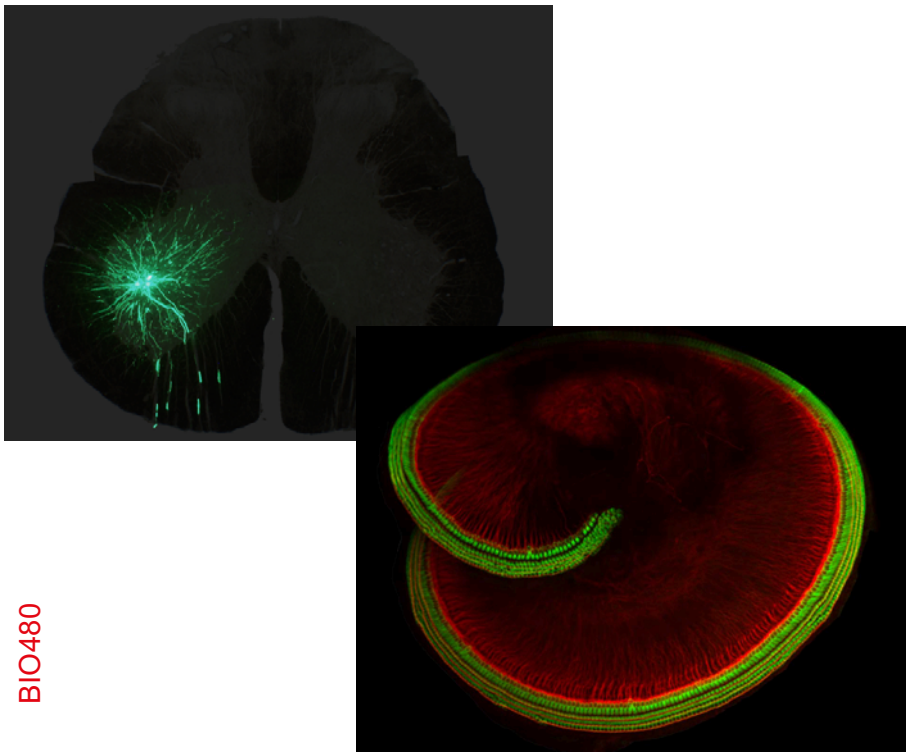
EPFL

Therapeutic applications in neurologic and sensory disorders



Bernard Schneider

BIO480
November 2024

Novel Therapeutic Approaches for CNS Diseases

- **CNS and Therapy Development**

  General principles

- **Aβ immunotherapy against Alzheimer's Disease**

- **Gene therapy for CNS diseases**

  Example of AAV as gene delivery system for the CNS

  Lipid Storage Diseases – *ex vivo* gene therapy for MLD

  Amyotrophic Lateral Sclerosis – RNAi against SOD1

- **Sensory organs:**

  Blindness functional rescue by optogenetic

  Deafness Rescue of cochlear function

Motoneuron Diseases

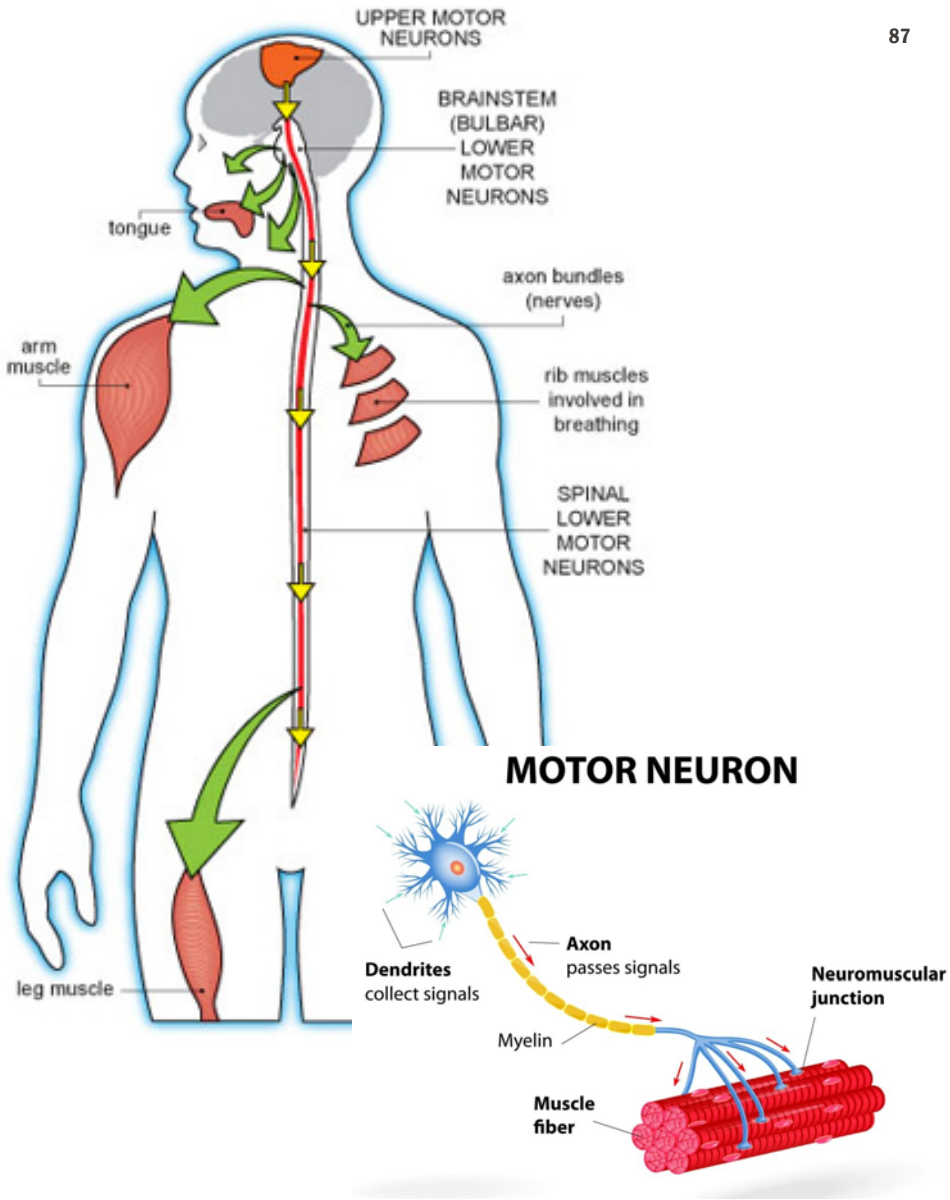
Major motoneuron disorders:

Spinal Muscular Atrophy (SMA)

- Affects mostly children
- Loss of lower motoneurons
- Caused by loss of SMN function
- Lack of muscle tone, fatal

Amyotrophic Lateral Sclerosis (ALS)

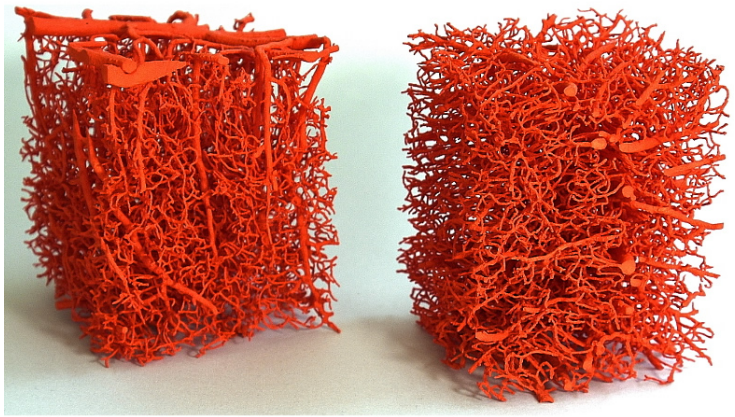
- Adult onset
- Loss of upper and lower motoneurons
- Complex etiology
- Near complete paralysis of skeletal musculature
- Fatal within 2-5 years



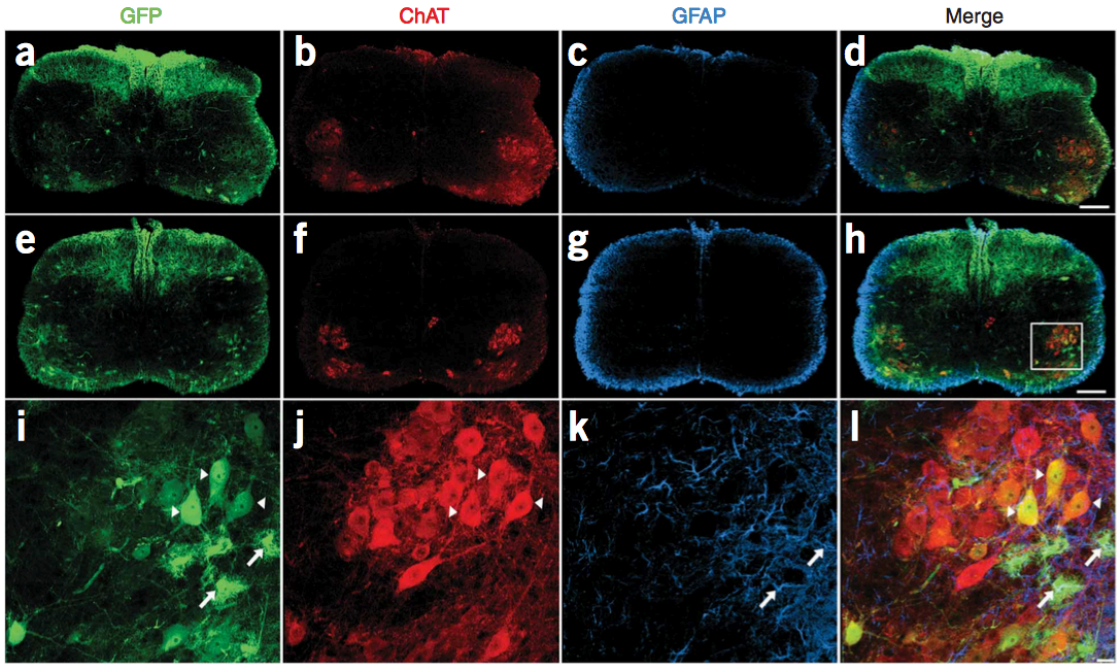
Intravenous injection of AAV for CNS gene delivery

AAV9 injected IV can pass the blood-brain barrier (spinal cord)

Brain vasculature

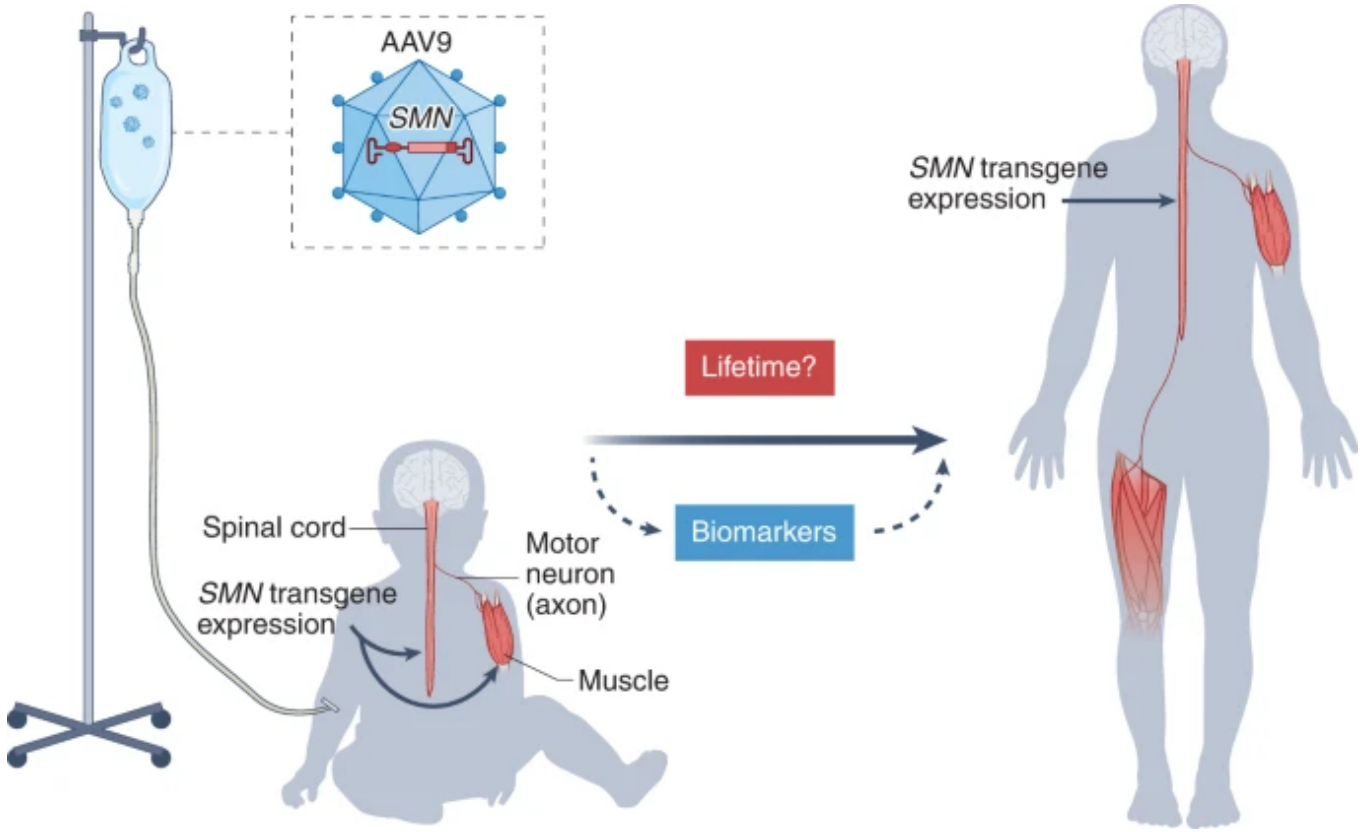


Intravenous AAV9 injection in mouse neonates



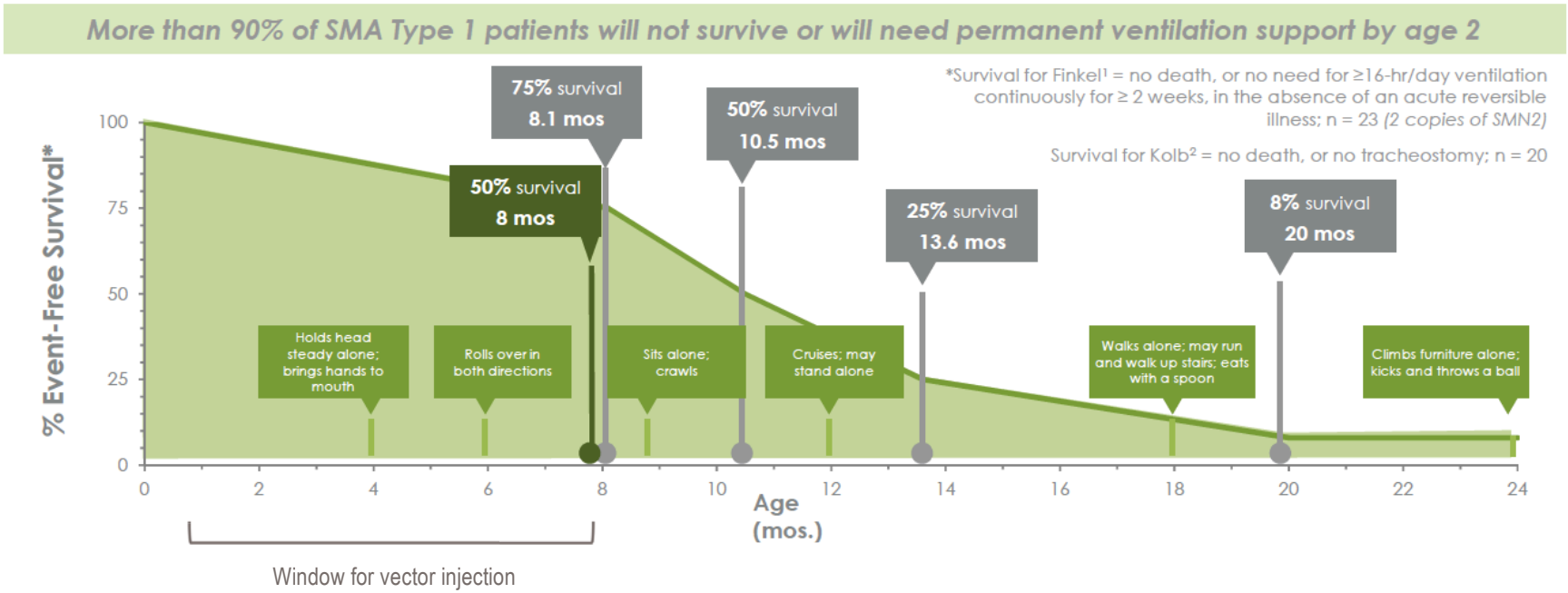
Foust KD, Nat Biotechnol 2009
Deverman BE, Nat Biotechnol 2016

Gene therapy for Spinal Muscular Atrophy



Spinal Muscular Atrophy: disease natural history

SMA type I: natural course of the disease



At 13.6 months of age:
only 25% of SMA I babies are expected to survive w/o treatment

Gene therapy for Spinal Muscular Atrophy

Clinical trial for Zolgensma (scAAV9-cba-flSMN)

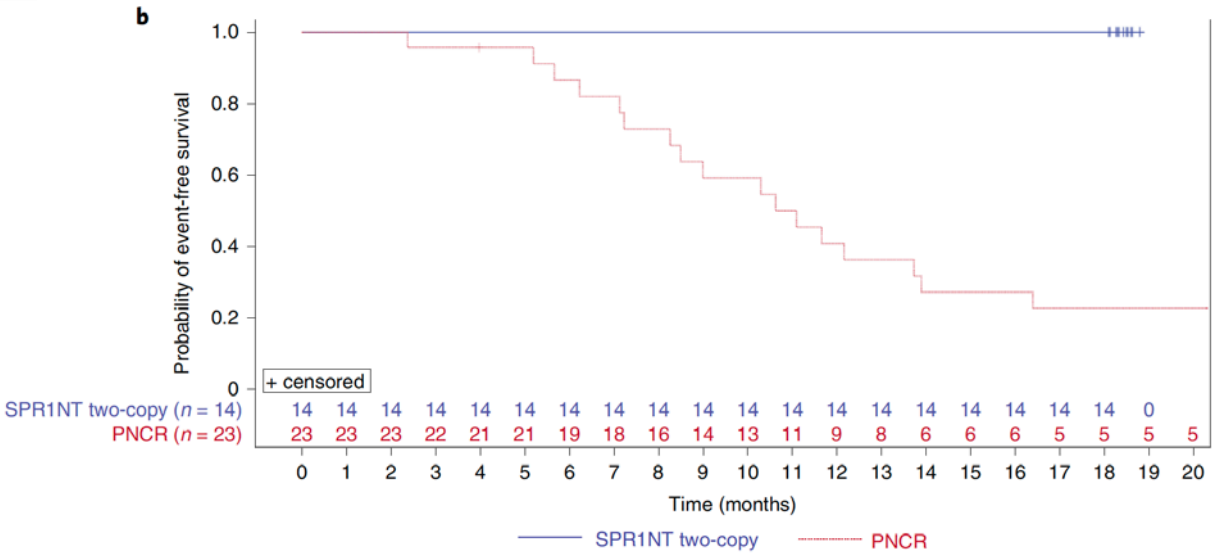
Patients: SMA type I, 2 copies of SMN2

Dosing: 1.1^{E}14 VG/kg body weight

Treatment: <1.5 months old, intravenous administration

Milestones achieved

Event-free survival



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Nature Medicine | VOL 28 | July 2022 | 1381–1389c

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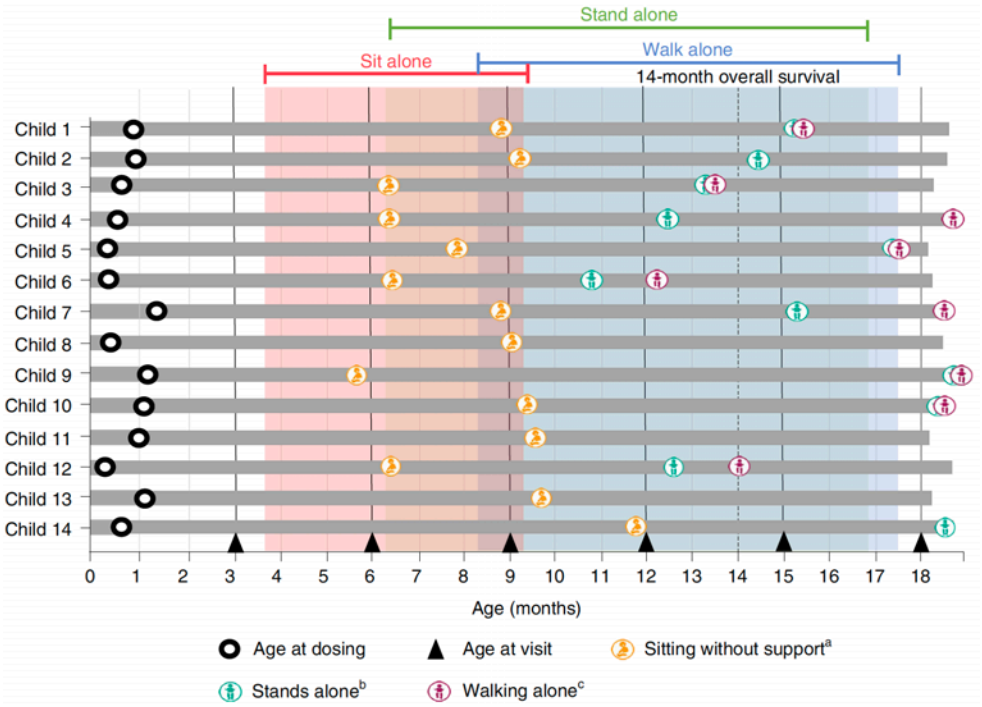
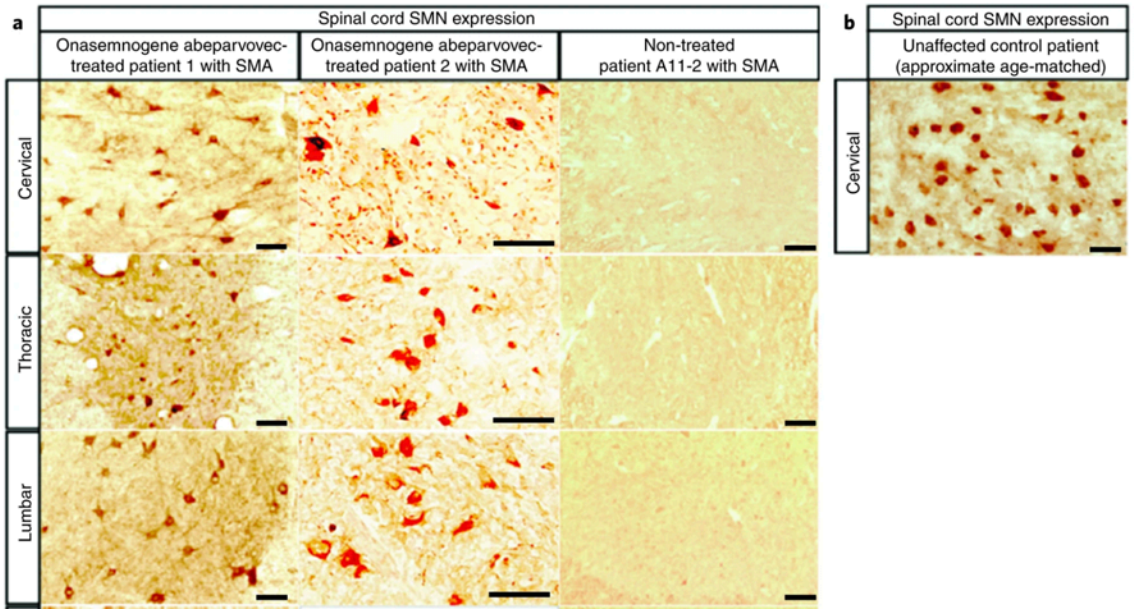


SMN expression is restored in various tissues



Nature Medicine | VOL 28 | July 2022 | 1381–1389c
Nature Medicine 2021 27(10):1701-1711

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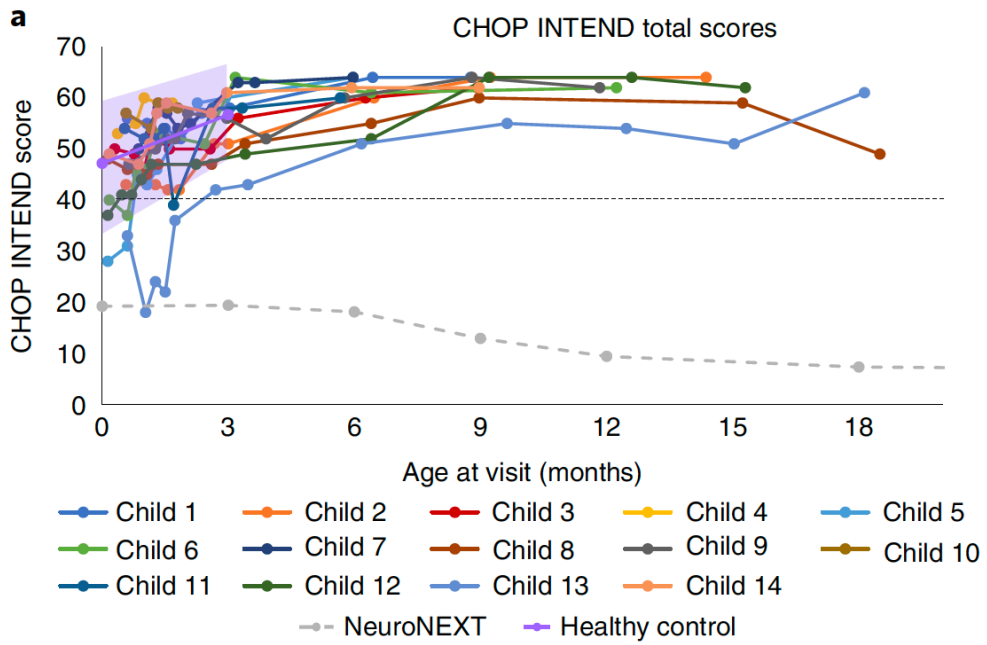
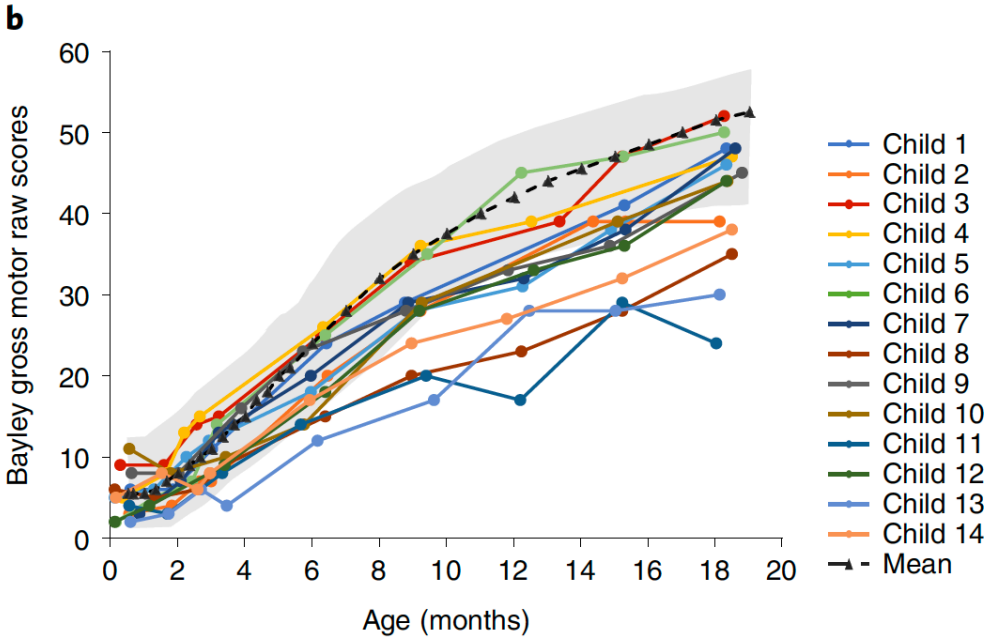




>1200 children treated with Zolgensma

- 79% were able to stand independently
- 7 were able to stand in the normal development window
- Cost: 2.1 M$

Nature Medicine | VOL 28 | July 2022 | 1381–1389c

Gene therapy: question 2

The intravenous injections of Zolgensma is the first effective disease-modifying gene therapy for a neurological disease.

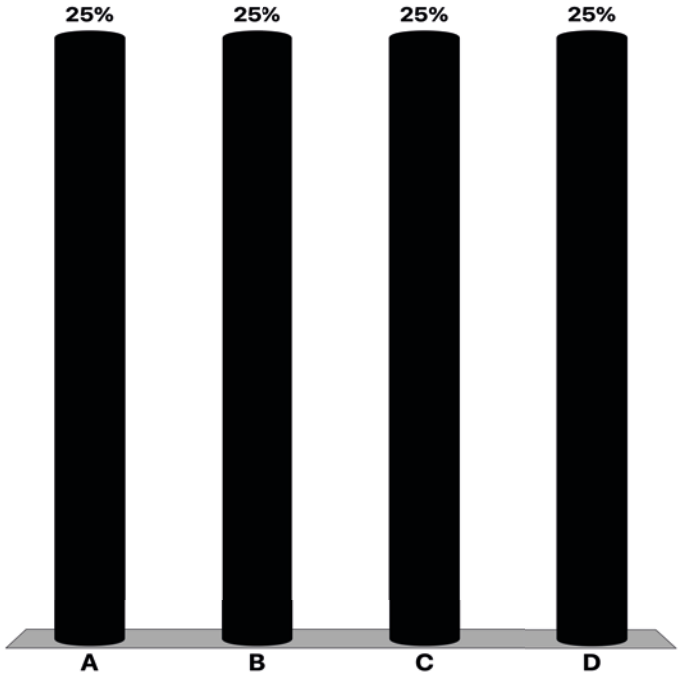
What do you think has been the parameter(s) critical for efficacy?

A. The use of a promoter allowing for SMN expression in key cell types

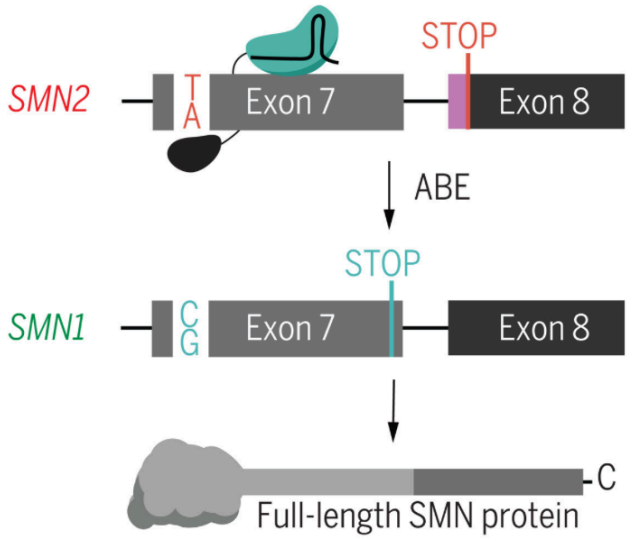
B. The use of a highly active SMN variant

C. The dose of vector injected

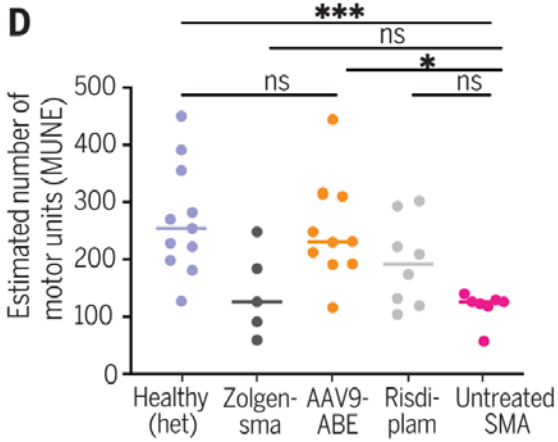
D. The use of an AAV capsid able to enter the central nervous system following peripheral injection

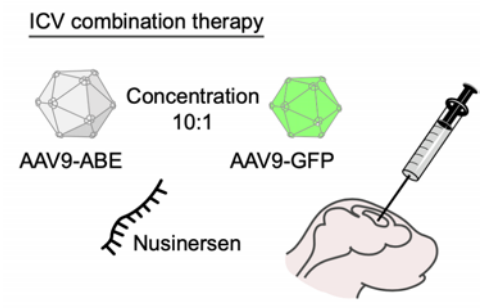


Base editing of SMN2 gene has therapeutic efficacy in SMA mice

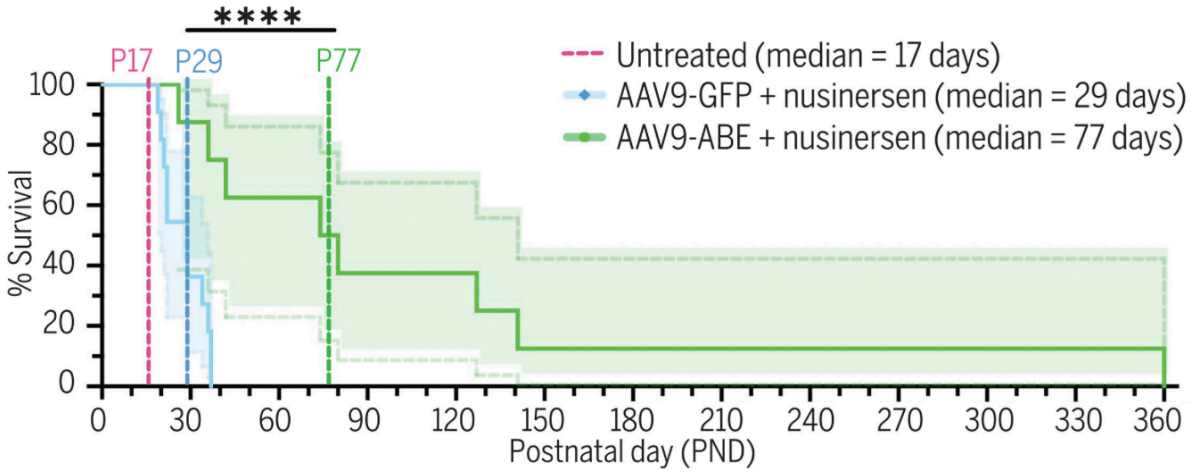


Neuroprotection
in response to genome base editing
leading to exon 7 inclusion





Enhanced survival in delta7 SMA mice



Science 2023, DOI: 10.1126/science.adg6518

Gene therapy for the CNS and sensory organs

- **Gene therapy for the CNS**

  General principles

- **Viral vectors**

  Adeno-Associated Viral vector

- **Applications of gene therapy in the CNS**:

  Lipid Storage Diseases – *ex vivo* gene therapy for MLD

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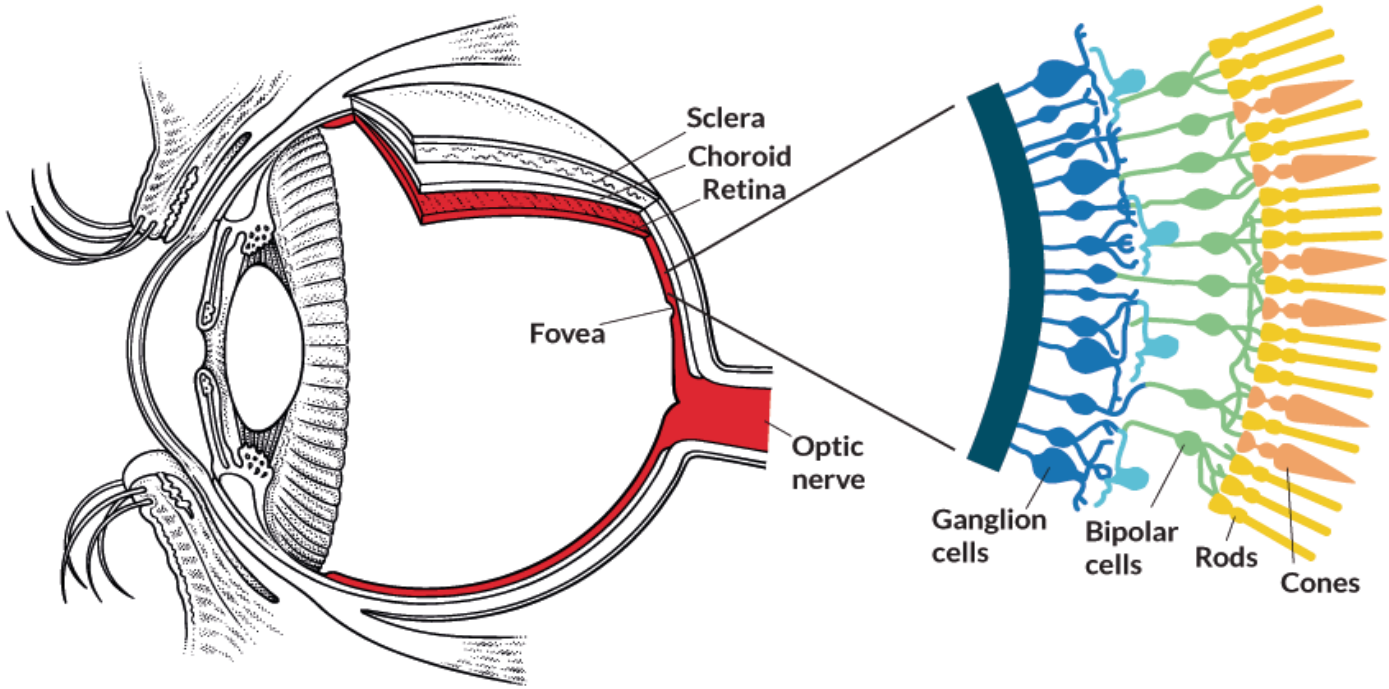
- **Sensory organs:**

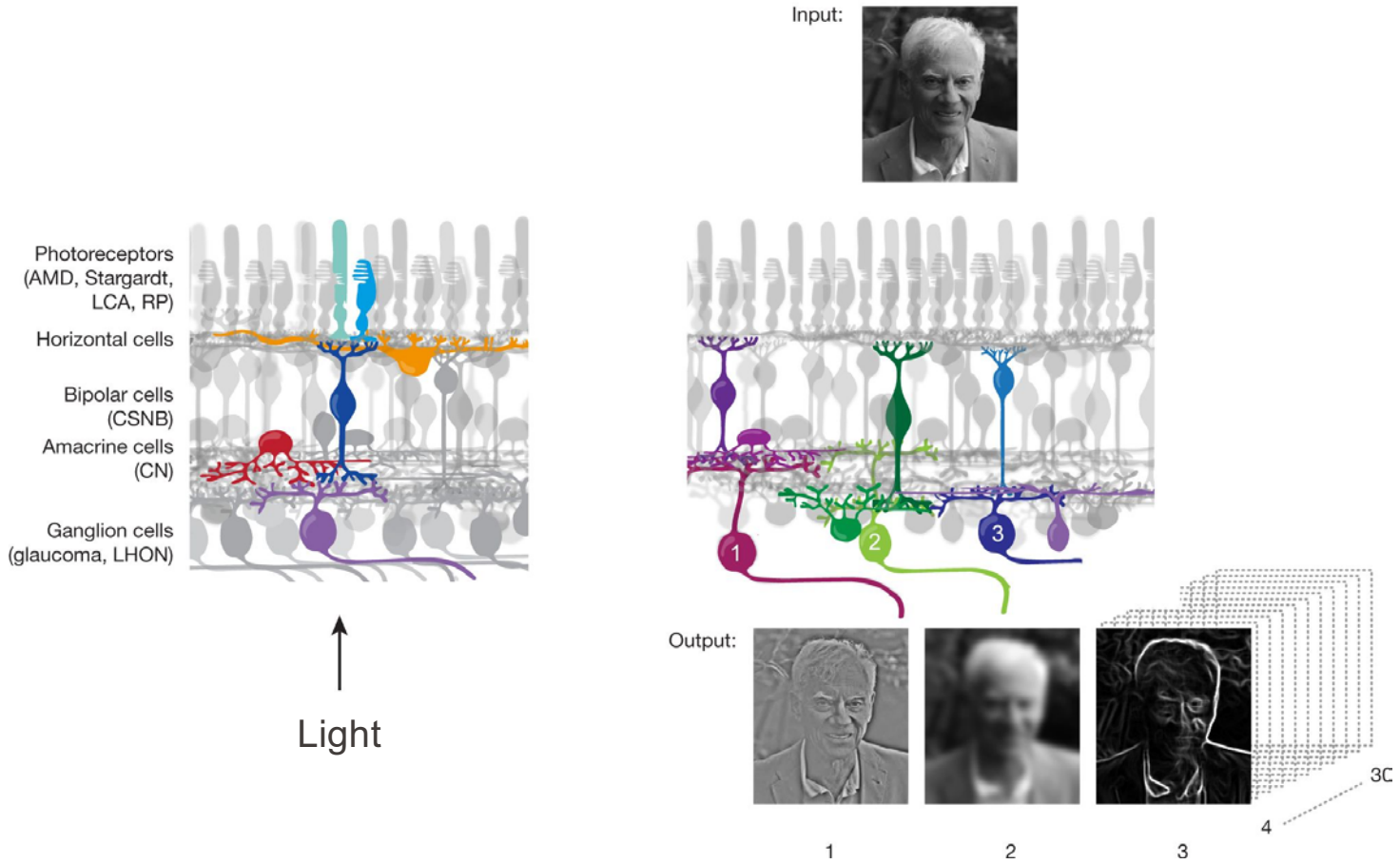
Blindness	enzyme replacement functional rescue by optogenetic
Deafness	inactivation of defective allele for protection of cochlear function

Eye function: physiology



Eye function: physiology

Cellular organisation of the retina



Retinal cell types are organized into about 30 circuits

↓

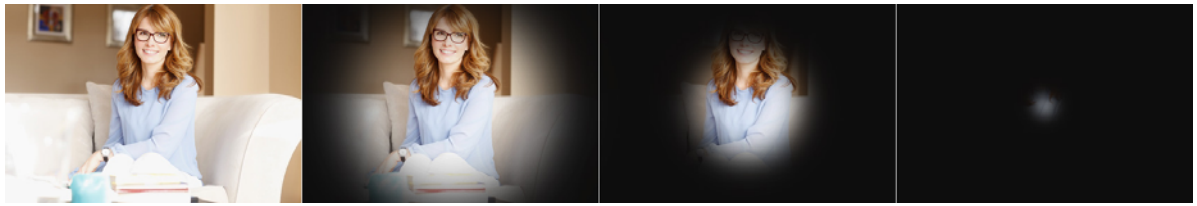
parallel image processor

Roska, B., Sahel, J. Restoring vision. Nature 557, 359–367 (2018) doi:10.1038/s41586-018-0076-4

Eye diseases

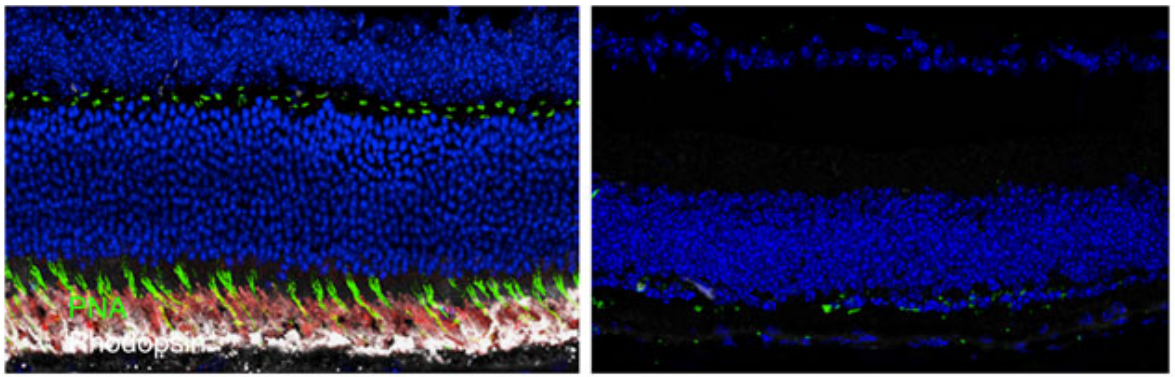
Retinal degeneration: retinitis pigmentosa

- 1.5 mio of people affected
- > 60 genes identified
- Blindness typically develops before 60 yrs of age.
- Rod-cone dystrophy



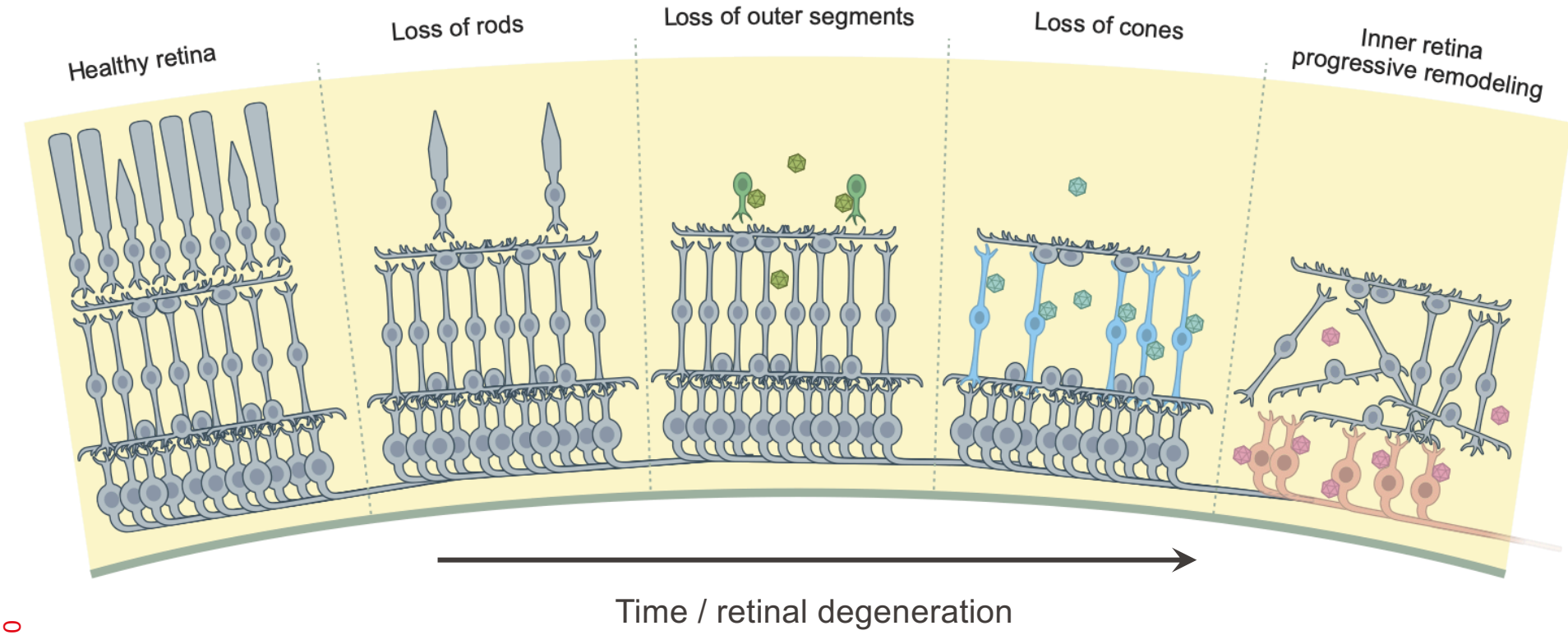
Normal retina

rd1/rd1 retina (Pde6b gene):
Photoreceptor degeneration



Eye diseases: gene therapy

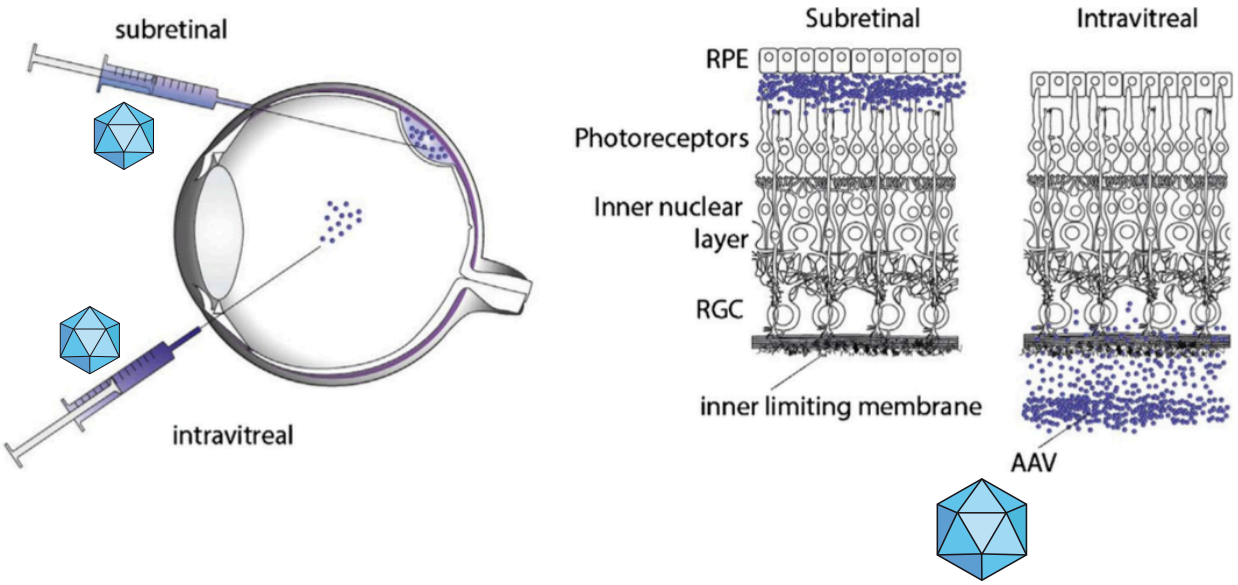
Progressive retinal degeneration in *Retinitis pigmentosa*



Kleinlogel et al., 2020, Physiol Rev 100: 1467–1525

Eye diseases: gene therapy

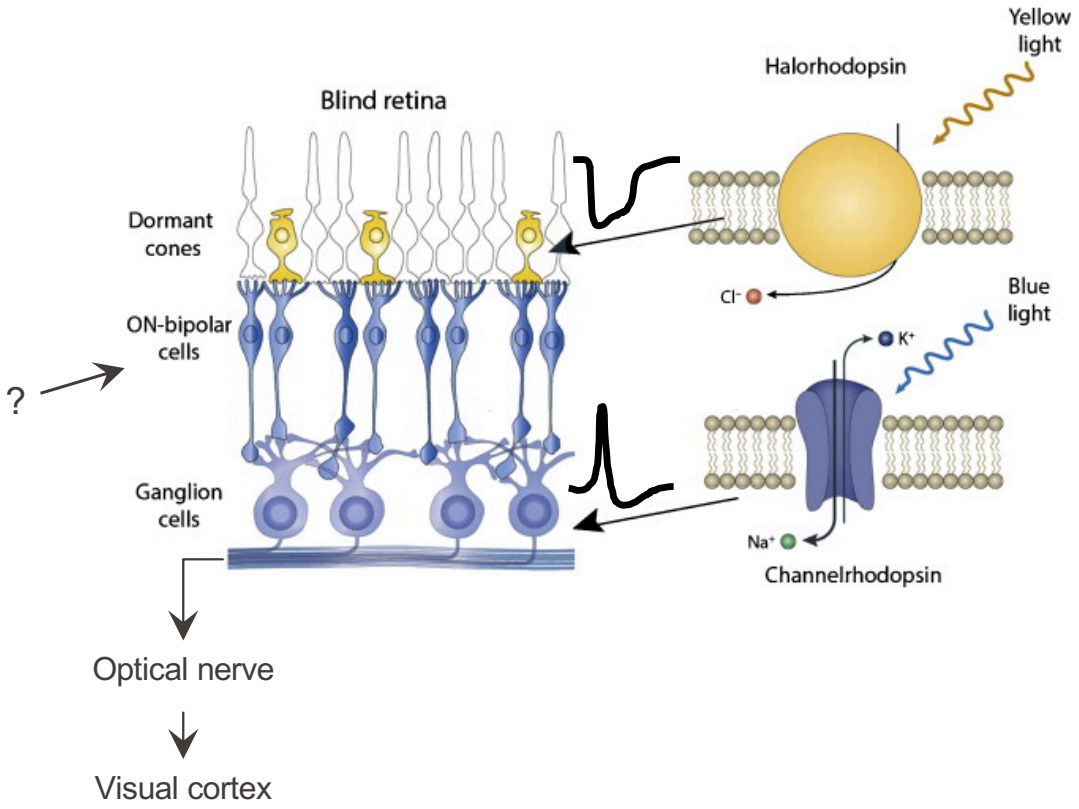
Gene therapy for the treatment of blindness: gene transfer to the retina with AAV vector

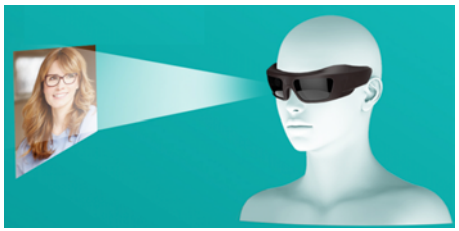


Dalkara D & Sahel J-A, Comptes Rendus Biologies 337(3), 2014

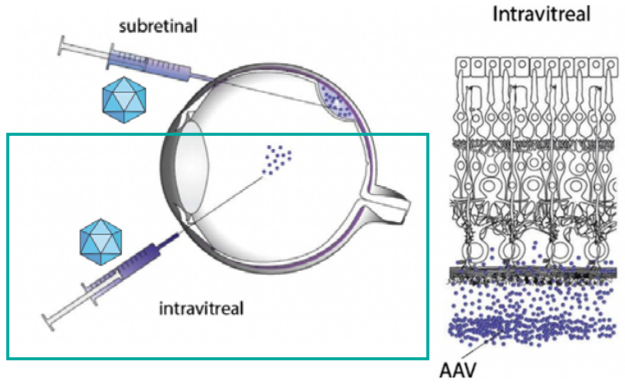
Eye diseases: gene therapy

Gene therapy for blindness: optogenetics for vision restoration





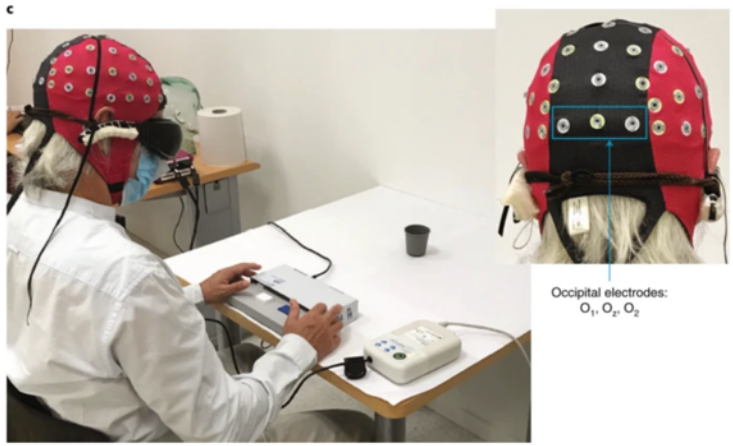
Amplifying glasses



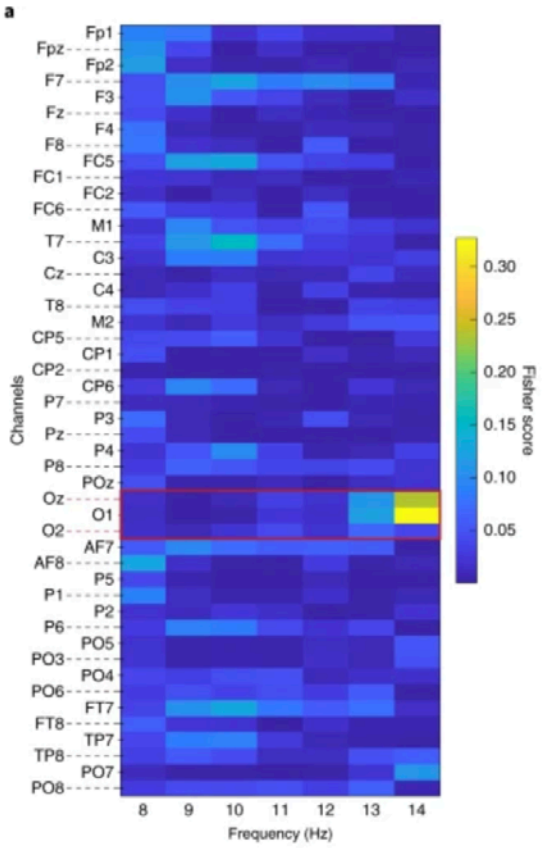
Dalkara D & Sahel J-A, Comptes Rendus Biologies 337(3), 2014

Partial recovery of visual function in a blind patient after optogenetic therapy

Retinitis pigmentosa: optogenetic vector (AAV2.7m8) encoding the light-sensing channelrhodopsin ChrimsonR via single intravitreal injection into the worse-seeing eye to target mainly foveal retinal ganglion cells.



Stimulus	Natural binocular: both eyes open without the light-stimulating goggles			Natural monocular: untreated eye covered, treated eye open without the light-stimulating goggles			Stimulated monocular: untreated eye covered, treated eye open and stimulated with the light-stimulating goggles		
	Perceive	Locate	Touch	Perceive	Locate	Touch	Perceive	Locate	Touch
Notebook, contrast = 40%	0/1	0/1	0/1	0/1	0/1	0/1	4/4	4/4	4/4
Notebook, contrast = 55%	0/1	0/1	0/1	0/1	0/1	0/1	4/5	4/5	4/5
Notebook, Contrast = 100%	0/1	0/1	0/1	0/1	0/1	0/1	4/4	4/4	4/4
Staple box, contrast = 40%	0/1	0/1	0/1	0/1	0/1	0/1	3/6	3/6	2/6
Staple box, contrast = 55%	0/1	0/1	0/1	0/1	0/1	0/1	2/5	2/5	1/5
Staple box, contrast = 100%	0/1	0/1	0/1	0/1	0/1	0/1	1/4	1/4	1/4



Nature Medicine volume 27, pages 1223–1229 (2021)

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Deafness	inactivation of defective allele for protection of cochlear function

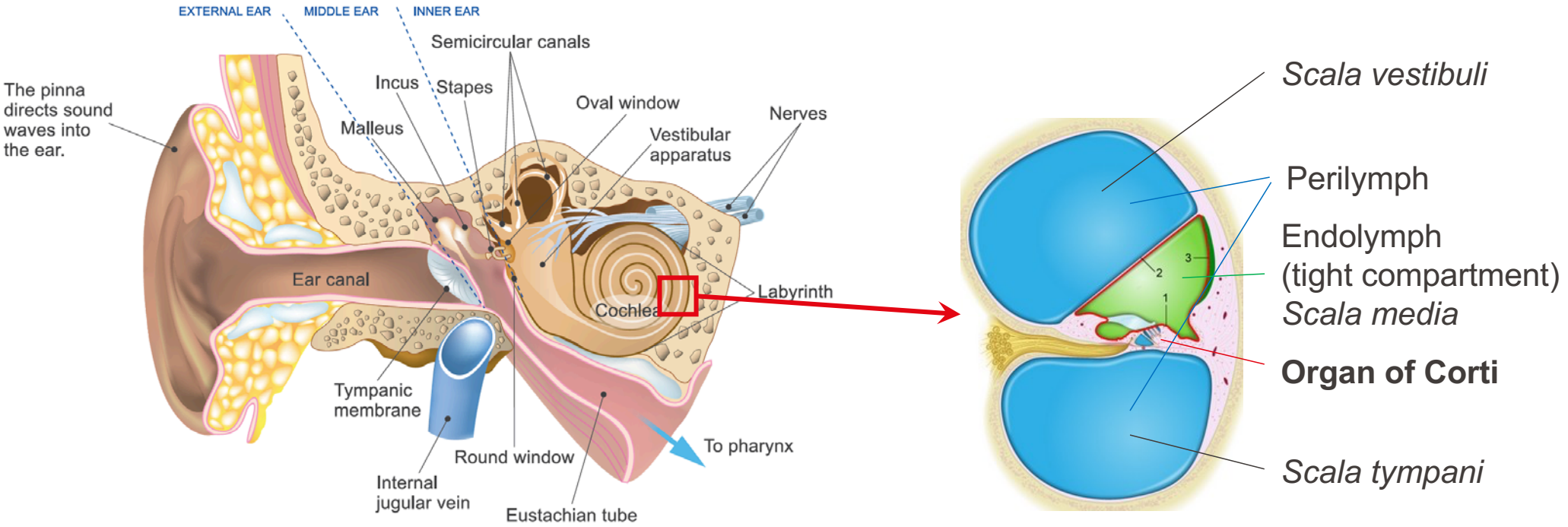
Ear diseases

Deafness: genetic causes and treatments

- Deafness affects 450 mio people worldwide, including 34 mio children.
- 26 mio people suffer from congenital hearing loss, 60% attributed to genetic factors.
- **Current state-of-the-art treatment for deafness: cochlear implants**

Inner ear physiology

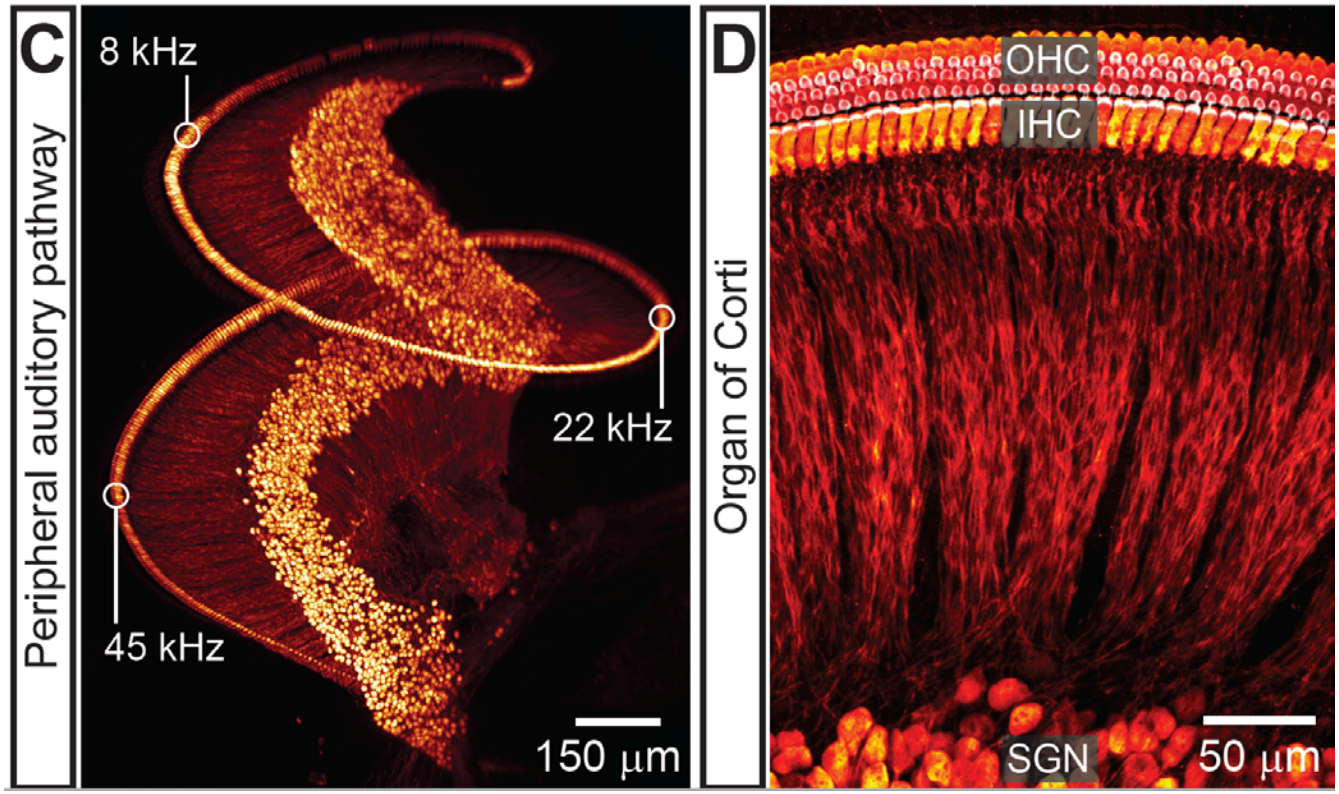
Inner ear anatomy and cochlear function



- http://www.cochlea.eu/en

Inner ear physiology

Linear tonotopical organization of the auditory pathway and organ of Corti



Outer hair cells

Inner hair cells

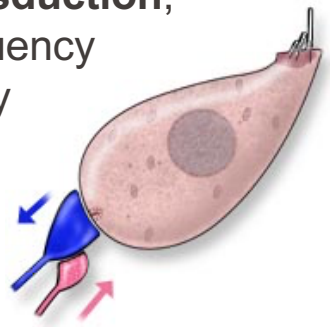
Spiral ganglion neurons

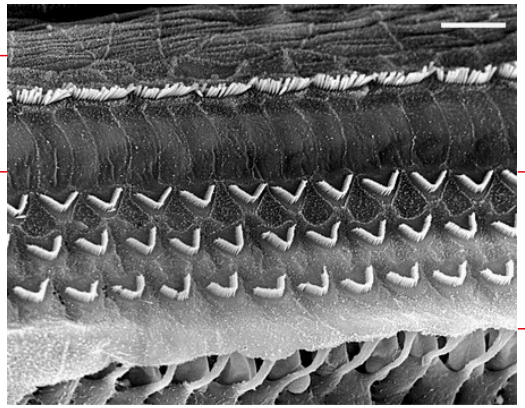
Michanski S, et al. PNAS 116: 6415–6424, 2019

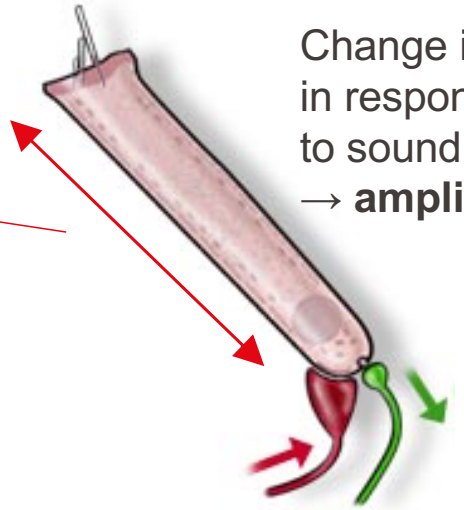
Inner ear physiology

Cochlear hair cells

Responsible for **signal transduction**, coding frequency and intensity

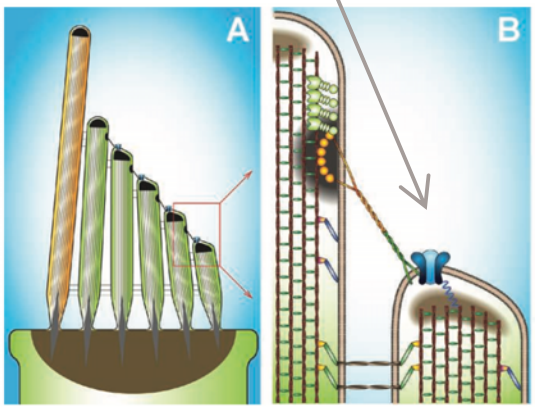


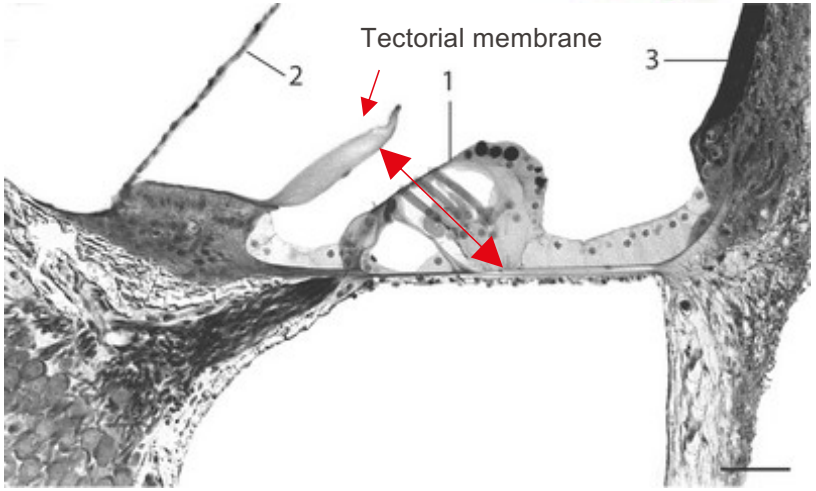




Change in shape in response to sound → **amplification**

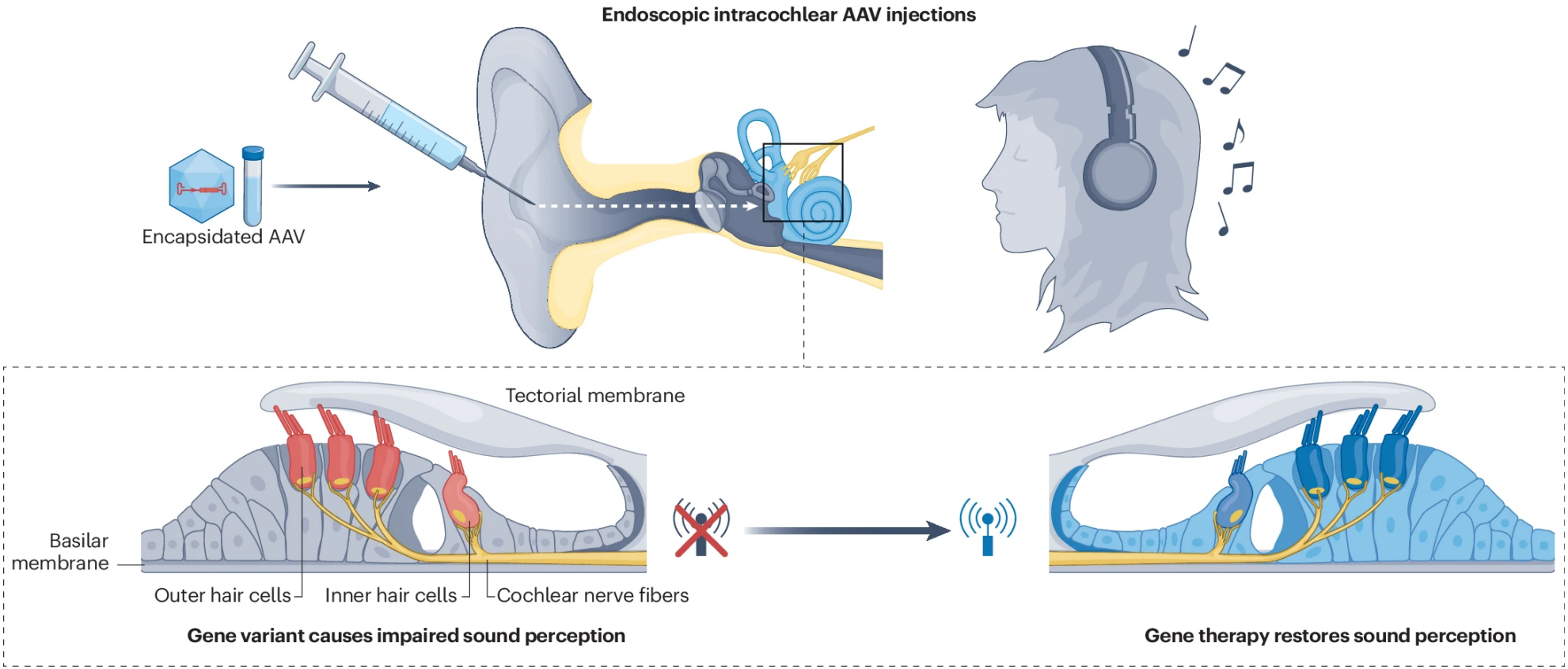
Mechanotransduction (TMC1 is part of the channel)





http://www.cochlea.eu/en

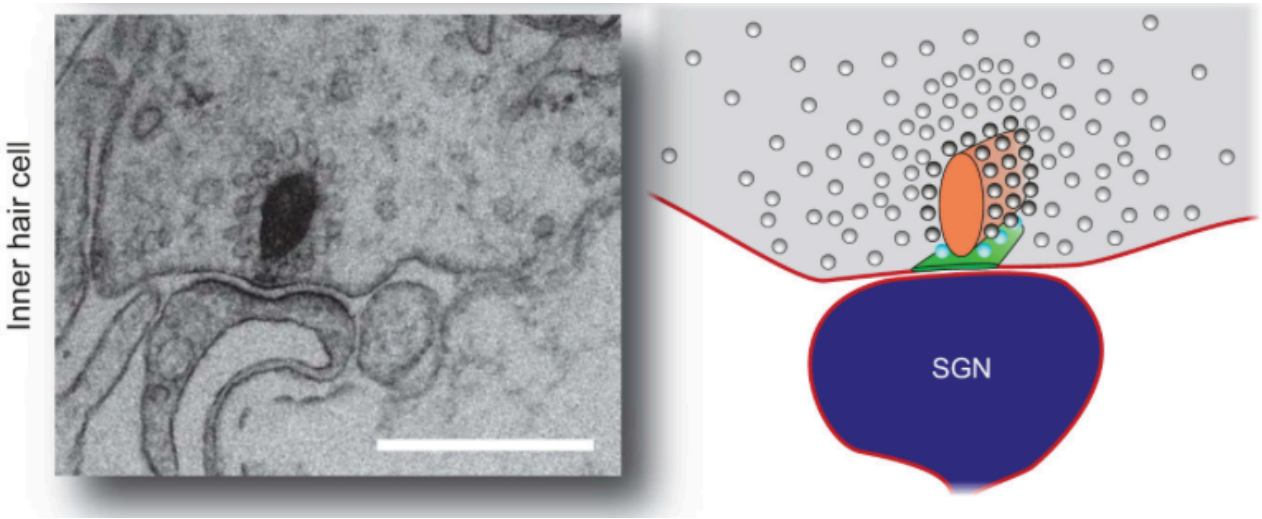
Gene Therapy for Deafness

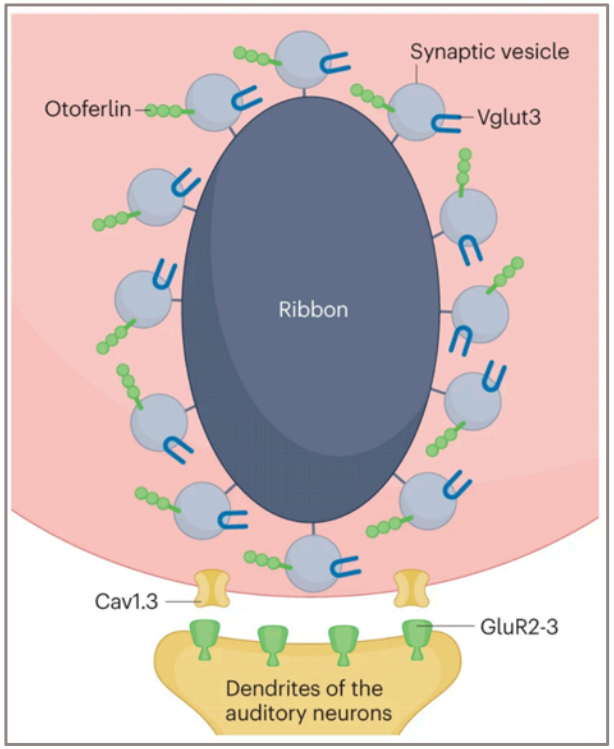


Nature Medicine volume 30, pages 1828–1829 (2024)

Otoferlin: a key factor in synaptic vesicle release in inner hair cells

- Mutations in the OTOF gene can lead to sensorineural hearing loss (DFNB9 ⇒ 2-8% of hereditary deafness).
- Impaired processing of sound signals, even with intact inner ear structures.

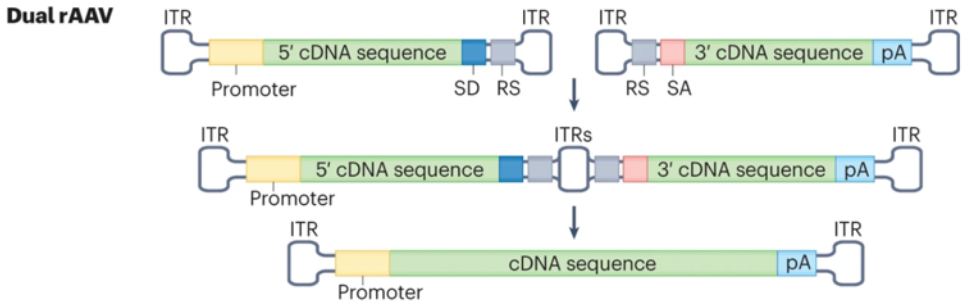




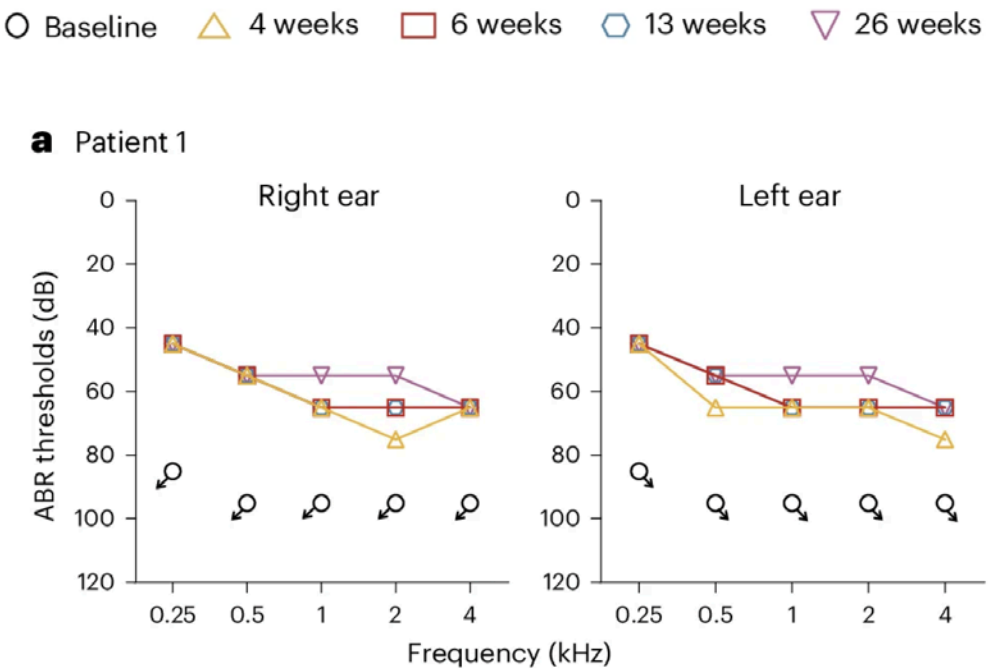
Nature Medicine volume 30, pages 1828–1829 (2024)
Nature Reviews Genetics volume 24, pages 665–686 (2023)

Gene Therapy for DFNB9

- Deafness caused by Otoferlin loss of function (DFNB9)
- Dual adeno-associated virus (AAV) serotype 1 carrying human *OTOF* transgene.
- Trans-splicing



Otoferlin coding sequence: ca. 3.7 kb



Nature Medicine volume 30, pages 1898–1904 (2024)
Nature Reviews Genetics volume 24, pages 665–686 (2023)

Gene therapy: ethical considerations

Ethical considerations for gene therapy applications

- « *Primum non nocere* »

- “Somatic” gene therapy (no modification of the germ line)
- Local administrations are preferred to systemic treatments
- Not applicable during embryonic development

- One-time treatment
- Long-term follow-up of the patients

Gene therapy: ethical considerations

Risk / benefits evaluation

- Secondary effects
- Biosafety

- Therapeutic benefits
- One-time treatment

- Disease severity?
- Existing alternative treatments?
- Is the treatment affordable?