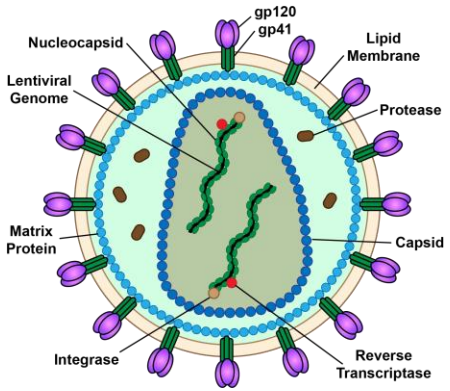
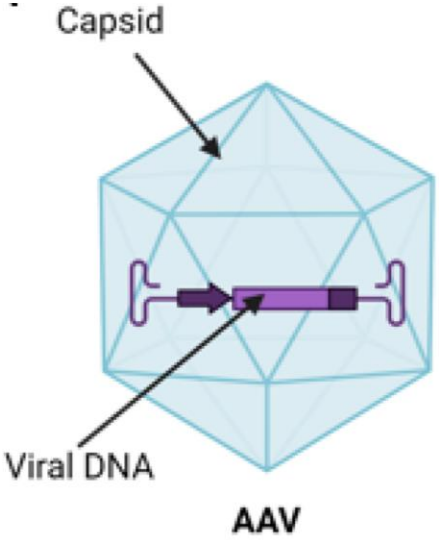
UniSR
Università Vita-Salute
San Raffaele

Lentiviral Vectors



Adeno-Associated Vectors

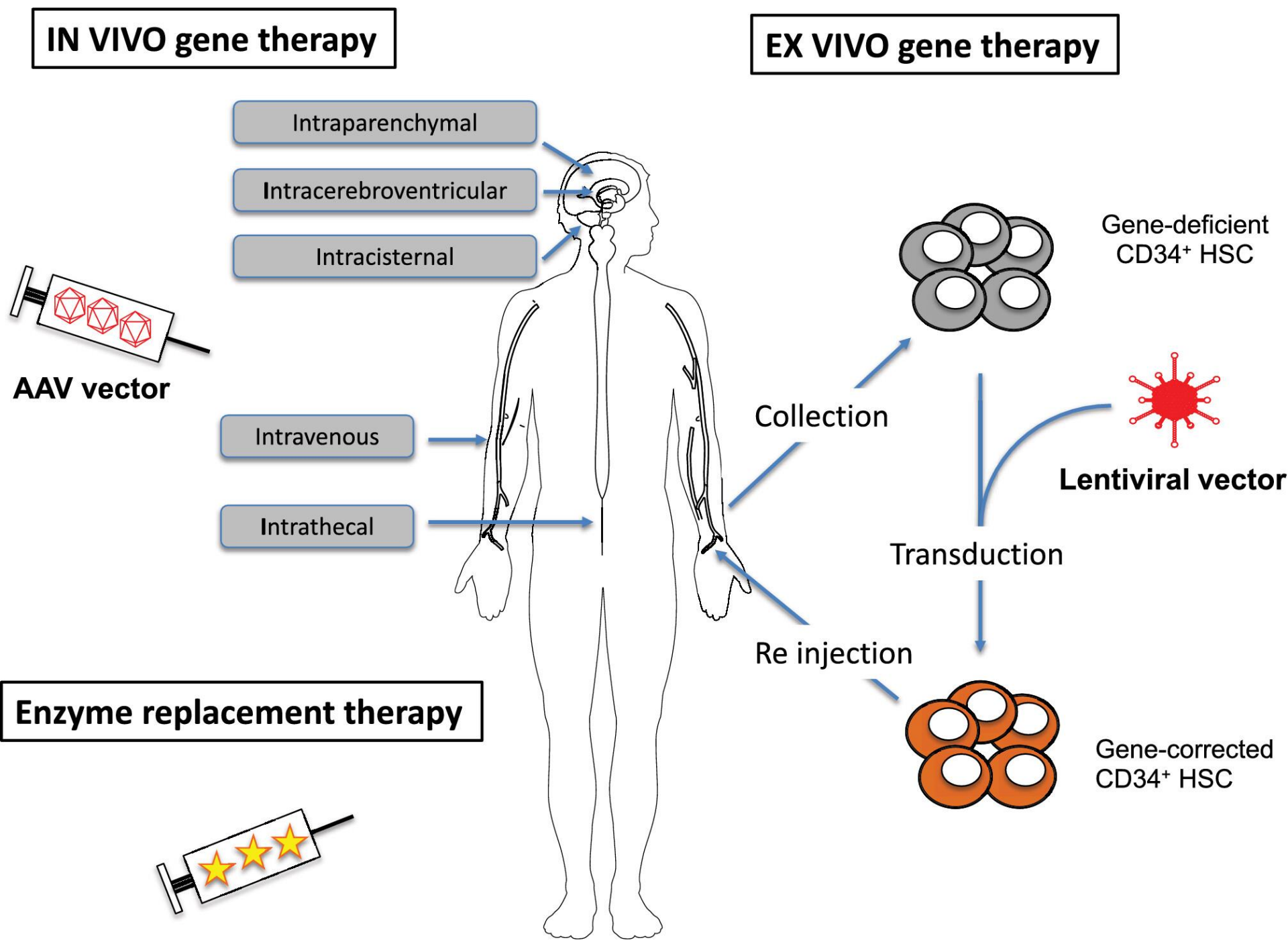


Tigem, Alberto Auricchio è il nuovo direttore

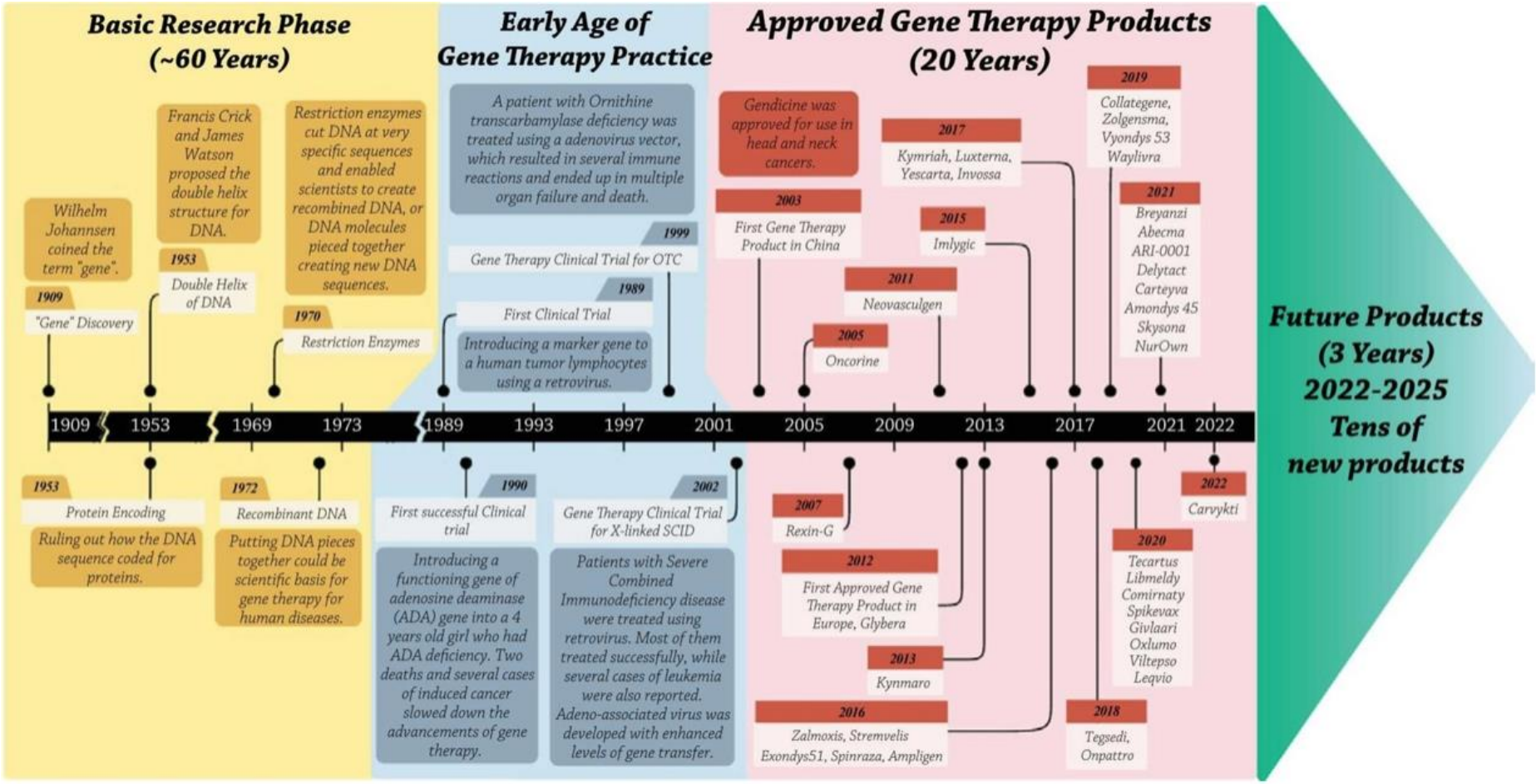
Si apre un nuovo capitolo di una storia lunga 30 anni: Andrea Ballabio, alla guida dell'Istituto fin dalla sua nascita nel 1994, passa il testimone

di Francesca Cerati

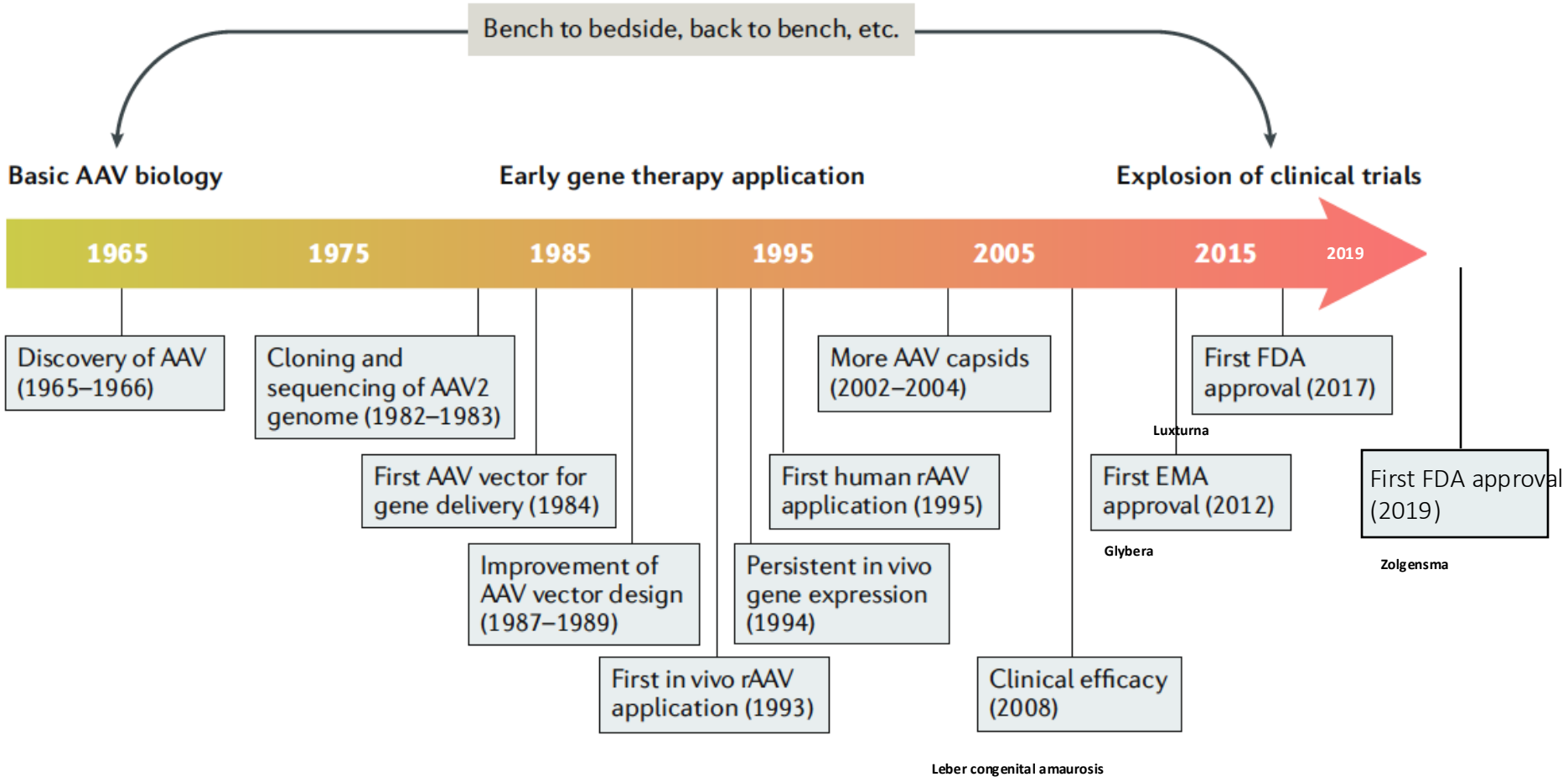
15 aprile 2024


IN VIVO gene therapy
EX VIVO gene therapy
Intraparenchymal
Intracerebroventricular
Intracisternal
AAV vector
Intravenous
Intrathecal
Enzyme replacement therapy
Collection
Re injection
Gene-deficient CD34+ HSC
Lentiviral vector
Transduction
Gene-corrected CD34+ HSC

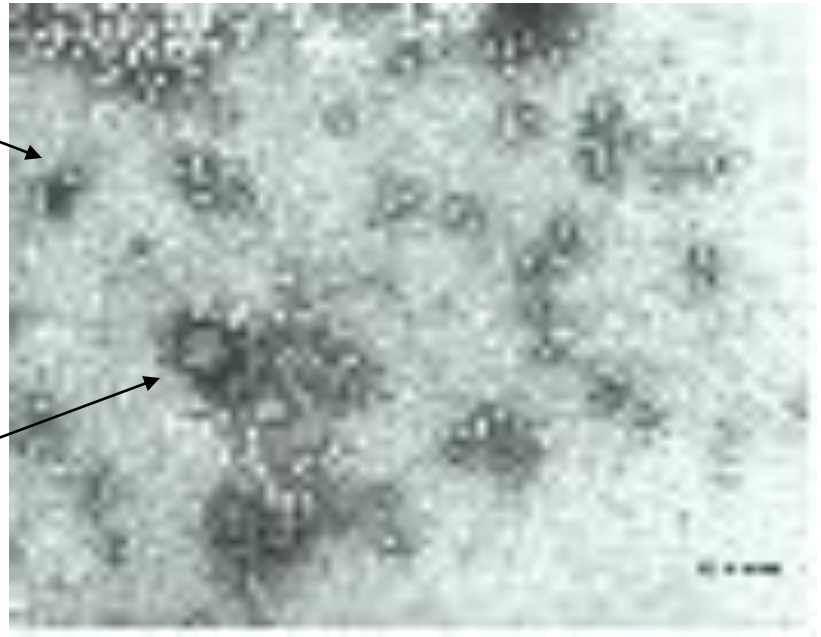
A glance at the journey of gene therapy



50 years of AAV



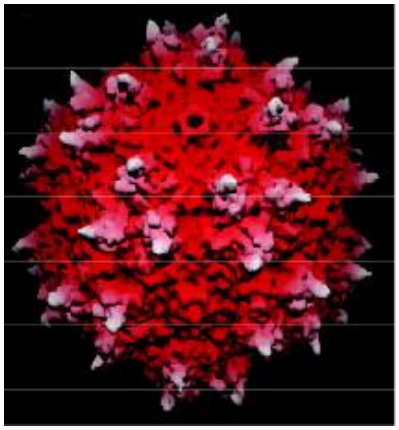
Adeno-associated virus (AAV)



Taxonomy
Family: Parvovirus
Subfamily: Parvoviridae
Genus: Dependovirus
Type: AAV 1-12

Morphology
Particles are icosahedral, non-enveloped,
18-26 nm diameter, 50% protein (VP1-3) 50% DNA.
Resistant to inactivation by solvents, pH and heat.

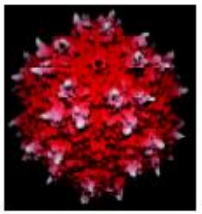
Genome
Linear, non-segmented, ssDNA ~5 kb.
AAVs package equal amounts of (+) and (-) strands.



Xie et al. 2002

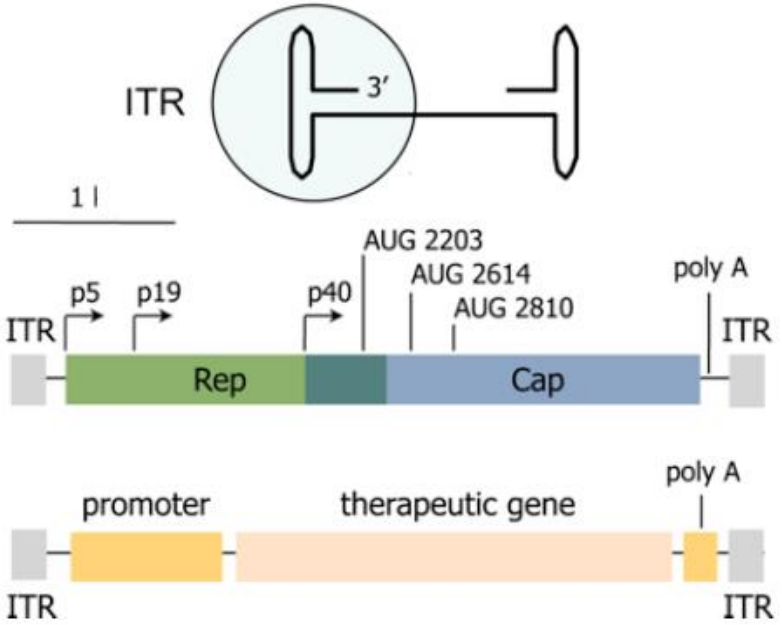
Gene transfer using Adeno-Associated Virus (AAV) vectors

1. Based on a widely diffused, non pathogenic virus
2. Vectors retain less that 10% of the viral genome
3. Vectors do not express any viral protein (not inflammatory and not immunogenic); long term ensured in vivo
4. Expression of the therapeutic gene can be driven by any desirable promoter
5. High titer vector preparations are obtained by virion purification
6. Mixing of different rAAV preparations results in the simultaneous expression of gene combinations in vivo

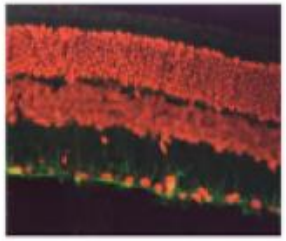


Xie et al. 2002

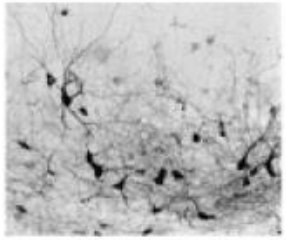
Family: Parvovirus
Genus: Dependovirus
Type: AAV 1-9
Size: 18-26 nm
Genome: ssDNA ~5 kb



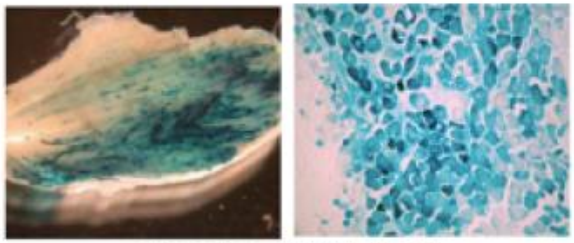
AAV vectors transduce with high efficiency post-mitotic tissues in vivo



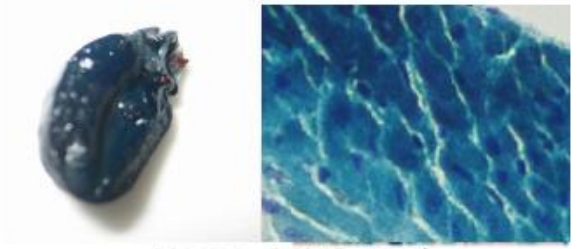
Retina, AAV2-GFP



Brain, AAV2-bcl2



Muscle, AAV8-βgal

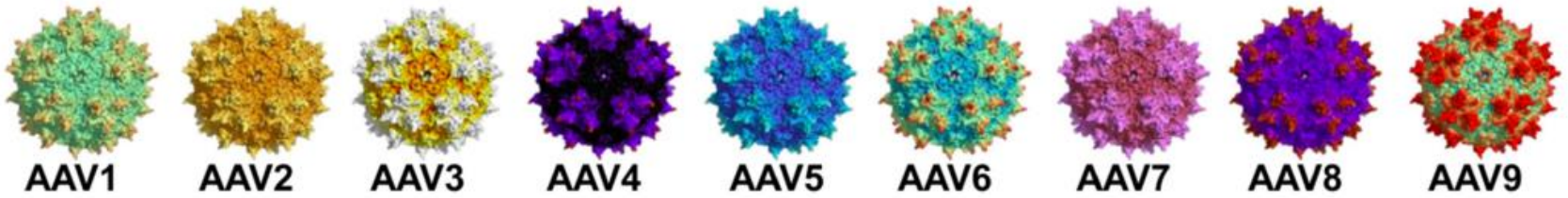


Heart, AAV9-βgal

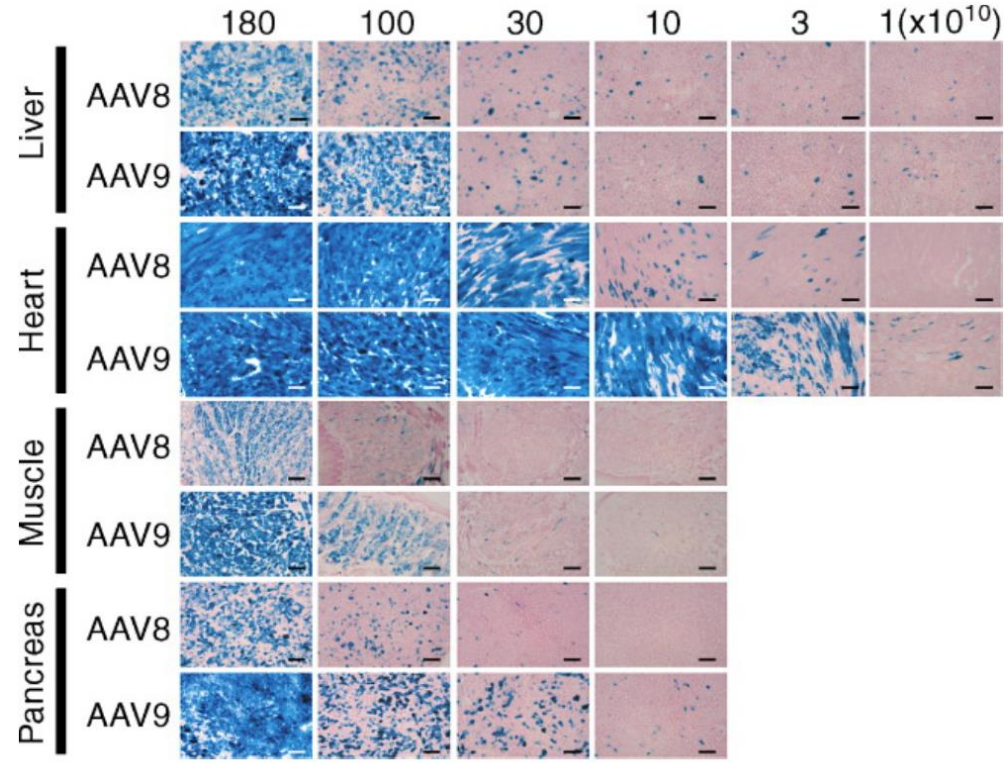
Recettori di alcuni Parvovirus

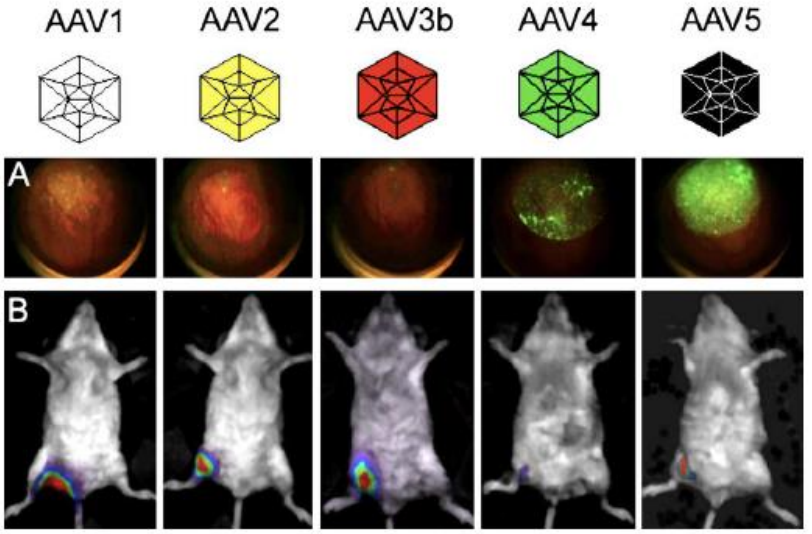
Parvovirus	Recettore
AAV1	Acido sialico (legami ⟨2-3-N e ⟨2-6-N)
AAV2	Proteoglicani contenenti eparan-solfati (HSPG) Corecettori: integrina ⟨v®5, FGFR1, HGF-R
AAV3	Proteoglicani contenenti eparan-solfati (HSPG)
AAV4	Acido sialico (legami ⟨2-3-O)
AAV5	Acido sialico (legami ⟨2-3-O e ⟨2-3-N) Recettore del PDGF (PDGFR)
AAV6	Acido sialico (legami ⟨2-3-N e ⟨2-6-N)
AAV7	Non noto
AAV8	Recettore della laminina (LamR)
AAV9	Non noto (LamR?)
Parvovirus B19	Antigene P dei globuli rossi
CPV (parvovirus canino)	Recettore della trasferrina Acido sialico (acido N-glicolil-neuraminico, NeuGC)
FPV (parvovirus della panleucopenia felina)	Recettore della trasferrina

Biodistribution of AAV serotypes 1-9 in mice



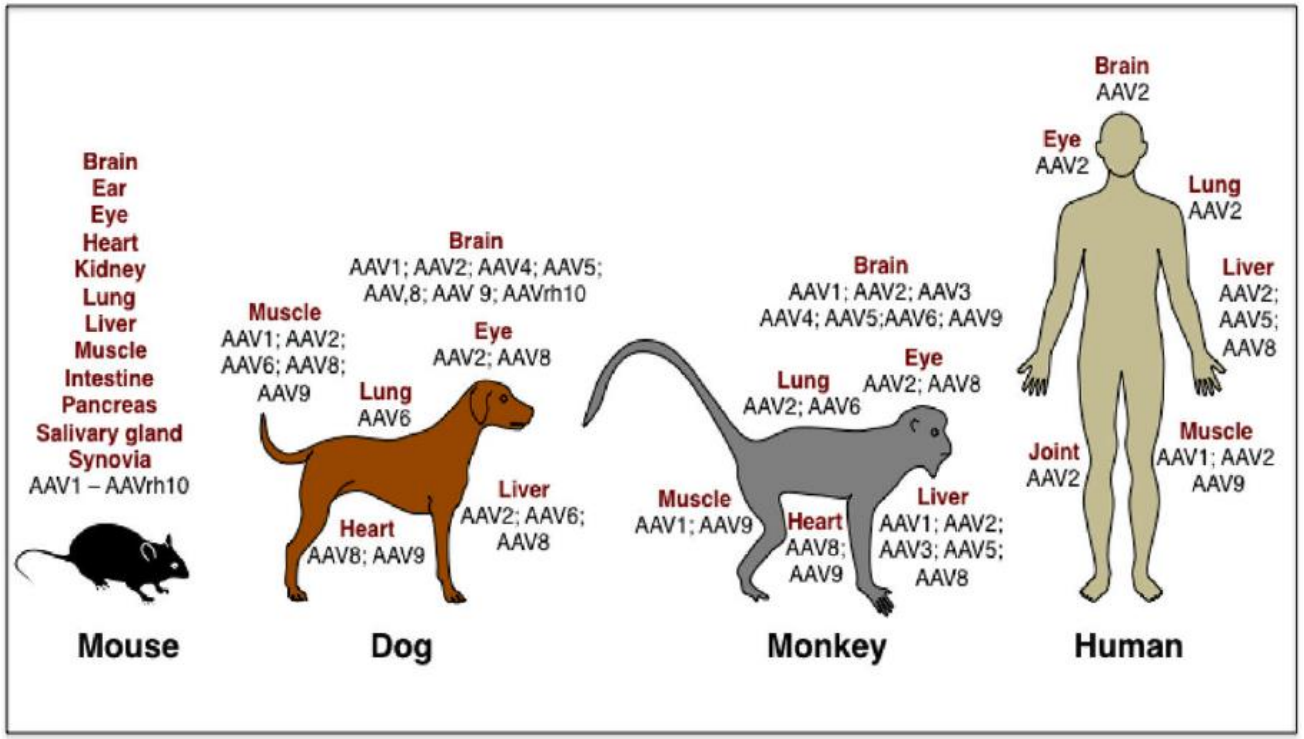
Mouse	AAV1	AAV2	AAV3	AAV4	AAV5	AAV6	AAV7	AAV8	AAV9
	Liver, heart, skeletal muscle	Liver, heart and muscle	Heart, Liver	Heart, lung, Liver	Liver	Liver, heart, skeletal muscle	Liver, skeletal muscle	Heart, Liver, brain, muscle	Liver, heart, brain, Lung, skeletal muscle



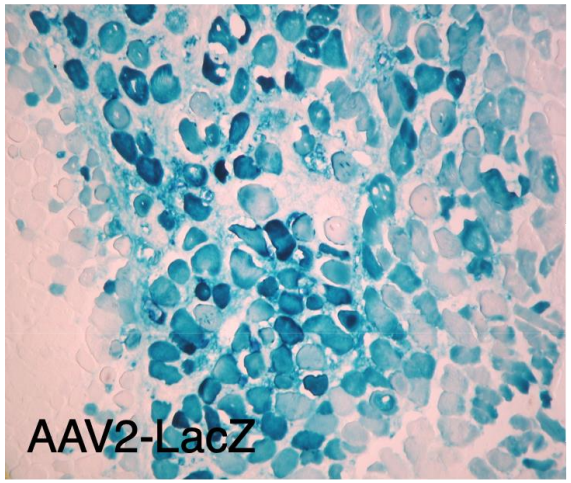


Criteria for the choice of the AAV serotype to use as a gene transfer vector

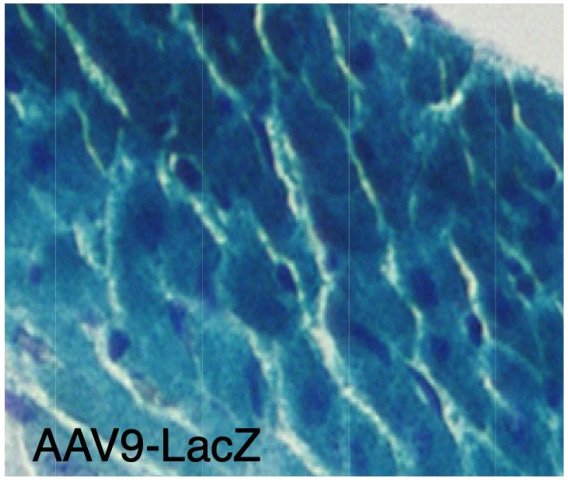
- ★ **Which cell/tissue types are being targeted**
- ★ The safety profile associated with the delivered gene
- ★ The choice of systemic versus local delivery
- ★ The use of tissue-specific or constitutively active promoters
- ★ Which animal species is the final target



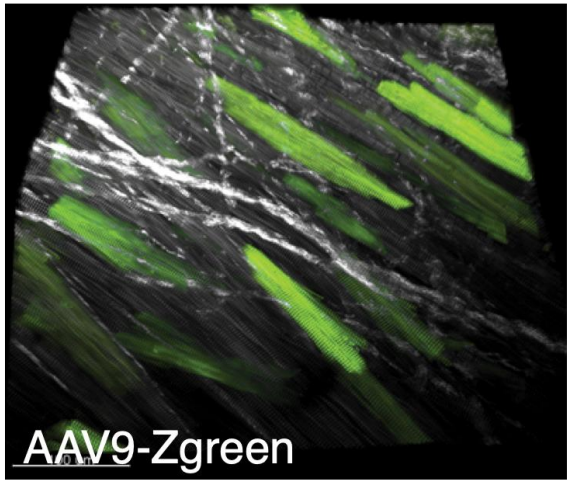
AAV efficiently transduces permissive tissues and promotes persistent transgene expression



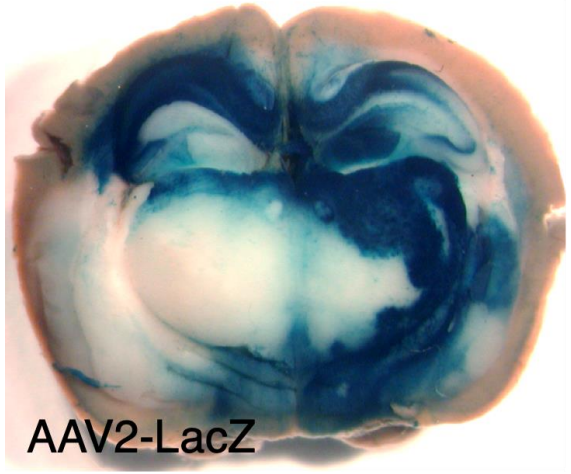
Skeletal muscle



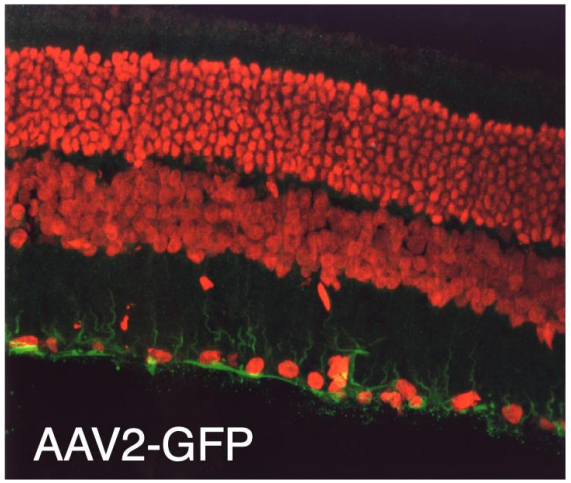
Heart



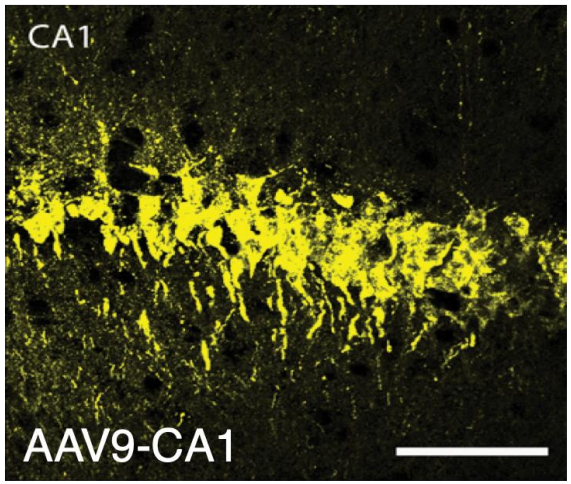
Cardiomyocytes



Brain

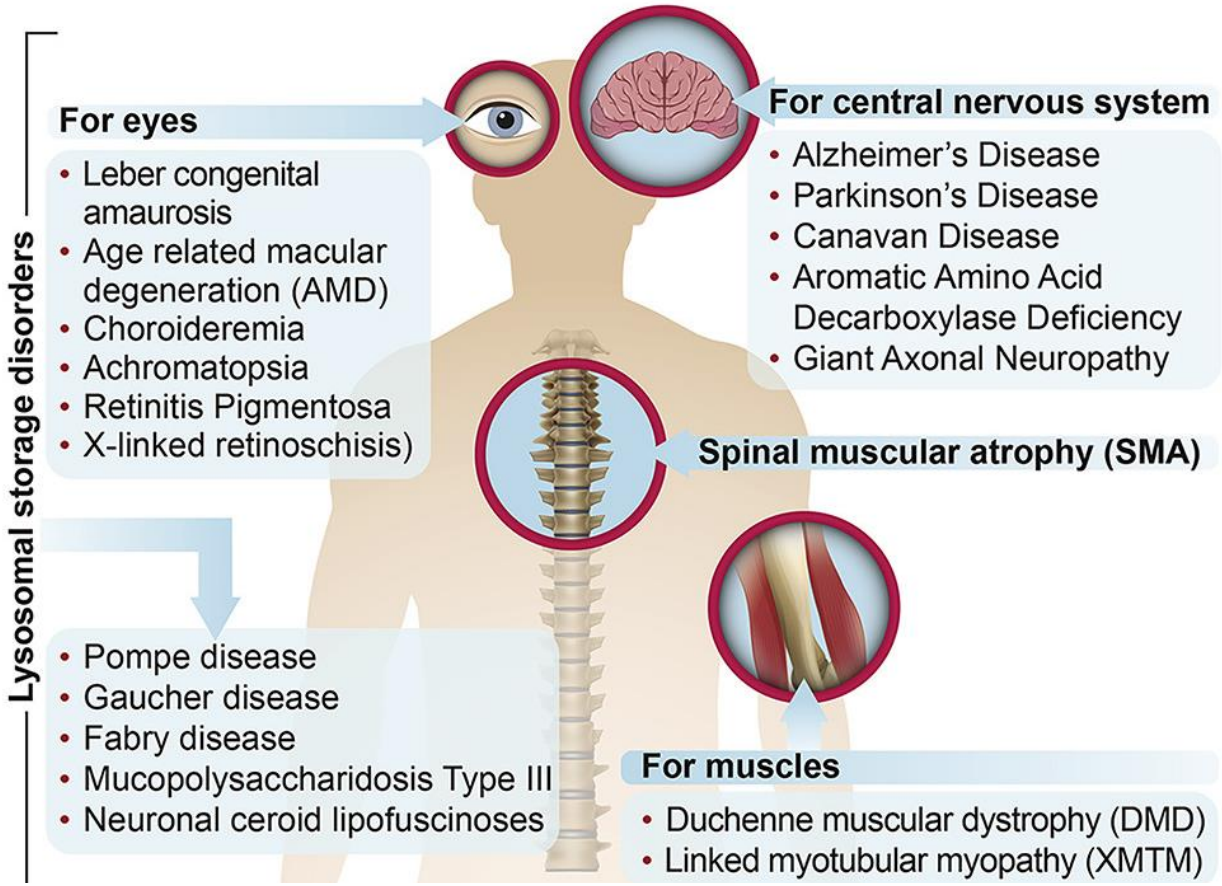


Retina



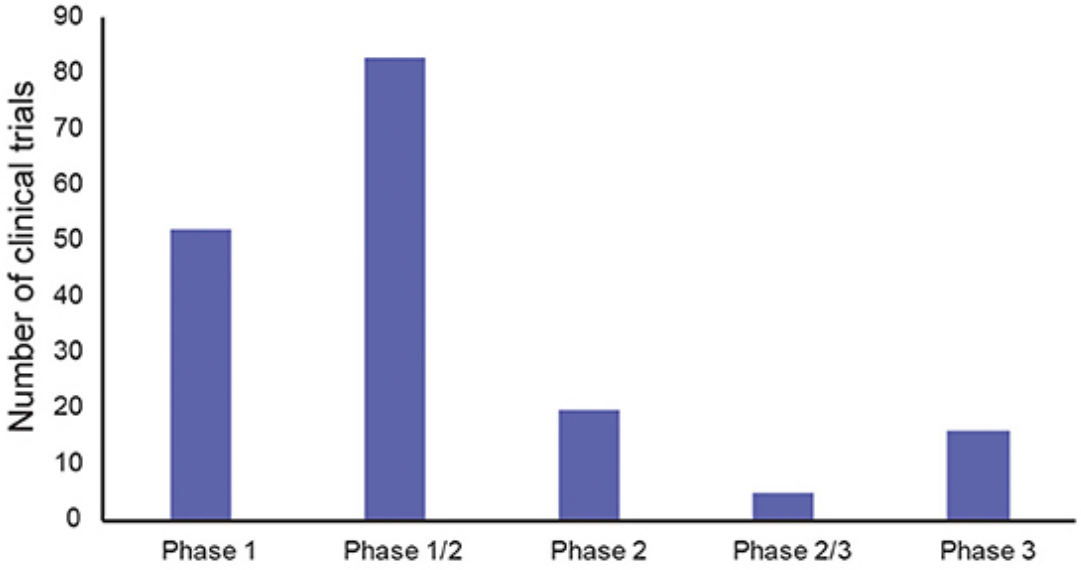
Neurons

In vivo Gene Therapy with AAVs

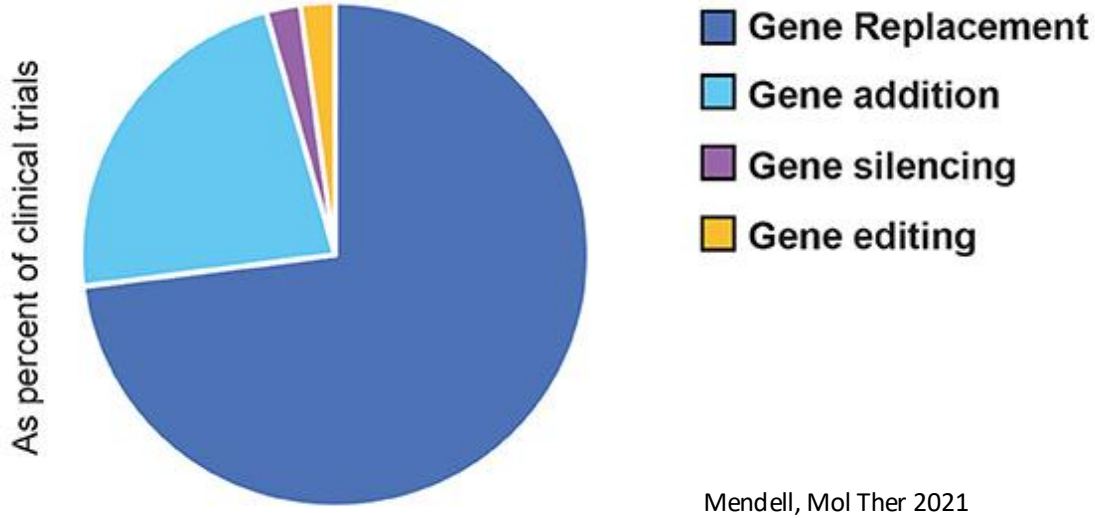


Retinal gene therapy						
Type 2 Leber congenital amaurosis	AAV2 vector; unilateral subretinal administration.	5	36	In all 5 patients, stable improvement in visual sensitivity seen.	NCT00516477	94, 97
Type 2 Leber congenital amaurosis	AAV2 vector; unilateral subretinal administration.	3	54 to 72	In all 3 patients, improvement in visual sensitivity seen at 6 months, which increased for 1 to 3 years and then declined.	NCT00481546	95
Type 2 Leber congenital amaurosis	AAV2 vector; unilateral subretinal administration.	12	36	In 6 patients, improvement in visual sensitivity seen, which peaked at 6 to 12 months and then declined.	NCT00643747	96
Liver-directed gene therapy						
Haemophilia B	AAV8 vector; intravenous administration.	10	16 to 48	No inhibitors; persistent FIX expression; in high-dose group, mean FIX levels of 5.1 ± 1.7% seen in all 6 treated patients.	NCT00979238	40
Haemophilia B	AAV8 vector; intravenous administration.	7	Up to 12	No inhibitors; persistent FIX expression in 1 patient.	NCT01687608	110

Current status of the clinical phases



Gene Therapy Approaches



Mendell, Mol Ther 2021

Gene therapy AAV products that have obtained the approval by FDA in USA and by Ema in Europe

Name	Marketing Authorization Holder	Disease	Viral Vector
GLYBERA Alipogene tiparvovec	UniQure Netherlands	LPLD Lipoprotein lipase Deficiency	AAV1
LUXTURNA Voretigene neparvovec	Spark Eupharma	RPE65 mutation-associated blindness	AAV2
ZOLGESMA Onasemnogene abeparvovec	Novartis	SMA spinal muscular atrophy	AAV9
UPSTAZA Eladocagene exuparvovec	PTC Therapeutics International Limited	Severe deficiency of aromatic L-amino acid decarboxylase (AADC)	AAV2
HEMGENIX Etranacogene dezaparvovec	CSL Behring LLC.	Haemophilia B (congenital Factor IX deficiency).	AAV5
ROCTAVIAN Valoctocogene roxaparvovec	BioMarin International Limited.	Haemophilia A (congenital Factor VIII deficiency)	AAV5

Peculiarities of the eye as a target for gene therapy

The eye is a site of immune-priviledge

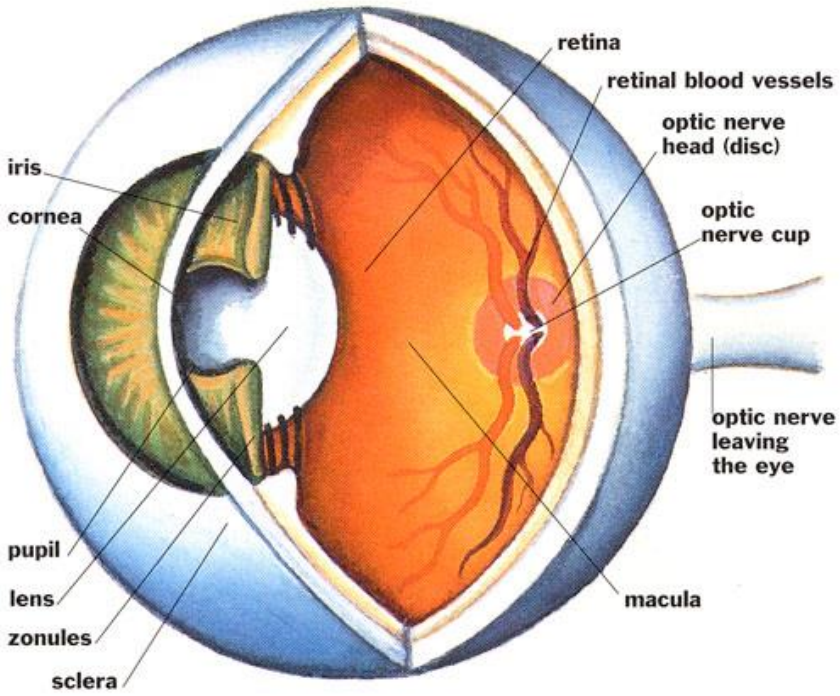
Most cells in the post-natal eye are terminally differentiated and prone to degenerative processes

Its compartmentalized anatomy (blood-retina barrier) enables local vector delivery in small volume with low likelihood of systemic dissemination

The eye is readily accessible for *in vivo* assessment by optical imaging and electrophysiological techniques

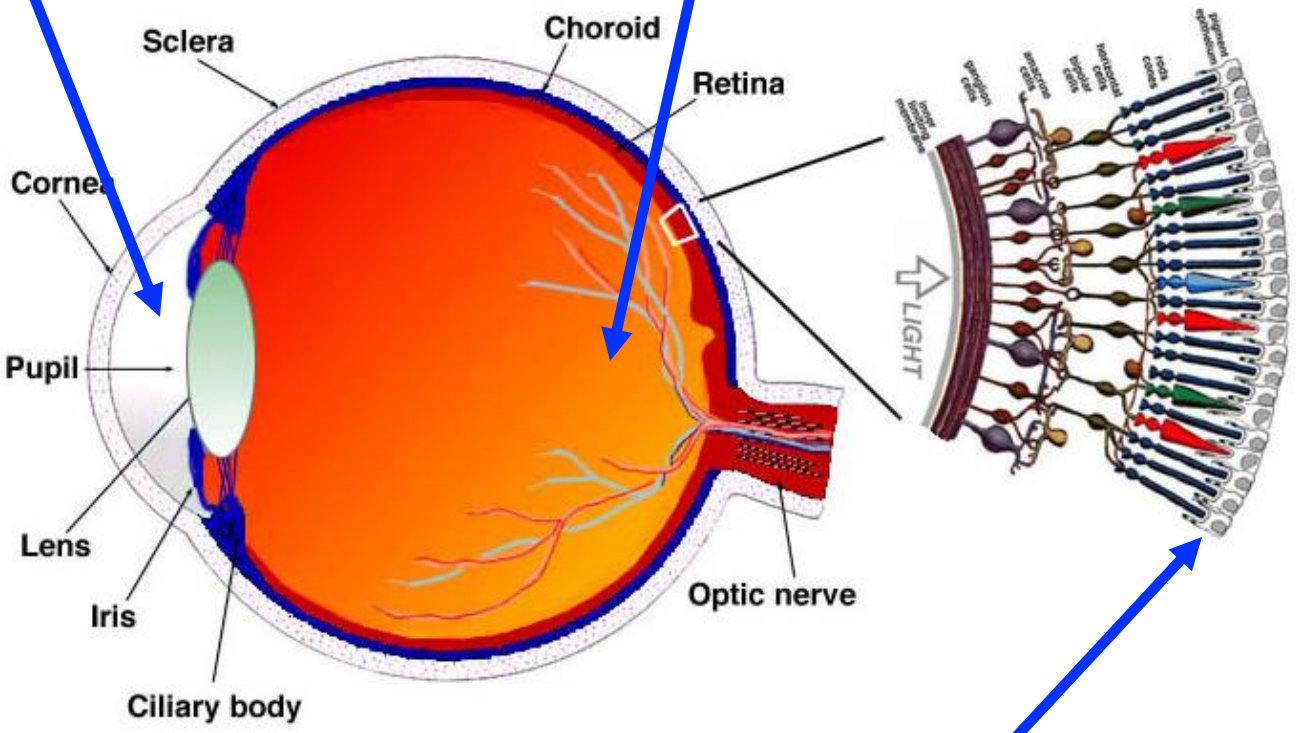
The results of the first clinical trials for ocular cancer and angiogenic disease have now been reported. One trial of gene replacement therapy for inherited retinal degeneration commenced recently and further such trials are expected to begin imminently

There are many animal models available



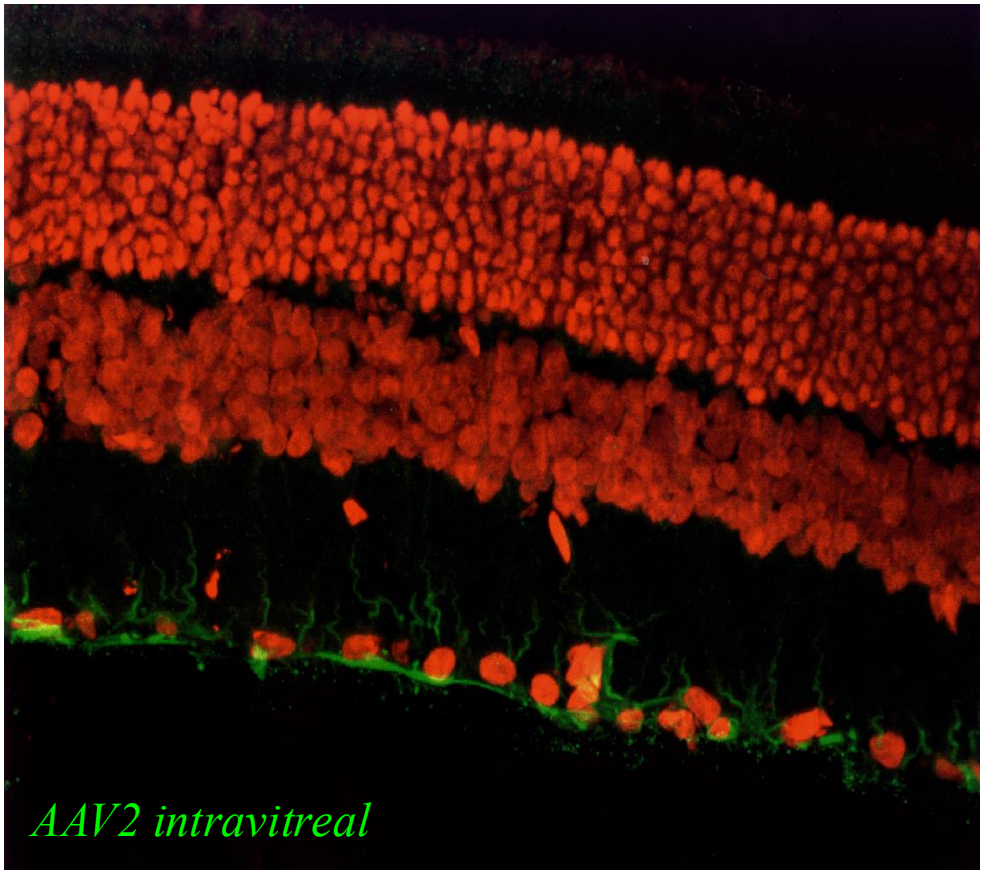
Into the anterior chamber - for corneal disease

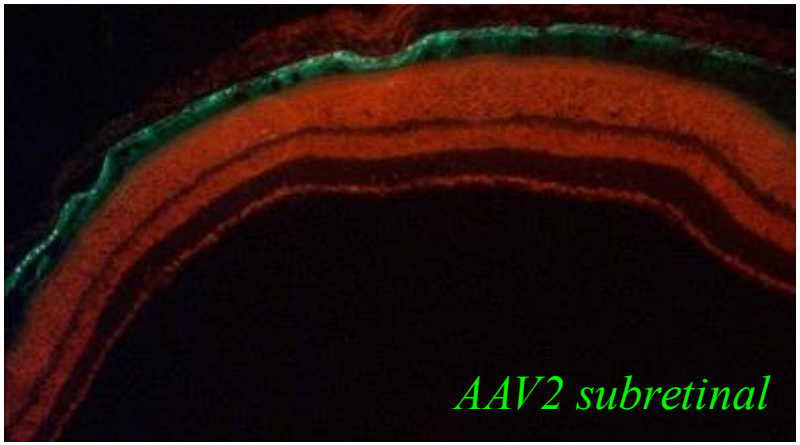
Intravitreal - anti-apoptotic or neurotrophic genes to protect RGC death in glaucoma

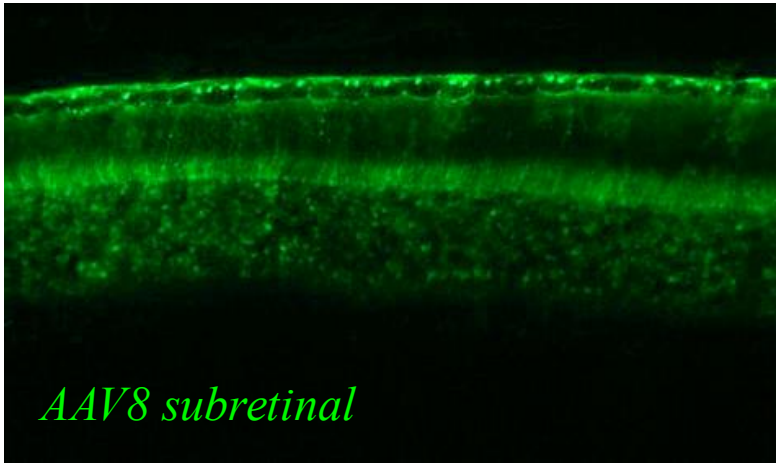


Sub-retinal (between photoreceptors and RPE) - for inherited retinal disorders, retinoblastoma and retinal neovascularization

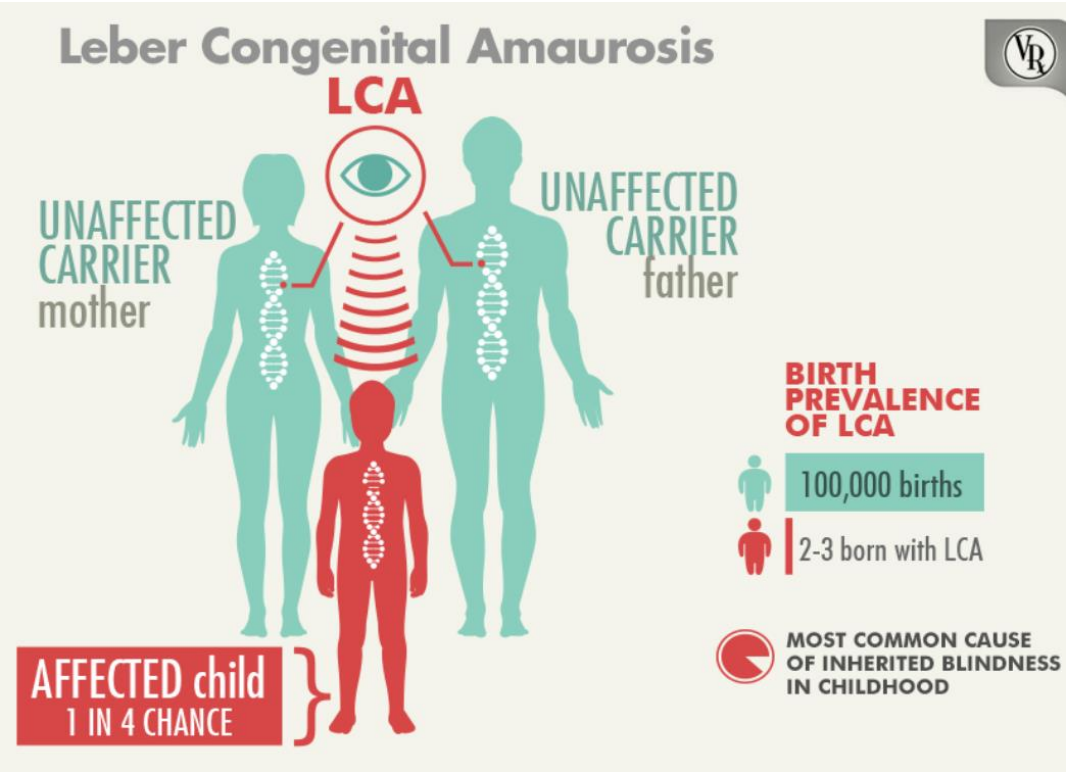
AAV is the only vector to efficiently transduce both RPE and photoreceptors

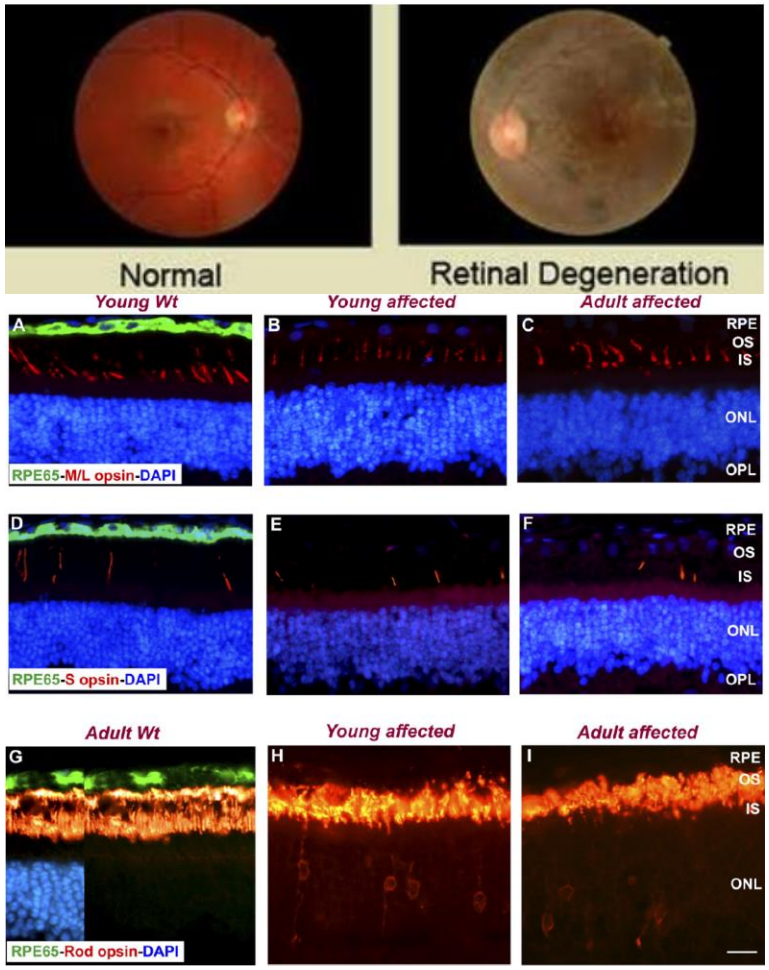






Leber Congenital Amaurosis

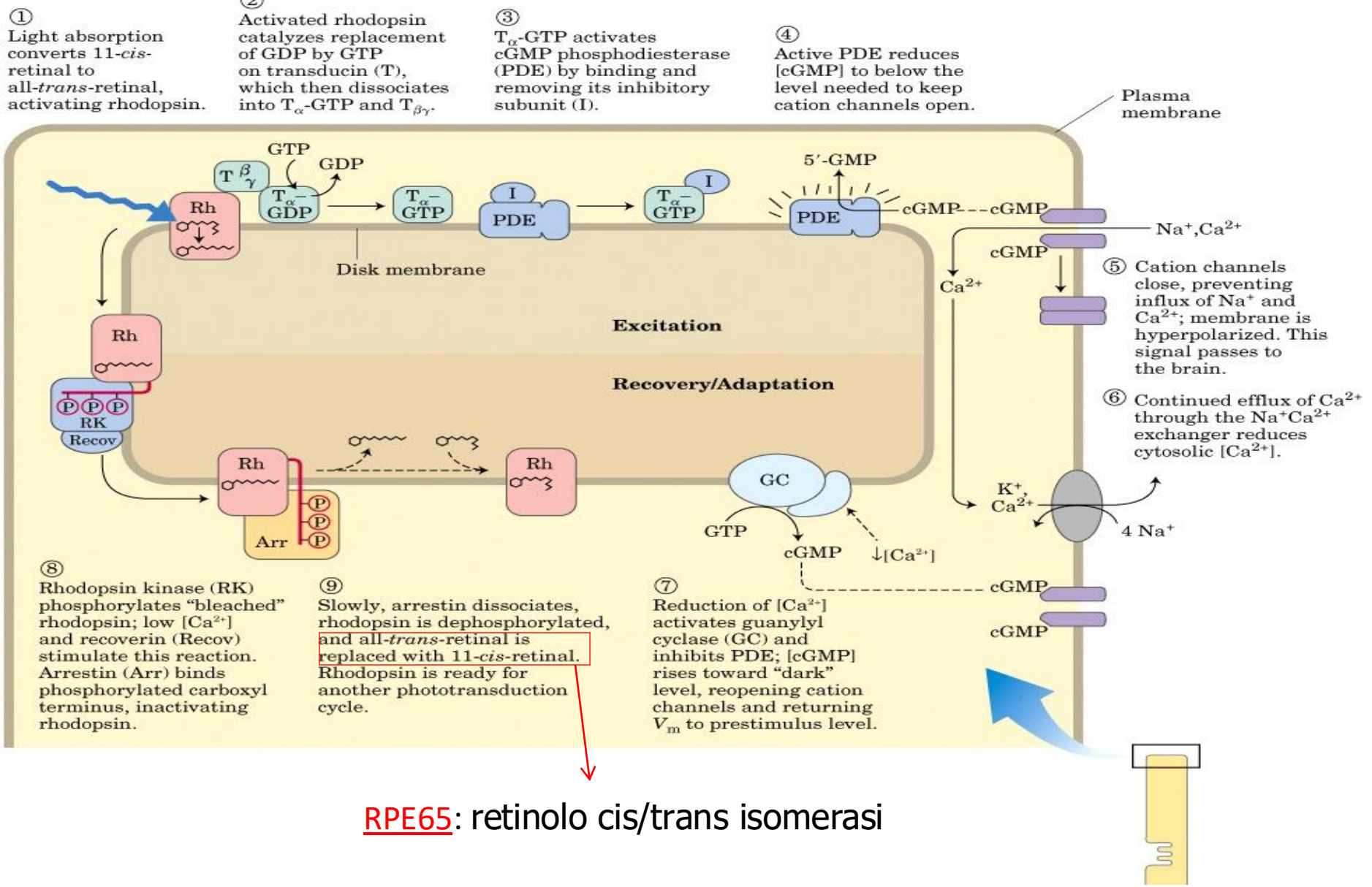




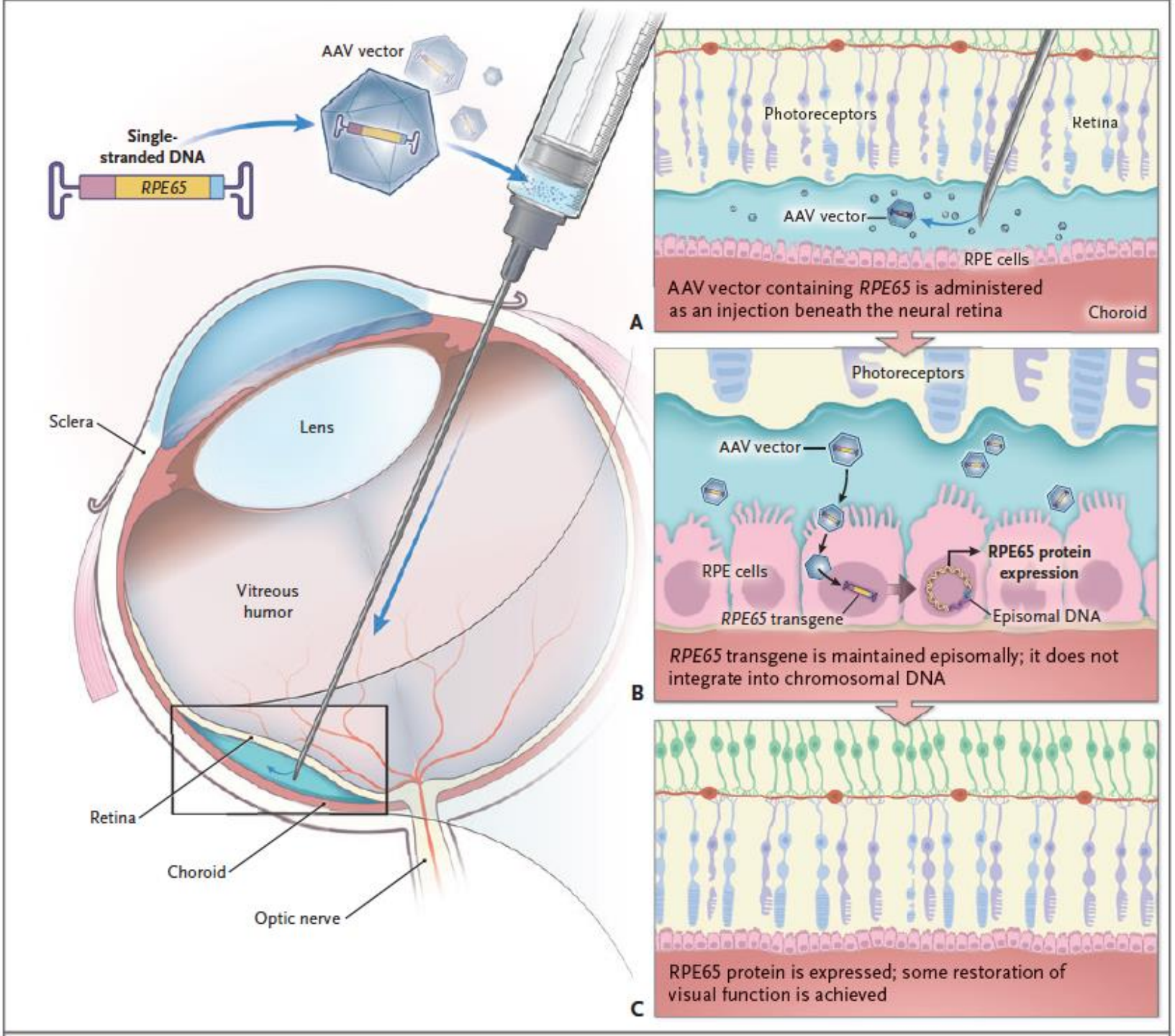
Vision loss in IR patients is due to the dysfunction/degeneration of retinal photoreceptor cells (PRs; rods and cones) and/or the retinal pigment epithelium (RPE)

Mutations in more than a dozen genes can cause LCA and *RPE65*-LCA is thought to represent about 6% of all LCA cases

Ciclo della fototrasduzione



RPE65: retinolo cis/trans isomerasi


AAV vector
Single-stranded DNA
RPE65
Sclera
Lens
Vitreous humor
Retina
Choroid
Optic nerve
Photoreceptors
Retina
AAV vector
RPE cells
AAV vector containing RPE65 is administered as an injection beneath the neural retina
Choroid
A
Photoreceptors
AAV vector
RPE cells
RPE65 protein expression
RPE65 transgene
Episomal DNA
RPE65 transgene is maintained episomally; it does not integrate into chromosomal DNA
B
RPE65 protein is expressed; some restoration of visual function is achieved
C

First AAV-Delivered Gene Therapy for Inherited Disease Approved by FDA

Luxturna is a recombinant adeno-associated virus of serotype 2 (rAAV2) expressing hRPE65. It is indicated for the treatment of patients with biallelic RPE65 mutation-associated retinal dystrophy.

One caveat: the injections cost $850.000 USD for patient (both eyes), making it one of the most expensive treatments in the world

> *In 41 patients in the clinical program, a single dose of Luxturna restored functional vision in these patients—and in a way that they were now able to conduct activities of daily living independently. The latest data, presented at the American Academy of Ophthalmology, suggests that one dose at three years and counting is still showing a sustained effect.*

- 30 patients treated in four independent trials
- The procedure was safe
- All trials showed significant improvements of both retinal and visual function
- Significant mobility improvement in navigation tasks
- The functional gain has been durable for as long as 3 years

Target disease	Vector	Sponsor	Phase
Leber congenital amaurosis 2	AAV2-hRPE65v2	Spark Therapeutics	I/II (follow on)
	AAV5-OPTIRPE65	MeiraGTx UK II Ltd	I, II
	AAV2-hRPE65v2-301	Spark Therapeutics	III
	AAV2-hRPE65v2-101	Spark Therapeutics	I/II
	AAV5-OPTIRPE65	MeiraGTx UK II Ltd	I/II
	AAV2.hRPE65p.hRPE65	University College, London	I/II, completed
	AAV2-hRPE65	Applied Genetic Technologies Corp	I/II, completed
	AAV2-hRPE65	University of Pennsylvania	I
	AAV2-hRPE65	Hadassah Medical Organization	I
	AAV4-hRPE65	Nantes University Hospital	I/II, completed

ZOLGENSMA

CORRIERE DELLA SERA / CRONACHE

LA VICENDA

Sofia, la bambina di Napoli curata con il farmaco più costoso al mondo

Ha 6 mesi e una malattia rara: per la terapia spesi 1,9 milioni. Il papà: «Per noi era un tunnel senza fine, finalmente ora possiamo sperare di vedere la luce»

di **Fulvio Bufi**

FARMACIA E BUSINESS

Novartis, il farmaco Zolgensma (atrofia spinale) diventa il più caro al mondo: costa 2,1 milioni di dollari

di **Redazione Economia** | 25 mag 2019

LOTTA ALL'EVASIONE

Lotteria degli scontrini, come funziona: dal codice per giocare alle estrazioni

LE AGEVOLAZIONI

Rottamazione, «saldo e stralcio»: nuove scadenze per 1,2 milioni di italiani

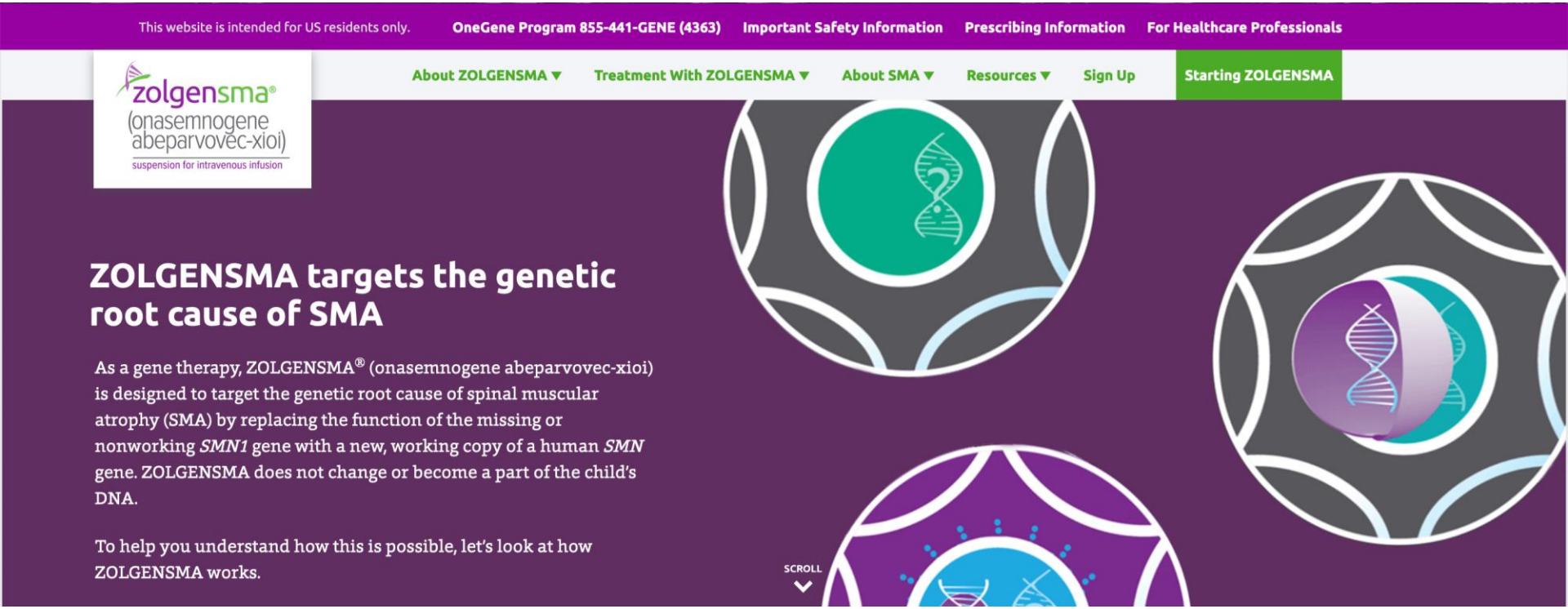
PAGAMENTI DIGITALI

Arriva il Cashback senza «Spid» e senza «App Io». Come fare per ottenerlo

L'INDAGINE

Smart working: così l'azienda può monitorare i dipendenti

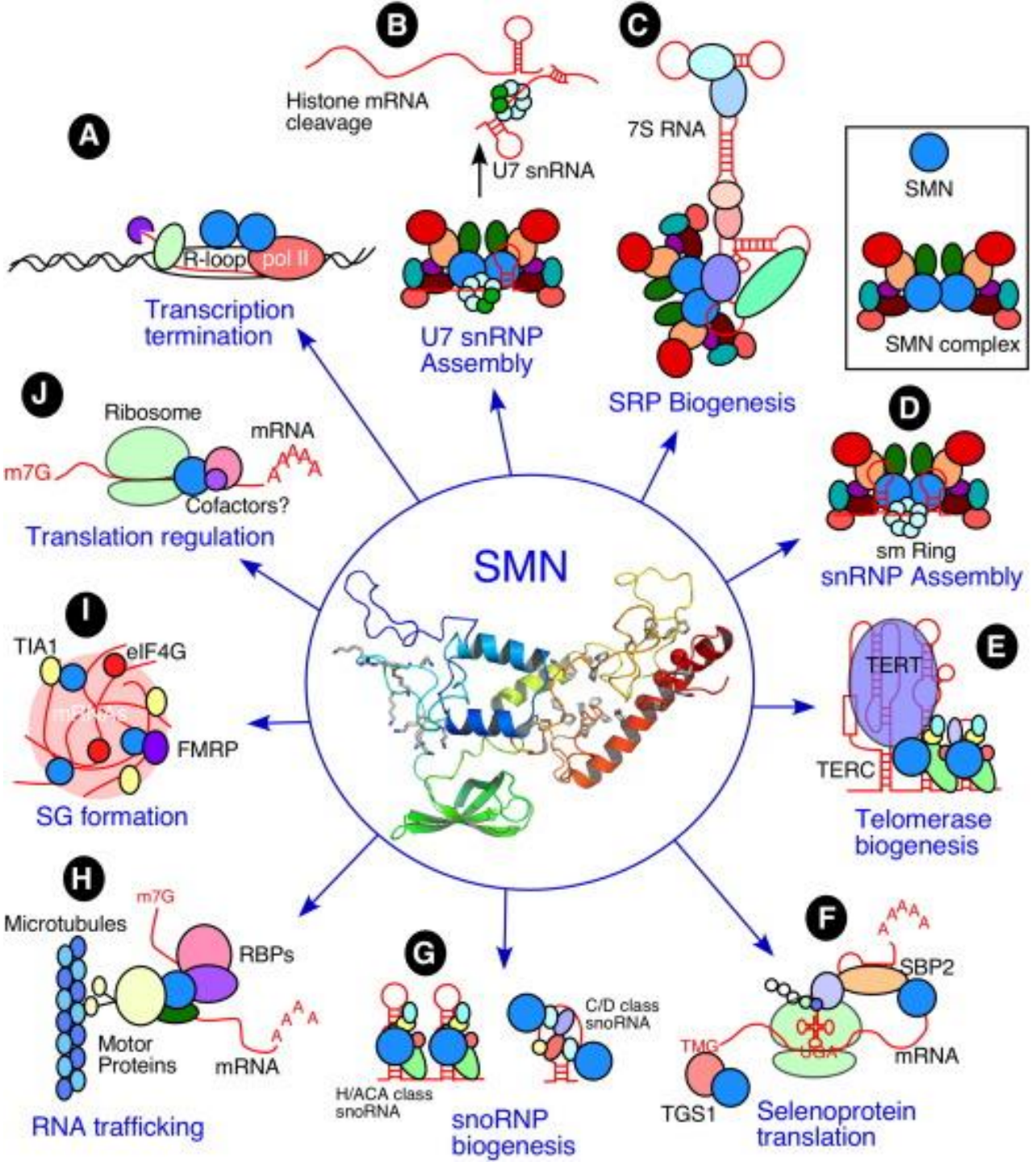
7 dicembre 2020



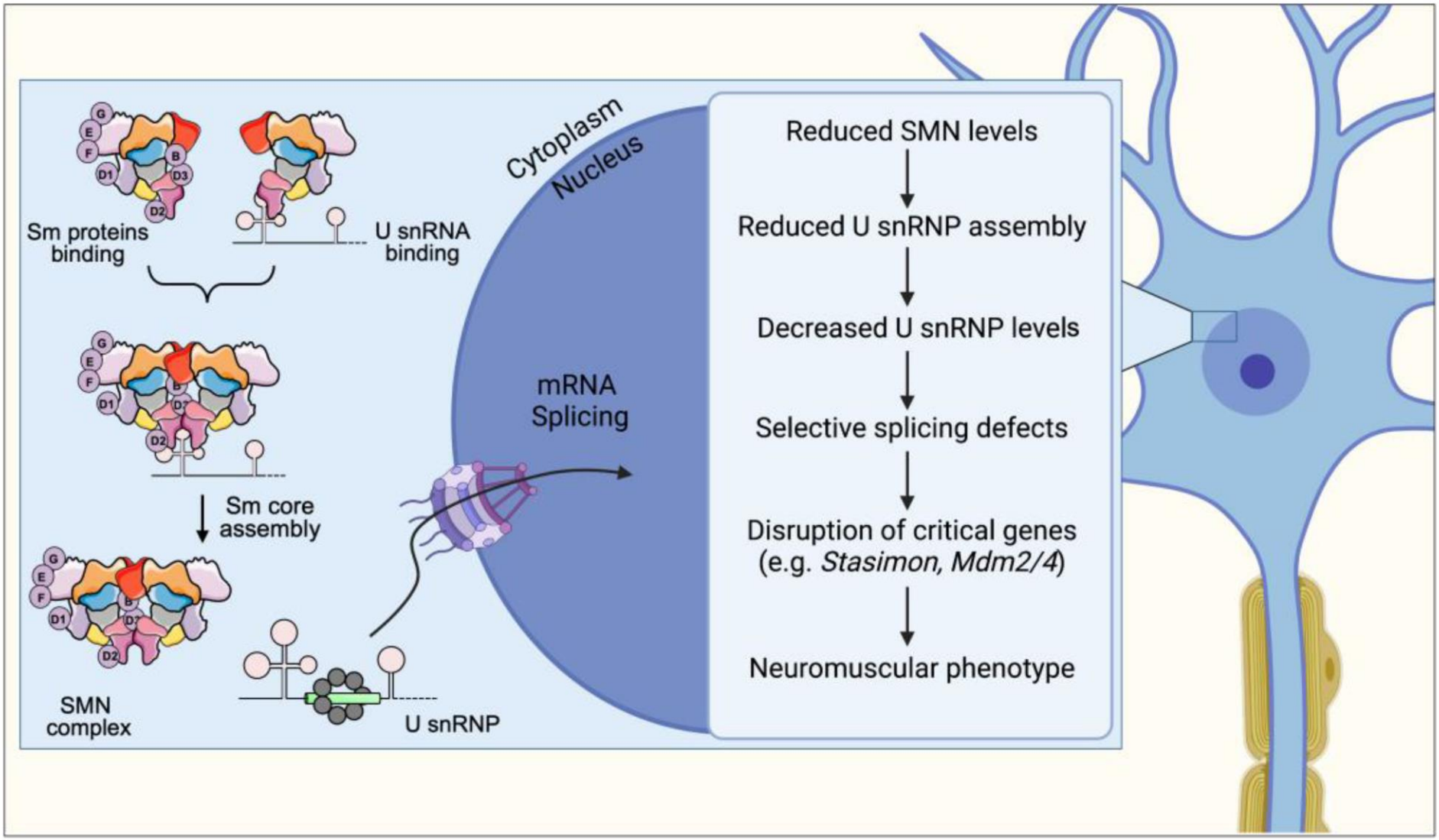
What is ZOLGENSMA?

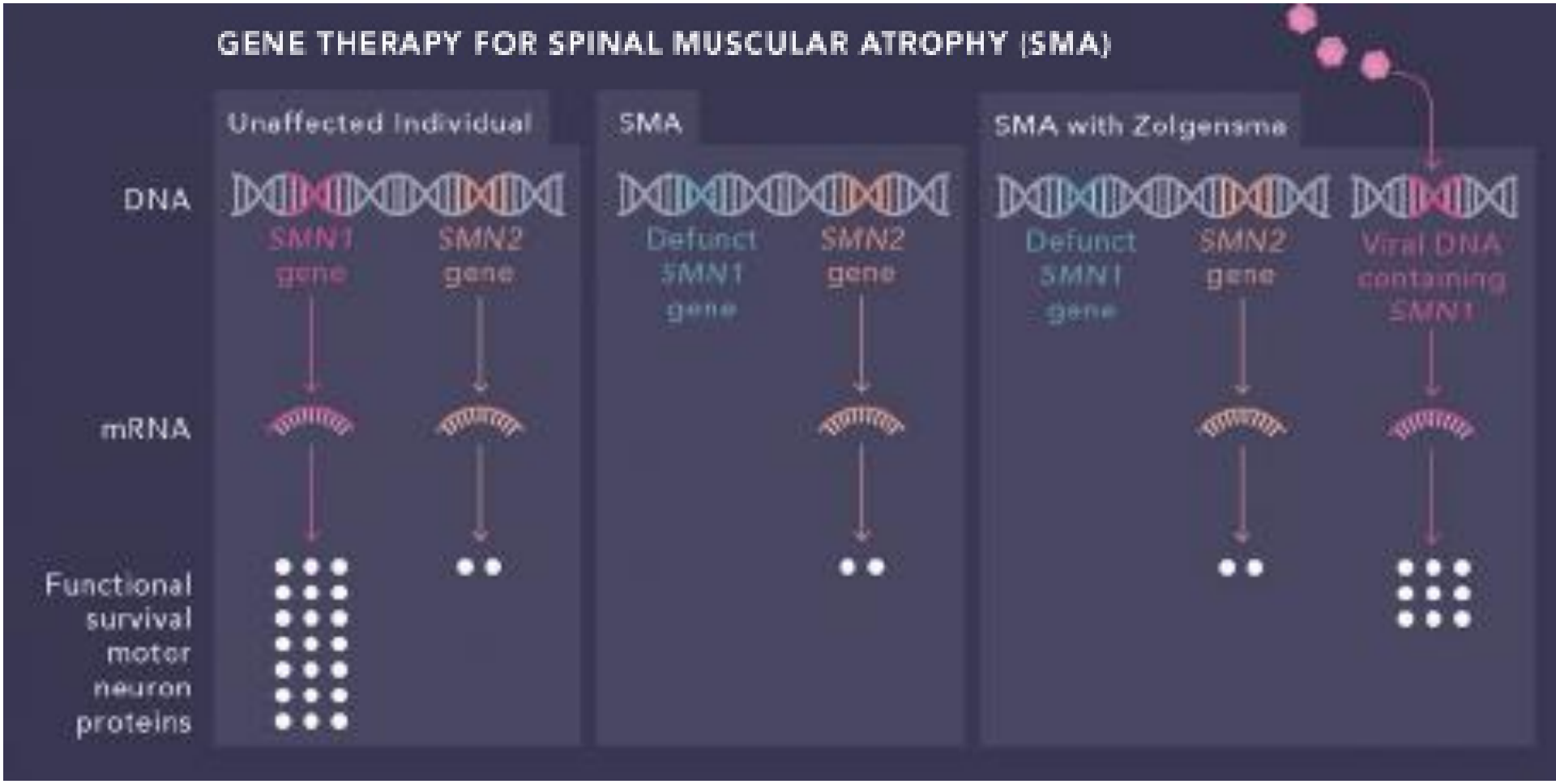
ZOLGENSMA is a prescription gene therapy used to treat children less than 2 years old with spinal muscular atrophy (SMA). ZOLGENSMA is given as a one-time infusion into a vein. ZOLGENSMA was not evaluated in patients with advanced SMA.

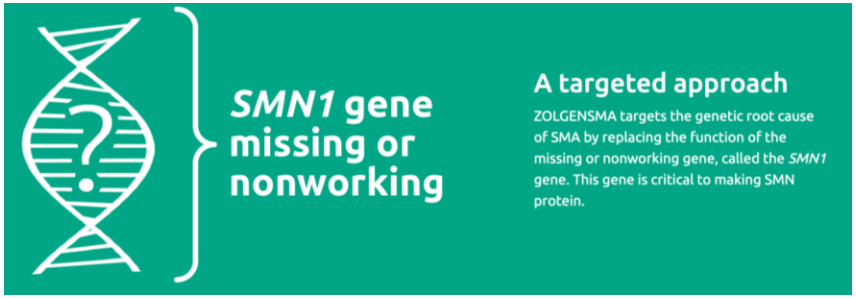
SMN protein


A
R-loop
pol II
Transcription termination
B
Histone mRNA cleavage
U7 snRNA
U7 snRNP Assembly
C
7S RNA
SRP Biogenesis
SMN
SMN complex
D
sm Ring
snRNP Assembly
E
TERT
TERC
Telomerase biogenesis
F
SBP2
mRNA
TMG
TGS1
Selenoprotein translation
G
C/D class snoRNA
H/ACA class snoRNA
snoRNP biogenesis
H
Microtubules
m7G
RBPs
Motor Proteins
mRNA
RNA trafficking
I
TIA1
eIF4G
FMRP
SG formation
J
Ribosome
mRNA
m7G
Cofactors?
Translation regulation
SMN

SMA aethiopathogenesis

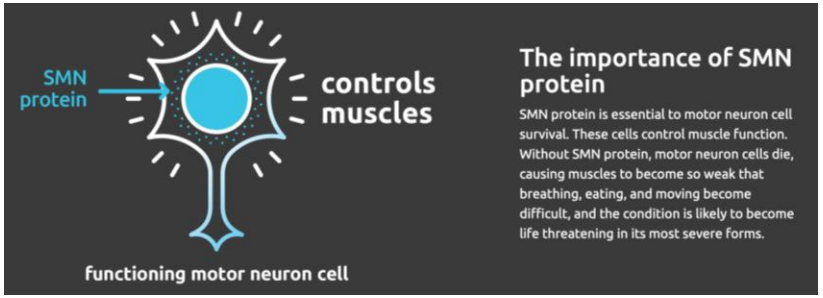



GENE THERAPY FOR SPINAL MUSCULAR ATROPHY (SMA)
Unaffected Individual
SMA
SMA with Zolgensma
DNA
mRNA
Functional survival motor neuron proteins
SMN1 gene
SMN2 gene
Defunct SMN1 gene
SMN2 gene
Defunct SMN1 gene
SMN2 gene
Viral DNA containing SMN1



A targeted approach

ZOLGENSMA targets the genetic root cause of SMA by replacing the function of the missing or nonworking gene, called the *SMN1* gene. This gene is critical to making SMN protein.

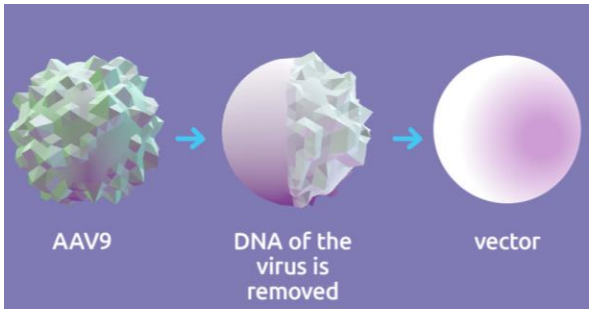


The importance of SMN protein

SMN protein is essential to motor neuron cell survival. These cells control muscle function. Without SMN protein, motor neuron cells die, causing muscles to become so weak that breathing, eating, and moving become difficult, and the condition is likely to become life threatening in its most severe forms.

The role of the vector

ZOLGENSMA is made up of a new, working copy of a human *SMN* gene that is placed inside a vector. A vector's job is to deliver the new, working *SMN* gene to the motor neuron cells in the body.



Delivery of the *SMN* gene

The vector that delivers the *SMN* gene is made from a virus called adeno-associated virus 9, or AAV9. This type of virus does not make people sick. To make the vector, the DNA of the virus is removed so that the new *SMN* gene can be put inside. Vectors are used because they can travel throughout the body and deliver the new, working gene to the cells where it is needed.

Production of SMN protein

When the new, working gene reaches its destination, it is ready to tell the motor neuron cells to start making SMN protein. This happens throughout the body, with many vectors delivering a new, working copy of the *SMN* gene to motor neuron cells. The new gene does not become part of the child's DNA.

Motor neuron cells maintained

With the motor neuron cells now able to make sufficient SMN protein, motor neuron cells that have not died may survive, function, and be maintained.

2022, 7 ottobre: Atrofia muscolare spinale di tipo 1: prima terapia genica in FVG effettuata dell'equipe servizio Malattie rare del Burlo

Il bimbo trattato è arrivato da noi a quattro mesi di vita con malattia già in stadio avanzato e grave compromissione di deglutizione e respiro. Dopo il trattamento, il decorso della malattia è stato bloccato e il bimbo anche se avrà bisogno di una carrozzina elettronica e dovrà essere sottoposto a ventilazione notturna, non è più in pericolo di vita.

Come spiegano i membri dell'equipe del servizio malattie rare del Burlo, la terapia genica in questione è relativamente semplice, poiché si tratta dell'infusione per via endovenosa di un vettore virale adeno-associato (denominato AAV9) che trasporta il gene mancante SMN1 nel sistema nervoso centrale.

Si tratta, inoltre, di una terapia innovativa e ancora altamente costosa (oltre un milione di euro).

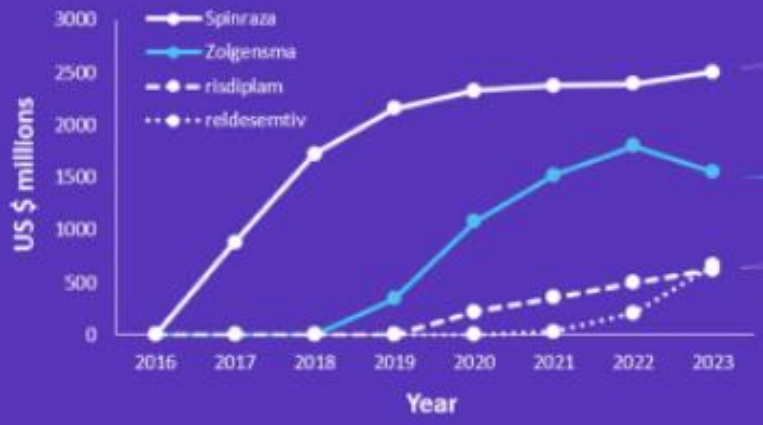
ZOLGENSMA FOR SPINAL MUSCULAR ATROPHY

SMA is most often **LETHAL** in childhood

90% rate of death or permanent ventilation at two years of age in children with type 1 SMA

ALL of the children were **ALIVE** at two years in the pivotal trial of Zolgensma

Price: $425,000 annually for five years = $2.125 million



Spinraza: The first ever drug for SMA, but dosed every four months intrathecally

Risdiplam & reldesemtiv: two potential competitors currently in phase II/III trials

Zolgensma: the second SMA market entrant, but the first ever SMA gene therapy. Only requires a single intravenous dose

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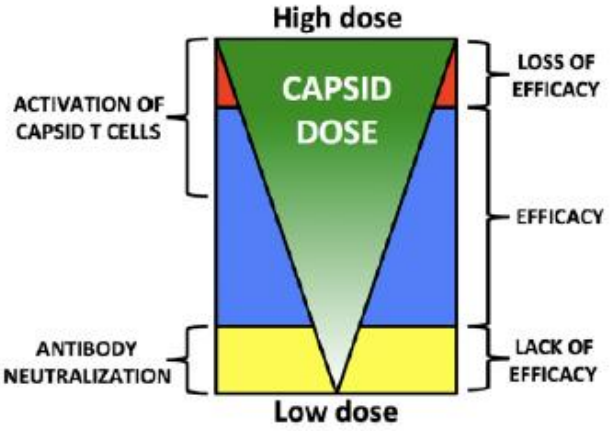
Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B

Amit C. Nathwani, M.B., Ch.B., Ph.D., Ulreke M. Reiss, M.D., Edward G.D. Tuddenham, M.B., B.S., Cecilia Rosales, Ph.D., Pratima Chowdary, M.B., B.S., Jenny McIntosh, Ph.D., Marco Della Peruta, Ph.D., Elsa Lheriteau, Ph.D., Nishal Patel, F.R.C.P., F.R.C.Path., Deepak Raj, M.B., B.S., Ph.D., Anne Riddell, B.Sc., Jun Pie, B.S.N., Savita Rangarajan, M.B., B.S., David Bevan, M.B., B.S., Michael Recht, M.D., Yu-Min Shen, M.D., Kathleen G. Halka, M.D., Etiena Basner-Tschakarjan, M.D. Ph.D., Federico Mingozzi, Ph.D., Katherine A. High, M.D., James Allay, Ph.D., Mark A. Kay, M.D., Catherine Y.C. Ng, M.S., Junfang Zhou, M.D., Maria Cancio, M.D., Christopher L. Morton, B.S., John T. Gray, Ph.D., Deokumar Srivastava, Ph.D., Arthur W. Nienhuis, M.D., and Andrew M. Davidoff, M.D.
N Engl J Med 2014; 371:1994-2004November 20, 2014DOI: 10.1056/NEJMoa1407309

Dose-dependent increase in circulating factor IX to a level that was 1 to 6% of the normal value over a median period of 3.2 years, with observation ongoing

Reduction of more than 90% in both bleeding episodes and the use of prophylactic factor IX concentrate.

In 10 patients with severe hemophilia B, the infusion of a single dose of AAV8 vector resulted in long-term therapeutic factor IX expression associated with clinical improvement. With a follow-up period of up to 3 years, no late toxic effects from the therapy were reported.



It will cost **US$3.5 million** for each dose, making it the most costly medication in the world. At first look, the price appears exorbitant, but a new examination of the drug's cost-effectiveness reveals that the life-span cost of continuous infusion of FIX for each individual with mild to chronic hemophilia B is between US$21 and $23 million

WORLD ANTI-DOPING AGENCY

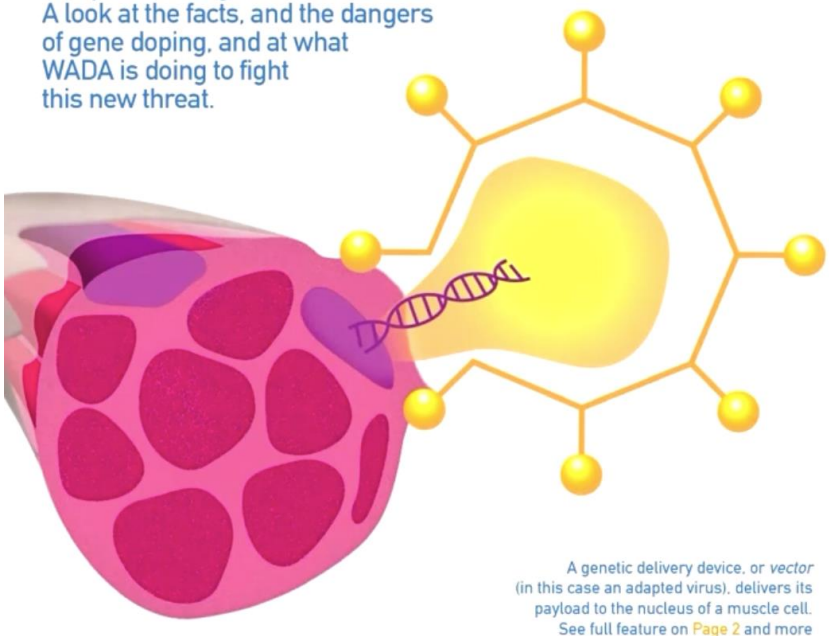
play true

ISSUE 1 - 2005

AN OFFICIAL PUBLICATION OF THE WORLD ANTI-DOPING AGENCY

Gene Doping

Science and sport converge once again as medical research charts the complexities of genetic treatment. A look at the facts, and the dangers of gene doping, and at what WADA is doing to fight this new threat.



A genetic delivery device, or *vector* (in this case an adapted virus), delivers its payload to the nucleus of a muscle cell.

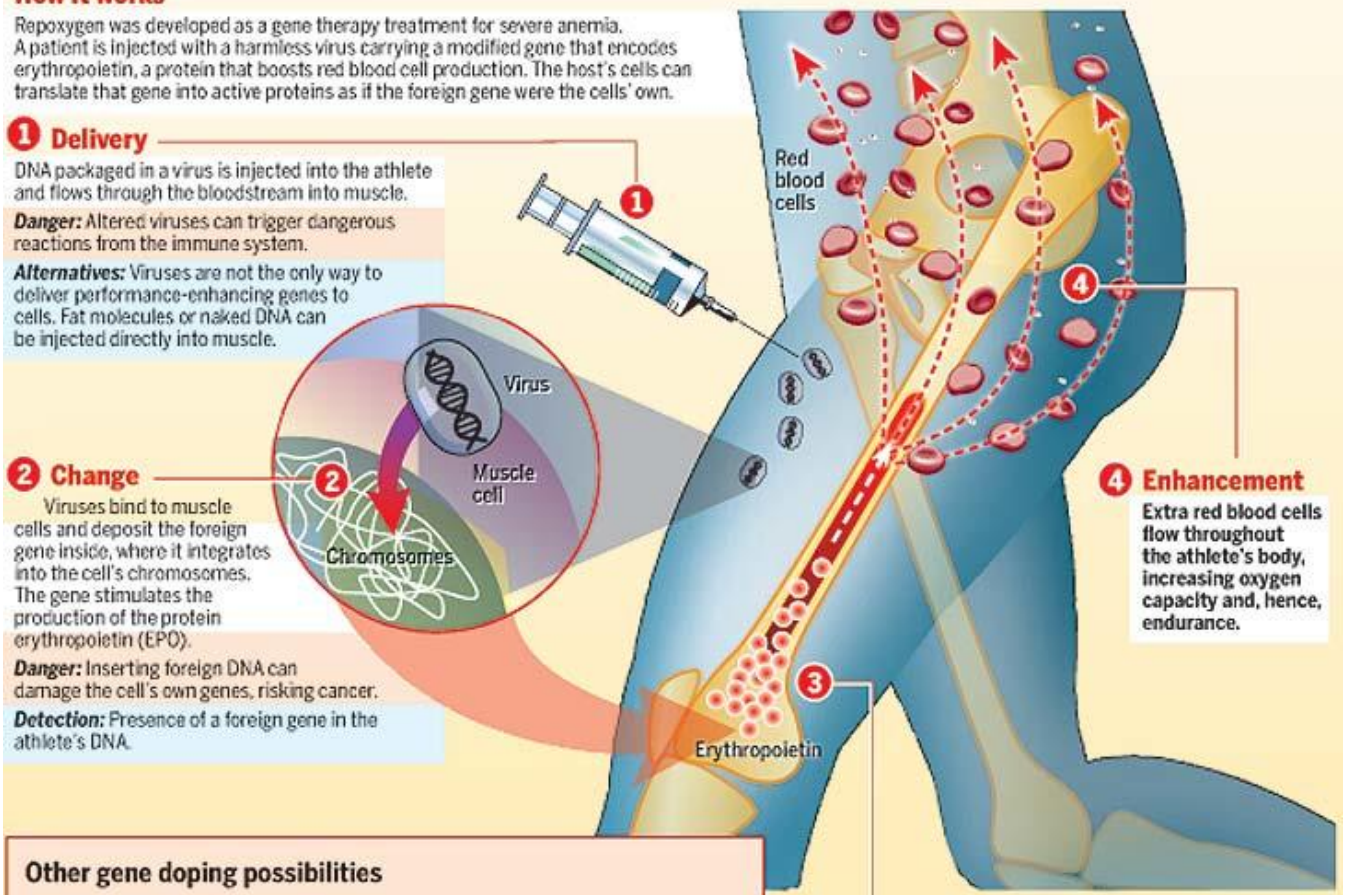
See full feature on Page 2 and more

Gene doping

Repoxygen is a new way to artificially enhance an athlete's performance — one that is hard to detect and with potentially permanent effects

How it works

Repoxygen was developed as a gene therapy treatment for severe anemia. A patient is injected with a harmless virus carrying a modified gene that encodes erythropoietin, a protein that boosts red blood cell production. The host's cells can translate that gene into active proteins as if the foreign gene were the cells' own.



Other gene doping possibilities

■ In 1988, H. Lee Sweeney and colleagues at the University of Pennsylvania School of Medicine injected mice with a virus carrying a gene that boosted production of insulin-growth factor 1 (IGF-1). The injected mice had 15% more muscle mass than untreated mice.

■ In 2004, Ronald Evans and colleagues at California's Salk Institute for Biological Studies engineered mice to have extra copies of the gene encoding a protein called peroxisome proliferator-activated receptor delta (PPAR-delta). These mice could run twice as far as unaltered mice.

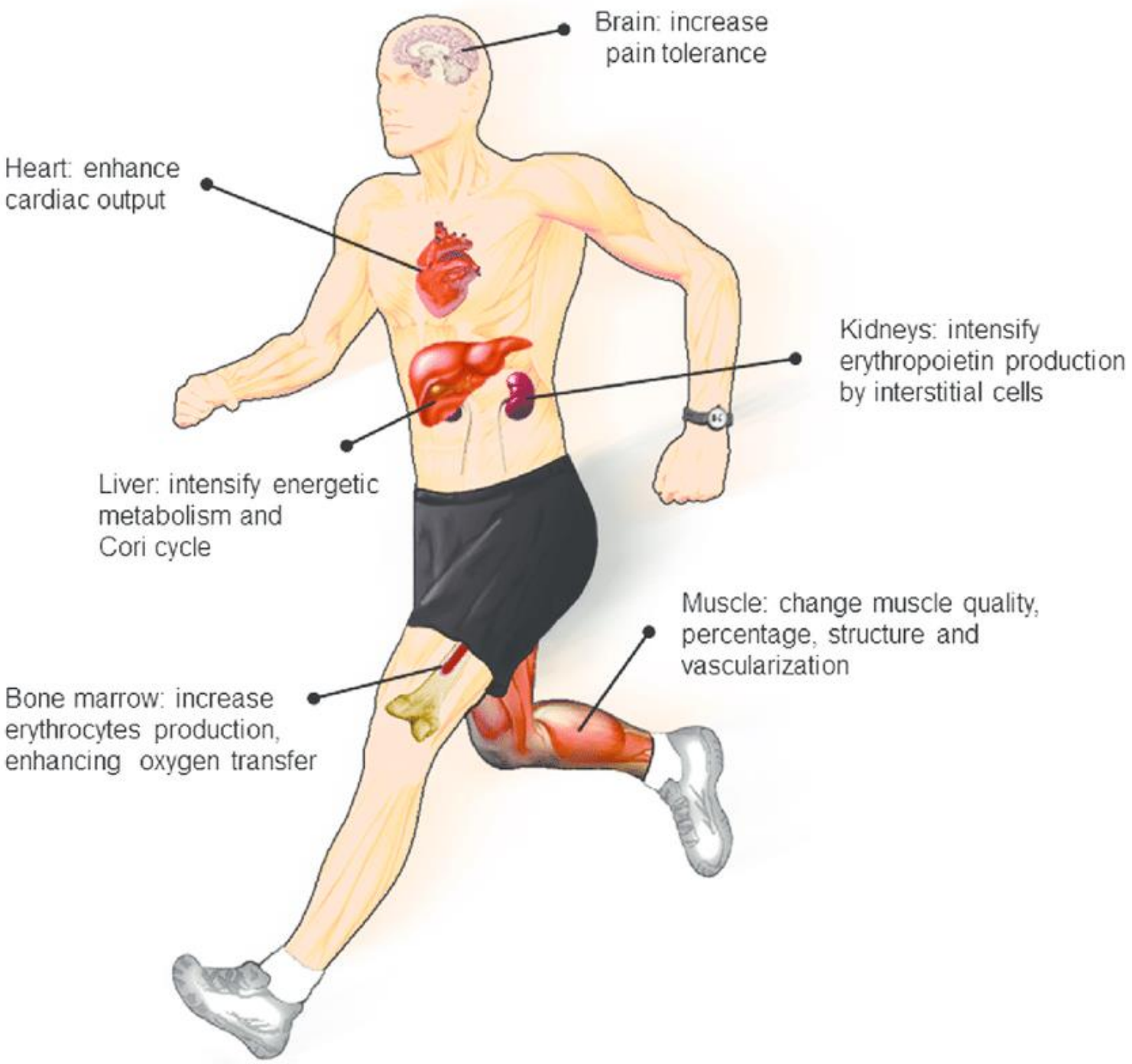
SOURCE: *Finding the Golden Genes*, Patrick Barry; www.sciencenews.org

SUSIE MAH/ SUN MEDIA

WORLD ANTI-DOPING AGENCY

Geni:

-EPO
-IGF1
-Inibitori della Miostatina


Brain: increase pain tolerance
Heart: enhance cardiac output
Kidneys: intensify erythropoietin production by interstitial cells
Liver: intensify energetic metabolism and Cori cycle
Muscle: change muscle quality, percentage, structure and vascularization
Bone marrow: increase erythrocytes production, enhancing oxygen transfer

Da 53 a 25 anni biologici: Liz Parrish, la prima donna a ringiovanire grazie alla terapia genetica

Liz Parrish, CEO di BioViva, sostiene di aver ridotto la sua età biologica di quasi 30 anni attraverso una terapia genetica sperimentale, suscitando dibattiti nel mondo scientifico.

Pubblicato il 7 Ottobre 2024 - 0:54 · **Angelo Petrone**

Il trattamento principale a cui si è sottoposta mira a estendere i suoi **telomeri**, oltre a includere un inibitore della **miostatina** per contrastare la perdita di massa muscolare.

Parrish non crede che il semplice allungamento dei telomeri possa essere la soluzione definitiva all'invecchiamento, osservando che alcune specie longeve hanno telomeri che si accorciano rapidamente e altre che li conservano più a lungo. La biologia umana è complessa e l'invecchiamento non può essere risolto da un'unica scoperta. Tuttavia, Parrish è convinta che il **prolungamento dei telomeri** giochi un ruolo importante in questa battaglia. Dopo il trattamento, ha incontrato leader politici e sanitari in tutto il mondo, raccogliendo interesse e curiosità, ma anche scetticismo sul suo approccio ancora non del tutto provato.

BioViva Science
bioviva-science.com

CONTACT
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Email: info@bioviva-science.com

BioViva

BioViva's CMV vector: a platform for better gene-therapy delivery

BioViva Science is a gene-therapy company focused on treating aging-related complex diseases with a new gene-therapy platform.

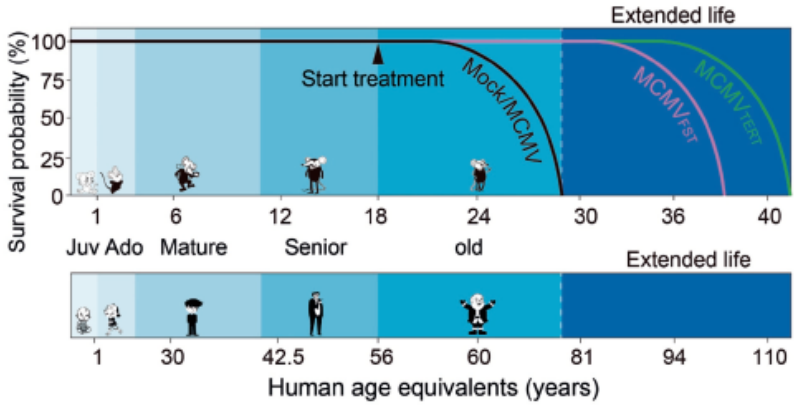

Fig. 1 | The survival curve of mice in each group was determined by a Kaplan–Meier survival curve. χ^2 test, $p<0.001$ TERT-IP vs. WT-IP and TERT-IN vs. WT-IN group at the 50% survival probability; $p<0.001$ FST-IP vs. WT-IP and FST-IN vs. WT-IN group at the 50% survival probability. $n=8$ per group. C57BL/6J mice and human age equivalence at the start of experimental treatment. MCMV, mouse cytomegalovirus; FST, follistatin; TERT, telomerase reverse transcriptase.

BioViva is building a gene-therapy platform using a cytomegalovirus (CMV) that be injected or delivered intranasally. Its established safety profile and lower immunogenicity make it redosable in animalmodels (Fig. 1). CMV does not integrate,which could reduce off-target effects. BioViva's early-stage CMV projects are looking at metabolic disease, frailty, cardiovascular disease, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD). "We are applying for two pre-investigational new drugs (INDs): one for our intranasal gene therapy for Alzheimer's disease and another to look at age-related metabolic dysfunction with secondary endpoints in age-related muscle loss. Once the gene therapies have reached proof of- concept studies in humans, Parrish sees many possibilities. "We would like to see our gene therapies reach the market, and we are flexible as to how this happens. We are open to licensing, partnerships, and joint ventures," said Parrish.


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For all skin types, especially suitable for mature skin
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