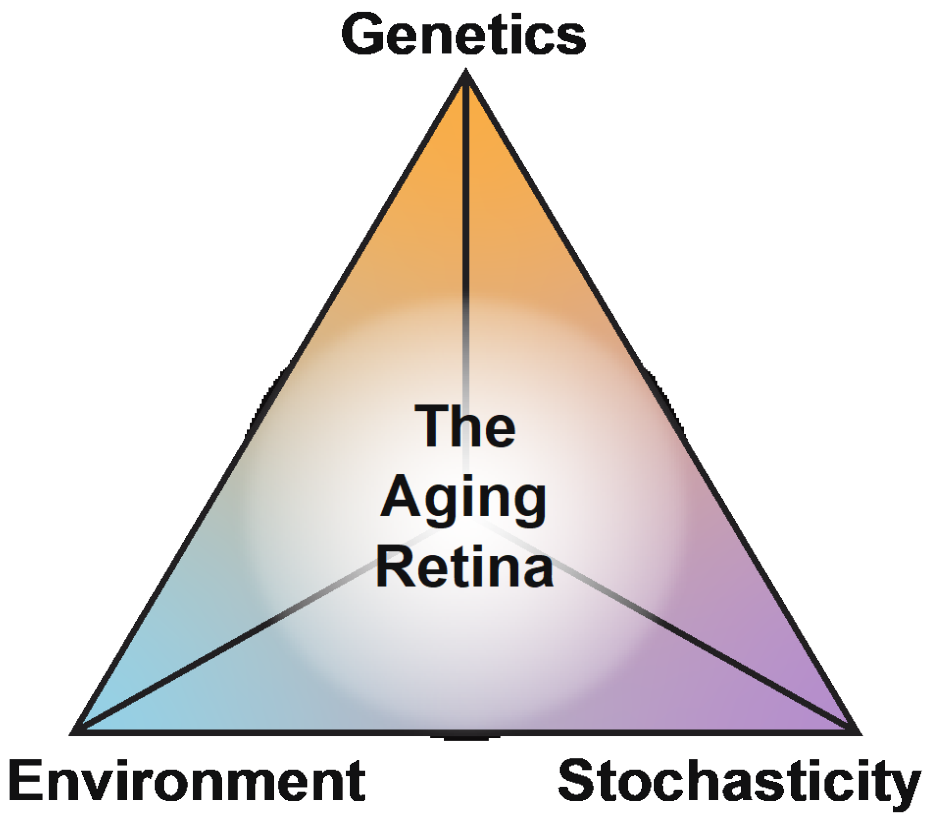
PLoS one

Distinct Signature of Altered Homeostasis in Aging Rod Photoreceptors: Implications for Retinal Diseases

Sunil K. Parapuram[1☯¤a], Radu I. Cojocaru[1,2☯], Jessica R. Chang[2,3☯¤b], Ritu Khanna[1], Matthew Brooks[1,2], Mohammad Othman[1], Sepideh Zareparsi[1¤c], Naheed W. Khan[1], Norimoto Gotoh[2], Tiziana Cogliati[2], Anand Swaroop[1,2*]

Aging of The Retina/Photoreceptors



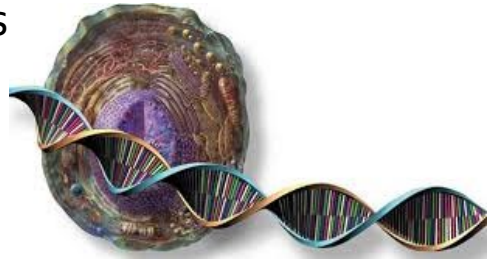
Campello et al. *Annu Rev Vis Sci.* 2021

Integrative Epigenomic Analysis of rod aging

Nrlp-EGFP

Flow-sorted photoreceptors
(98% purity)

3 12 18 24
months



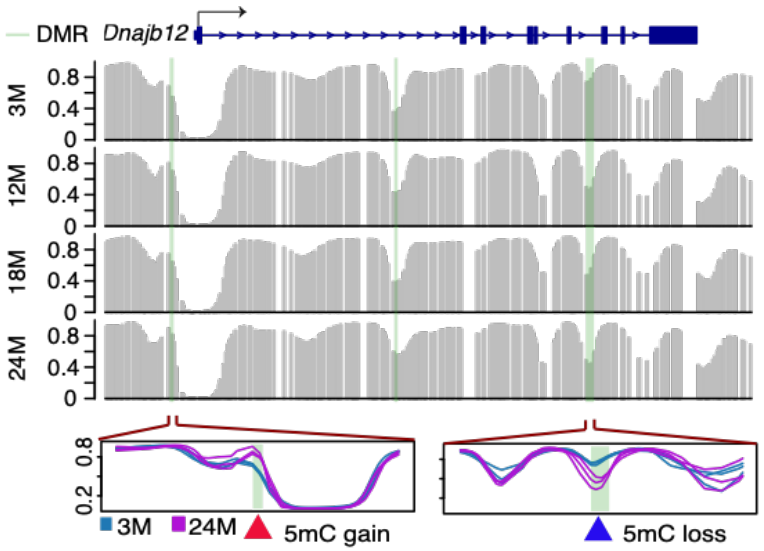
- **Whole-genome-bisulfite sequencing**
- ATAC-seq
- RNA-seq
- CUT&RUN

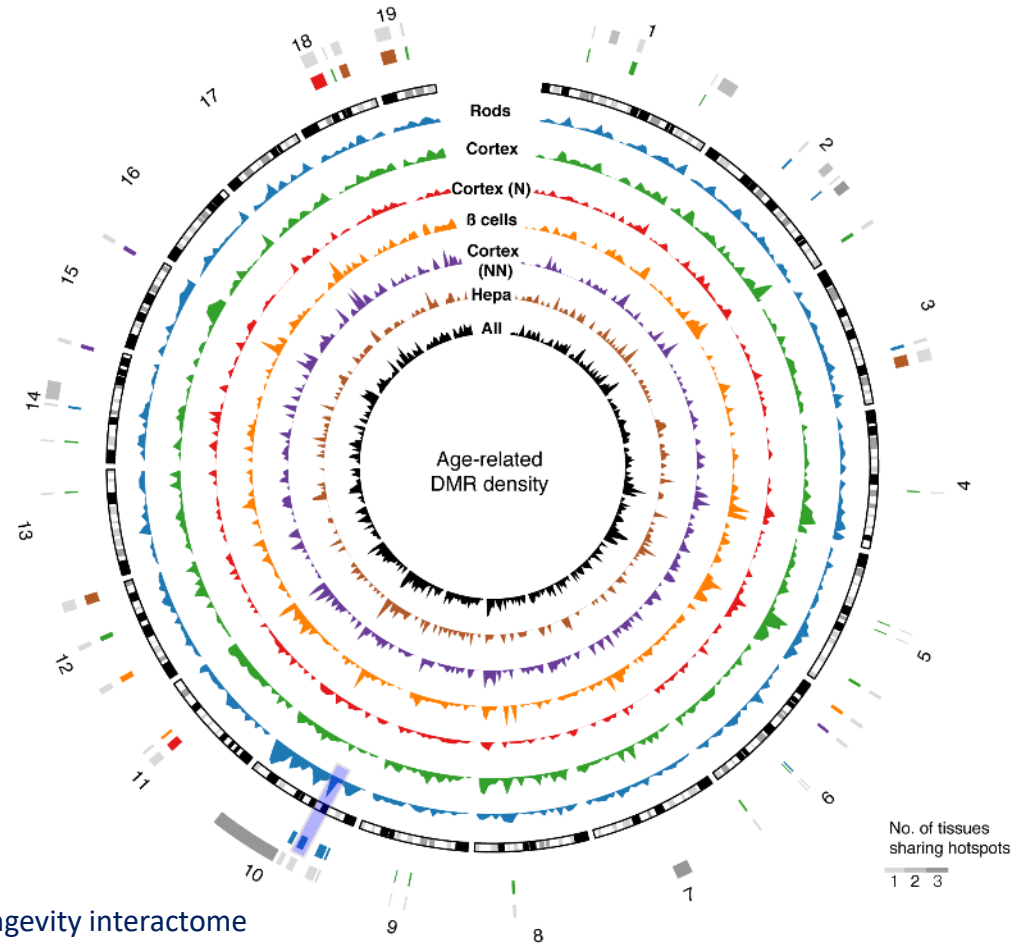
Akimoto et al. *PNAS* 2006

Corso-Díaz et. al., *Cell Reports* 31:107525, 2020

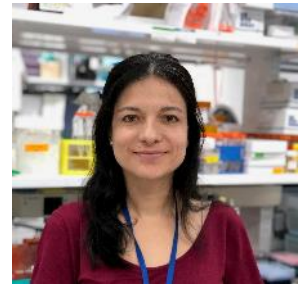
DNA methylation changes in aging rods

DMRs 3M vs 24M



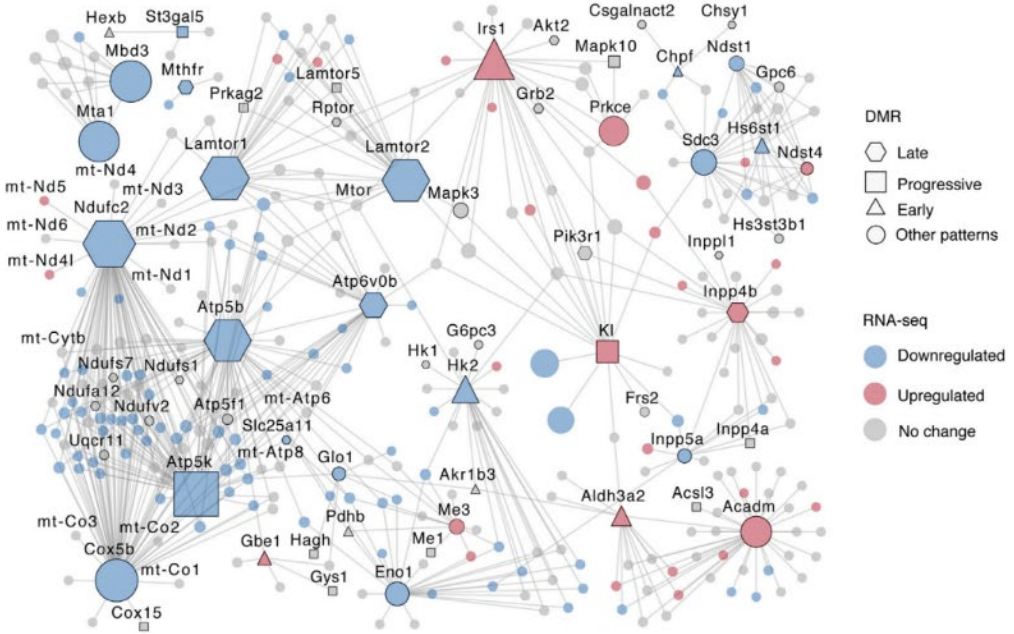


Longevity interactome

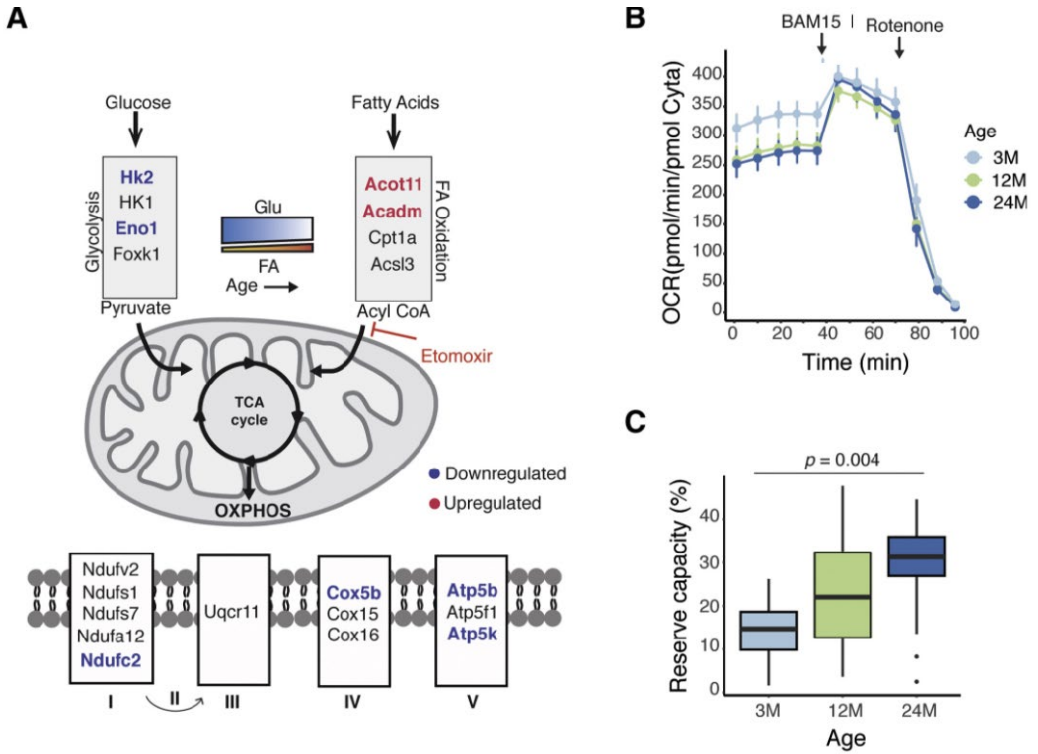


Corso-Díaz et al., *Cell Reports* 31:107525, 2020

Changes in methylated regions are associated with Rod-specific and Universal Aging Pathways



A subnetwork showing association with Metabolic Genes

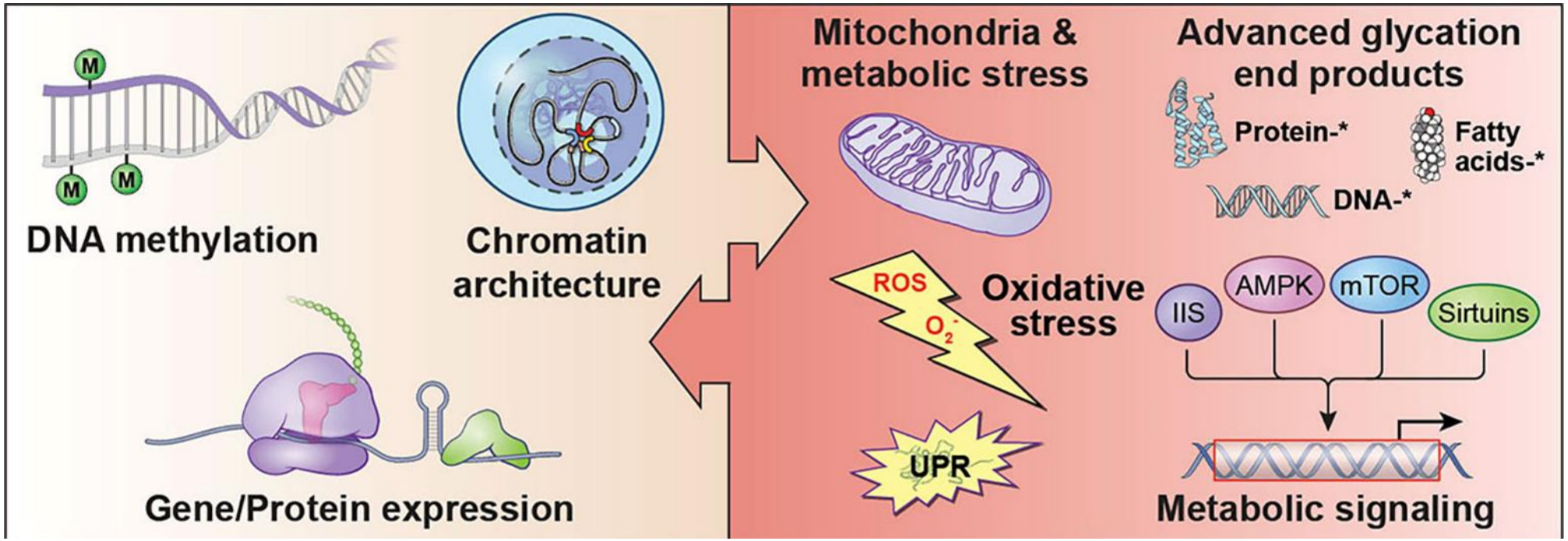


Decrease in oxygen consumption and enhanced FA dependency

Epigenome and Metabolic Dysregulation in Retinal Aging

Features of our genome

Cellular changes



Campello et al. *Annu Rev Vis Sci.* 2021

Summary and Hypothesis

- DNA methylation (epigenome) changes occur with age at gene regulatory regions in rod photoreceptors
- Age-related changes in methylation are associates with gene expression changes in cell type-specific and shared aging pathways
- Mitochondria and metabolic dysregulation is observed in aging rods

Can manipulating the epigenome impact mitochondrial function and reduce the impact of aging on retinal/rod function

Mediterranean Diet and Human Retinal Aging

Received: 15 August 2019 | Revised: 20 October 2019 | Accepted: 3 January 2020
DOI: 10.1002/alz.12077

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FEATURED ARTICLE

Adherence to a Mediterranean diet and cognitive function in the Age-Related Eye Disease Studies 1 & 2

Tiarnán D. Keenan[1] | Elvira Agrón[1] | Julie A. Mares[2] | Traci E. Clemons[3] | Freekje van Asten[4] | Anand Swaroop[4] | Emily Y. Chew[1] | for the AREDS and AREDS2 Research Groups[†]

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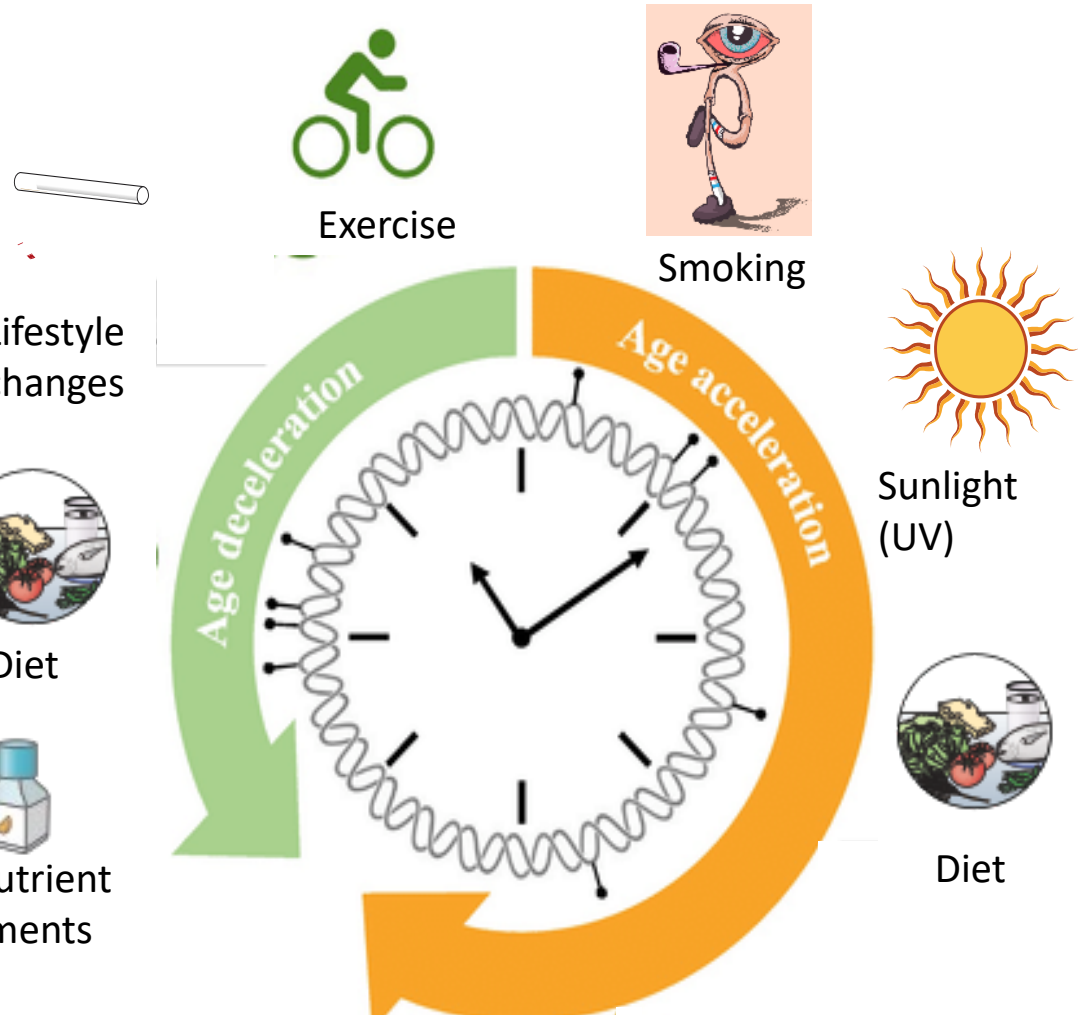
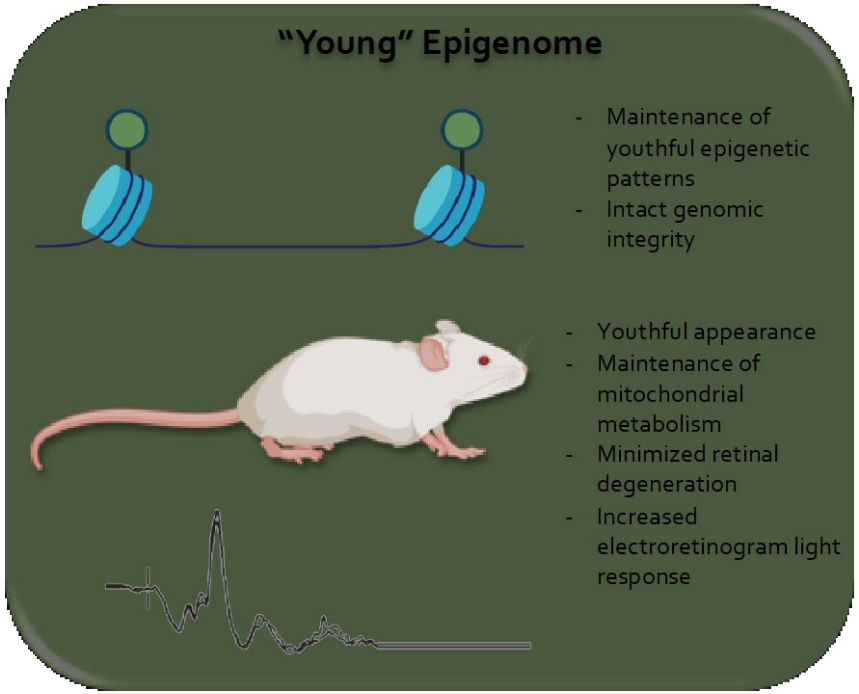
Adherence to the Mediterranean Diet and Progression to Late Age-Related Macular Degeneration in the Age-Related Eye Disease Studies 1 and 2

*Tiarnán D. Keenan, BM BCh, PhD,[1,‡] Elvira Agrón, MA,[1,‡] Julie Mares, PhD,[2] Traci E. Clemons, PhD,[3] Freekje van Asten, MD, PhD,[4] Anand Swaroop, PhD,[4] Emily Y. Chew, MD,[1] for the Age-Related Eye Disease Studies (AREDS) 1 and 2 Research Groups**



Prevent Blindness
Focus on Eye Health National Summit

Can Healthy Diet Slow Down the Impact of AGING?



1 year old

EXPERIMENTAL DIETS

Mediterranean Diet
High Fat Diet

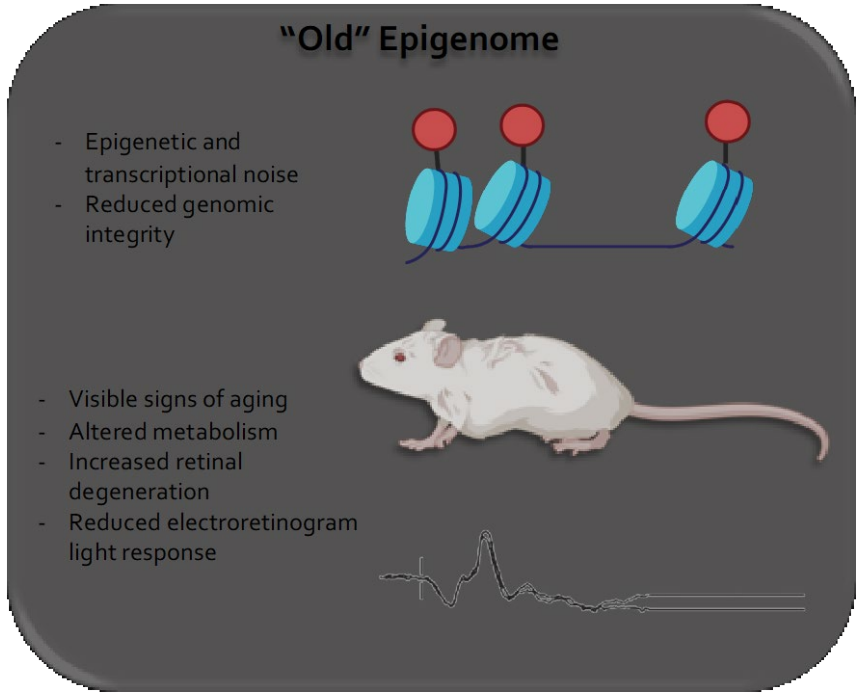
AREDS(2) Supplements
B-Vitamin Supplements

FUNCTIONAL AND MOLECULAR ASSESSMENTS

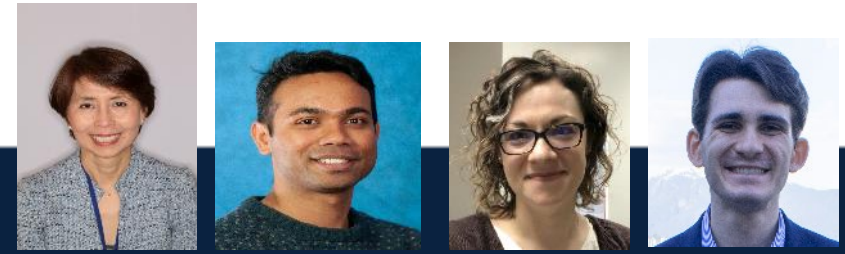
Structure & Function
Electroretinogram
Histology

Biochemical Assays
Mitochondrial function
Lipid and FA profiling

Genomic Analyses
Genome-wide methylation
Chromatin accessibility
Transcriptome



2 years old



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