SEMINARIS DE RECERCA 2019 SEMINARIS TECNOLÒGICS

1er Seminari Tecnològic 2019

Teràpia Gènica amb Vectors Adenoassociats

M. Chillon

Grupo de Terapia Génica para enfermedades neurodegenerativas y desmielinizantes

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[3] Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain
[4] Unidad Producción de Vectores (UPV)

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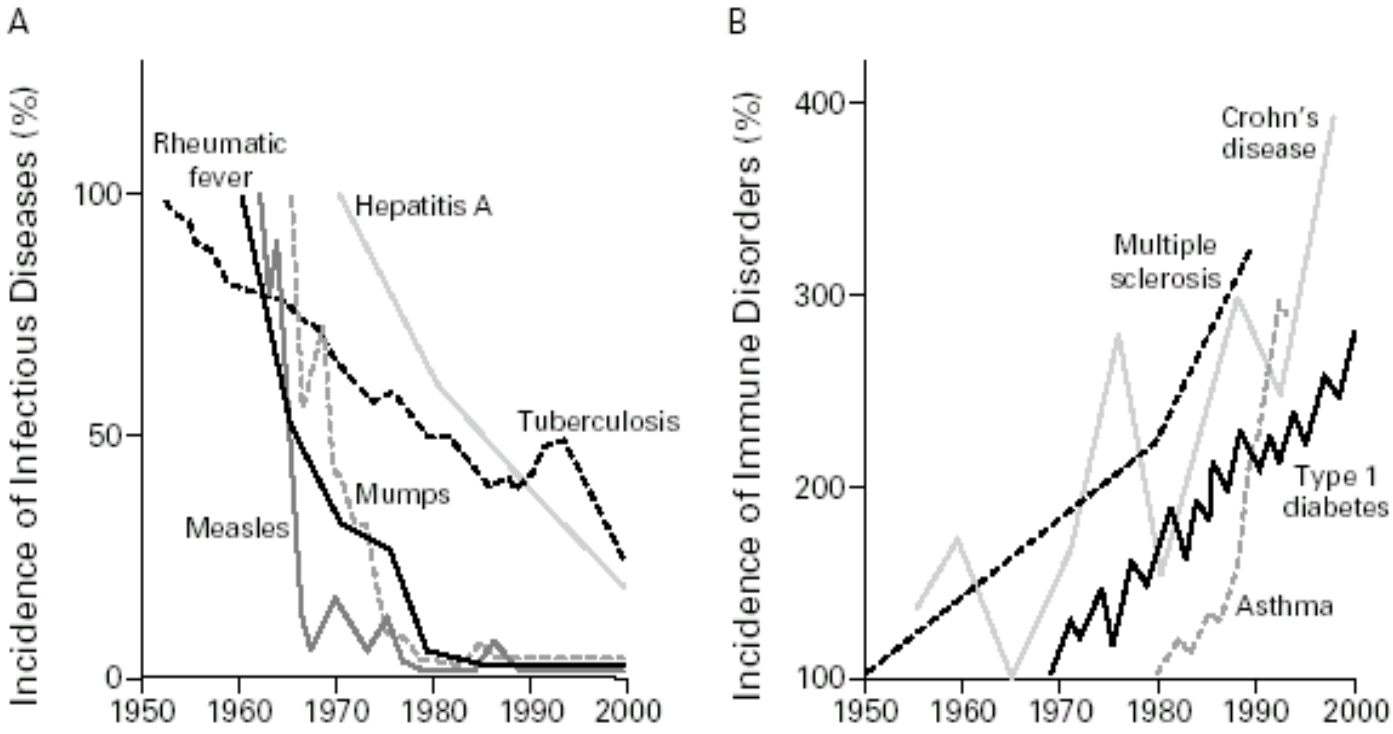
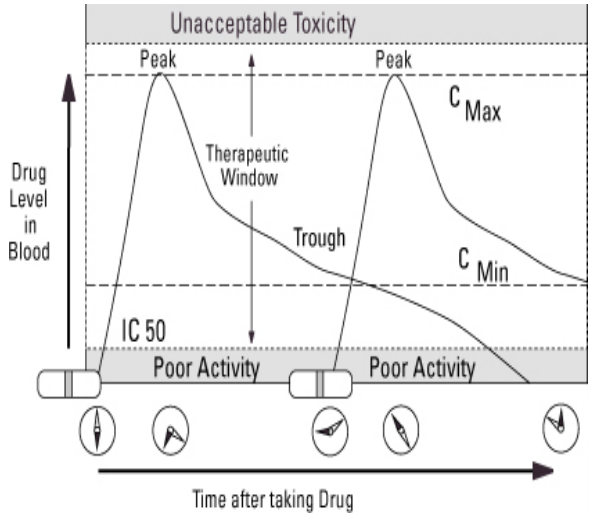
April 2nd, 2019

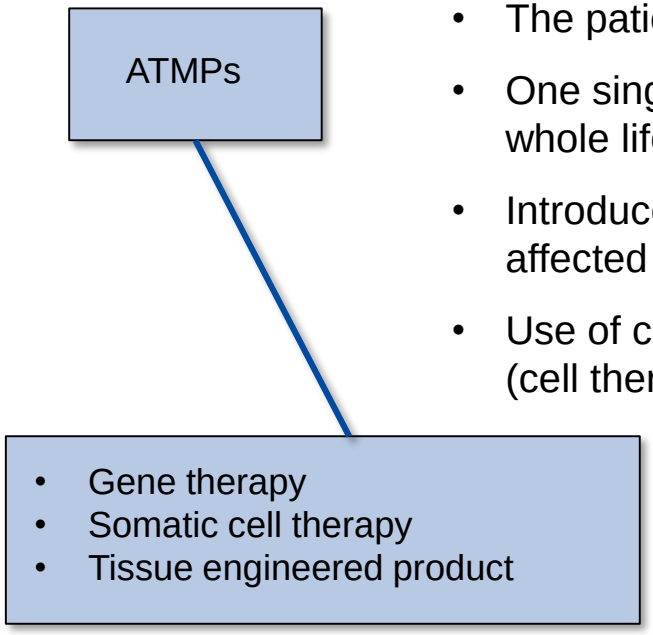

A
Incidence of Infectious Diseases (%)
100
50
0
1950
1960
1970
1980
1990
2000
Rheumatic fever
Hepatitis A
Tuberculosis
Mumps
Measles
B
Incidence of Immune Disorders (%)
400
300
200
100
Crohn's disease
Multiple sclerosis
Type 1 diabetes
Asthma

Some limitations of current therapies

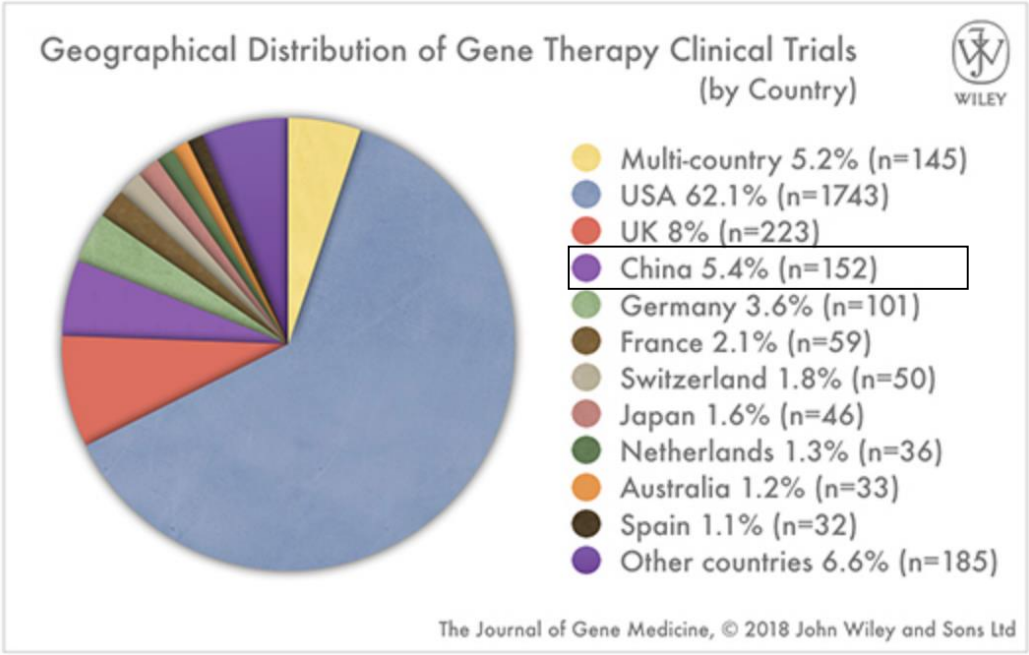
- Drugs usually administered systemically may cause long-term side effects.
- In some cases the drug does not reach the target organ efficiently, as often happens in the brain and the blood brain barrier.



ATMPs (Advanced-Therapy-Medicinal-Products)



- The patient's own cells produce the drug.
- One single dose may be enough for whole life treatment
- Introduce the therapeutic gene in the affected patient cells (gene therapy)
- Use of cells of corrected or healthy cells (cell therapy) or tissues.


Geographical Distribution of Gene Therapy Clinical Trials
(by Country)
WILEY
Multi-country 5.2% (n=145)
USA 62.1% (n=1743)
UK 8% (n=223)
China 5.4% (n=152)
Germany 3.6% (n=101)
France 2.1% (n=59)
Switzerland 1.8% (n=50)
Japan 1.6% (n=46)
Netherlands 1.3% (n=36)
Australia 1.2% (n=33)
Spain 1.1% (n=32)
Other countries 6.6% (n=185)
The Journal of Gene Medicine, © 2018 John Wiley and Sons Ltd

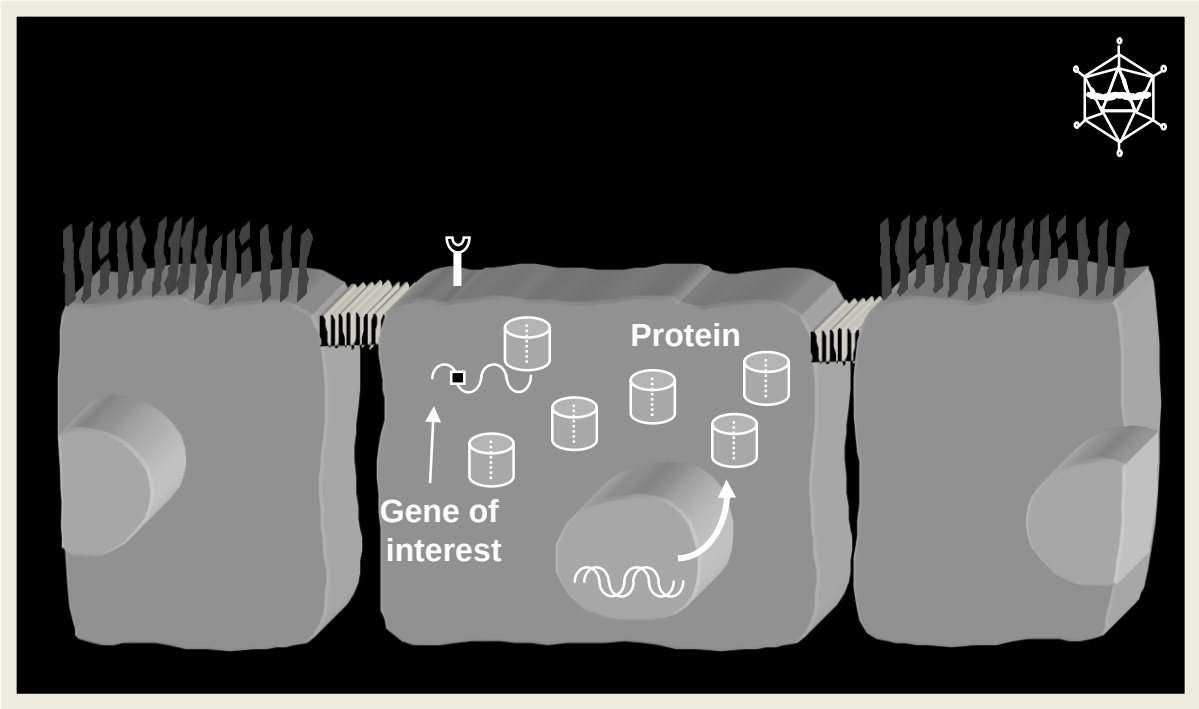
Successful gene therapy trials in humans

Some Gene Therapy Successes

Disorder	Disease type	Patients benefiting	First publication
X-SCID	Immunodeficiency	17/20	2000
ADA-SCID	Immunodeficiency	26/37	2002
Adrenoleukodystrophy	Neurologic	2/4*	2009
Leber's congenital amaurosis	Blindness	28/30	2008
Wiskott-Aldrich syndrome	Immunodeficiency	8/10	2010
β-thalassemia	Hemoglobinopathy	1/1	2010
Hemophilia	Coagulation	6/6	2011?

*Includes a patient treated too recently to see benefit

What is geGene Therapy ?

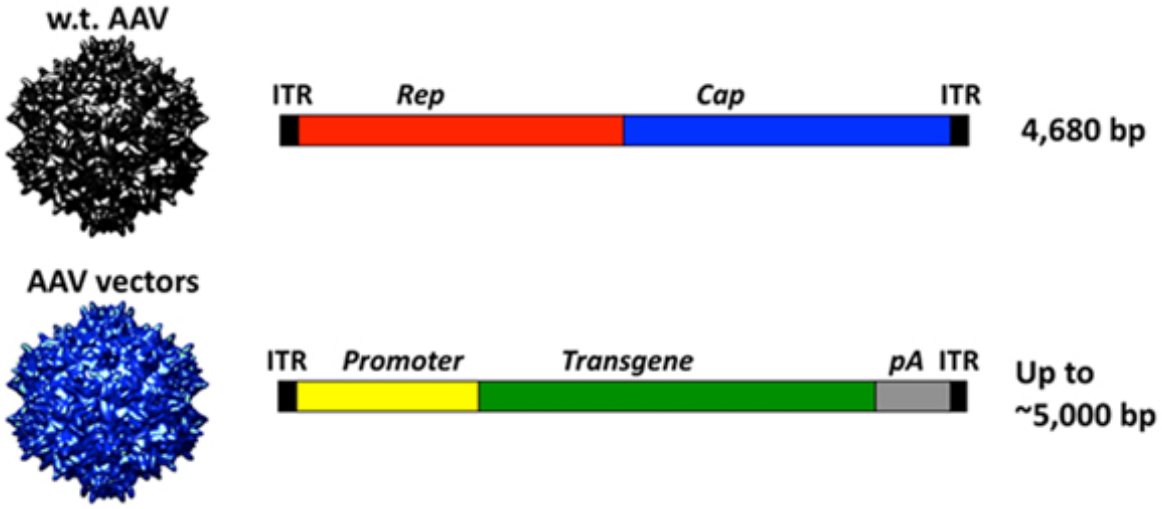


The use of genetic material (DNA, RNA) therapeutically

- It does not exist an ideal vector for all the diseases

AAV Vectors

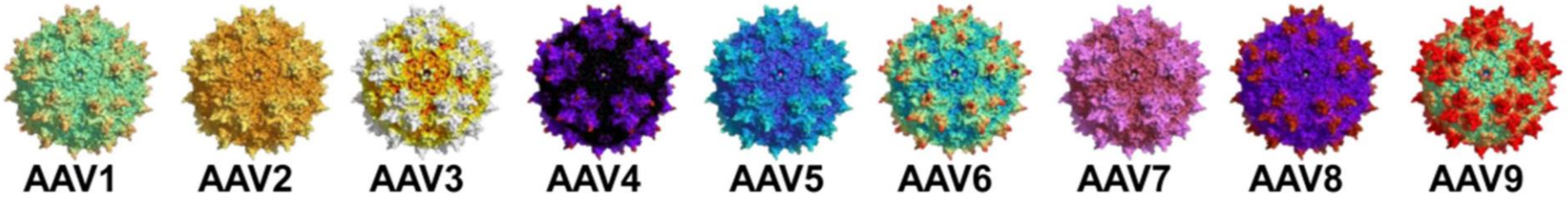
- Biosafety level 1
- Do not contain viral genes
- Easily to produce at large scale and GMP conditions



Ex vivo and in vivo Gene Transfer with AAV vectors: Advantages

- AAV vectors are classified as BLS-1
- Generation of AAVs vectors is very flexible and in high titers.
- For non-dividing cells as neurons or muscle fibres AAV vectors are highly recommended.
- Gene editing or integrative systems are currently used in combination with these vectors to achieve long-term expression in dividing cells (both ex vivo and in vivo approaches).
- Relatively low induction of immune response
- Currently used in human trials

Vectors with tropism to specific cell types

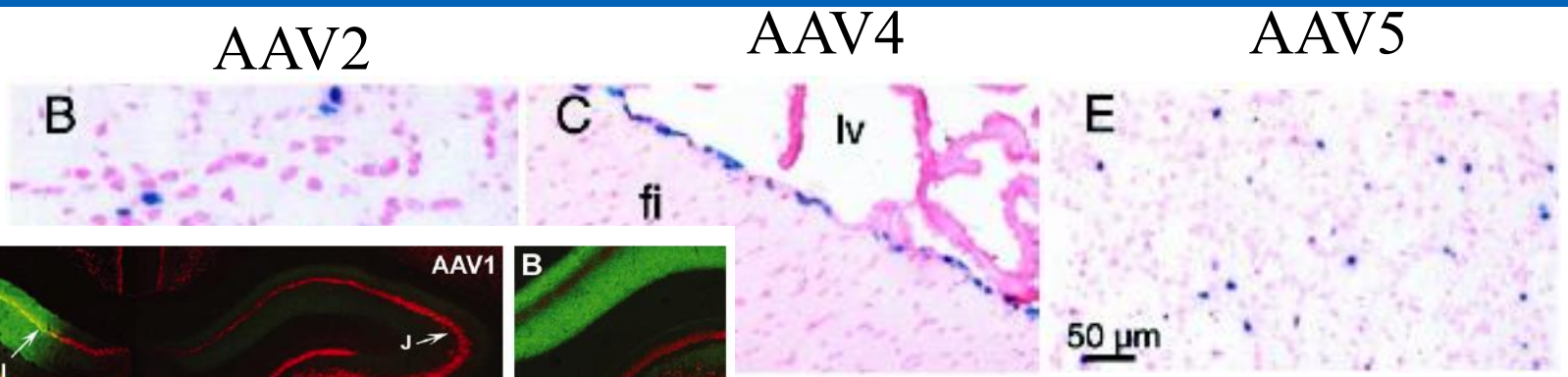


AAV1	AAV2	AAV3	AAV4	AAV5	AAV6	AAV7	AAV8	AAV9
Liver, heart, skeletal muscle, brain	Liver, heart and muscle	Heart, Liver	Heart, lung, Liver	Liver, brain	Liver, heart, skeletal muscle	Liver, skeletal muscle	Heart, Liver, brain, muscle	Liver, heart, brain, Lung, skeletal muscle

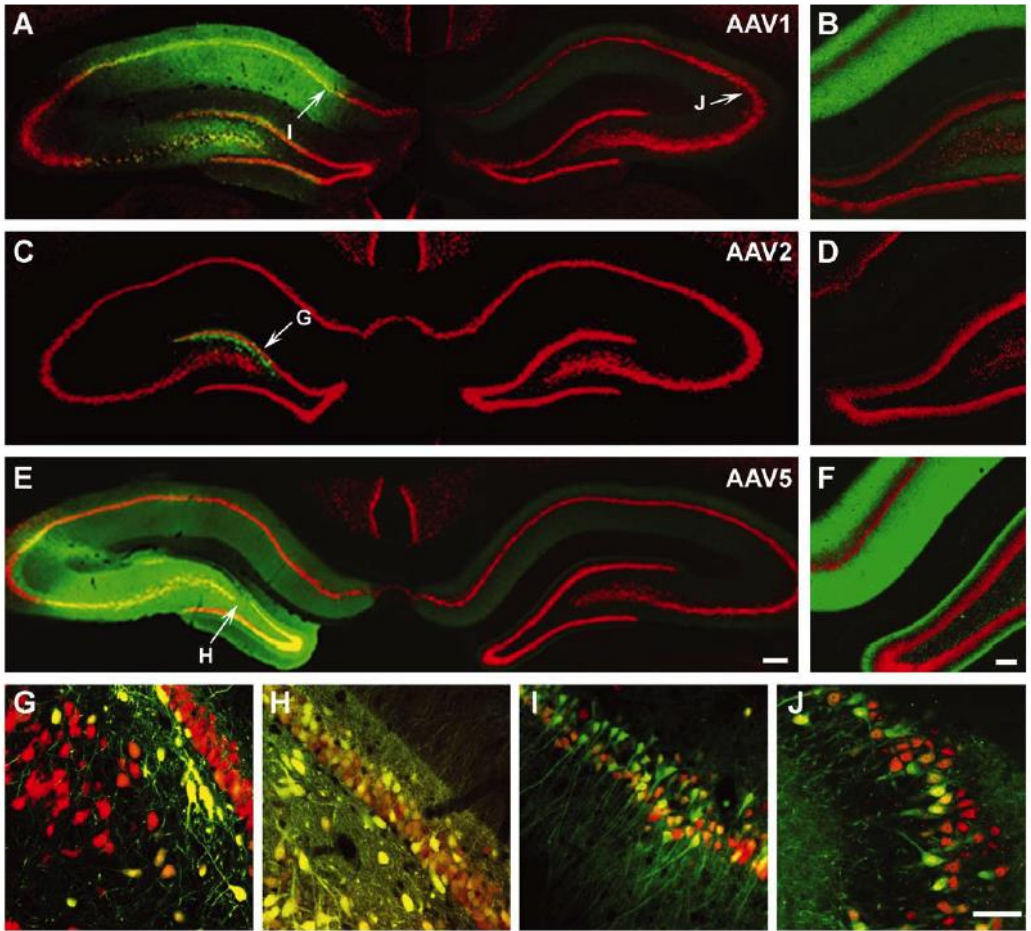
Characteristics of CNS important for gene transfer

- Nowadays, there is not a specific cure for many diseases affecting the Nervous System.
- Among them are neurodegenerative diseases such as mucopolysaccharidosis type VII or Alzheimer disease, immune diseases such as multiple sclerosis, and disorders associated with aging as dementia.
- CNS is protected by the Blood Brain Barrier
- Neurons are completely differentiated, quiescent, thus not all gene transfer vectors will be able to infect them

Different AAV Serotipes transduced different types of cells in the CNS



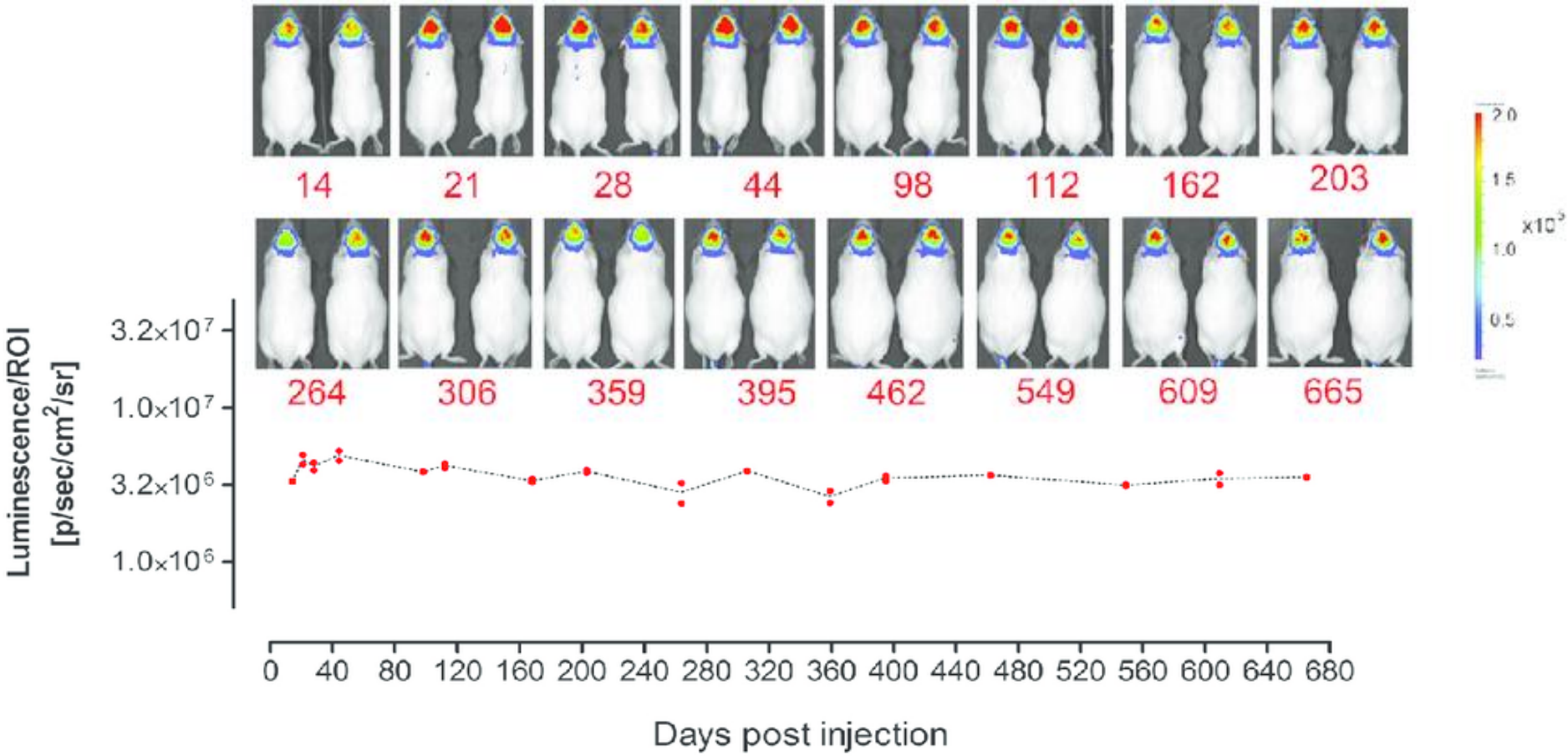
Davidson BL et al. PNAS 2000



High efficiency in transducing neurons
Biosafety
Easy to produce at high titer
Low immunogenicity
Long term expression
Some serotypes may cross the BBB

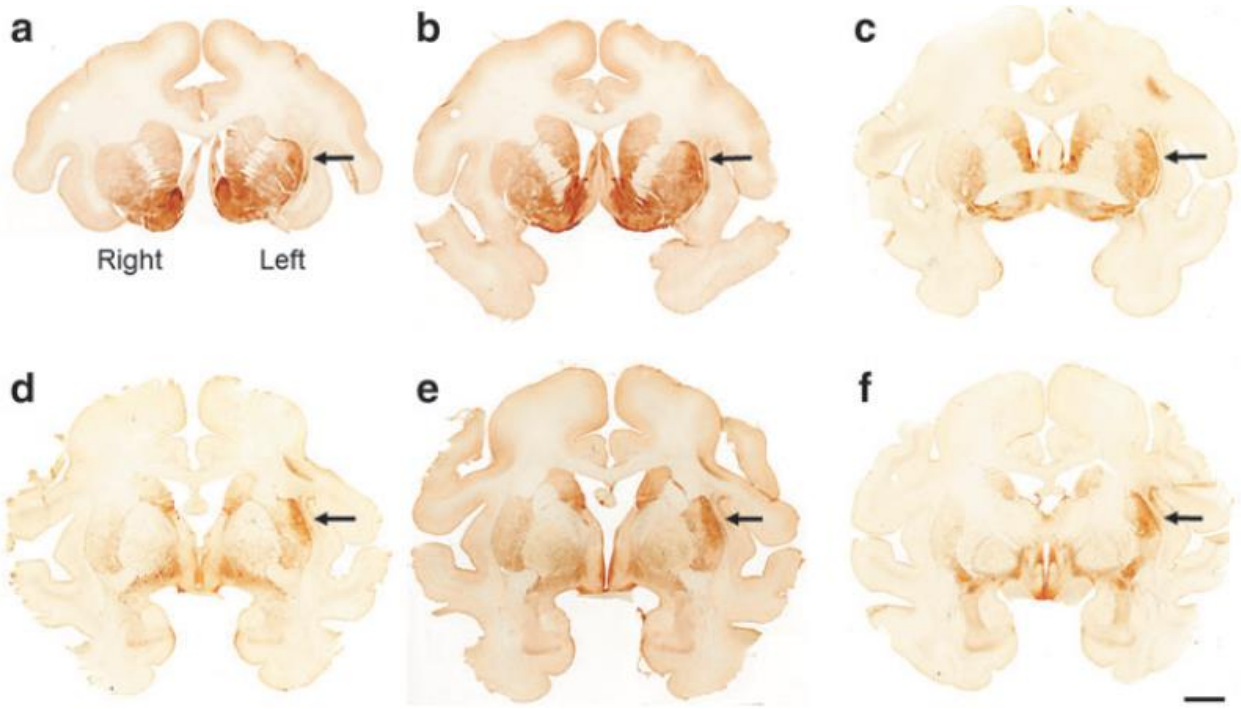
Mol Ther 2004, 2:302-17

One single dose = long-term expression



- One single dose treatment: one single administration, years of treatment.
- Possibility to deal with chronic diseases.

AAV stability in the Central Nervous System



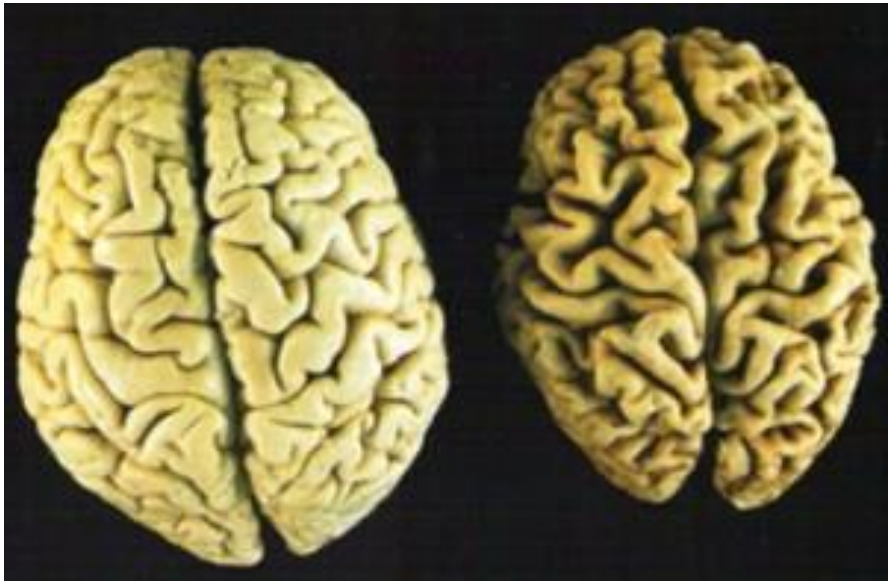
Persistent Expression of Dopamine-Synthesizing Enzymes 15 Years after Gene Transfer in a Primate Model of Parkinson's Disease

Yoshihide Sehara,[1] Ken-ichi Fujimoto,[2] Kunihiko Ikeguchi,[2] Yuko Katakai,[3] Fumiko Ono,[4] Naomi Takino,[5] Mika Ito,[5] Keiya Ozawa,[6] and Shin-ichi Muramatsu[1,5,6*]

HUMAN GENE THERAPY CLINICAL DEVELOPMENT DOI: 10.1089/humc.2017.010

Cognitive decline and aging

Many animal species, with a significative shorter half-life than humans, show similar cognitive decline at the end of life, indicating that specific biological processes rather than the length of lifetime are the main responsibles for brain aging.



Factors that may increase longevity

- Rapamicin, immunosupressor drug that increases lifetime in mice
- Caloric restriction, increases resistance to stress and reduces oxidative damage and inflammation in mice. May increase half-life up to 50%.

- Genetic background and healthy diets are more important for longevity than caloric restriction.

- Telomerases, protects chromosomal integrity
- Stem cells, participate in tissue regeneration.
- Pro-longevity factors as sirtuins or Klotho

Klotho: Antiaging protein

- Protein associated with longevity. Produced in kidney and brain.
- Discovered in mutant mice with a severe aging phenotype at muscular, vascular and mental levels.

RESEARCH ARTICLE

Suppression of Aging in Mice by the Hormone Klotho

Hiroshi Kurosu,[1] Masaya Yamamoto,[1] Jeremy D. Clark,[1] Johanne V. Pastor,[1] Animesh Nandi,[1] Prem Gurnani,[1] Owen P. McGuinness,[3] Hirotaka Chikuda,[4] Masayuki Yamaguchi,[4] Hiroshi Kawaguchi,[4] Iichiro Shimomura,[5] Yoshiharu Takayama,[2] Joachim Herz,[2] C. Ronald Kahn,[6] Kevin P. Rosenblatt,[1] Makoto Kuro-o[1]*

but then began to manifest multiple age-related disorders observed in humans, including ectopic calcification, skin atrophy, muscle atrophy, osteoporosis, arteriosclerosis, and pulmonary emphysema. *KL*$^{-/-}$ mice suffered premature death around two months of age.

The *Klotho* gene encodes a single-pass transmembrane protein that is detectable in limited tissues, particularly the distal convoluted tubules in the kidney and the choroid plexus in the brain. Because a defect in the *Klotho* gene leads to systemic age-dependent

Journal of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2011 July;66A(7):794–800
doi:10.1093/gerona/glr058

Advance Access published on April 7, 2011

Plasma Klotho and Mortality Risk in Older Community-Dwelling Adults

Richard D. Semba,[1] Anne R. Cappola,[2] Kai Sun,[1] Stefania Bandinelli,[3] Mansi Dalal,[1] Candace Crasto,[1] Jack M. Guralnik,[4] and Luigi Ferrucci[5]

REJUVENATION RESEARCH
Volume 17, Number 2, 2014

DOI: 10.1089/rej.2013.1523

Association of Klotho Polymorphisms with Healthy Aging: A Systematic Review and Meta-Analysis

Danilo Di Bona,[1,2] Giulia Accardi,[1] Claudia Virruso,[1] Giuseppina Candore,[1,2] and Calogero Caruso[1,2]

Functions of Klotho in the CNS

In CNS the KO Klotho mice have memory deficits, alterations in axonal transport, less synapsis in hippocampus, hippocampal degeneration, and deficit in myelin production.

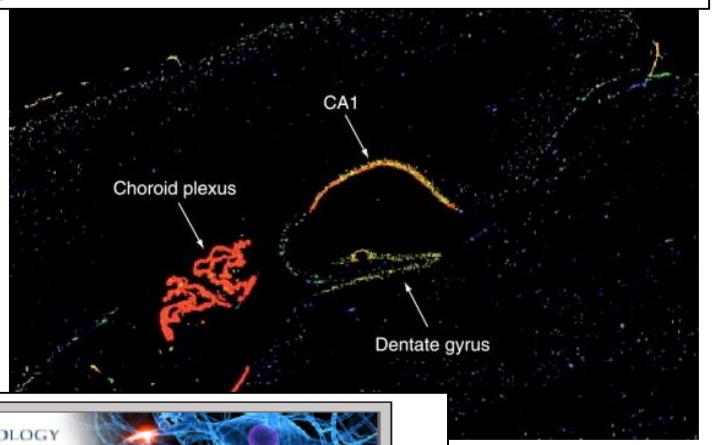
- Neuroprotector factor against oxidative stress
- Neuromodulation of the synapsis
- Myelinating factor
- Axonal transport
- Cognitive enhancer

The Journal of Neuroscience, January 30, 2013 • 33(5):1927–1939 • 1927

Cellular/Molecular

The Antiaging Protein Klotho Enhances Oligodendrocyte Maturation and Myelination of the CNS

Ci-Di Chen,[1] Jacob A. Sloane,[2*] Hu Li,[3*] Nurgul Aytan,[4*] Eustathia L. Giannaris,[5*] Ella Zeldich,[1] Jason D. Hinman,[6] Alpaslan Dedeoglu,[4] Douglas L. Rosene,[5] Rashmi Bansal,[7] Jennifer I. Luebke,[5] Makoto Kuro-o,[8] and Carmela R. Abraham[1]



Cell Reports
Article

OPEN ACCESS
CellPress

Life Extension Factor Klotho Enhances Cognition

Dena B. Dubal,[1,2,*] Jennifer S. Yokoyama,[2] Lei Zhu,[1,2] Lauren Broestl,[2] Kurtresha Worden,[1,2] Dan Wang,[2] Virginia E. Sturm,[2] Daniel Kim,[1] Eric Klein,[3] Gui-Qiu Yu,[1] Kaitlyn Ho,[1] Kirsten E. Eilertson,[4,12] Lei Yu,[5] Makoto Kuro-o,[6,7] Philip L. De Jager,[8,9,10] Giovanni Coppola,[3] Gary W. Small,[3] David A. Bennett,[5] Joel H. Kramer,[2] Carmela R. Abraham,[11] Bruce L. Miller,[2] and Lennart Mucke[1,2,*]

Neurobiology:

The Neuroprotective Effect of Klotho is Mediated via Regulation of Members of the Redox System

Ella Zeldich, Ci-Di Chen, Teresa A. Colvin, Erin A. Bove-Fenderson, Jennifer Liang, Tracey B. Tucker Zhou, David A. Harris and Carmela R. Abraham

J. Biol. Chem. 2014, 289:24700-24715.
doi: 10.1074/jbc.M114.567321 originally published online July 18, 2014

Klotho as a diagnostic tool

Table 1
Characteristics of participants in the three study groups.

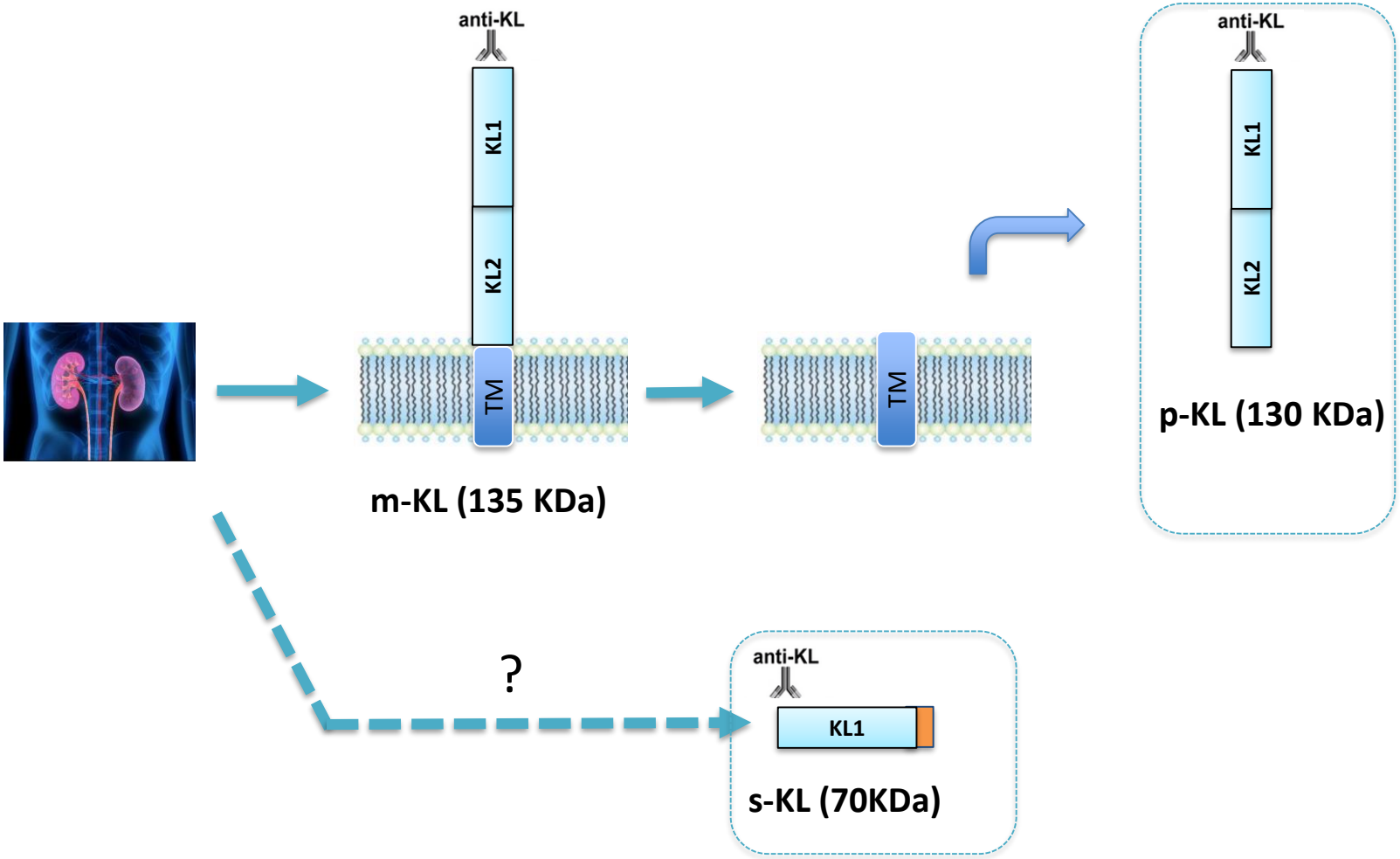
Characteristic[a]	Alzheimer's disease ($n = 20$)	Normal older adults ($n = 20$)	Normal younger adults ($n = 20$)	P^{b}
Age, years	76.9 (73.8, 80.1)	76.8 (74.2, 79.4)	30.1 (27.0, 33.2)	<0.0001
Sex				
Male	10	10	10	1.00
Female	10	10	10	
MMSE score	22.1 (21.1, 23.1)	28.6 (28.2, 29.1)	Not measured	<0.0001
CSF klotho (pg/mL)	664 (603,725)	776 (705,828)	922 (844, 1100)	0.001

[a] Mean (95% CI) shown for continuous variables
[b] For continuous variables, by ANOVA.

Semba et al, 2014

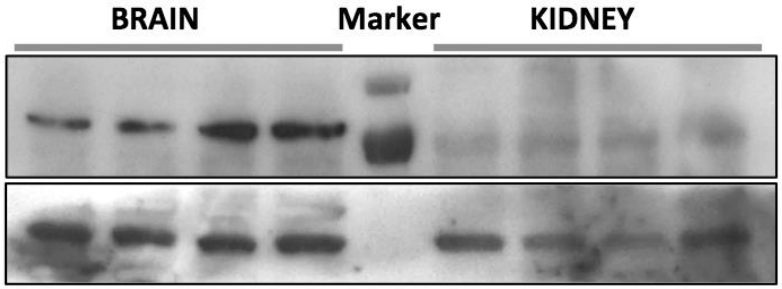
- En humanos, los niveles de klotho levels se reducen con la edad, y esta reducción es más evidente en pacientes de Alzheimer

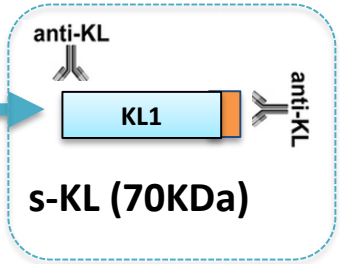
Klotho isoforms



Secreted Klotho isoform

- Our group reported recently that the secreted Klotho isoform is produced and stable. It is expressed in the CNS, and could be considered the specific brain isoform of klotho.



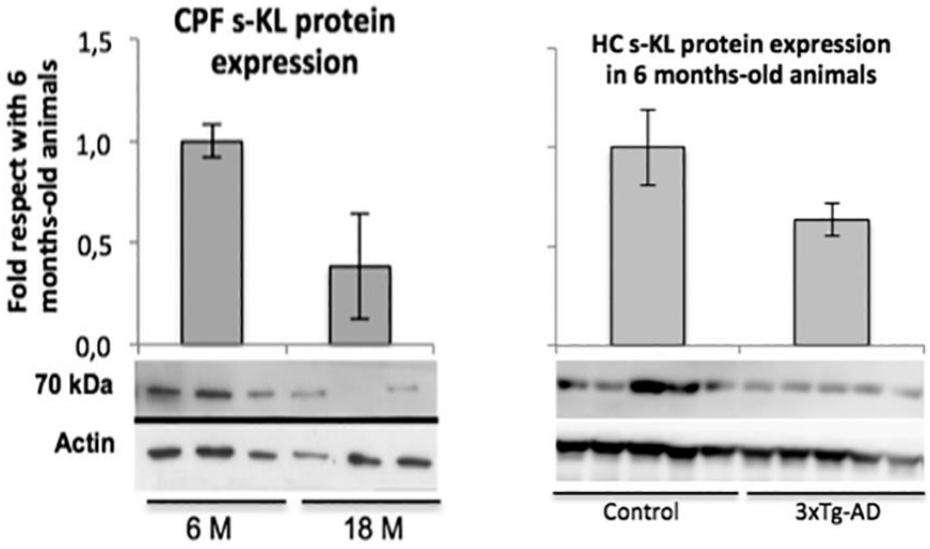


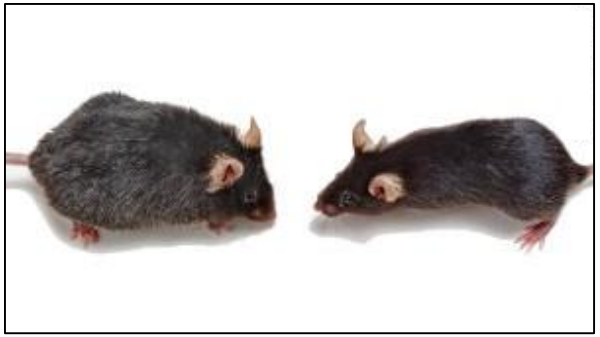
- It is unknown which klotho functions in brain are exclusive of s-KL

A. Masso, Plos One, 2015

Secreted Klotho in CNS

- We analyzed the levels of sKL in different mice models of aging
- We analyzed HC, Cx, CxPf y CB





1. sKL levels decay during aging
2. sKL levels decay rapidly in AD, and this reduction is statiscally significant BEFORE tha apparition of beta-amyloide plaques and cognitive deficits

Cause or consequence?

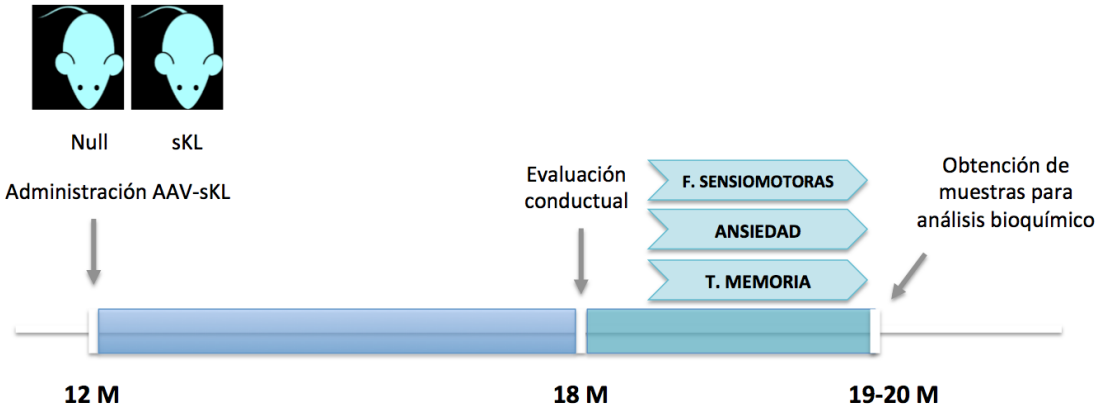
A. Masso, Plos One 2015

Secreted Klotho as a therapeutic molecule

- It has been demosntrated a significant correlationship between Klotho and connitive performance.
- The question is: Is Klotho the cause or the consequence of it?

We have long experience in manipulating genetically the levels of a specific protein in vivo

Secreted Klotho as a therapeutic molecule

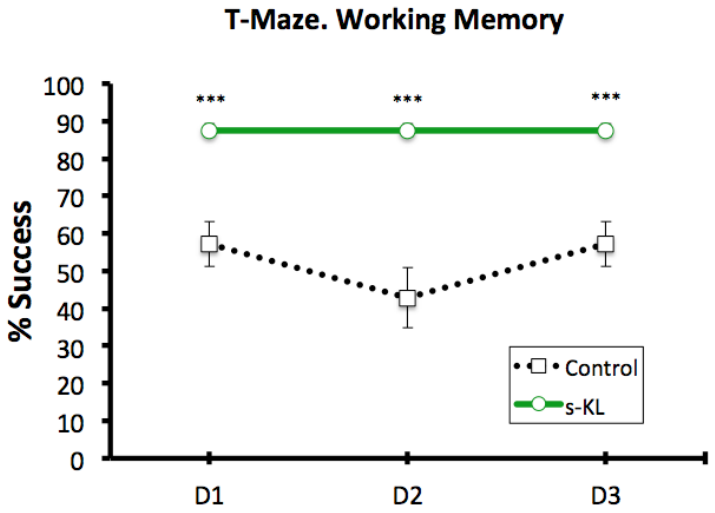


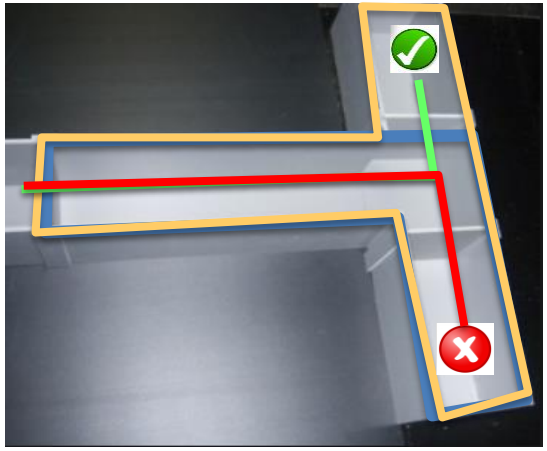
www.viralvector.eu

- ✓ Murine model of natural aging. Treatment at 12m of age and evaluation at 18m.
- ✓ Disponibility of an efficient AAV vector to transduce neurons, without scondary effects.
- ✓ We have a candidate gene(Klotho, sKL). Pleiotropic. Secreted isoform.
- ✓ Administration of a single dose

Secreted Klotho as a therapeutic molecule

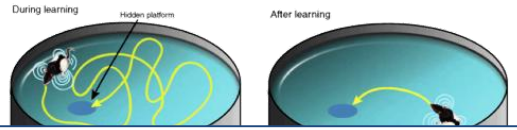
T-maze: increase in CNS s-KL expression can significantly improve the score compared to control group, as checked by less errors to choice the non-visited arm of the maze (p = 0,0018)

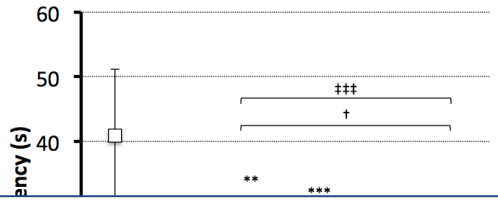




Secreted Klotho as a therapeutic molecule

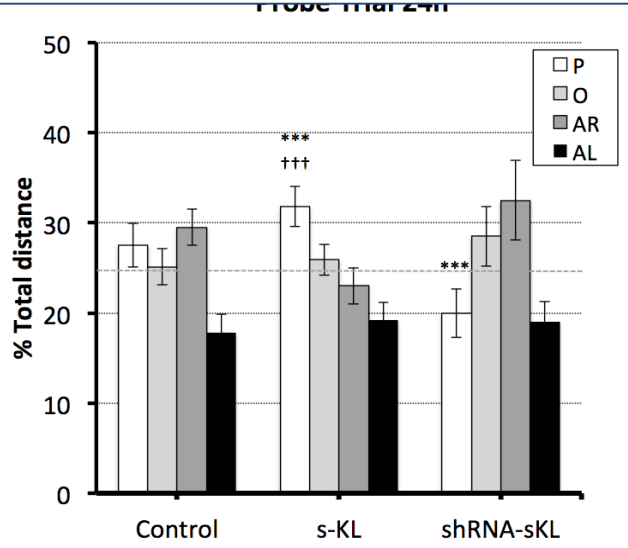
Water-maze: To assess long-term memory retention. s-KL group prioritize much more efficiently the Plat quadrant compared to control group (*p<0.01*), indicating that increased levels of s-KL in the CNS have a significant effect on long-term memory, improving its performance.

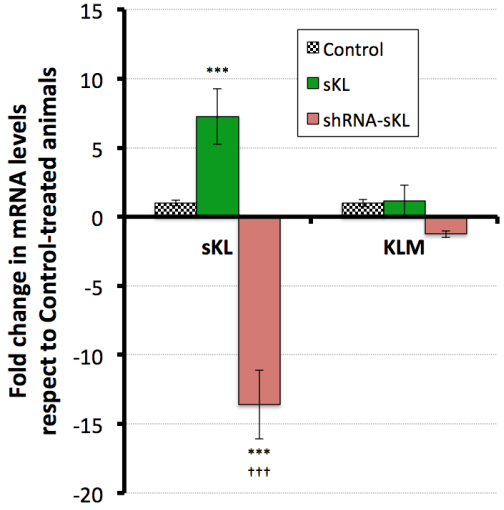




1) Long-term expression of AAV-secreted Klotho vectors specifically in the CNS enhances cognitive performance in aged naive animals

2) No secondary effects observed

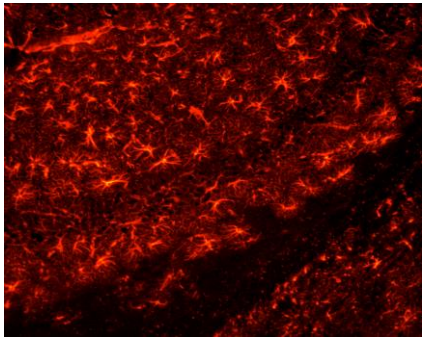


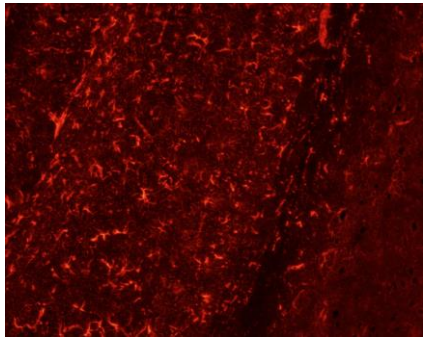


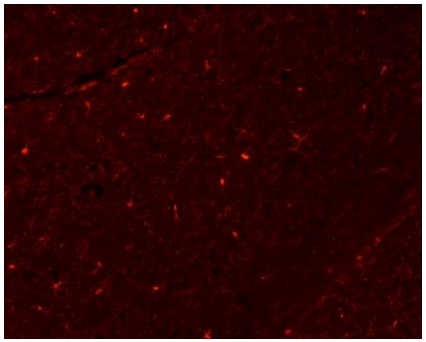
Secreted-Klotho isoform protects against age-dependent memory deficits in aged animals

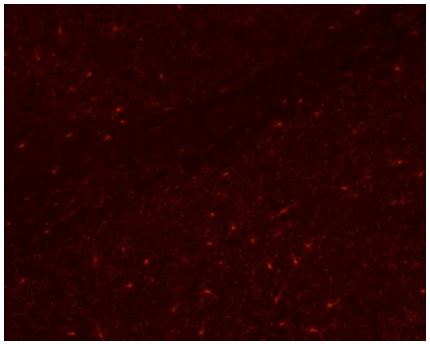
WT-AAV/Null

WT-AAV/sKL

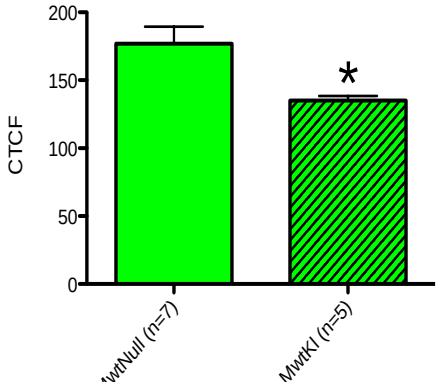




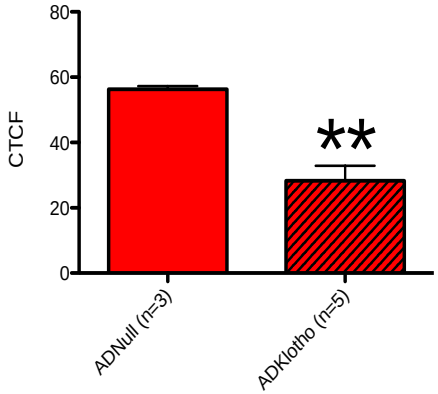




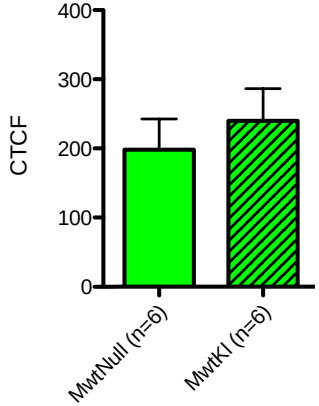
GFAP (CA1 – stratum radiatum)



Iba1 (CA1 – stratum radiatum)



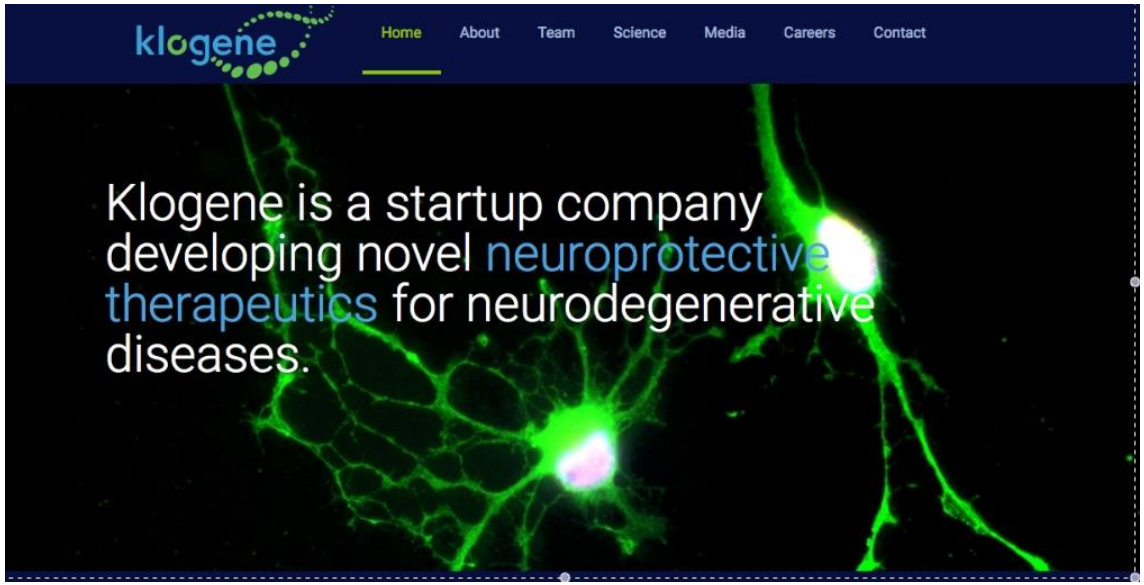
NeuN (CA1)



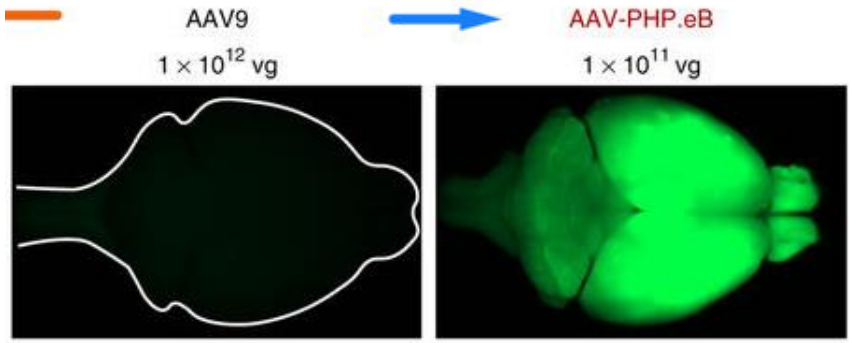
Summary and perspectives

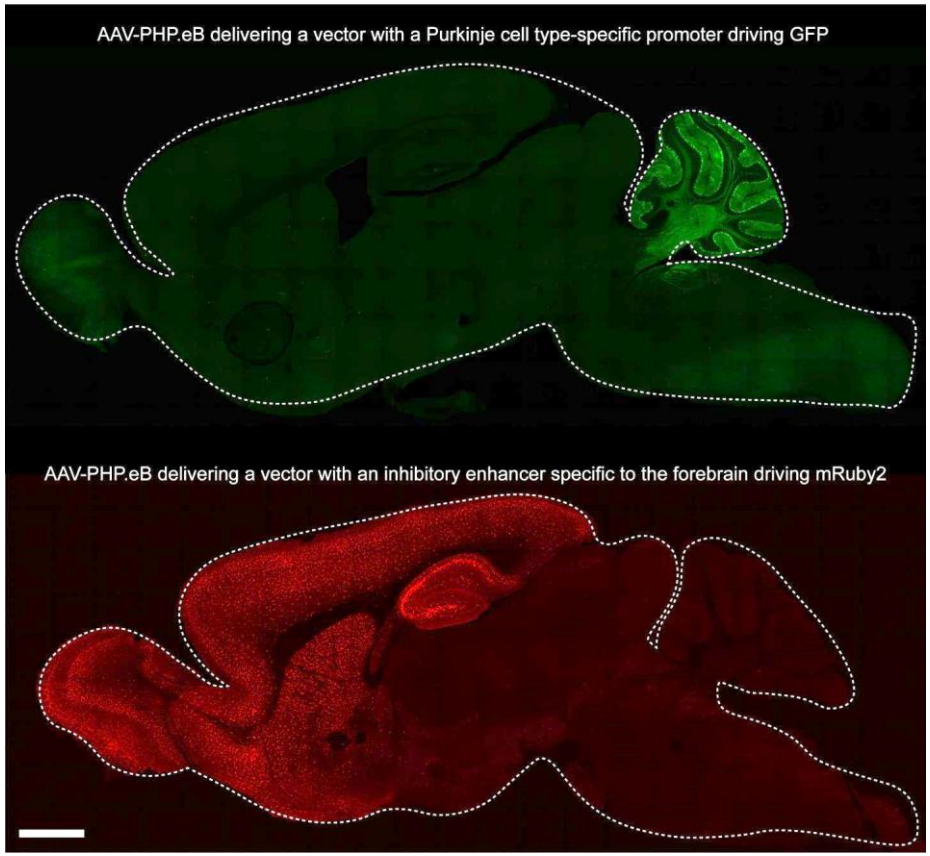
- Long-term expression of secreted Klotho specifically in the CNS enhances cognitive performance in aged naive animals

- ➢ Determine if other parameters such as mielination, synapsis, neuronal viability, etc, are also improved
- ➢ Test the effect of klotho as a therapeutic protein in animal models of AD.

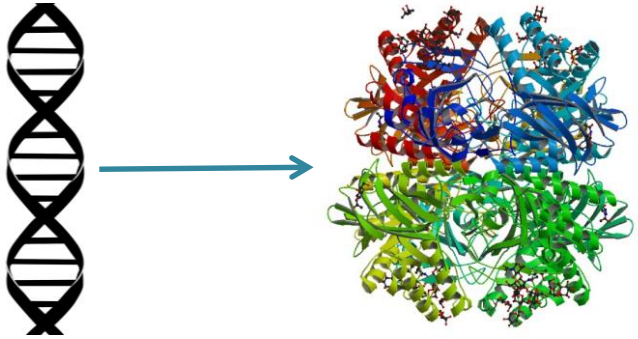


AAV and Blood Brain Barrier





Mucopolysaccharidosis VII

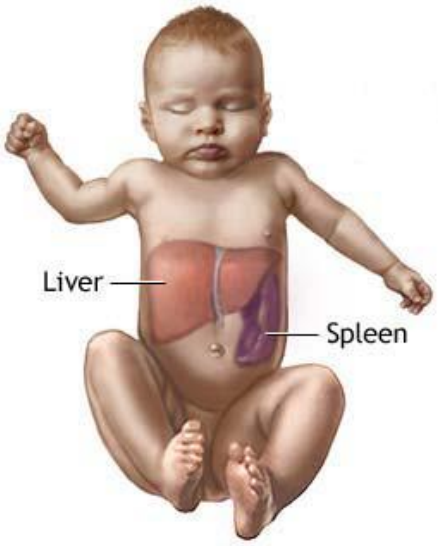


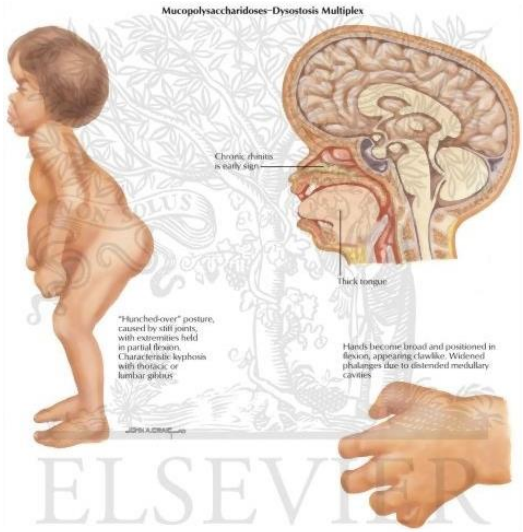
GUSB

β-Glucuronidase

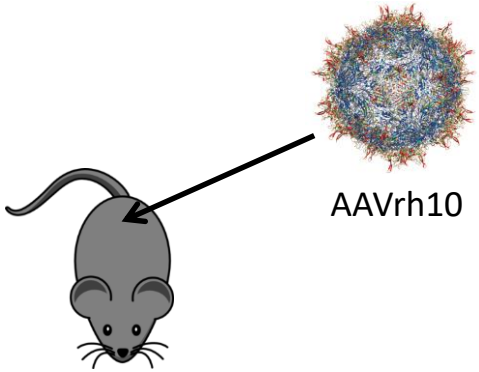
Incidence: 1:250,000 births

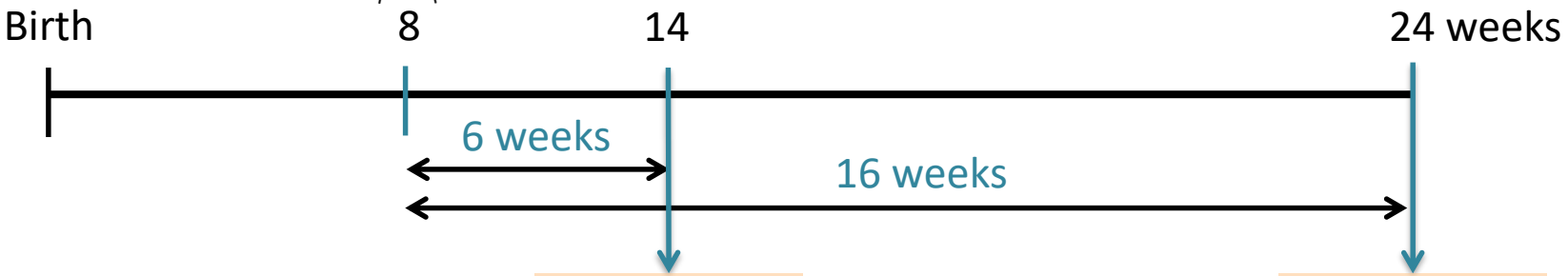
Wide range of clinical severity and disease onset





Experimental Design





Short term
3.5 months

Long term
6 months

n = 8 to 12

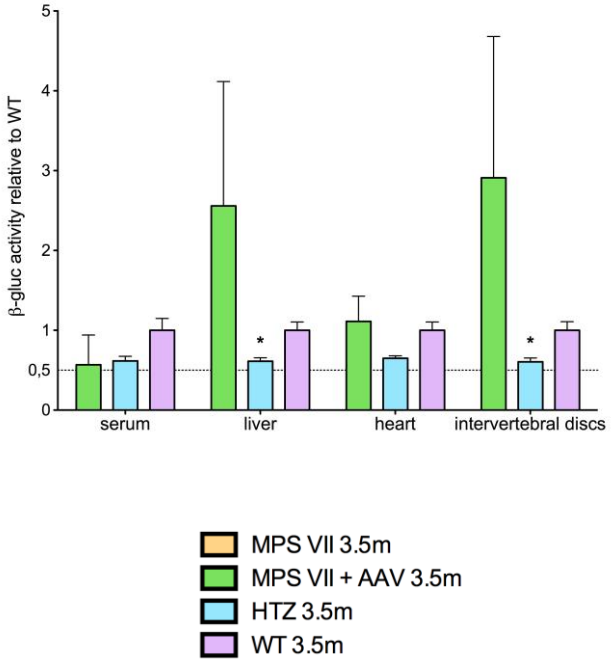
MPS VII half life:
4.2 months

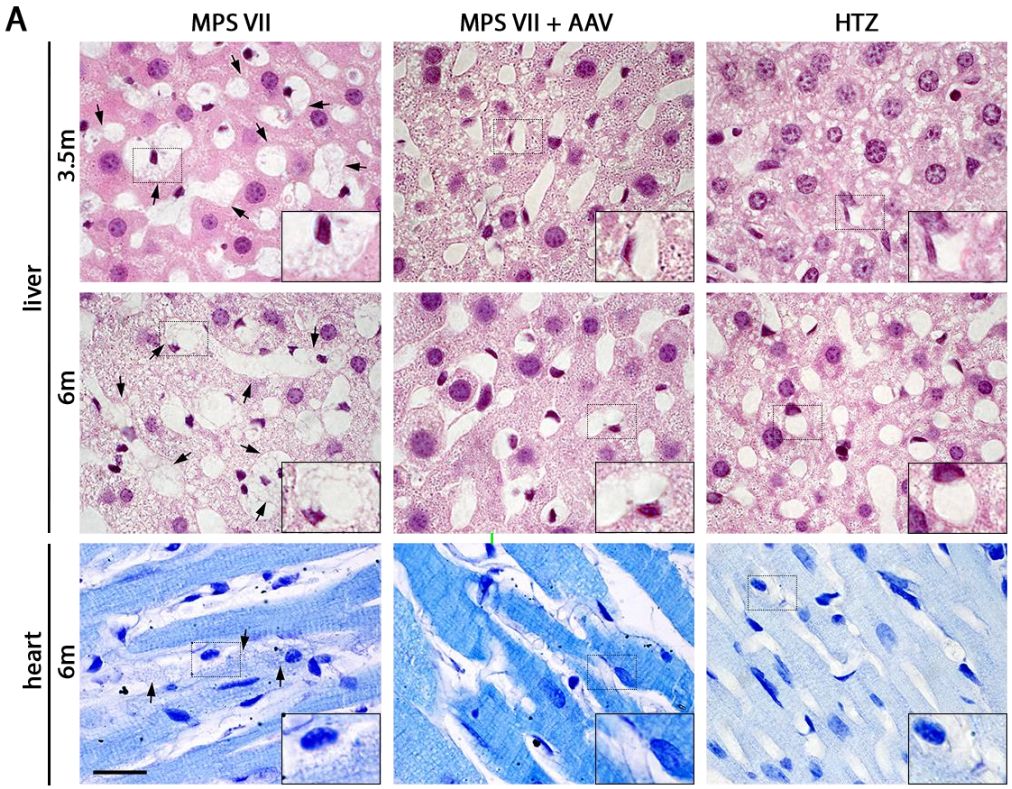
- MPS VII 3.5m
- MPS VII + AAV 3.5m
- HTZ 3.5m
- WT 3.5m

- MPS VII 6m
- MPS VII + AAV 6m
- HTZ 6m
- WT 6m

Biochemical and histopathological correction

- Biochemical and histopathological correction in peripheral tissues (liver and heart)

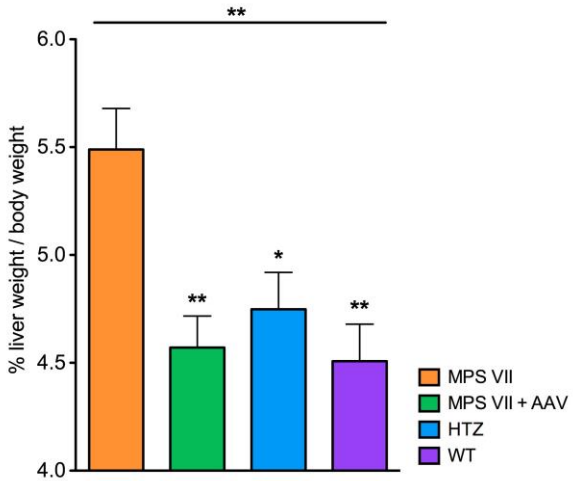


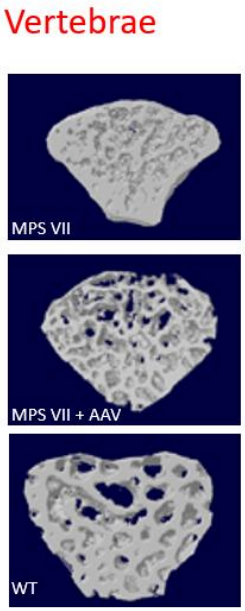


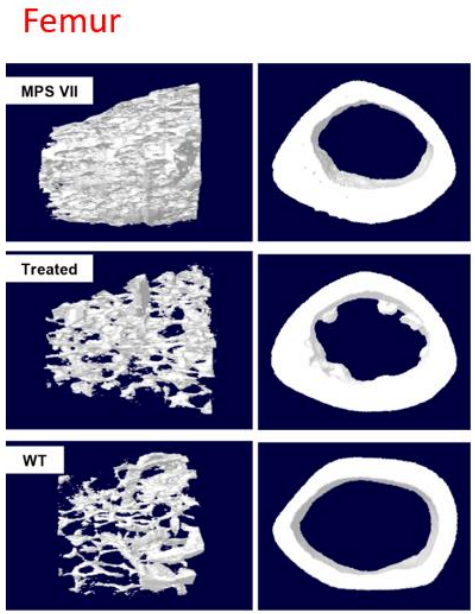
Scale bar: 20 µm

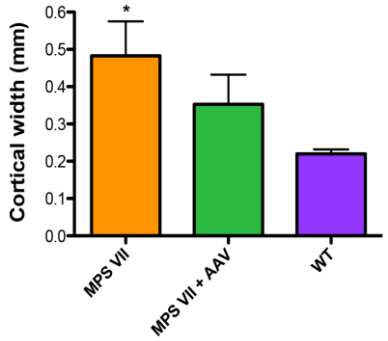
Biochemical and histopathological correction

- Biochemical and histopathological correction in peripheral tissues (liver and heart)
- Hepatomegaly correction and skeletal partial recovery



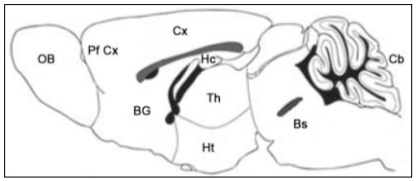


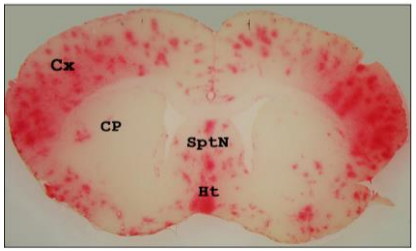


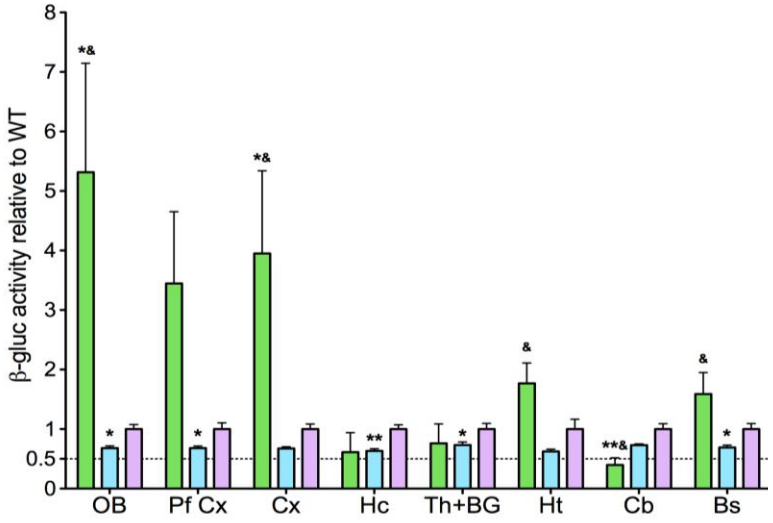


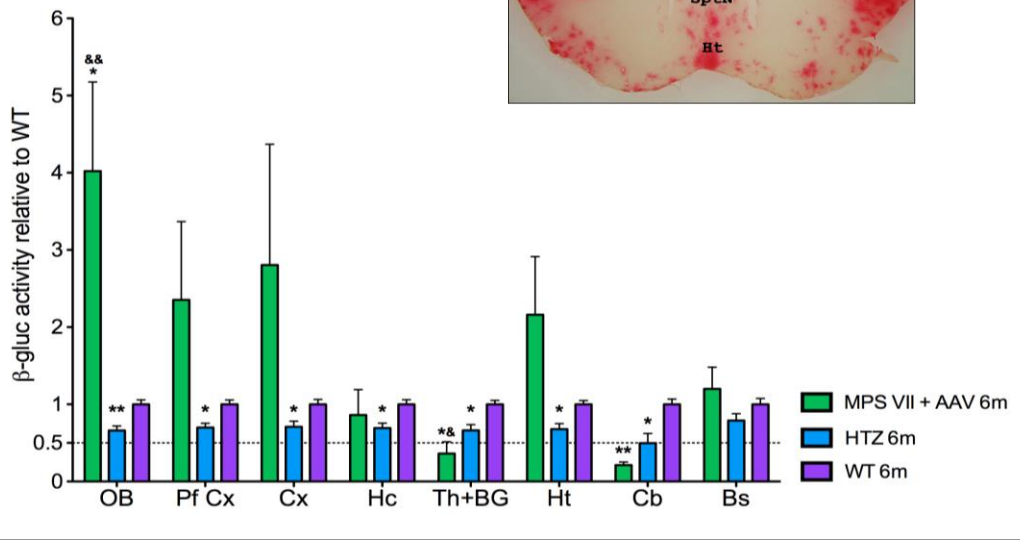
Biochemical and histopathological correction

- Biochemical and histopathological correction in peripheral tissues (liver and heart)
- Hepatomegaly correction and skeletal partial recovery
- CNS biochemical correction



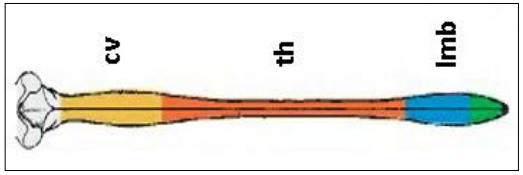


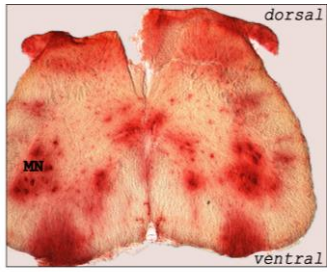


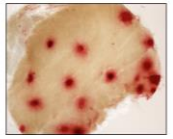


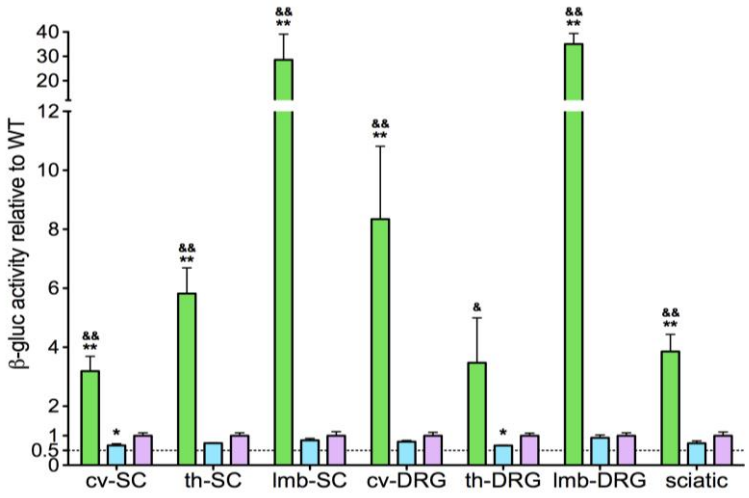
Biochemical and histopathological correction

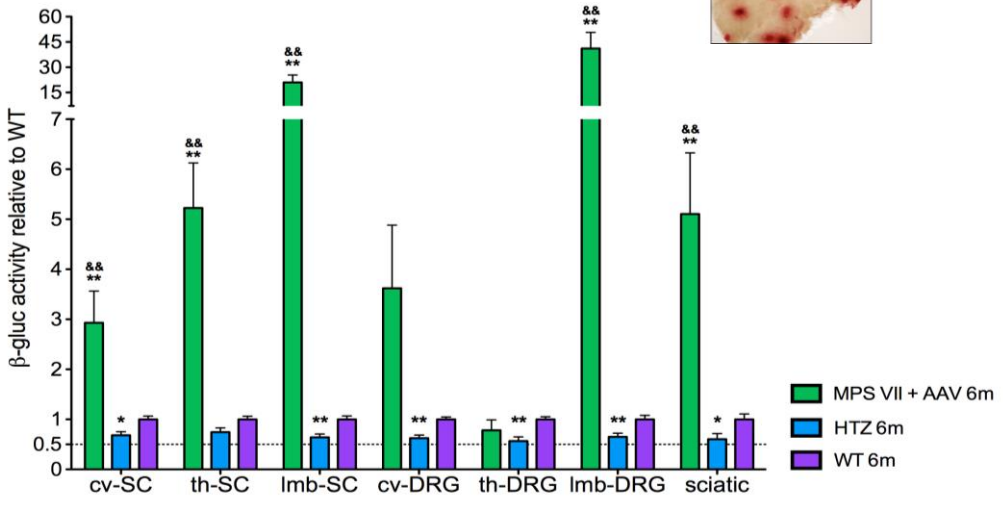
- Biochemical and histopathological correction in peripheral tissues (liver and heart)
- Hepatomegaly correction and skeletal partial recovery
- CNS biochemical correction
- Spinal cord: biochemical correction





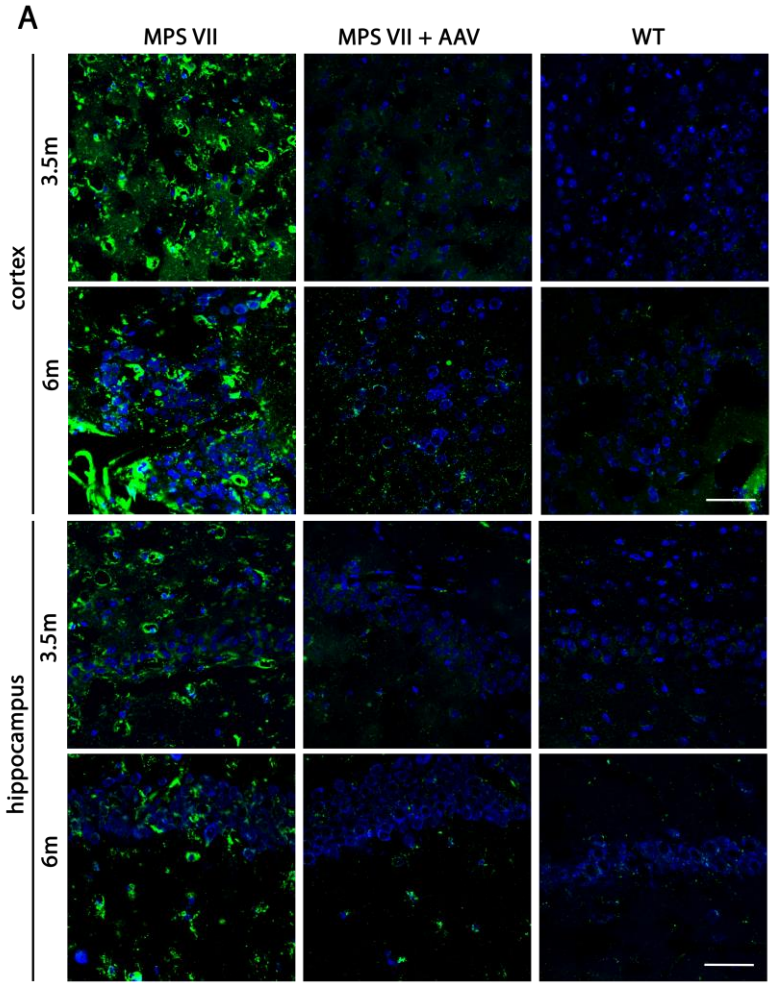






Biochemical and histopathological correction

- Biochemical and histopathological correction in peripheral tissues (liver and heart)
- Hepatomegaly correction and skeletal partial recovery
- CNS biochemical correction
- Spinal cord: biochemical correction
- Lysosomal distension (LAMP-1 accumulation)



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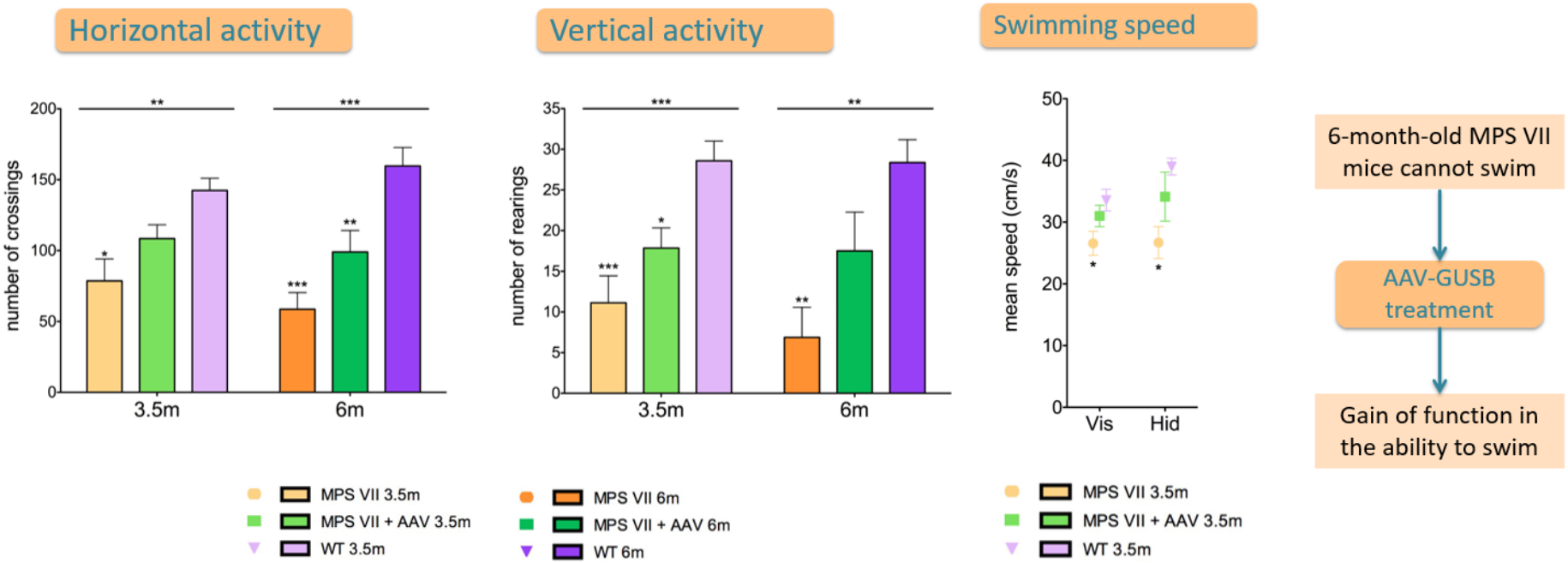
- CNS biochemical correction
- Spinal cord: biochemical correction
- Lysosomal distension (LAMP-1 accumulation)
- Behavioral studies



Biochemical and histopathological correction

- Biochemical and histopathological correction in peripheral tissues (liver and heart)
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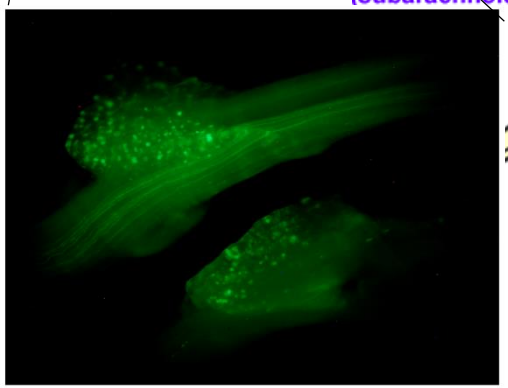
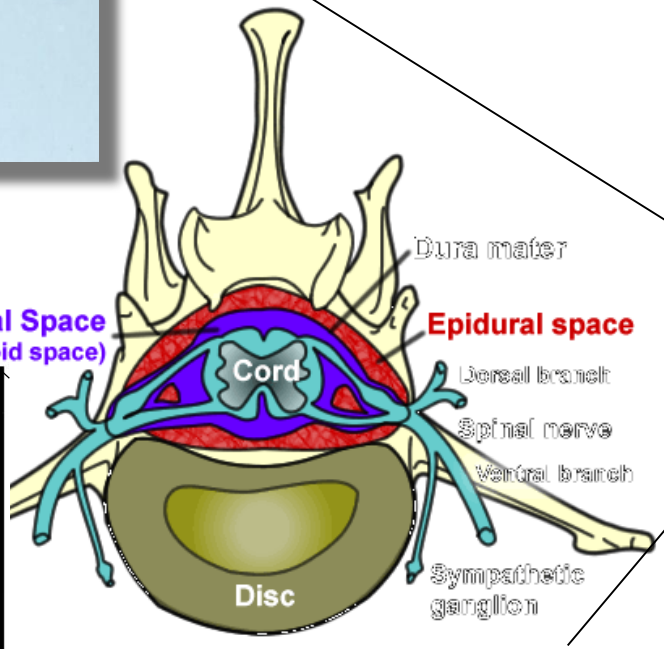
- CNS biochemical correction
- Spinal cord: biochemical correction
- Lysosomal distension (LAMP-1 accumulation)
- Behavioral studies

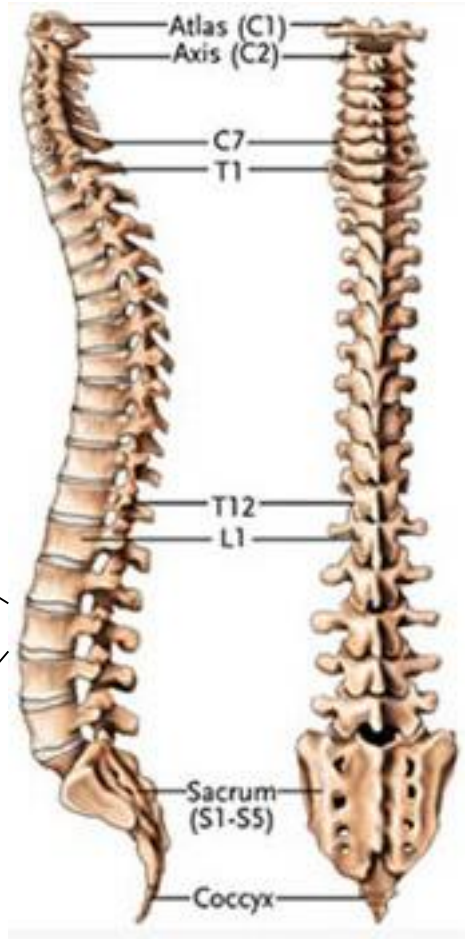
Perspectives:

- Test AAV vectors able to cross the BBB
- Check the effect of the immune response when overexpressing proteins in patients with absence of target protein

Gene therapy in PNS



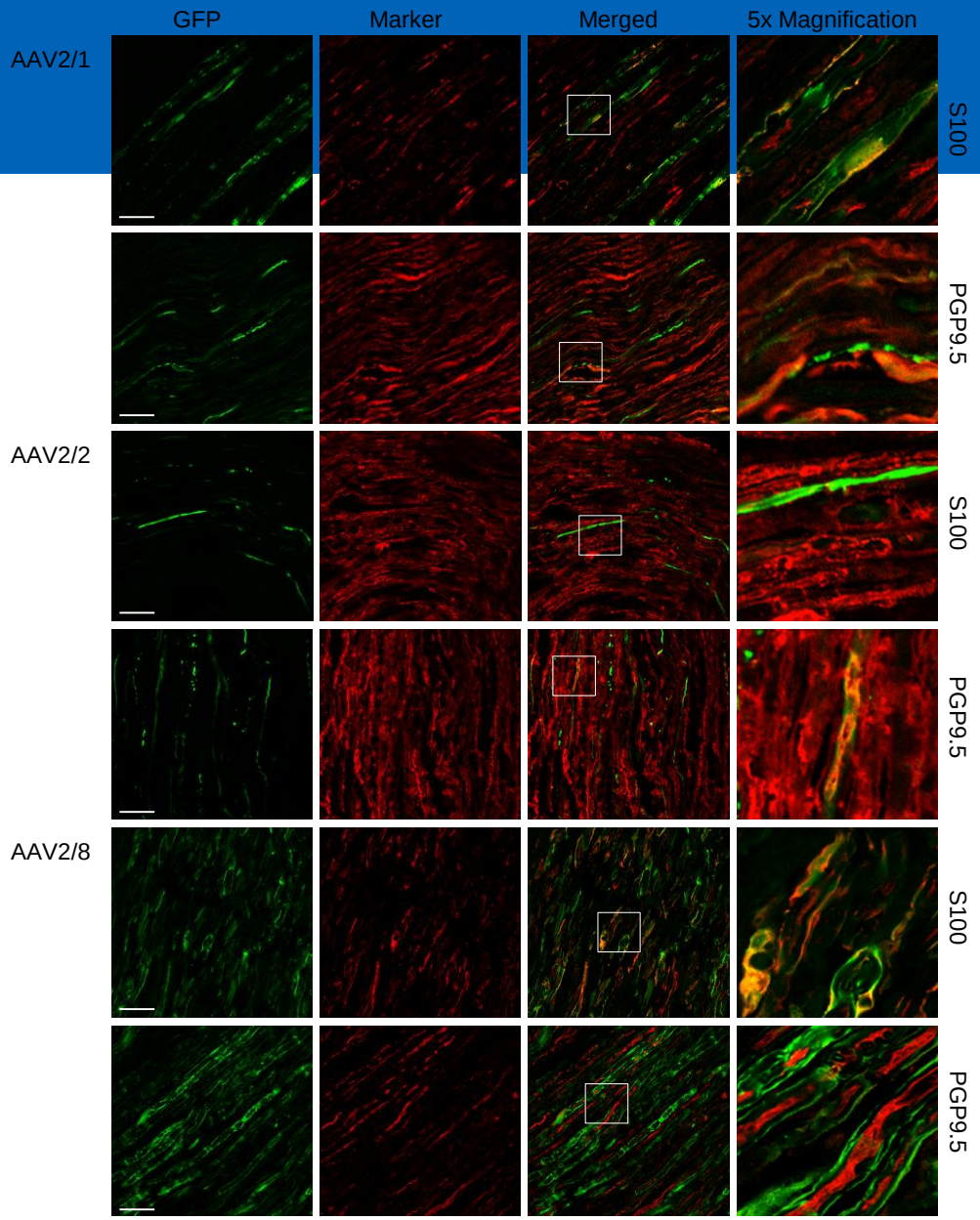




Figures kindly provided by Assumpcio Bosch

AAV vectors for peripheral nerve regeneration

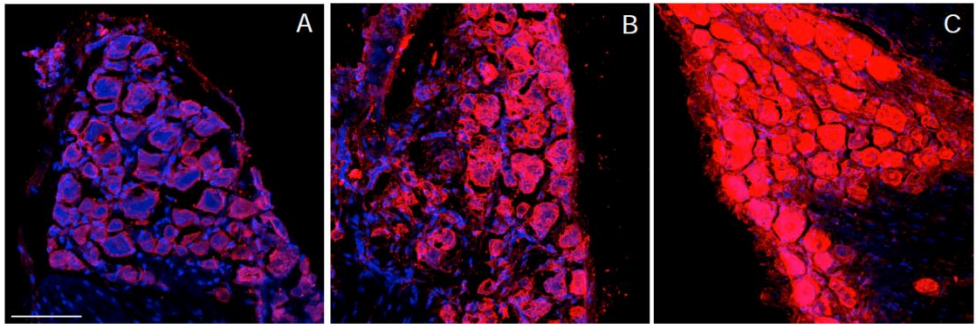
Serotype	Transduced cell type
AAV1	Neurons/Schwann cells
AAV2	Neurons
AAV8	Schwann cells

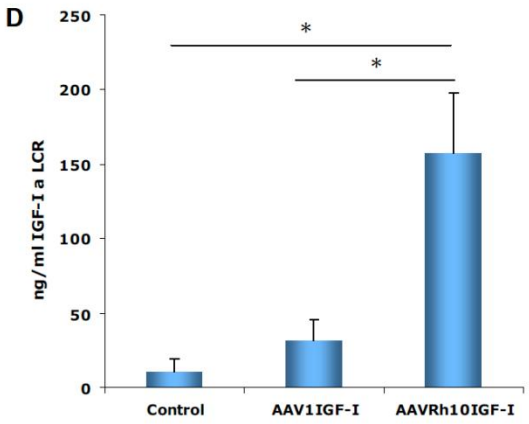


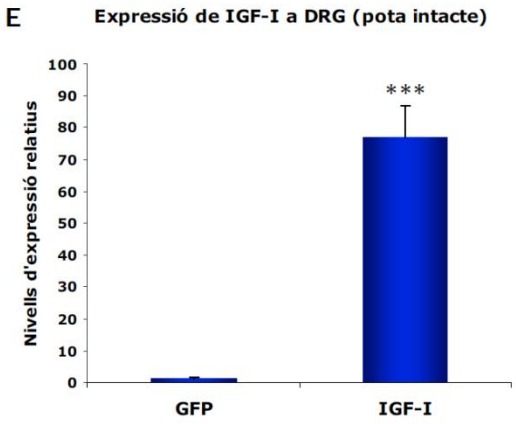
Gene Therapy (2011) 18, 622–630

Targeting the PNS by viral gene therapy vectors

Diabetic polyneuropathy

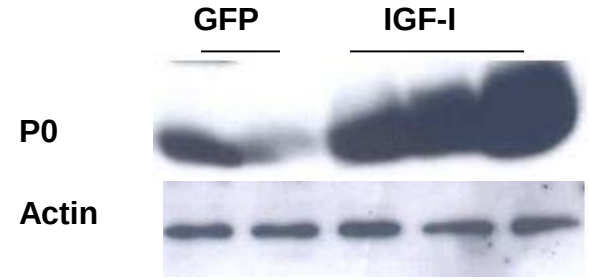






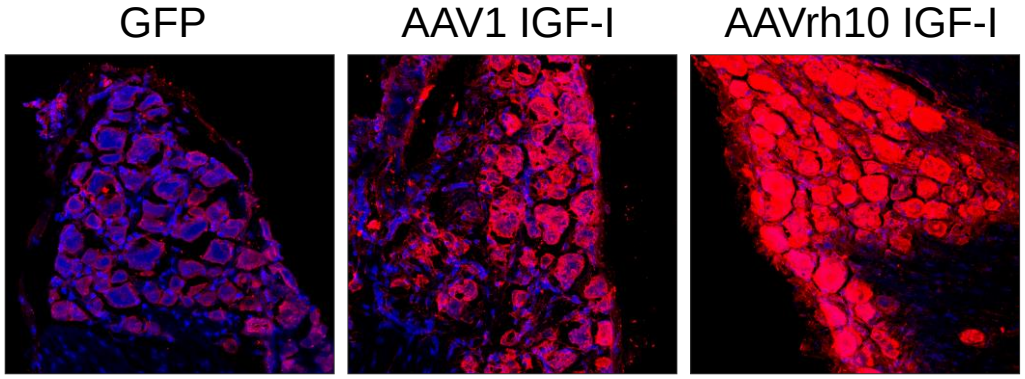
- Regeneration

- Myelination



Homs et al, Gene Ther. 2011
Homs et al. J Peripher Nerv Syst. 2011
Ariza et al, Neuroscience. 2014

AAVrh10-IGF-I improves regeneration and myelination in injured sciatic nerve

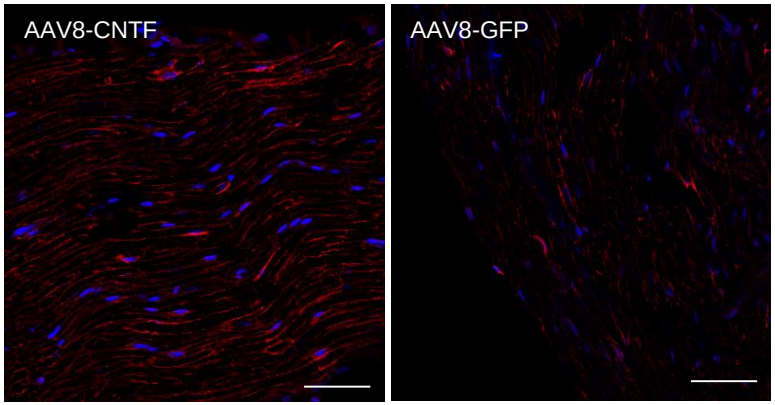


Tractament / *Paràmetre*	**AAVrh10-GFP** (n=7)		**AAVrh10-IGF-I** (n=15)	
Setmana p.i	**3**	**4**	**3**	**4**
Múscul plantar				
CMAP (mV)	6.6 ± 0.9	6.3 ± 0.6	6.3 ± 0.3	5.5 ± 0.3
MNCV (m/s)	34.7 ± 2.1	36.7 ± 3.2	41.3 ± 2.2	42.3 ± 2.6
Nervi digital				
CNAP (μV)	29.2 ± 3.0	19.0 ± 3.1	36.3 ± 3.0	31.2 ± 2.6 [a]
SNCVp (m/s)	40.2 ± 1.7	44.6 ± 2.8	44.1 ± 2.8	46.7 ± 2.4
SNCVd (m/s)	28.1 ± 1.4	24.8 ± 0.9	28.6 ± 0.9	25.6 ± 0.6

AAVrh10
Increased motor nerve conduction velocity and sensory compound nerve action potentials

Molecular Therapy — Methods & Clinical Development (2014) 1, 7

AAV vectors for peripheral nerve regeneration



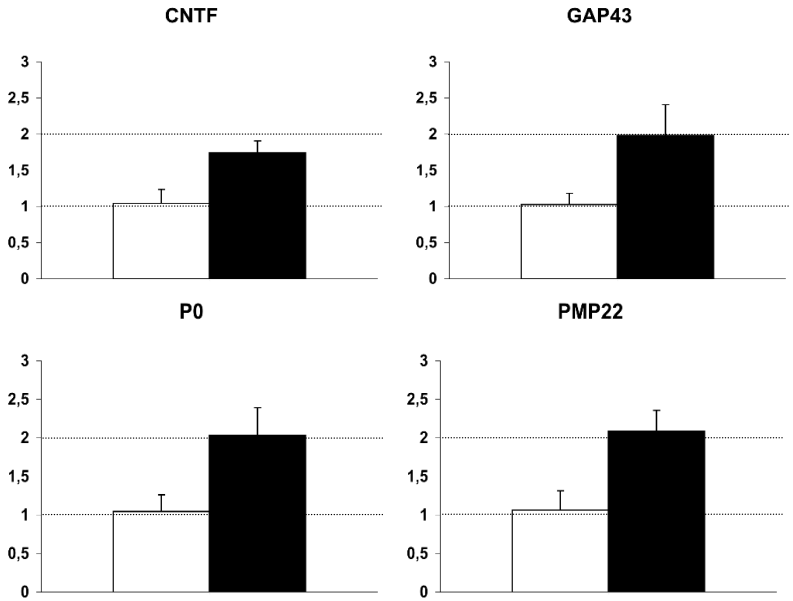


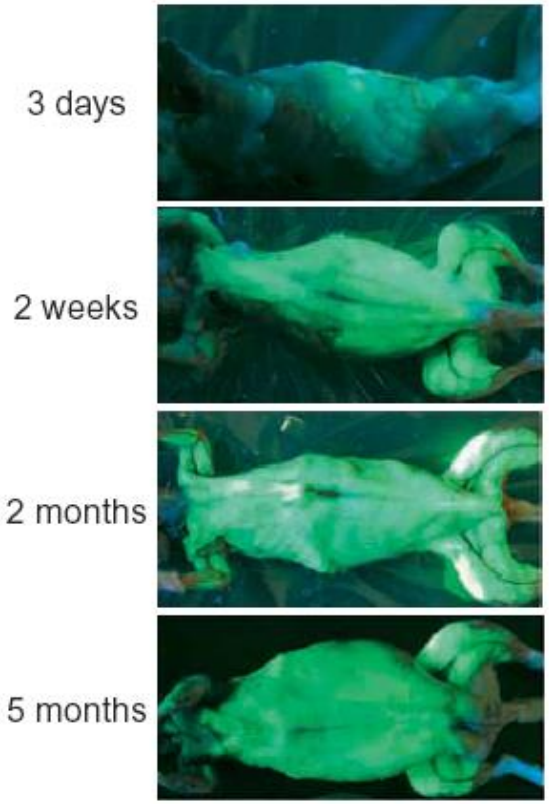
Table 1 Electrophysiological tests for animals injected with AAV8-GFP or AAV-CNTF intrasciatically

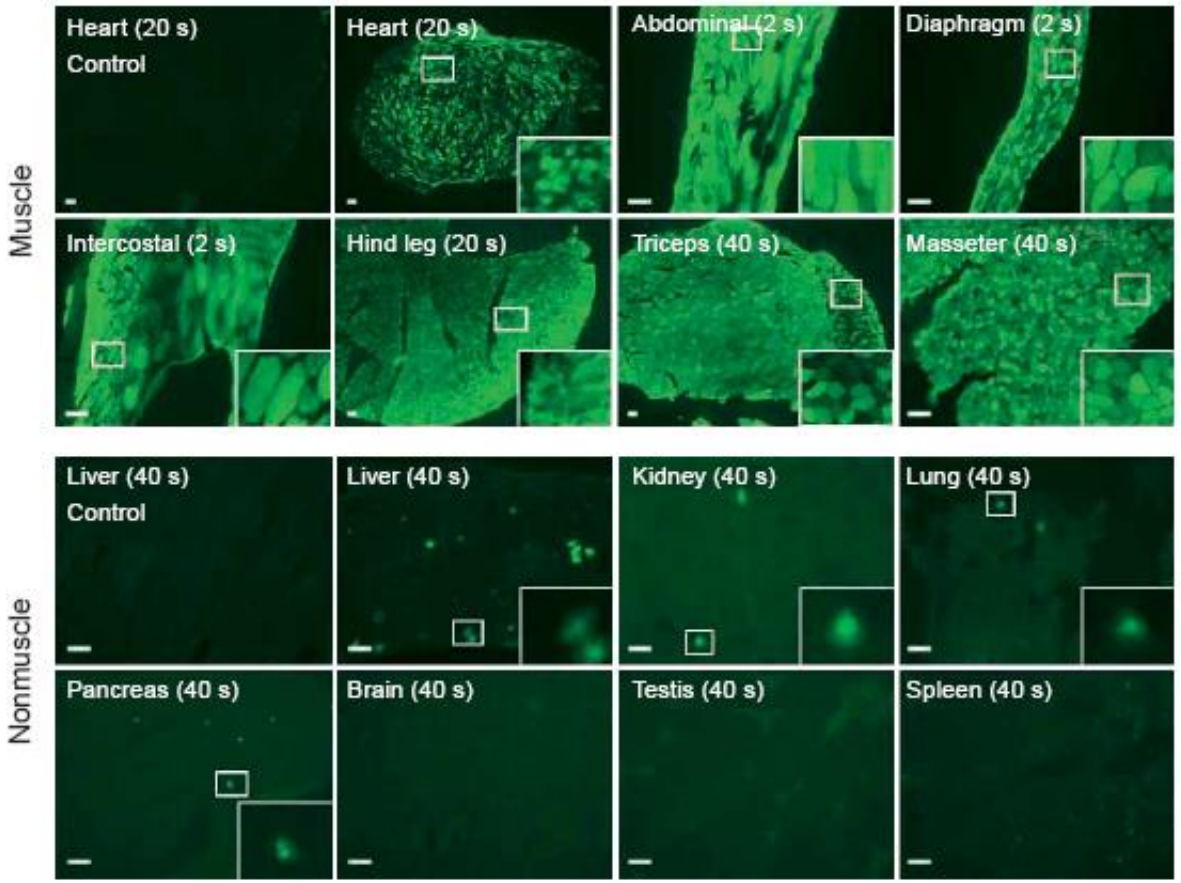
Target/parameter	*17 dpi*		*24 dpi*		*30 dpi*	
	+GFP	*+CNTF*	*+GFP*	*+CNTF*	*+GFP*	*+CNTF*
Ant tibialis muscle						
Latency (ms)	4.1 ± 0.3	4.1 ± 0.6	2.6 ± 0.2	2.2 ± 0.2	1.9 ± 0.1	1.9 ± 0.2
CMAP (mV)	3.8 ± 1.9	4.3 ± 1.6	7.6 ± 1.7	12.4 ± 1.6	14.7 ± 1.3	20.5 ± 1.7*
Plantar muscle						
Latency (ms)	11.2 ± 1.0	11.3 ± 0.9	5.3 ± 0.6	5.0 ± 0.4	3.9 ± 0.3	3.8 ± 0.2
CMAP (mV)	0.06 ± 0.06	0.07 ± 0.05	0.56 ± 0.17	0.89 ± 0.37	1.3 ± 0.4	1.9 ± 0.5
Nociception						
Pinprick score	0.5 ± 0.5	0.7 ± 0.5	2.2 ± 0.3	2.5 ± 0.5	4.5 ± 1.5	5.5 ± 0.5

Abbreviations: Ant, anterior; CMAP, compound muscle action potential; dpi, days after injury.
*$P<0.05$ vs +GFP.
$n=4$ per group.
Data are expressed as mean ± s.e.m.

Gene Therapy (2011) 18, 622–630

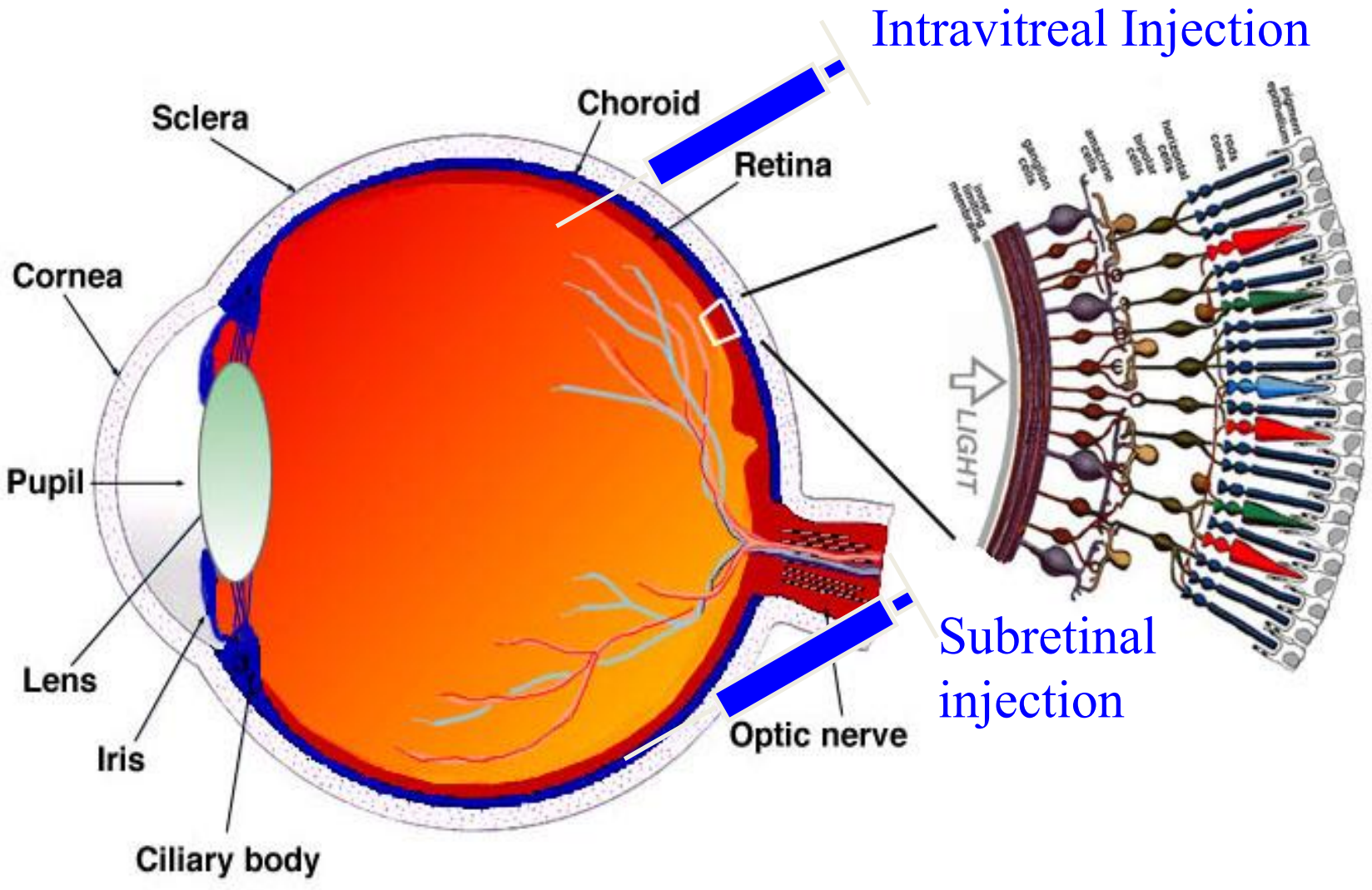
AAV for diseases affecting muscle



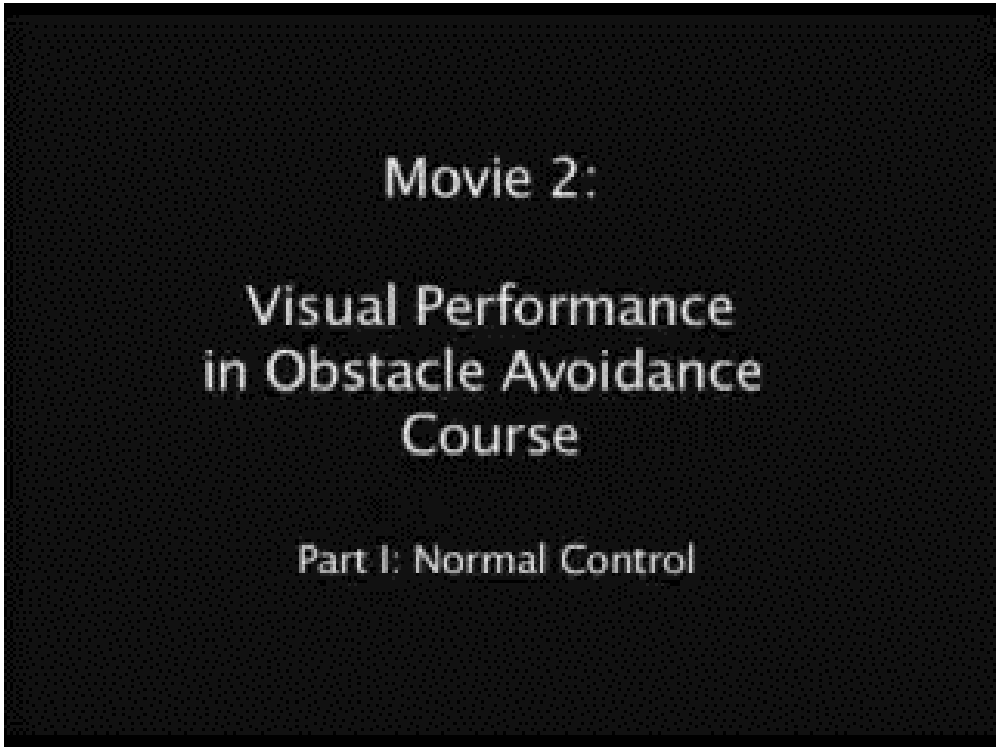


Wang et al, Nature Biotechnology, (2005) 23(3):321-328

AAVs for diseases affecting eye



Scotopic: Visió baixa lluminositat
Achromatopsia: bastons bé. Veuen amb poca llum
cons afectats: no color, no veuen amb molta llum



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FDA News Release

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

Luxturna is the first gene therapy approved in the U.S. to target a disease caused by mutations in a specific gene

Luxturna is approved for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy that leads to vision loss and may cause complete blindness in certain patients.

- Pfizer has dosed the first patient in a trial of a DMD gene therapy acquired as part of its $700 million takeover of Bamboo Therapeutics in 2016.
- Roche has just acquired Sparks Therapeutics for $4.300 miilion

Teràpia Gènica amb Vectors Adenoassociats

TAKE HOME MESSAGE

- Gene therapy allows specific and efficent control of the expression of specific gene(s)
- Gene therapy allows basic research as well as preclinical/clinical research for monogenic or monogenic diseases, but also to other diseases
- AAV vectors allows long-term safe gene expression with just one single administration
- Several diseases have been cured and more clinical trials are currently in progress

Viral Vector Production Unit (UPV)

UAB Universitat Autònoma de Barcelona

UABCEI CAMPUS D'EXCEL·LÈNCIA INTERNACIONAL

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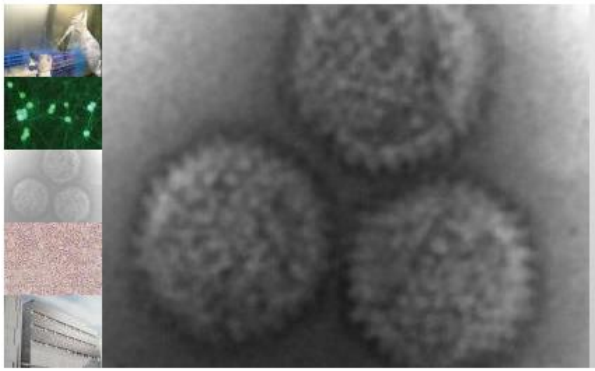
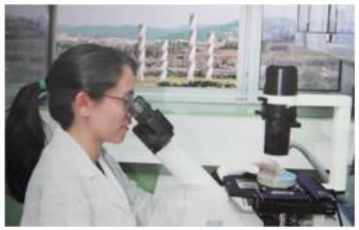


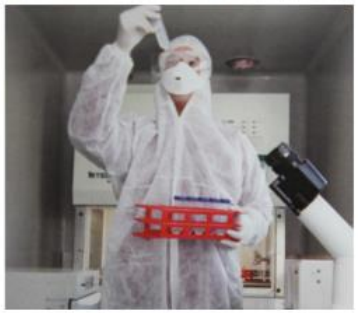
UPV produces recombinant adenoviruses: human and canine

The **Viral Vector Production Unit (UPV)** currently produces several adenovirus (human and canine) and adeno-associated virus (AAV) serotypes.

Viral vectors are widely used tools for gene transfer and gene expression. Their use is an attractive choice given their high transduction efficiency, and the ease and flexibility to genetically express or inhibit one gene or a combination of genes in specific areas and periods of time, while avoiding compensation phenomena or other drawbacks associated with animal models. Despite the availability of standardized procedures for their application in both in vitro and in vivo, and their low risk level when used in a controlled setting, the production of viral vectors requires the application of specialized techniques, access to expensive equipment and biological safety laboratories.

UPV is a technological platform at the Universitat Autònoma de Barcelona. It has Biological Safety Level 2 and 3 facilities and it is staffed by experienced and highly qualified personnel. Since its opening in 2003 it has been dedicated to the design, development, production and purification of more than 400 viral vectors for basic research and gene therapy pre-clinical studies for both public and private research laboratories.





News

Contact

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web site:
www.viralvector.eu