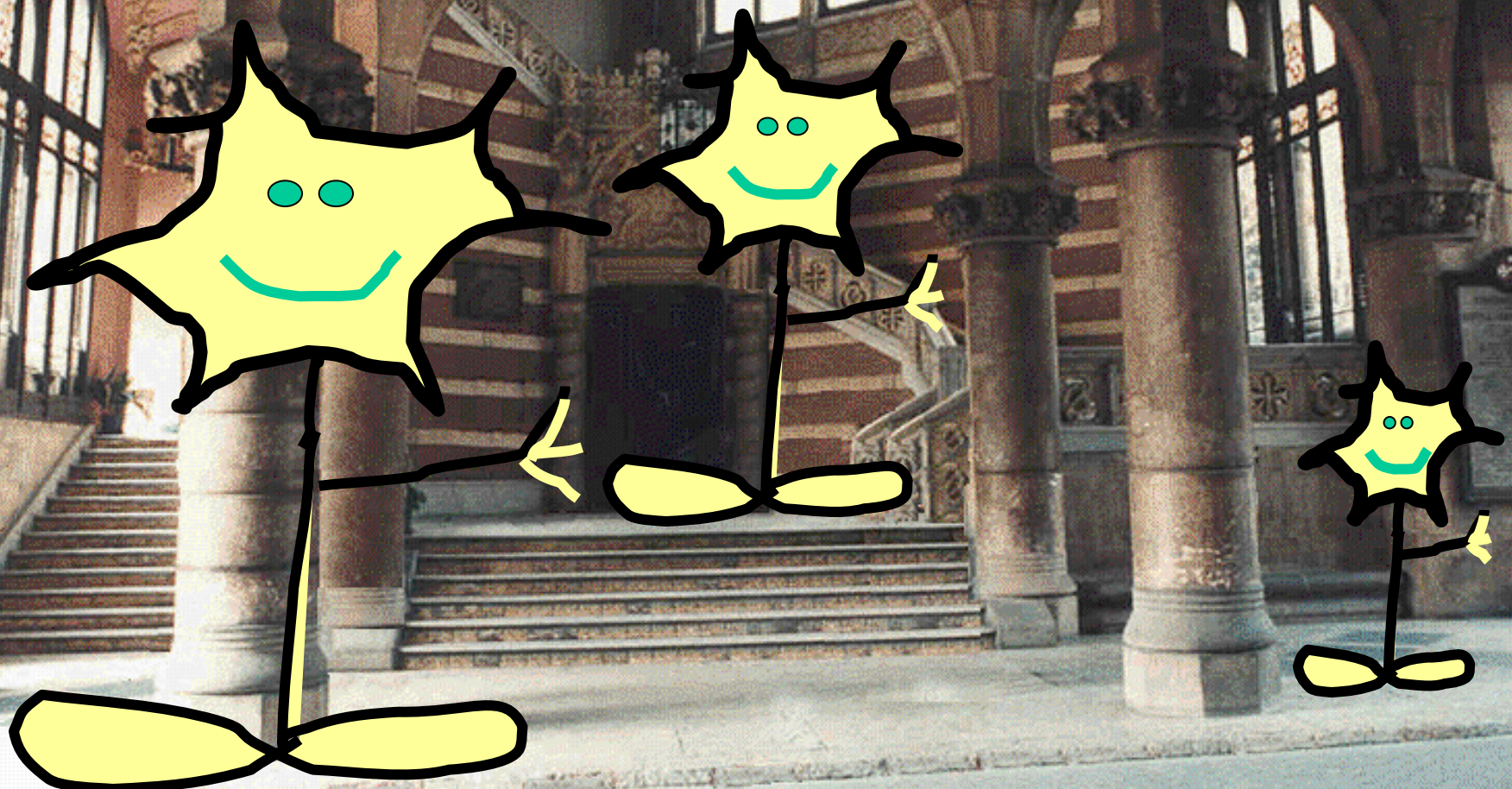


Atrofia muscular espinal

Presente y futuro de la investigación



Puesta al día de la AME

- Introducción
- Genética molecular: gen determinante y modificador
- Estrategias terapéuticas
- Consideraciones para ensayos clínicos

Conocimiento de la AME en los últimos 150 años



Descripción de la enfermedad

1850-1890

Diagnóstico clínico-
Clasificación

1950-80

Diagnóstico genético 1990-1999

Investigación
translacional

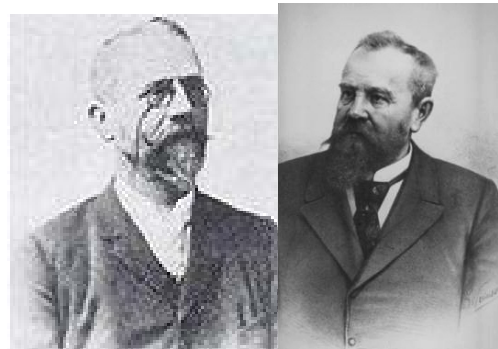
2000 →

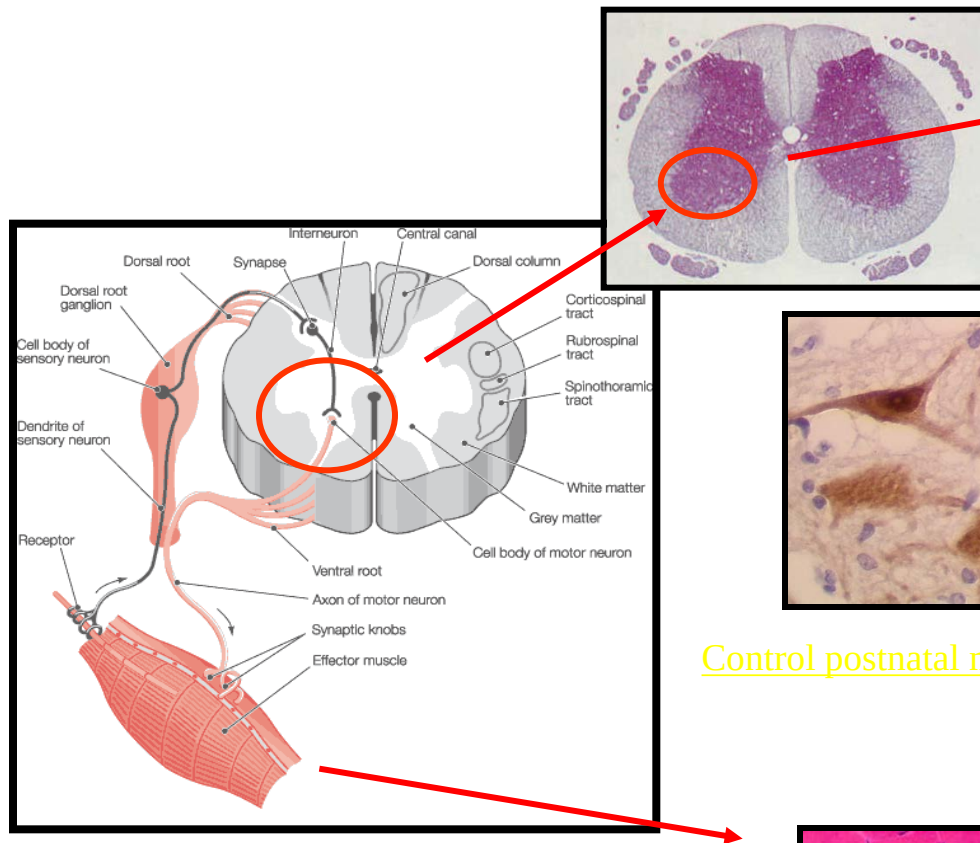
Protocolos de
tratamiento

???



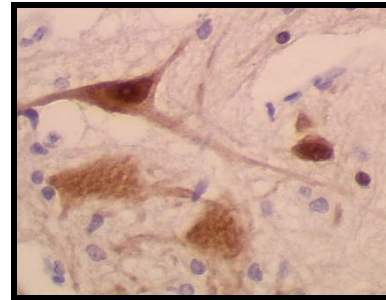
Descubrimiento
del gen en
1995!



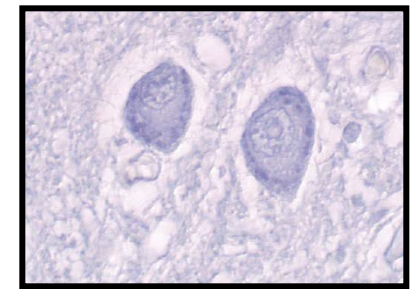


Anterior Horn of the
Spinal Cord

Spinal Cord Biopsy

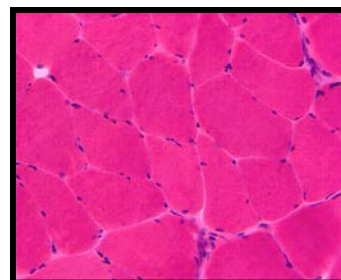


Control postnatal motor neurons

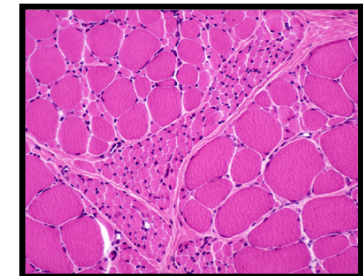


SMA postnatal motor neurons

Muscle Biopsy



Control postnatal muscle



SMA postnatal muscle

Soler et al., Brain, 2002

MOTOR MILESTONES IN SMA



NEVER SIT



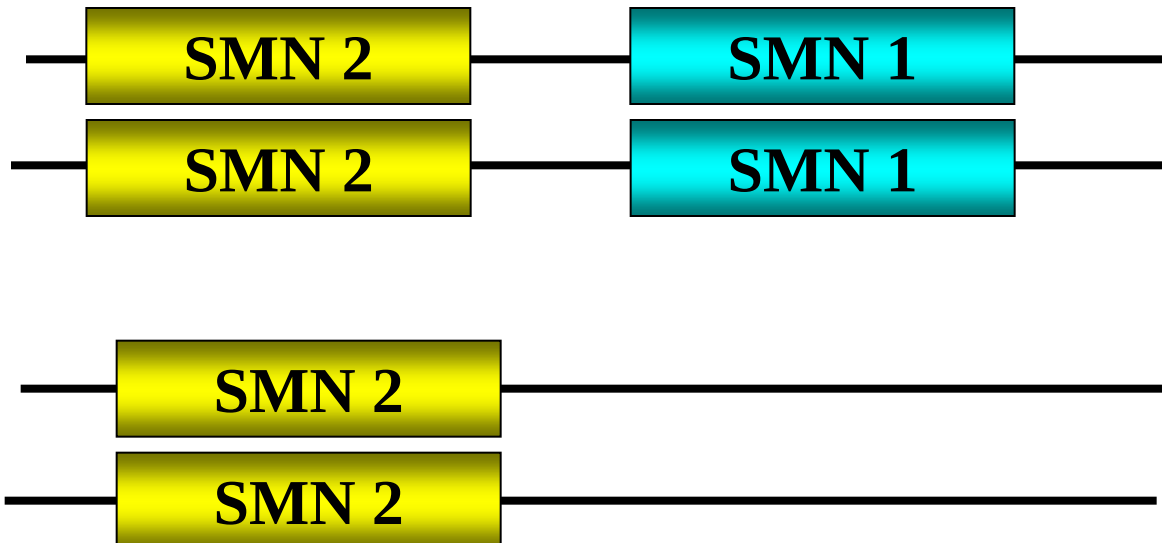
NEVER WALK



LOSS OF WALKING

Incidence 1/6000 newborns

Loss or mutations in Survival Motor Neuron 1 (SMN1)



SMA classification



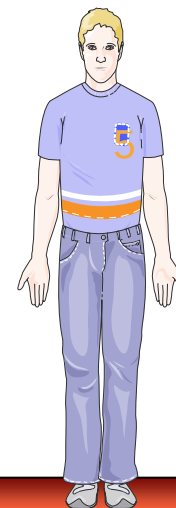
TIPO IV Adult

TIPO III - Kugelberg -Welander

TIPO II - Intermediate

TIPO I - Werdnig-Hoffmann

TIPO 0 Congenital



Birth

18 months

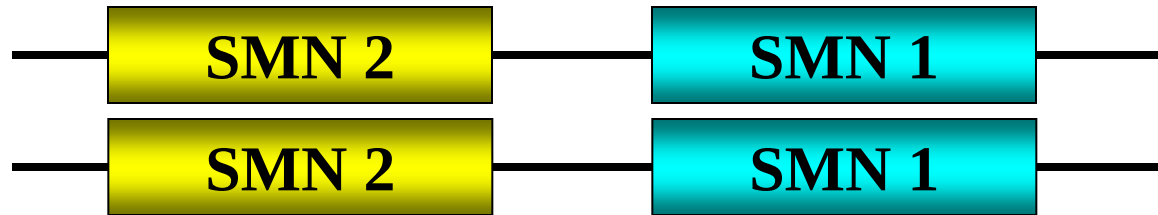
6months

2-3 years

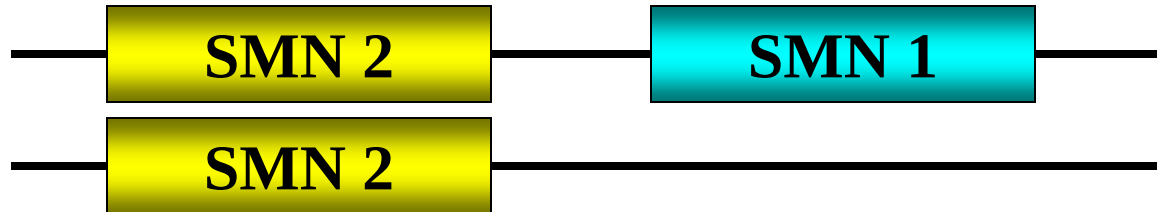
ADULT LIFE

POBLACION

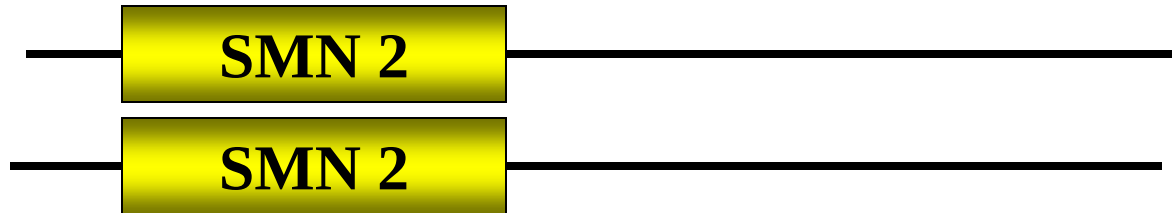
90%



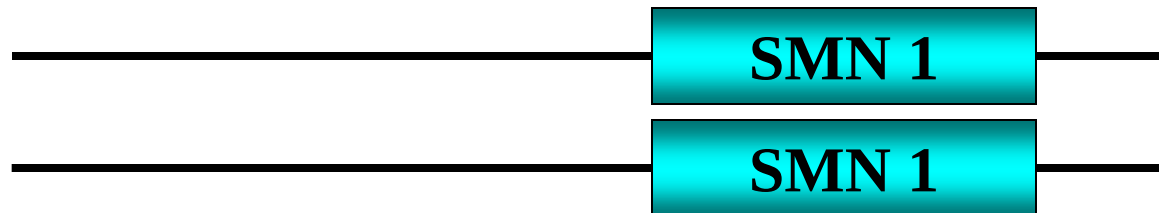
2%



AME



5-10%

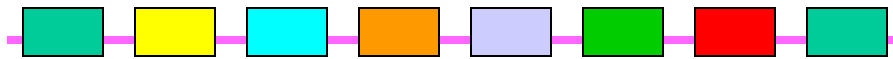
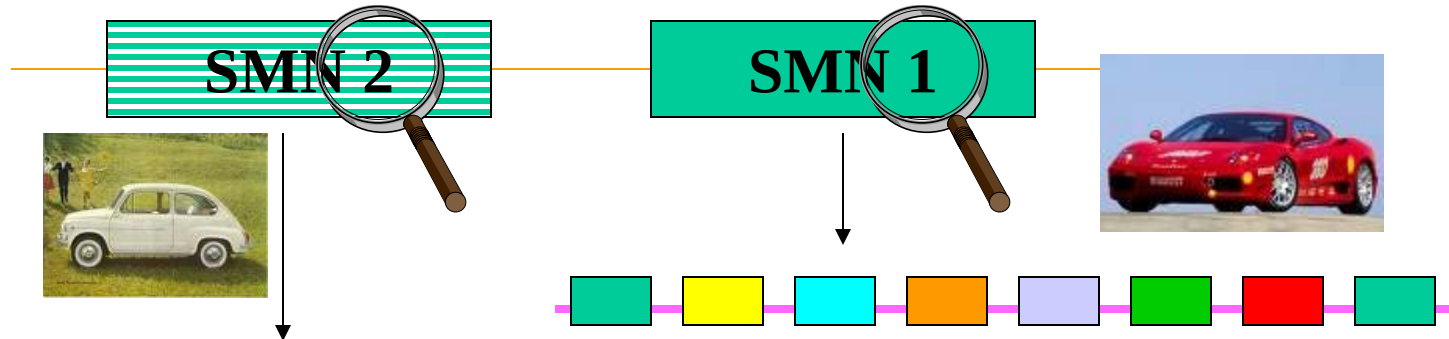


0%

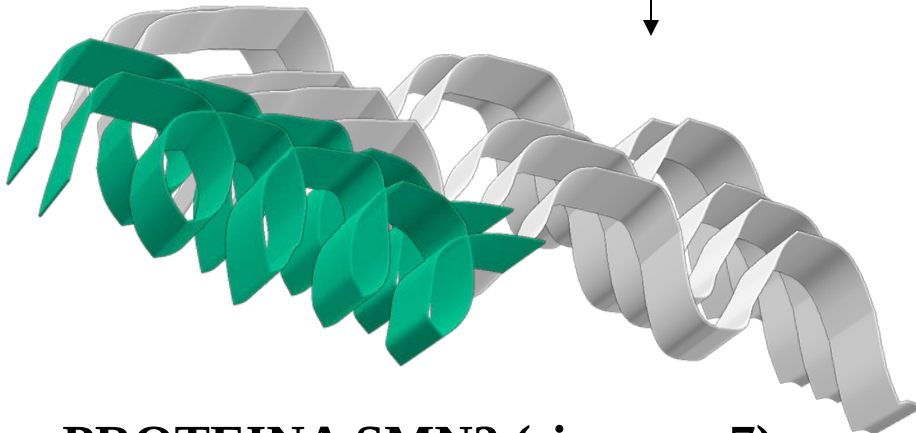


SMN = SURVIVAL MOTOR NEURON

ADN

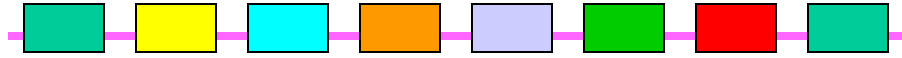


**ARN
mensajero**

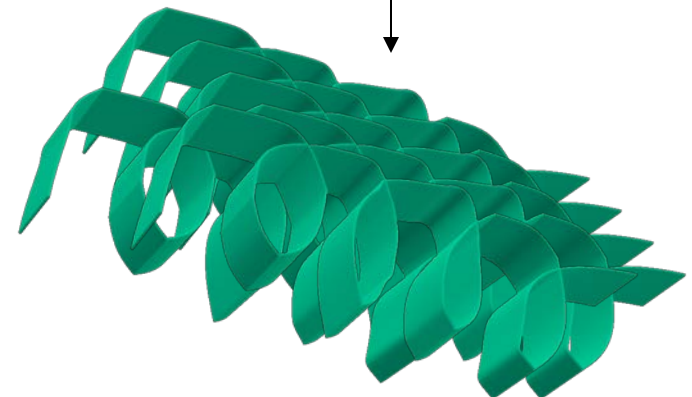


PROTEINA SMN2 (sin exon 7)

inestable y parcialmente funcionante



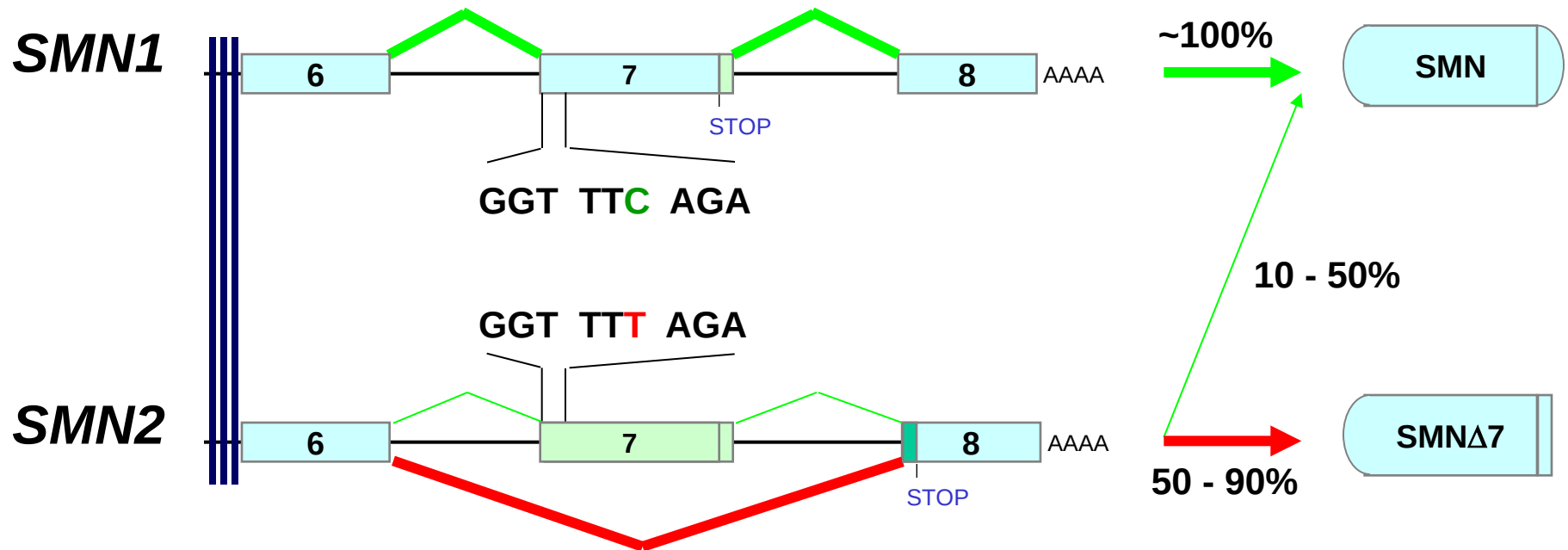
EXONES



PROTEINA SMN1 (completa)

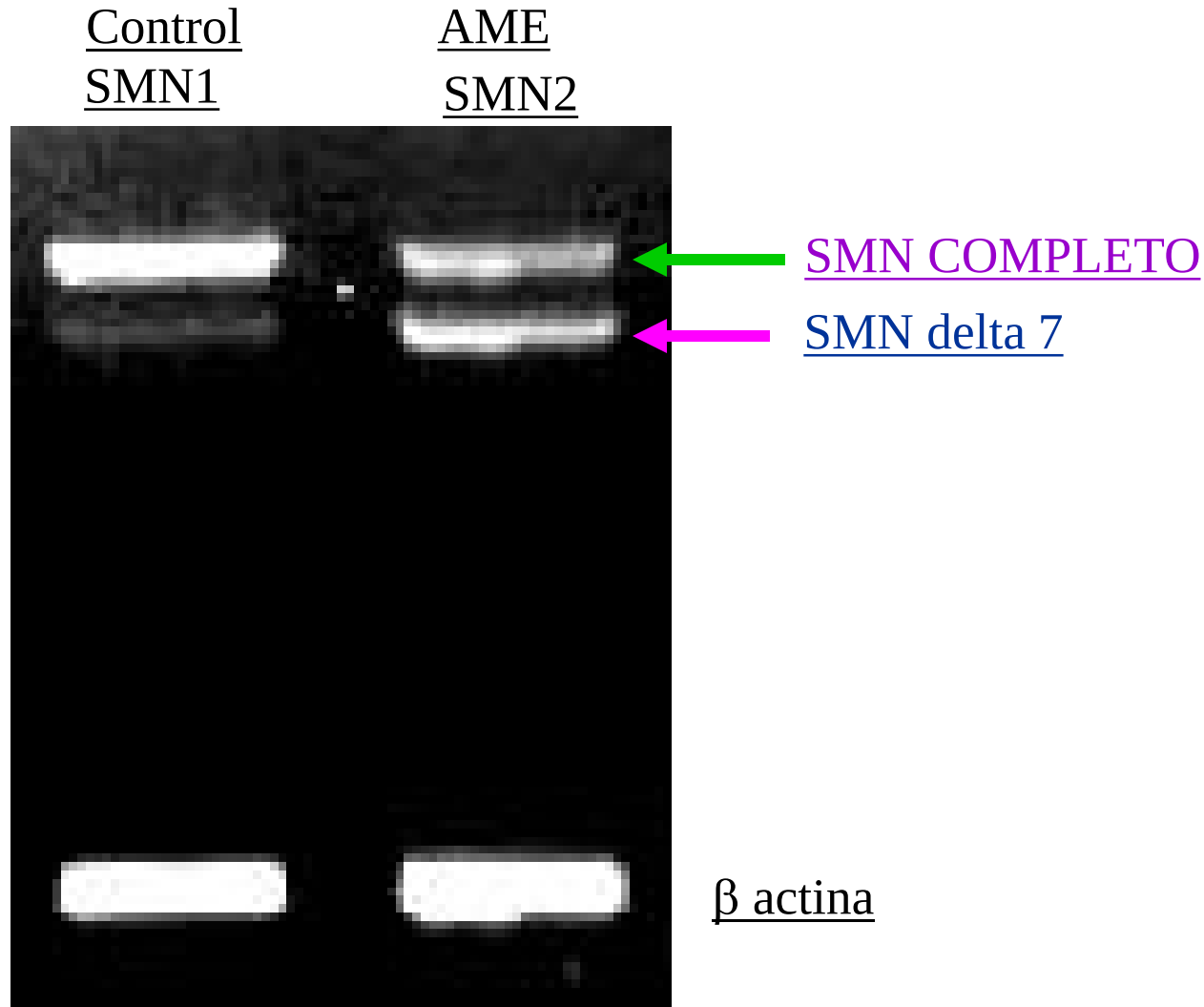
totalmente funcionante

Un pequeño cambio en la secuencia hace que se excluya el exon 7 de *SMN2*



TTC oTTT codifican para Fenilalanina

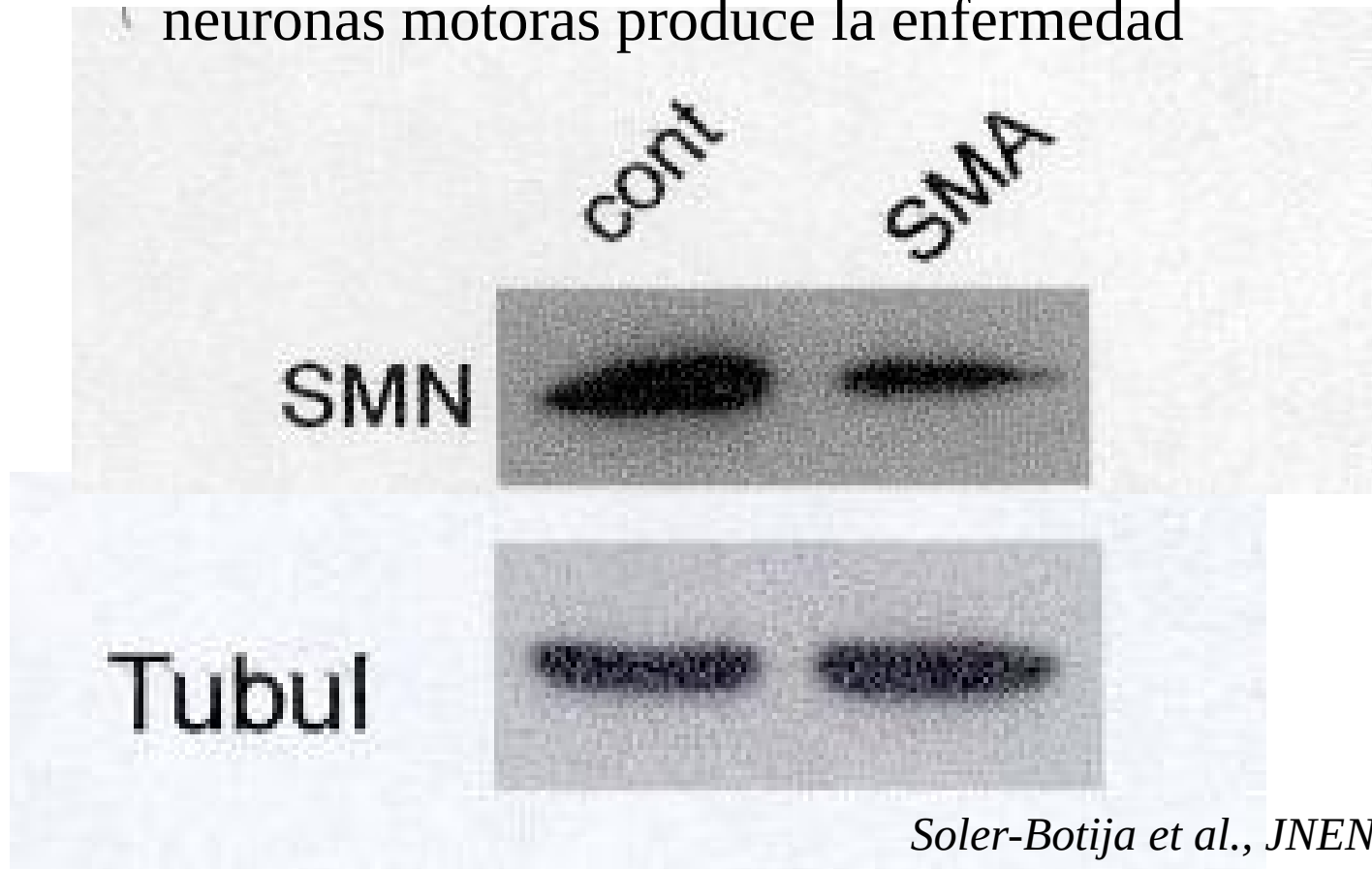
RNA MEDULA ESPINAL



Soler-Botija et al., JNEN, 2005

PROTEINA MEDULA ESPINAL

Una disminución de la cantidad de proteína SMN en las neuronas motoras produce la enfermedad



Soler-Botija et al., JNEN, 2005

El gen SMN2 es capaz de producir algo de proteína SMN funcional pero no alcanza para evitar la enfermedad



El gen determinante SMN1

***Las mutaciones en el gen SMN1
(deleciones, puntuales) están
presentes en los afectados de la
enfermedad***

SMA in Spain

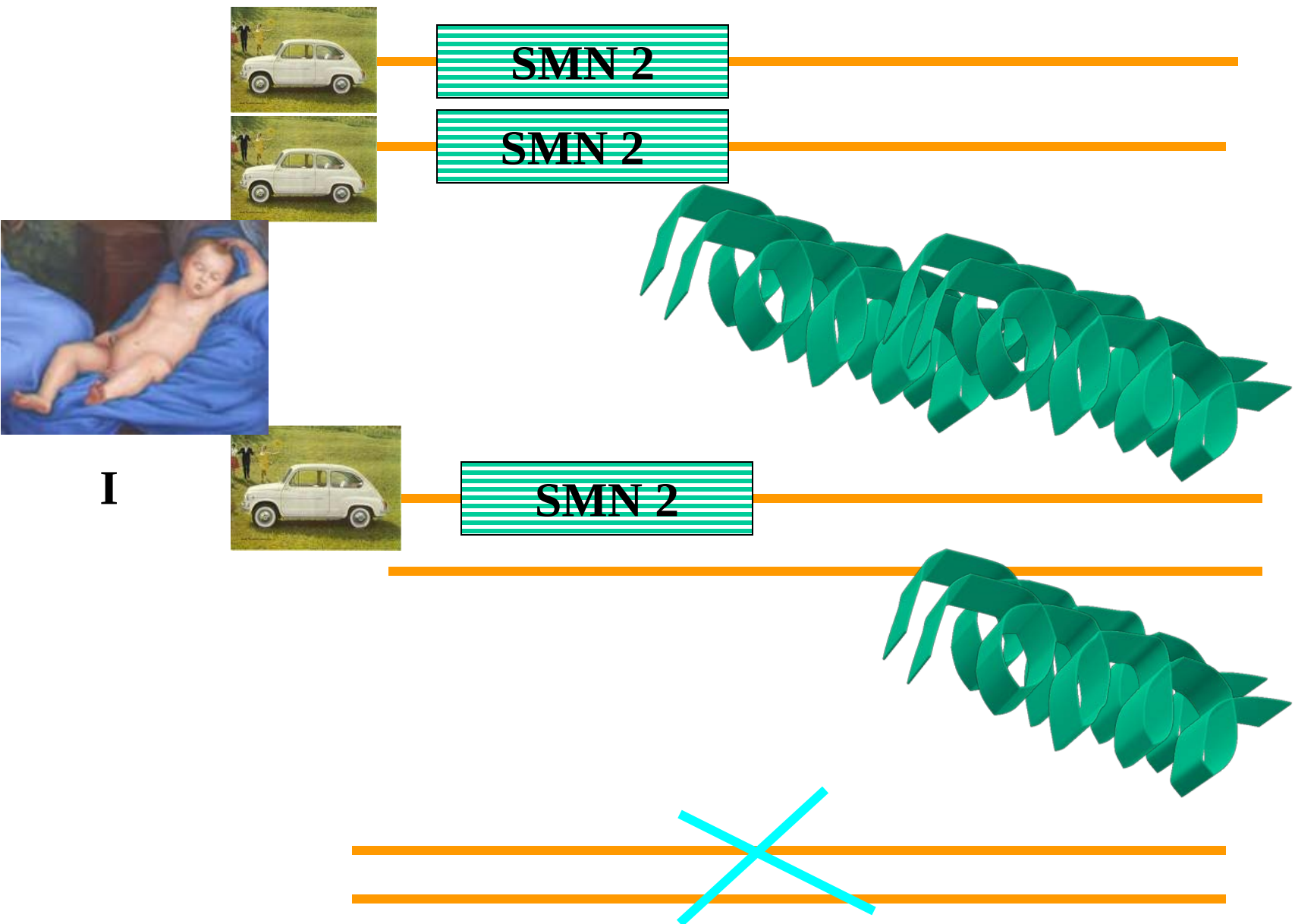
- 671 (90%) homozygous absence SMN1exon 7 and 8
- 37 (5%) homozygous absence SMN1exon 7 only (hybrid genes)
- 14 (1.9%) c.399_402delAGAG mutation in exon 3
 - 12 One SMN1 copy / 2 consanguineous
- 14 (1.9%) One SMN1 copy + mutations in SMN1 exons
- 9 (1.2%) One SMN1 copy +unknown mutation
- *A total of 54 different point mutations have been described in 120 unrelated patients all over the world*
- *25 missense, 18 frameshift, 6 splice-site, 5 non-sense*

(Alias et al., 2009)



El gen modificador SMN2

Todos los pacientes con AME tienen al menos una copia del gen SMN2 (cuya función no evita la aparición de la enfermedad), y cuanto más copias tiene un paciente, el fenotipo es en general menos grave.



Ningún paciente se ha descrito con ausencia de los dos genes SMN



II / III



SMN 2

SMN 2

SMN 2



SMN 2

SMN 2

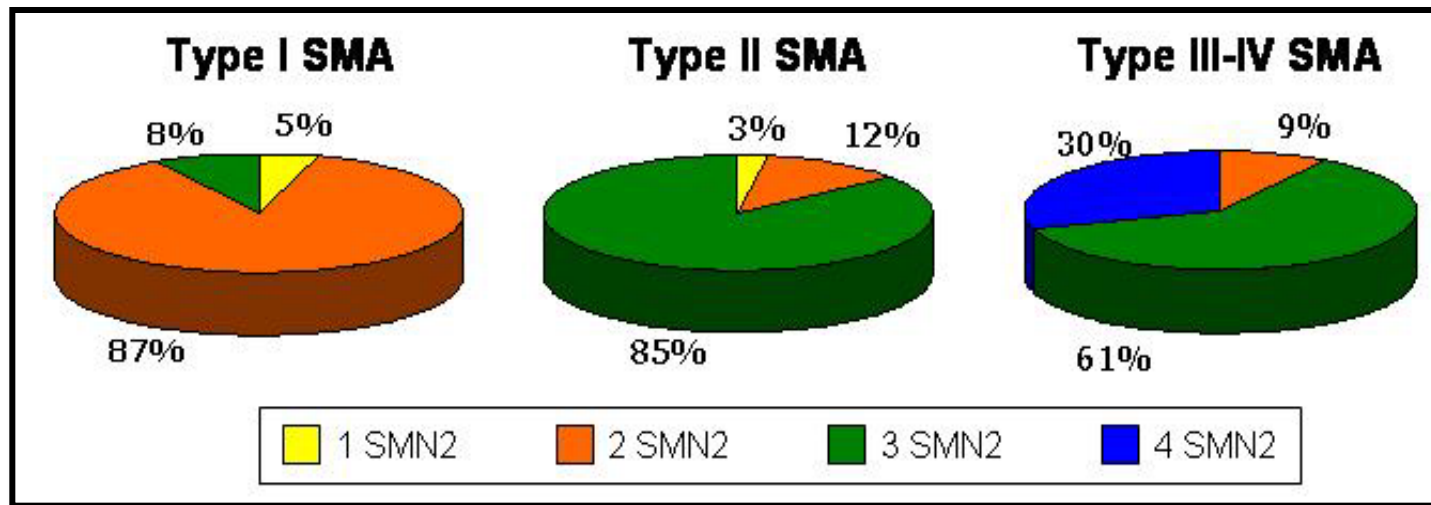
SMN 2

SMN 2



Clasificación : fenotipo y nº de copias SMN2

	1 SMN2	2 SMN2	3 SMN2	4 SMN2	
Type I SMA	12	220	19	0	251
Type II SMA	4	18	132	0	154
Type III-IV SMA	0	10	69	34	113
	16	248	220	34	518

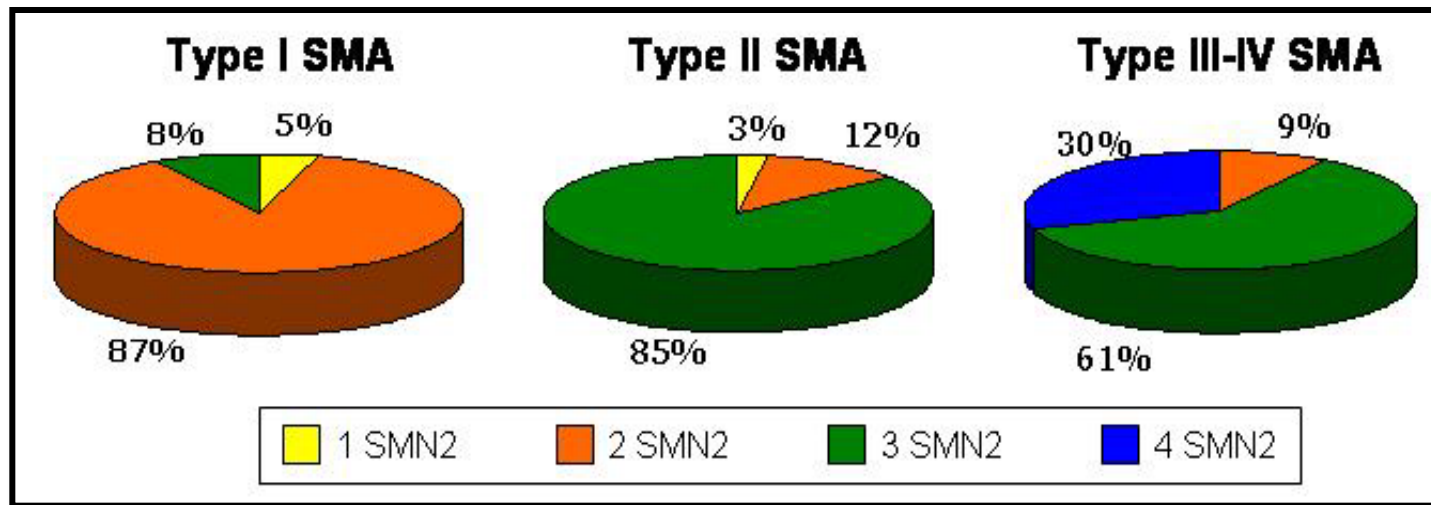


- Existe una correlación inversa entre el número de copias SMN2 y la gravedad de la enfermedad, aunque no es absoluta.

Bernal et al., en preparación

Clasificación : fenotipo y nº de copias SMN2

	1 SMN2	2 SMN2	3 SMN2	4 SMN2	
Type I SMA	12	220	19	0	251
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Type III-IV SMA	0	10	69	34	113
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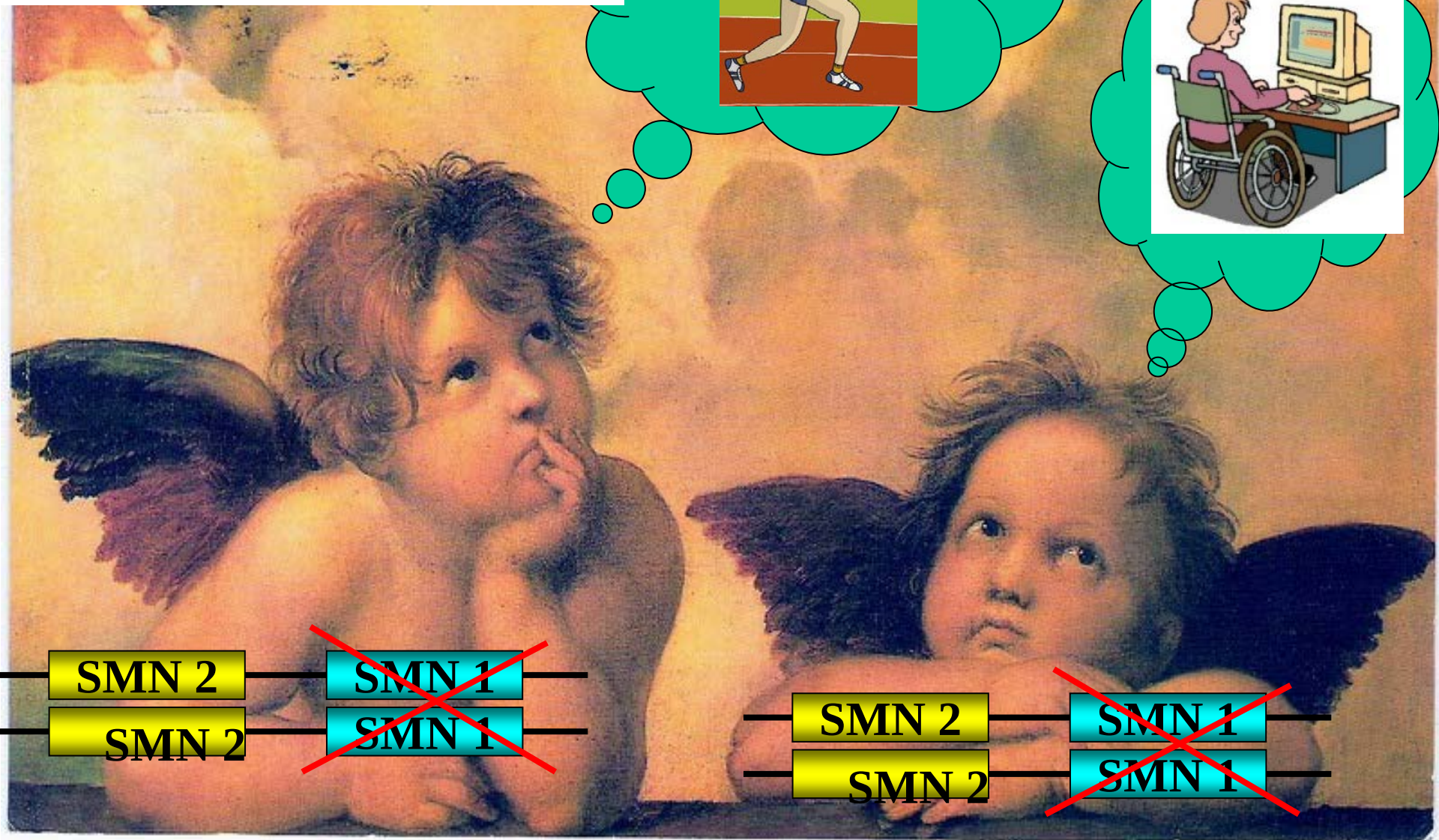


- Existe una correlación inversa entre el número de copias SMN2 y la gravedad de la enfermedad, aunque no es absoluta.

Bernal et al., en preparación

I. Cuscó
M. J. Barceló
R. Rojas-García
I. Illa
J. Gámez
C. Cervera
A. Pou
G. Izquierdo
M. Baiget
E. F. Tizzano

**SMN2 copy number predicts acute
or chronic spinal muscular atrophy
but does not account for intrafamilial
variability in siblings**





Discordancias fenotípicas

***Pacientes graves (tipo I) con 3
copias de SMN2***

***Pacientes moderados-leves (tipo
II-III) con 2 copias de SMN2***

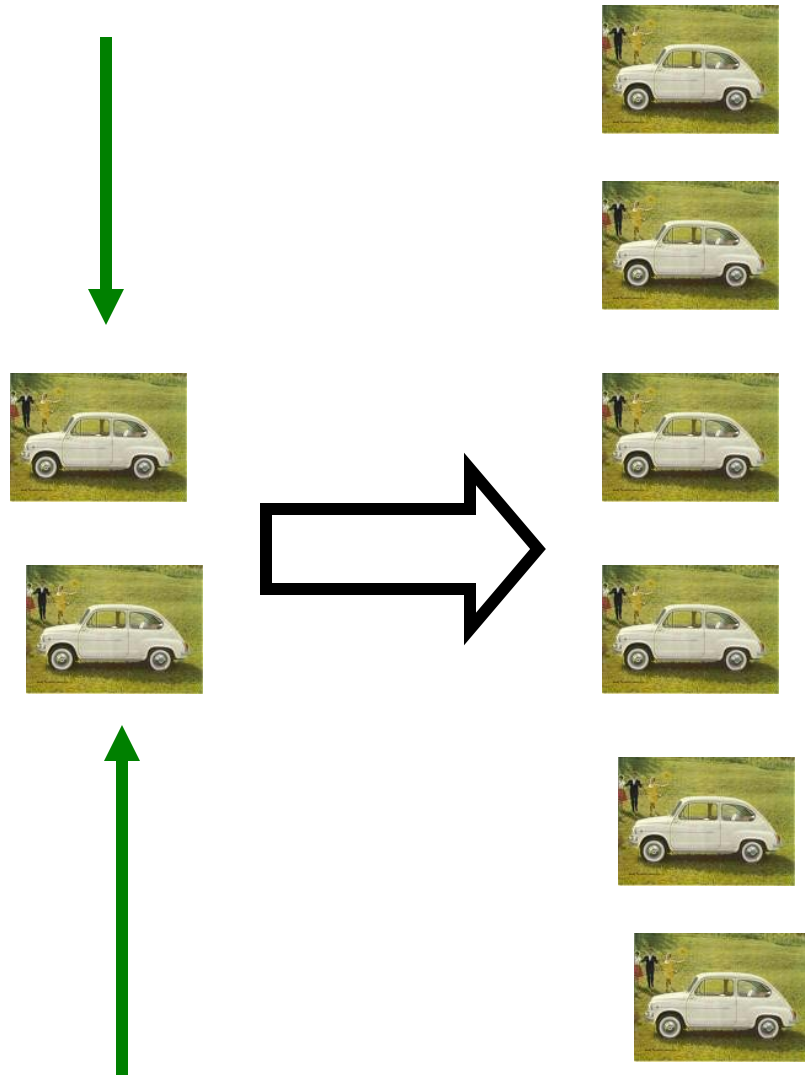
***Hermanos haploidenticos pero
con evolución diferente***

Características de la AME

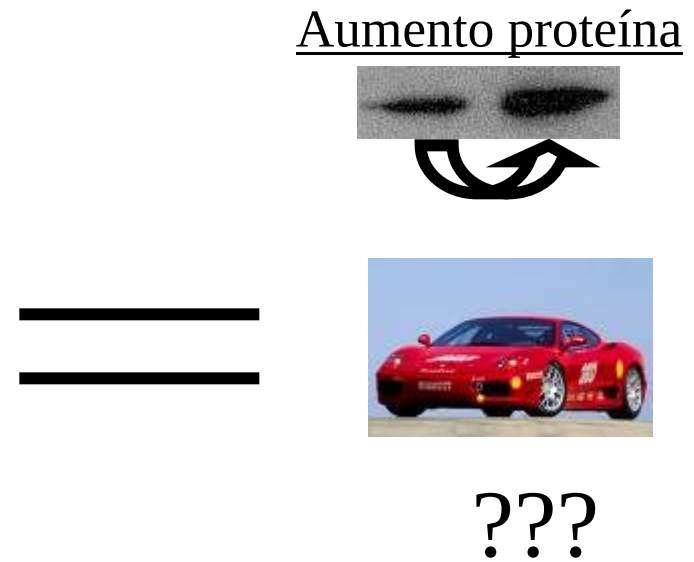
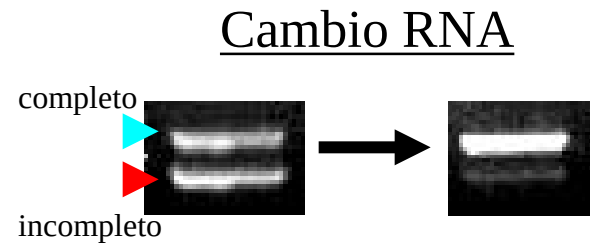
- Es una enfermedad de dos genes, la mutación en el SMN1 la determina y el número de copias de SMN2 modifica el fenotipo.
- La disminución de la proteína SMN es la causa de la enfermedad que parece iniciarse en la neurona motora y/o unión neuromuscular.
- La presencia y estudio del gen SMN2 puede servir de herramienta terapéutica.



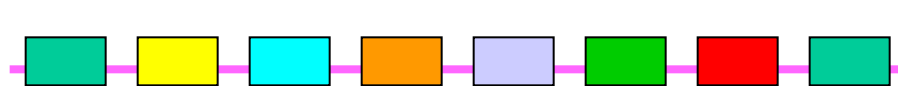
TERAPIA FARMACOLOGICA



TERAPIA FARMACOLOGICA



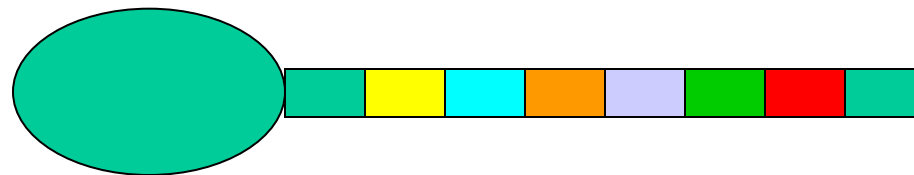
SMN2
upregulation



VPA, Phenylbutyrate, Hydroxyurea, , Salbutamol

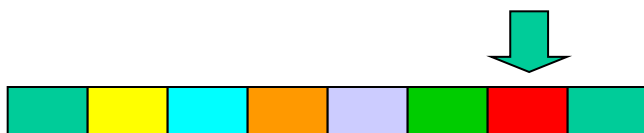
Increasing
RNA

Capping



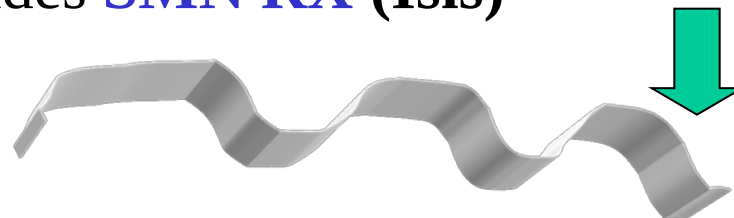
RG3039 (Repligen Corporation).

Including exon 7 in SMN2 transcripts.



Antisense oligonucleotides SMN RX (Isis)

SMN protein stabilization



Readthrough ALB-111
(NINDS)

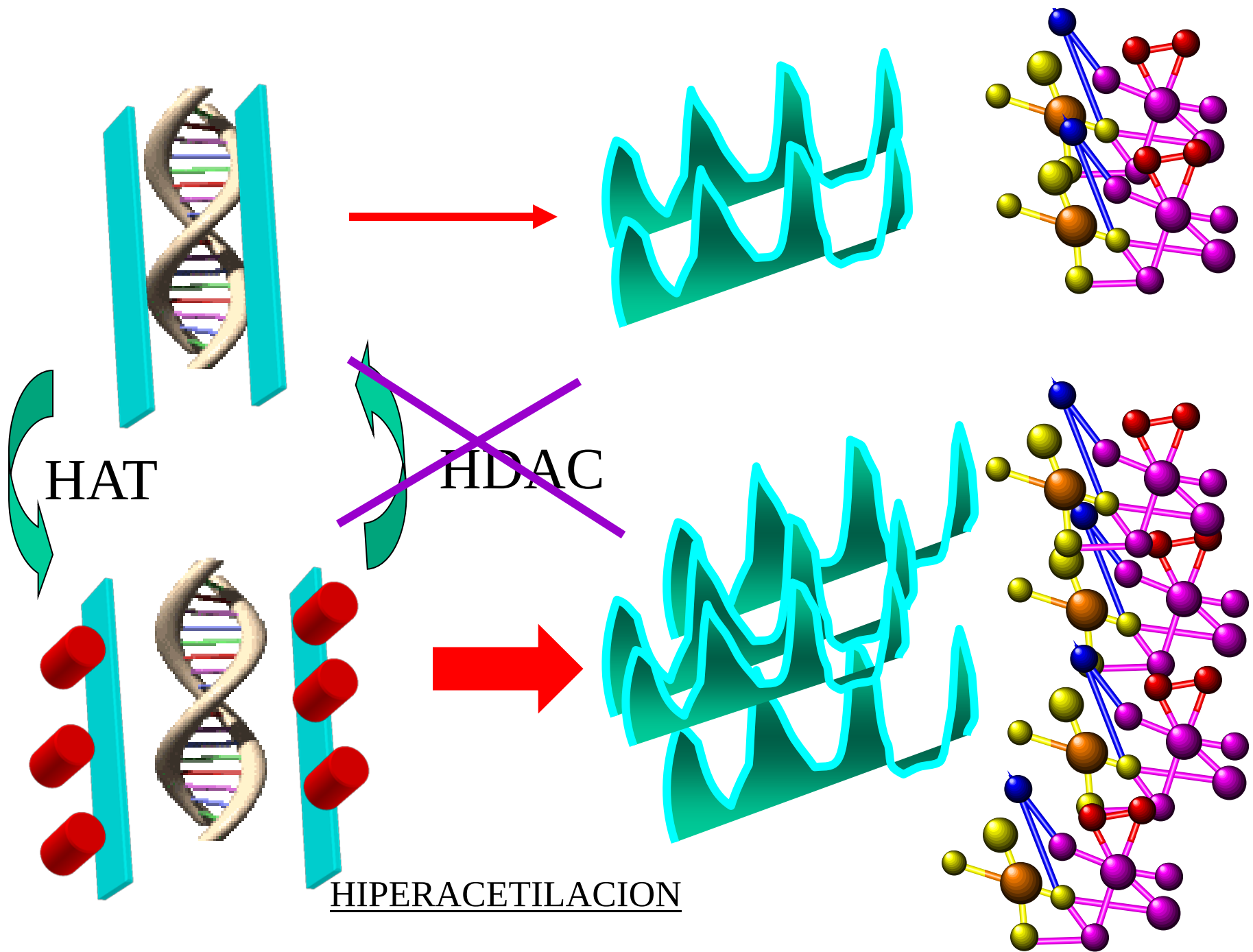
FARMACOLOGICA



Fármaco que active SMN2

Neuroprotección

Proteger y estimular músculo



PBA has been investigated in a double-blind placebo-controlled trial in 107 children with type II SMA. VPA–carnitine has been administered to 42 type II SMA children in a multi-centre phase II trial. A double-blind placebo-controlled trial with HU in 28 type II SMA and 29 type III SMA patients has recently been completed. **Results from these three clinical trials have not revealed a clear benefit of these drugs for the patients.**

Valproic acid increases the SMN2 protein level: a well-known drug as a potential therapy for spinal muscular atrophy

L. Brichth^{1,2}, Y. Hofmann¹, E. Hahnen³, F. A. Siebzebruhl³, H. Raschke¹, I. Blumcke³, I. Y. Eyupoglu⁴ and B. Wirth^{1,2,*}

¹Institute of Human Genetics, University of Bonn, Wilhelmstrasse 31, 53111 Bonn, Germany, ²Institute of Human Genetics, University of Cologne, Kerpener Str. 34, 50931 Cologne, Germany, ³Institute of Neuropathology, University Erlangen-Nuremberg, Krankenhausstrasse 8-10, 91054 Erlangen, Germany and ⁴Department of Neurosurgery, University Erlangen-Nuremberg, Schwabachanlage 6, 91054 Erlangen, Germany

Received May 8, 2003; Revised and Accepted July 25, 2003

European Journal of Human Genetics (2004) 12, 59–65
© 2004 Nature Publishing Group All rights reserved 1018-4813/04 \$25.00
www.nature.com/ejhg

Phenylbutyrate increases SMN expression *in vitro*: relevance for treatment of spinal muscular atrophy

Catia Andreassi¹, Carla Angelozzi¹, Francesco D Tiziano¹, Tiziana Vitali¹, Eleonora De Vincenzi¹, Alma Boninsegna², Marcello Villanova³, Enrico Bertini⁴, Antonella Pini⁵, Giovanni Neri¹ and Christina Brahe^{*,1}

Hydroxyurea Enhances *SMN2* Gene Expression in Spinal Muscular Atrophy Cells

Susanna M. Grzeschik, PhD,¹ Madhuri Ganta, PhD,¹ Thomas W. Prior, PhD,² William D. Heavlin, PhD,³ and Ching H. Wang, MD, PhD¹

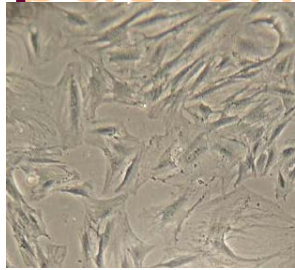
Downloaded from jmg.bmj.com on 2 June 2009

Short report

Salbutamol increases SMN mRNA and protein levels in spinal muscular atrophy cells

C Angelozzi, F Borgo, F D Tiziano, A Martella, G Neri, C Brahe

Tratamiento in vitro en células de ~~pacientes~~

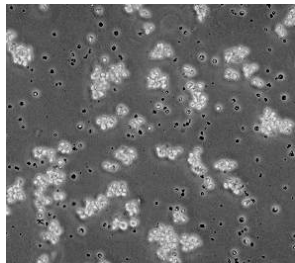
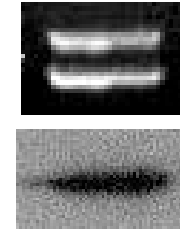


Fibroblastos

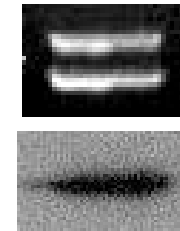
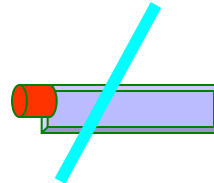
Responden



NO Responden



Linfoblastos



VARIABILIDAD INDIVIDUAL

Responden a uno si y a otro no

Algunos casos necesitan más dosis

Responden en una célula pero no en otra

Algunas casos necesitan dos fármacos

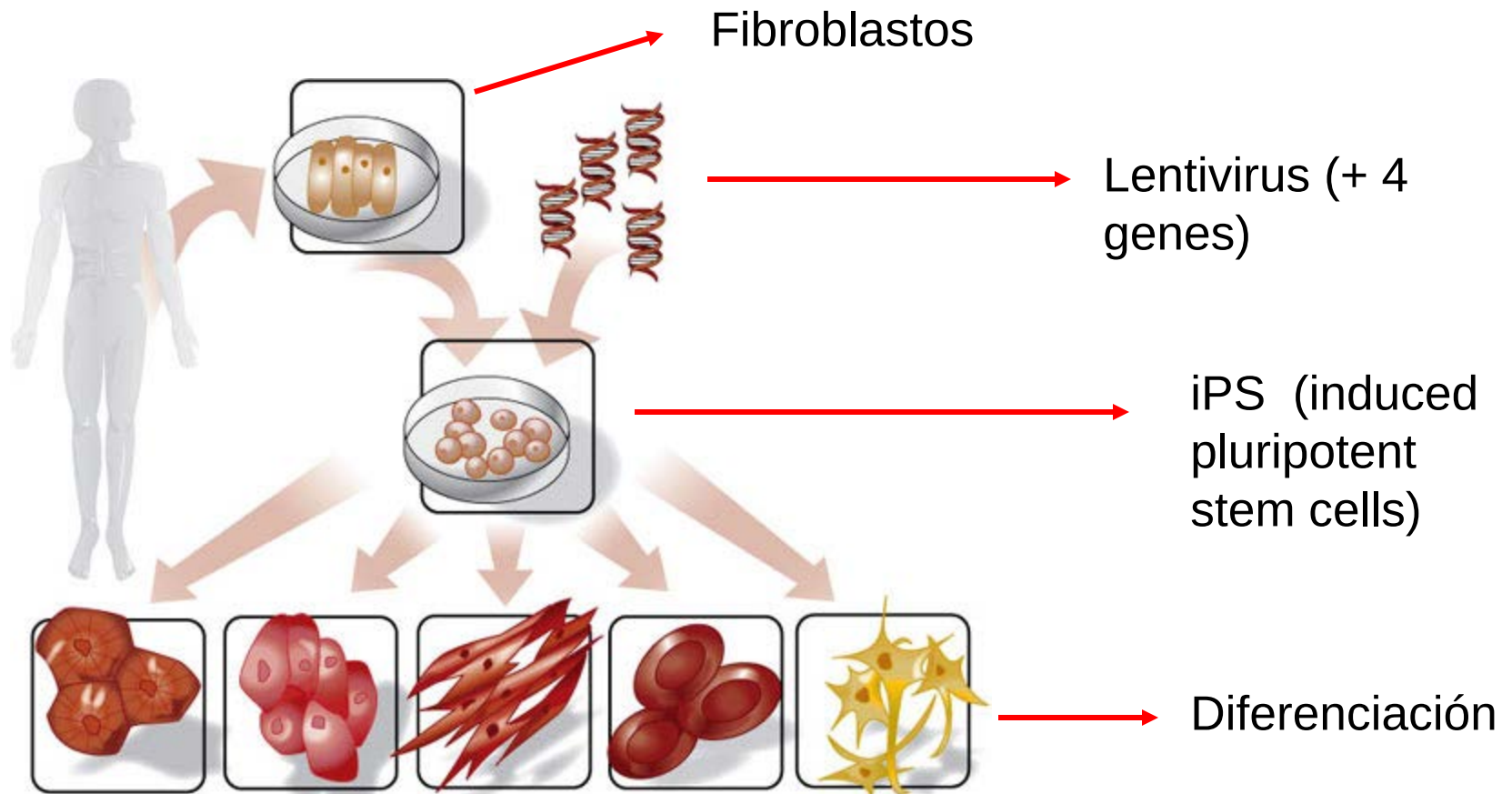
Hermanos responden diferente

Terapia personalizada

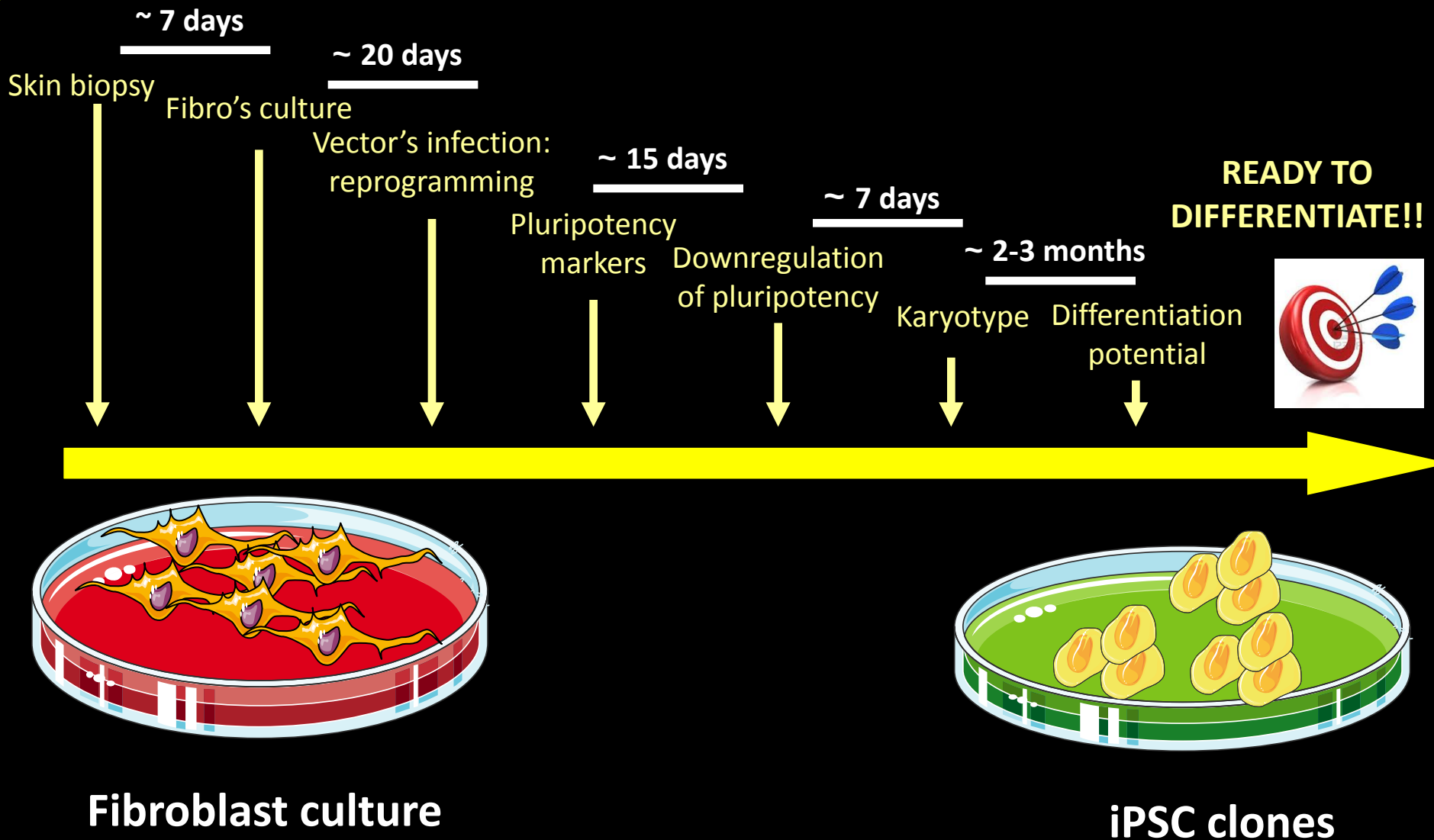
- Existen responders y no responders a la terapia farmacológica de incremento del SMN
- Hay diferencias intrapaciente según el tipo celular
- Estratificar los pacientes según la respuesta in vitro
- Necesidad de establecer modelos neuronales de pacientes

Induced pluripotent stem cells from a spinal muscular atrophy patient

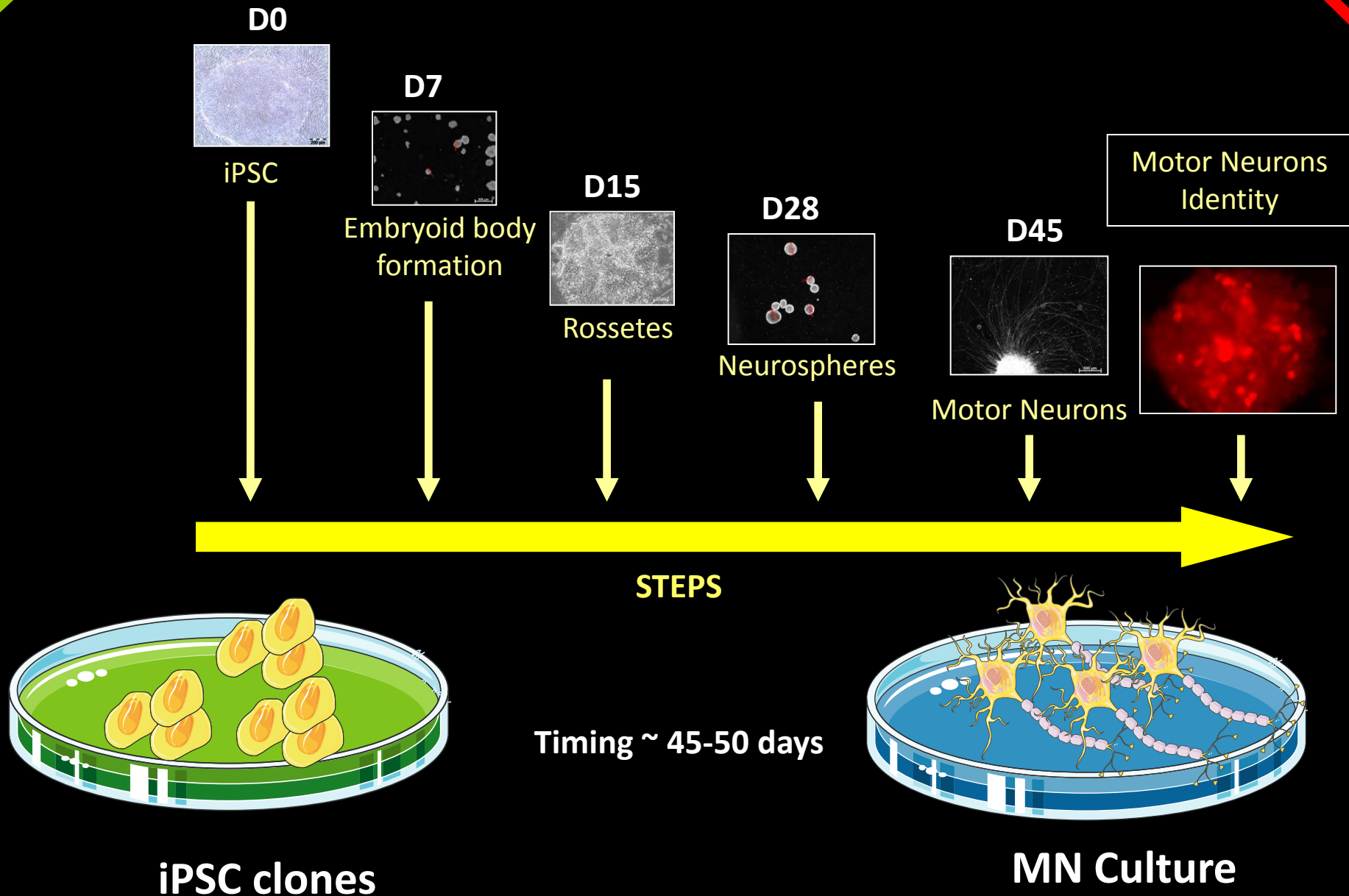
Allison D. Ebert^{1,2}, Junying Yu³, Ferrill F. Rose Jr⁴, Virginia B. Mattis⁴, Christian L. Lorson⁴, James A. Thomson^{2,3,5} & Clive N. Svendsen^{1,2,5,6}

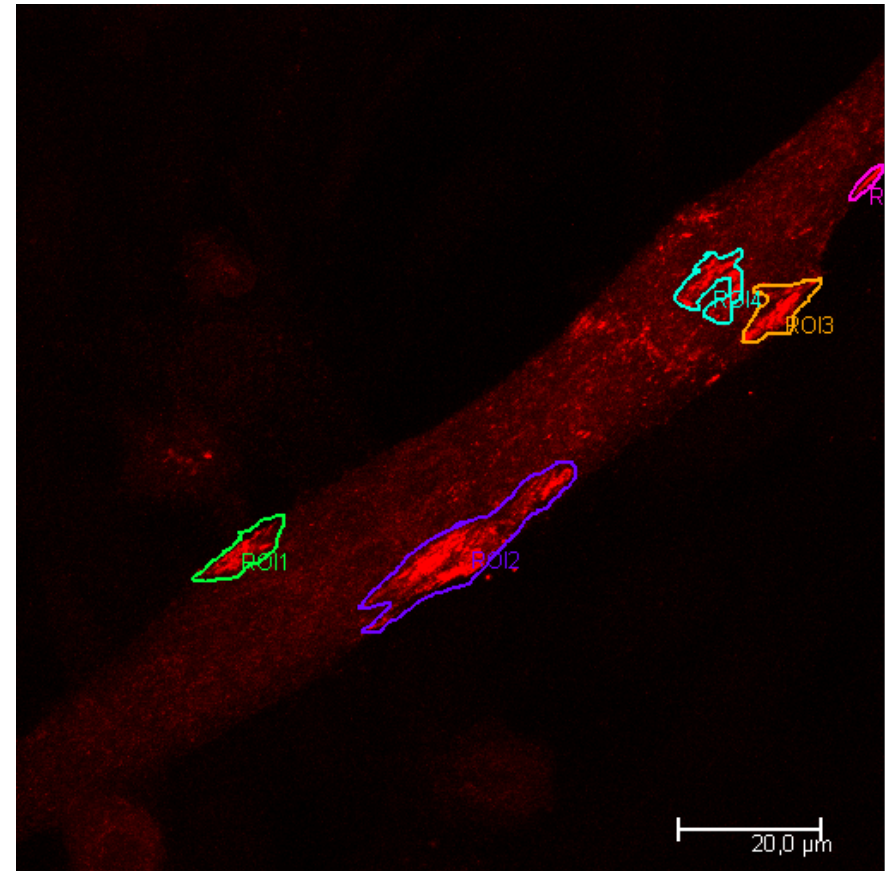
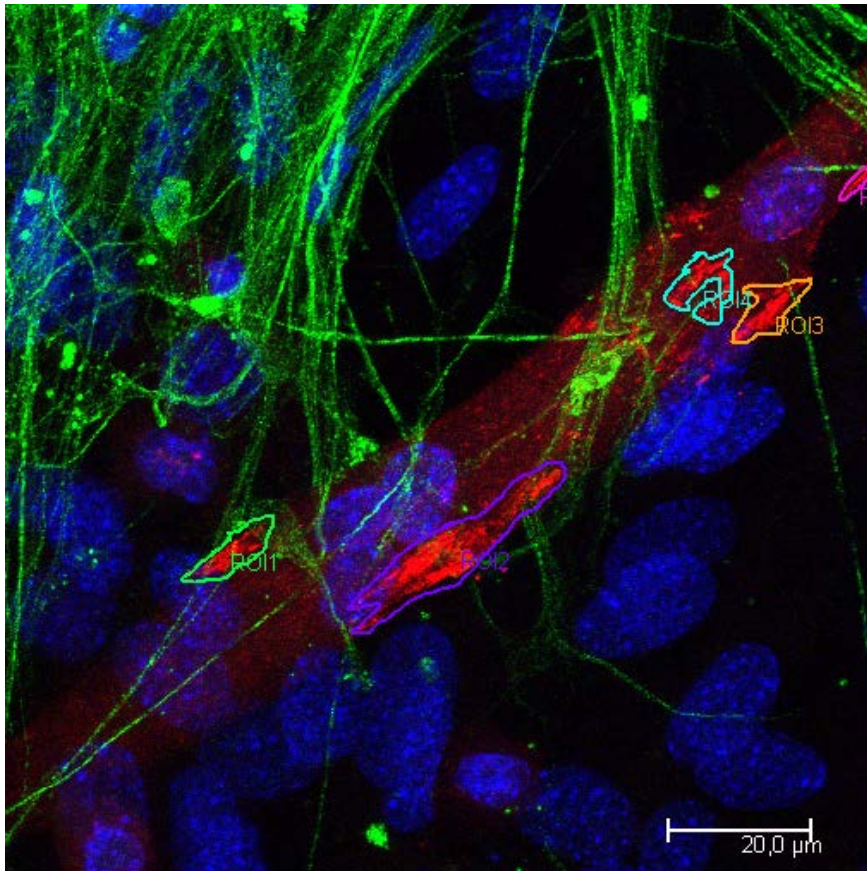


iPSC Generation SUMMARY



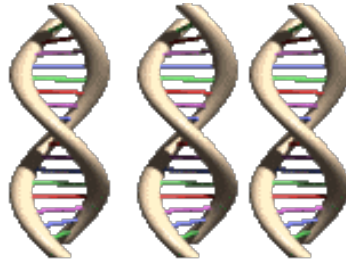
2. iPSC Differentiation SUMMARY





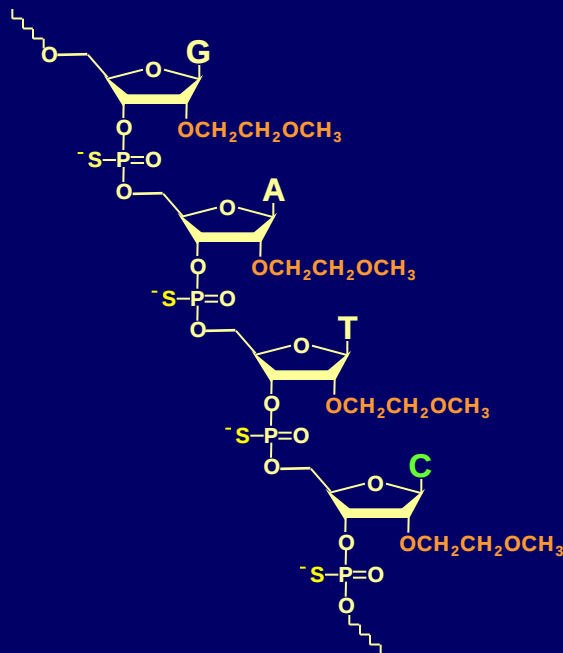
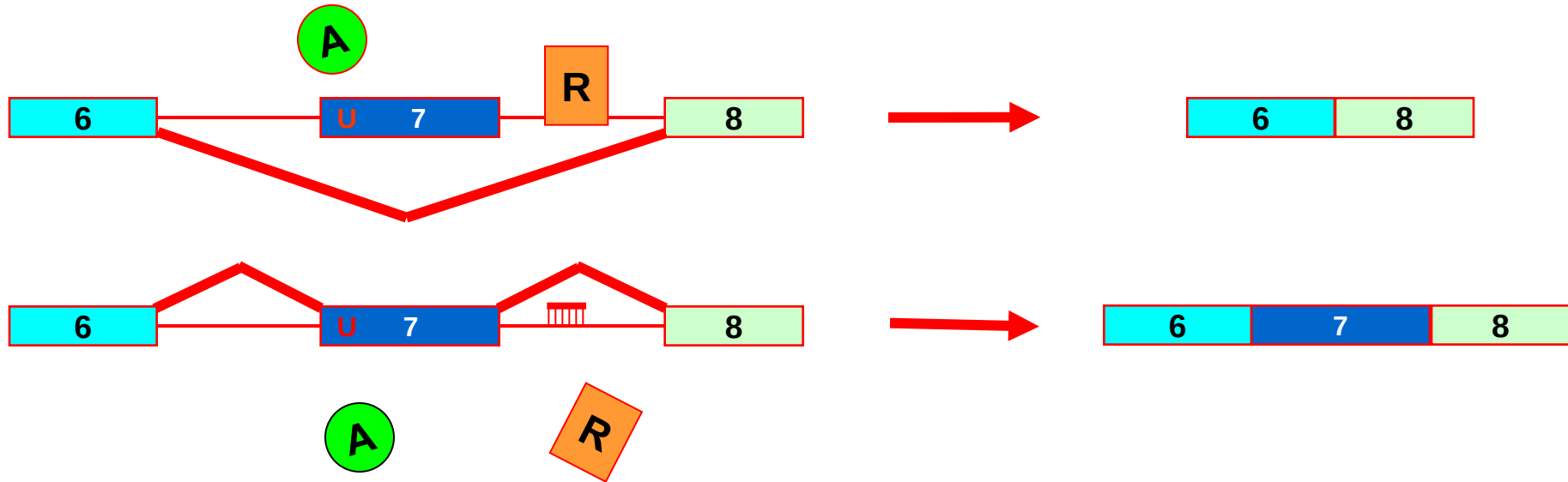
Boza et al., (sometido)

GENETICA



**Incrementar RNA, incluir el exón 7
Transferir copias normales gen a la
medula espinal**

Método para aumentar la inclusión del exon 7



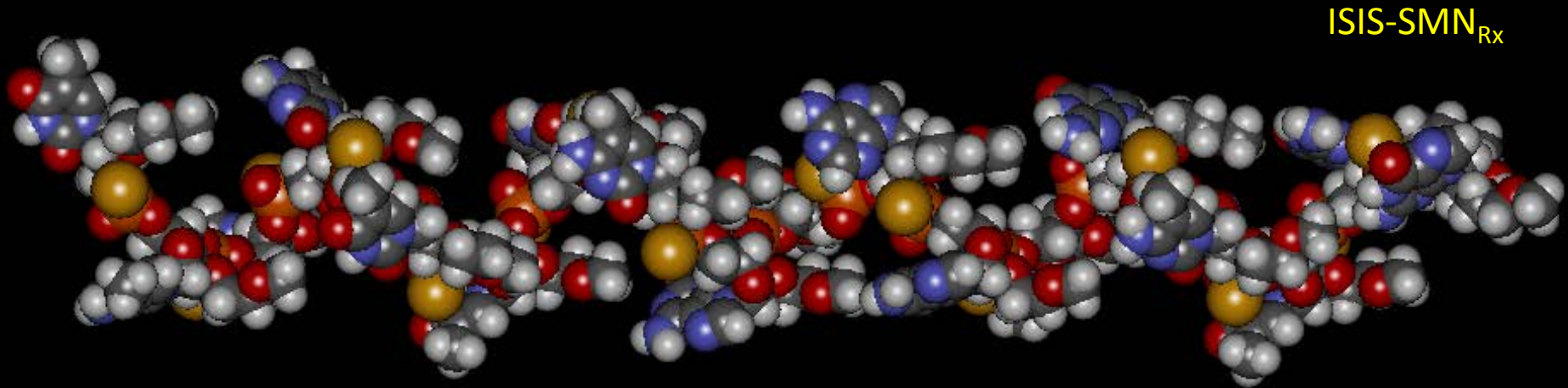
2'-O-(2-methoxyethyl) ribose

phosphorothioate

5-methyl cytosine



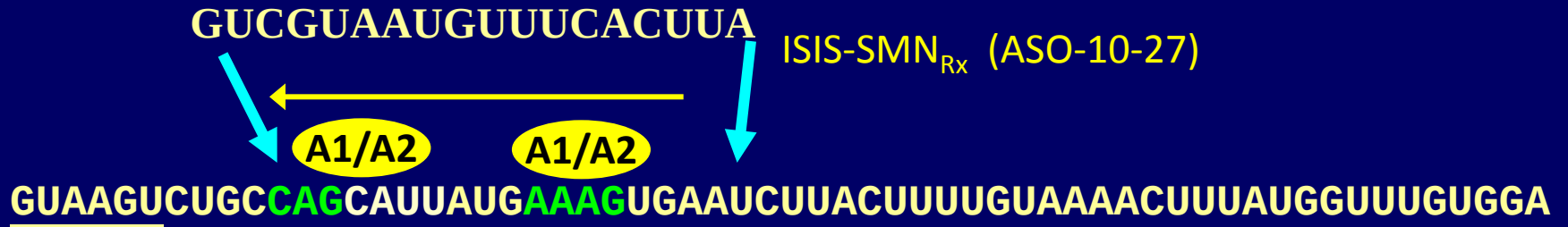
ISIS-SMN_{Rx}: nuevo fármaco en investigación



18mer; MW 7127

- Hua et al (2007) *PLoS Biol* 5: e73
- Hua et al (2008) *Am J Hum Genet* 82: 834
- Hua et al (2010) *Genes Dev* 24: 1634
- Passini et al (2011) *Science Transl Med* 3: 72ra18
- Hua et al (2011) *Nature* 478: 123

Terapia antisentido o antisense

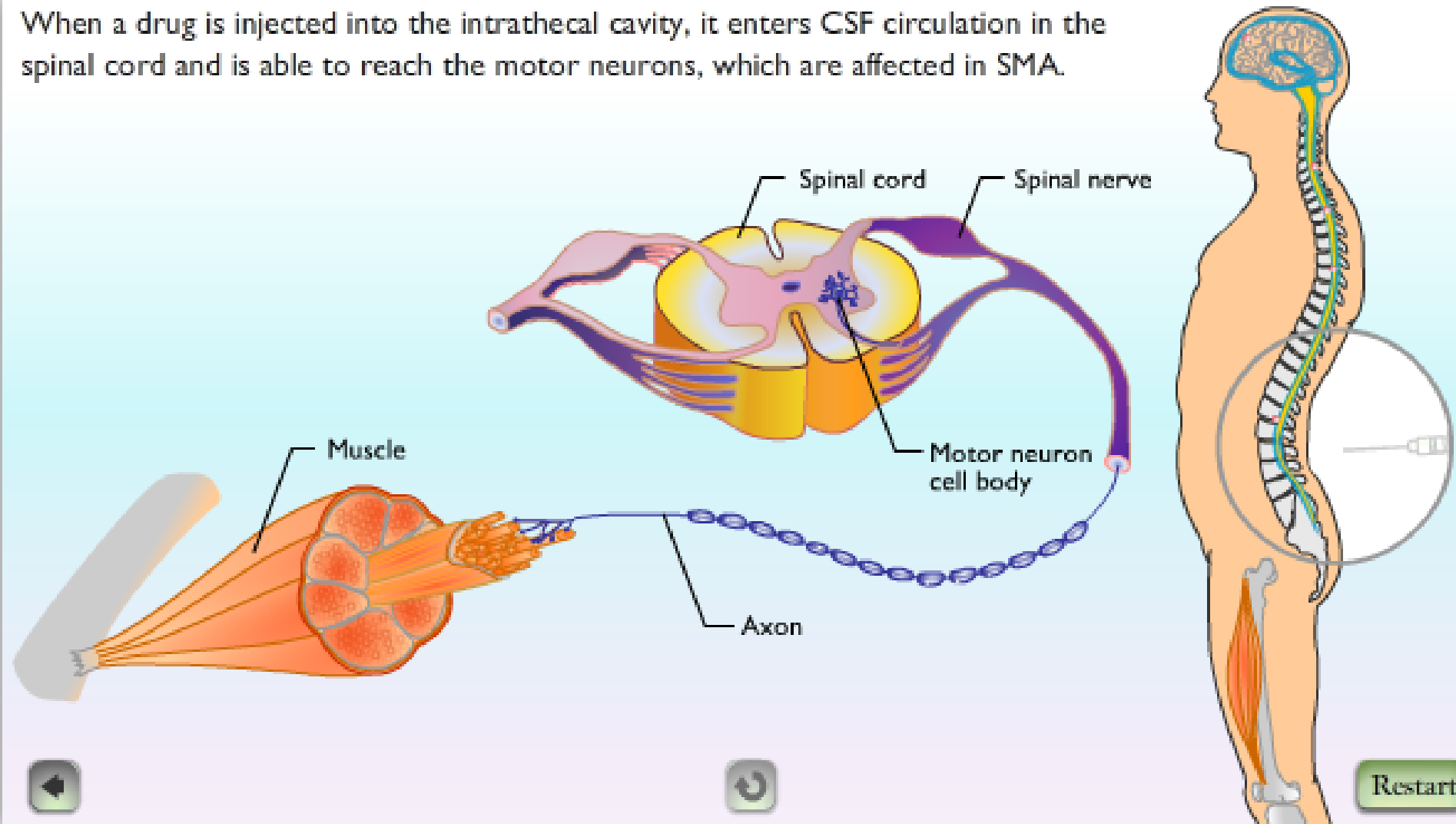


A nine-day-old untreated SMA mouse (left) and a nine-month-old SMA mouse given Isis's antisense therapy (right).



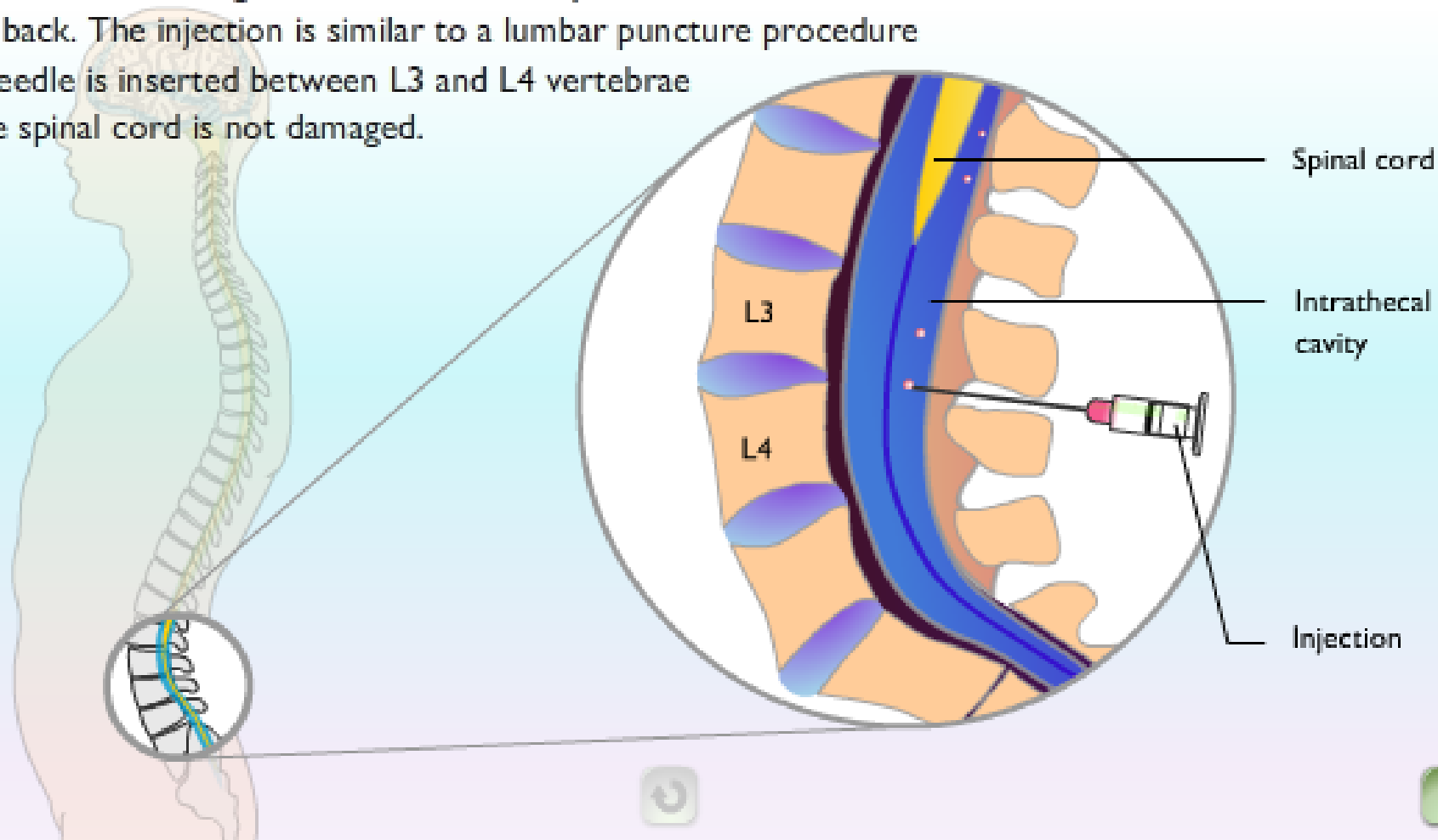
Intrathecal drug delivery

When a drug is injected into the intrathecal cavity, it enters CSF circulation in the spinal cord and is able to reach the motor neurons, which are affected in SMA.



Intrathecal drug delivery

In a technique called intrathecal drug delivery, a drug can be injected into the CSF, where it flows through the intrathecal cavity between the vertebrae of the lower back. The injection is similar to a lumbar puncture procedure where a needle is inserted between L3 and L4 vertebrae so that the spinal cord is not damaged.





A prof. Darryl De Vivo 2

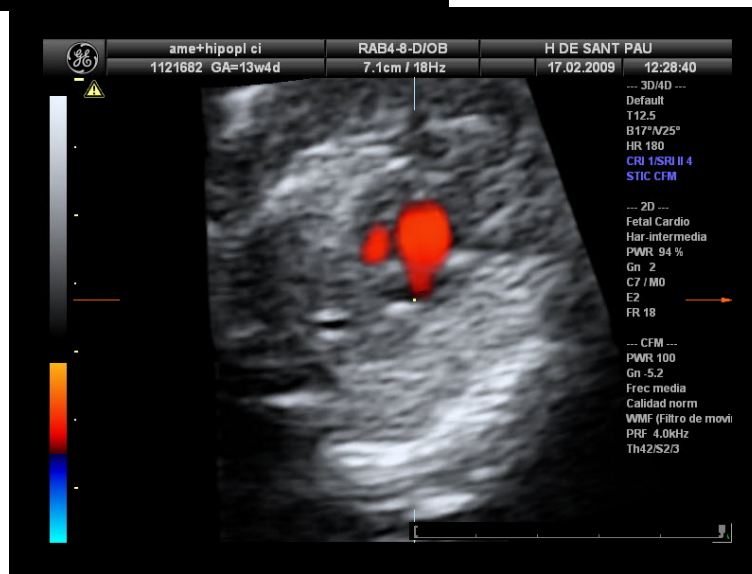
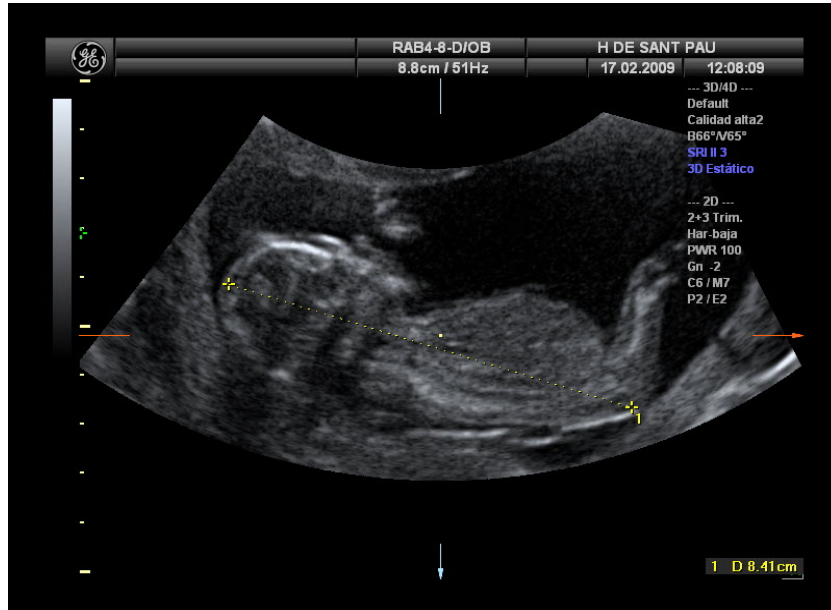
Petizione al Presidente Napolitano per avviare in Italia lo studio di fase I con il farmaco ISIS-SMNRx nei pazienti con atrofia muscolare spinale.

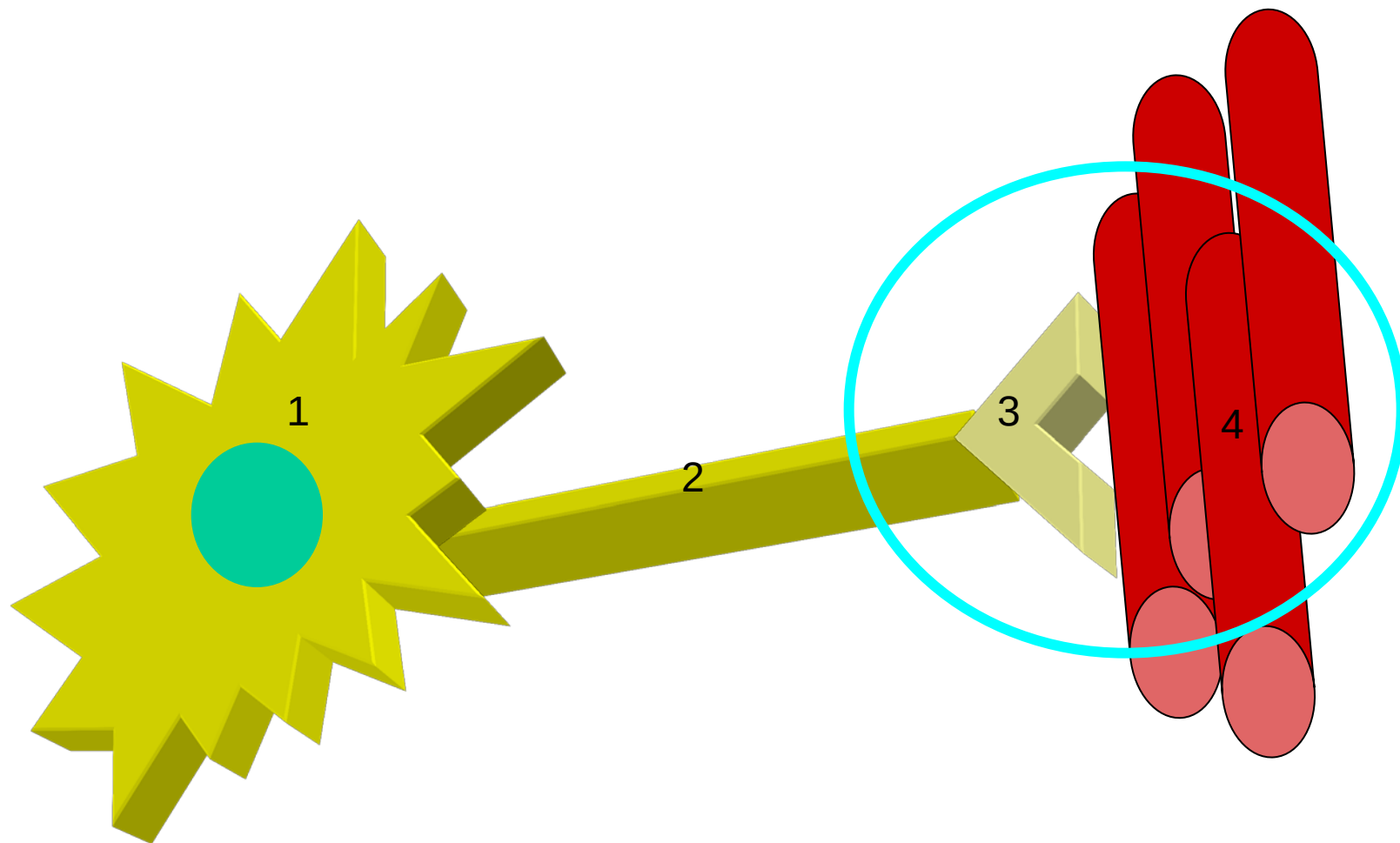
Christian ha 15 mesi ed è affetto da una malattia gravissima: l'atrofia muscolare spinale. L'unica speranza di salvezza per il piccolo Christian è un farmaco che viene sperimentato negli Usa, ma solo per chi ha tra i 2 e i 15 anni di età. Ma i genitori Pasquale e Nadia, che vivono a Serre (Salerno), combattono per il loro bambino e oggi hanno deciso di lanciare un appello al presidente della Repubblica, Giorgio Napolitano, al Papa ed altri, affinché li aiuti a fare avere il farmaco per il loro bambino. Attualmente si è in fase di arruolamento ma la sperimentazione sarà solo negli Usa. Mentre al Columbia University Medical Center la scelta dei pazienti è già cominciata negli altri due, il Children's Hospital Boston e il Children's Medical Center di Dallas l'arruolamento dovrebbe cominciare a breve.

Terapia en otras neuronas? Tejidos periféricos?

- Músculo
- Unión neuromuscular
- Cardiovascular (cardiopatías congénitas, fenómenos de necrosis vascular, trastornos de conducción?)
- Neuronas sensoriales-propioceptivas/interneuronas?
- Hígado (evidencia en ratones, Hau, 2011)

SMA case with 5mm NT, Hypoplasia of left heart and one SMN2 copy.





Journal of Pathology

J Pathol (2012)

Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/path.4080

ORIGINAL PAPER

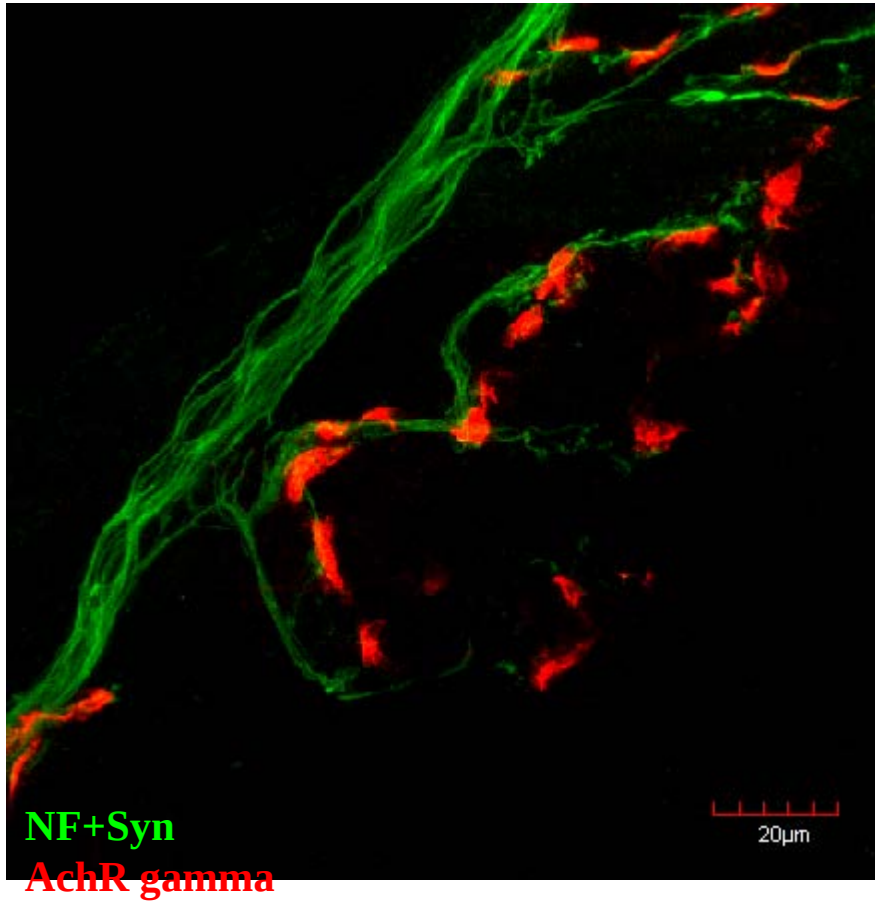
Synaptic defects in type I spinal muscular atrophy in human development

Rebeca Martínez-Hernández,¹ Sara Bernal,¹ Eva Also-Rallo,¹ Laura Alías,^{1,2} M^aJesús Barceló,^{1,2} Marta Hereu,³ Josep E Esquerda³ and Eduardo F Tizzano^{1,2*}

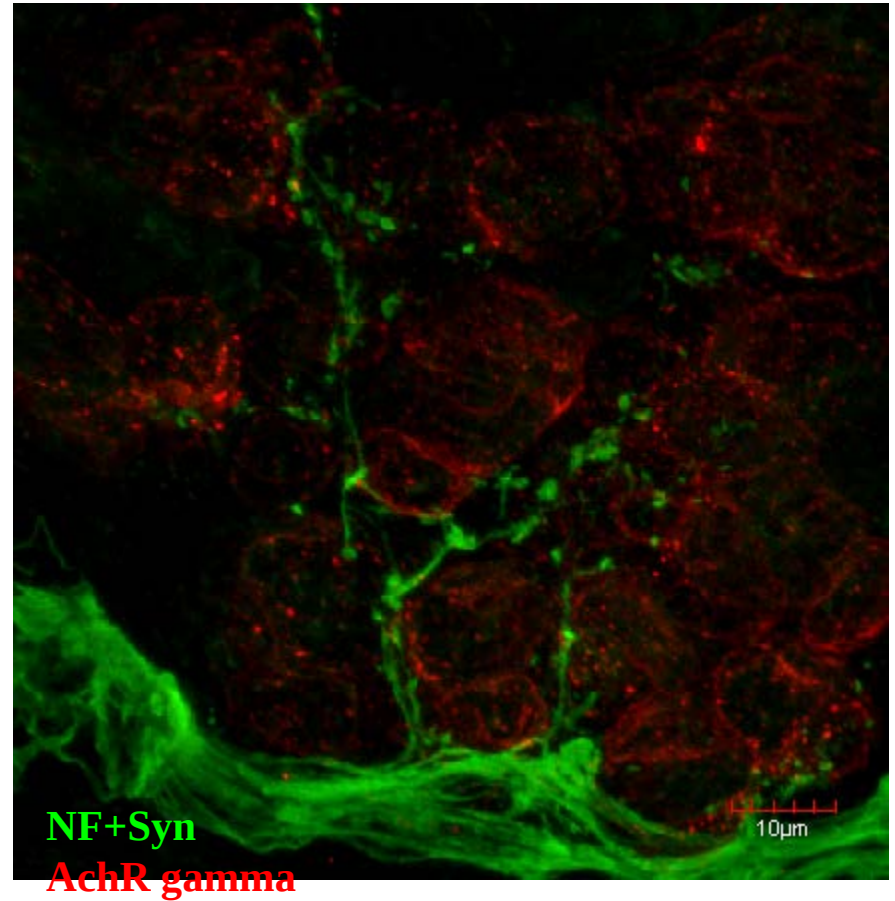


AXONS - ENDPLATES

Diaphragm 14 weeks Motor Endplates



CONTROL



SMA

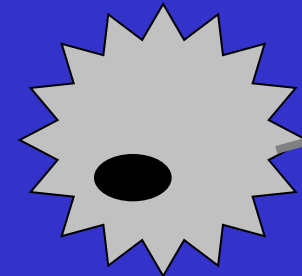
All the studies points to:

Motor neuron

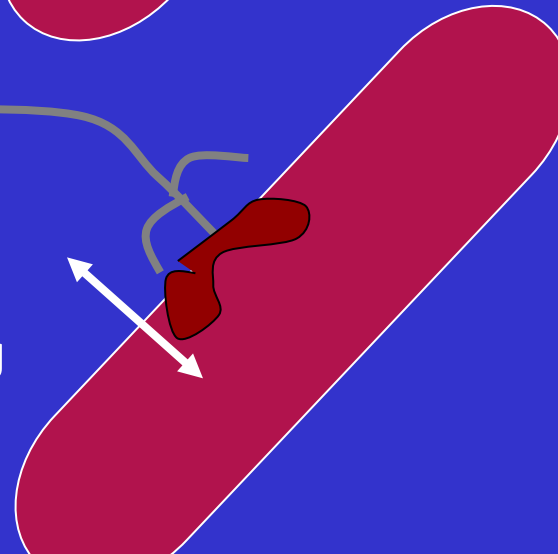
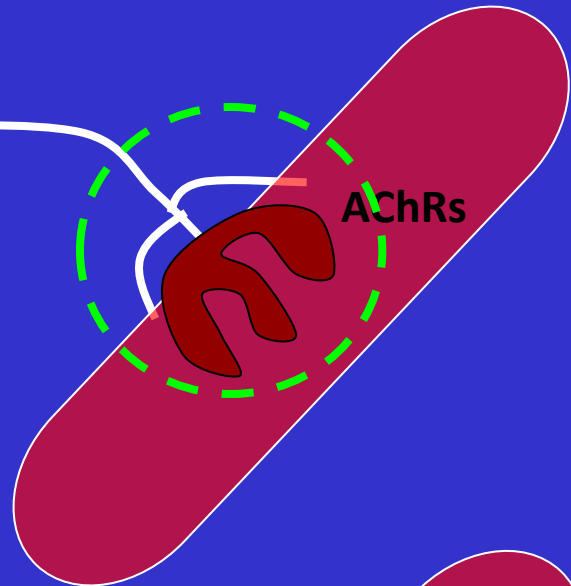
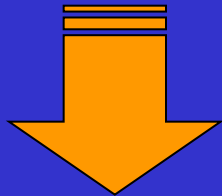
Muscle

Destabilization of the NMJ

AChRs



Defects in the maintenance of the NMJ



Recently reported

Neurons other than motor neurons could contribute to the motor defects in SMA?

In a *Drosophila* model a sensory-motor defect has been demonstrated

In mice models has been demonstrated that loss of sensory-motor synapses is a consequence of MN dysfunction

SMN Is Required for Sensory-Motor Circuit Function in *Drosophila*

Cell

Wendy L. Imlach,^{1,2} Erin S. Beck,^{1,3} Ben Jiwon Choi,^{1,2} Francesco Lotti,^{1,2} Livio Pellizzoni,^{1,2} and Brian D. McCabe^{1,2,3,*}

An SMN-Dependent U12 Splicing Event Essential for Motor Circuit Function

Francesco Lotti,^{1,3,5} Wendy L. Imlach,^{2,3,5} Luciano Saieva,^{1,3} Erin S. Beck,^{2,3} Le T. Hao,⁴ Darrick K. Li,^{1,3} Wei Jiao,^{1,2,3} George Z. Mentis,^{1,3} Christine E. Beattie,⁴ Brian D. McCabe,^{1,2,3,*} and Livio Pellizzoni^{1,3,*}

Neurobiology of Disease

The Journal of Neuroscience
The Official Journal of the Society for Neuroscience

Survival Motor Neuron Protein in Motor Neurons Determines Synaptic Integrity in Spinal Muscular Atrophy

Tara L. Martinez,^{1,3,4} Lingling Kong,^{1,*} Xueyong Wang,⁴ Melissa A. Osborne,⁵ Melissa E. Crowder,¹ James P. Van Meerbeke,¹ Xixi Xu,¹ Crystal Davis,⁵ Joe Wooley,¹ David J. Goldhamer,⁶ Cathleen M. Lutz,⁵ Mark M. Rich,⁴ and Charlotte J. Sumner^{1,2}

Motor Neuron Rescue in Spinal Muscular Atrophy Mice Demonstrates That Sensory-Motor Defects Are a Consequence, Not a Cause, of Motor Neuron Dysfunction

Rocky G. Gogliotti,^{1,2} Katharina A. Quinlan,³ Courtenay B. Barlow,^{1,2} Christopher R. Heier,¹ C. J. Heckman,³ and Christine J. DiDonato^{1,2}

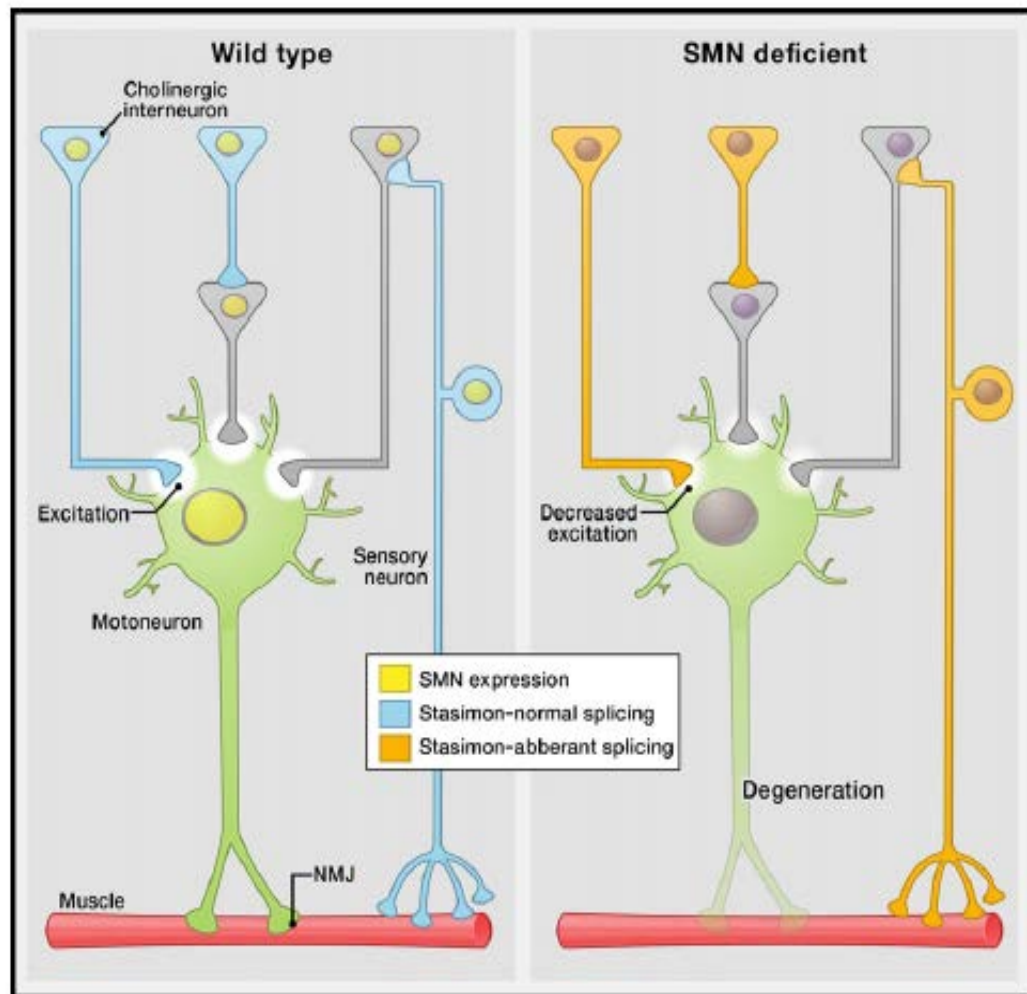


Figure 1. Circuit Basis for Selective Degeneration of Motoneurons in a *Drosophila* Model of SMA

In a *Drosophila* SMA model proprioceptive neurons and interneurons do not produce enough neurotransmitters (cholinergic). Blocking the potassium channels (thus enlarging action potential and increasing neurotransmitters in synapsis) with dalfampridine (4-aminopyridine) muscle size and motor function improved.

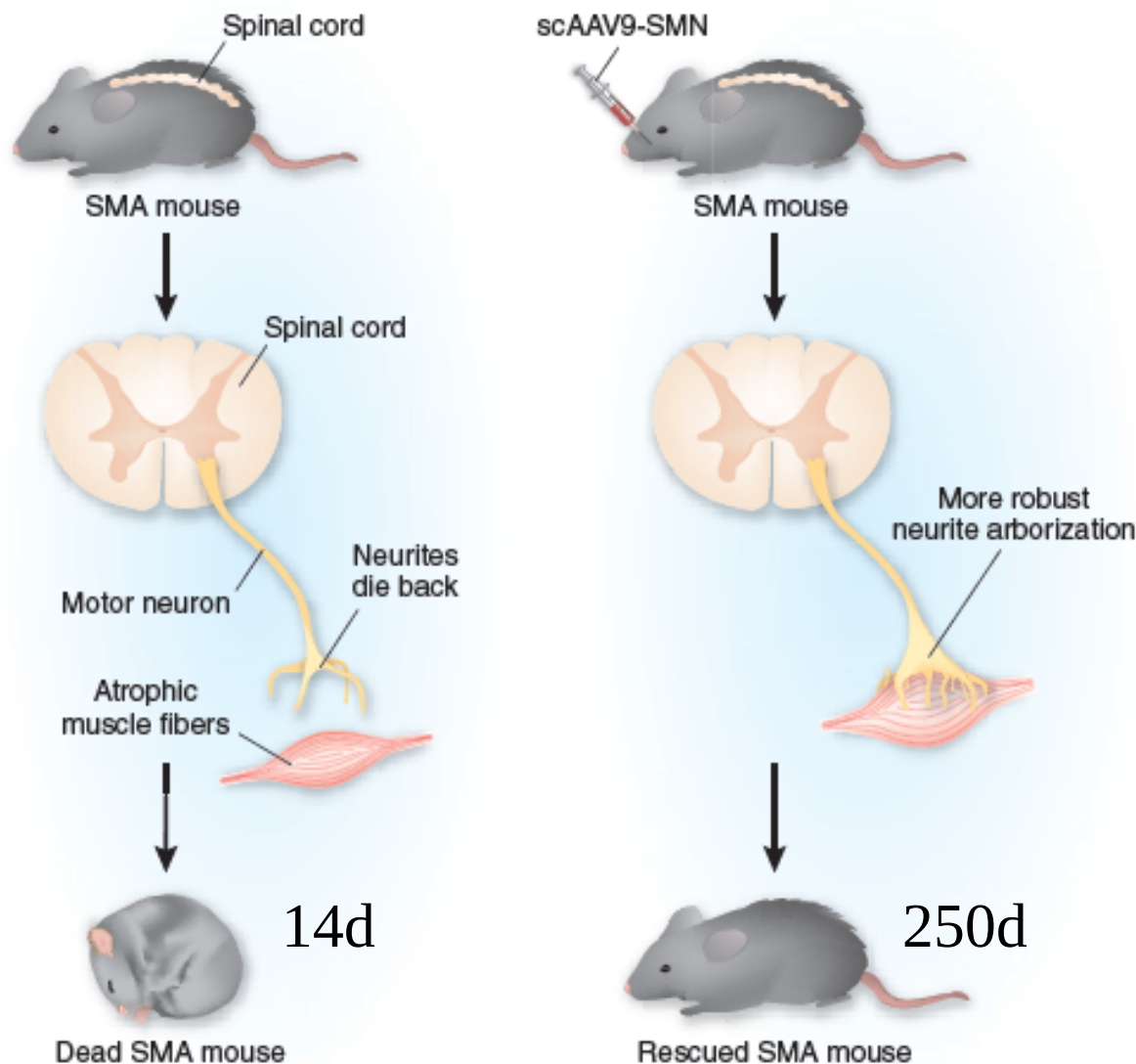
Motor neurons sensitive to diminished excitation? Network dysfunction instead a cell-autonomous alteration?

Estrategias terapéuticas AME



Transferir copias normales del gen SMN1 a la médula espinal (terapia génica).

- AAV9 que pasa la barrera hematoencefálica
- Aumenta la supervivencia cuando se administra muy precozmente al ratón SMA.
- Se está estudiando en primates



Gene therapy of SMA mice with scAAV9-SMN

Foust et al.,
Nature
Biotechnology,
2010

Figure 1 Gene therapy for mice with spinal muscular atrophy (SMA). SMA mice (null for the murine SMN gene and homozygous for variants of human SMN transgenes) are born with a normal motor neuron complement. However, the motor neurons undergo rapid attrition, likely a result of synaptic failure and denervation with attendant muscular atrophy. The mice become wasted and succumb at two weeks of age (left), analogous to an untreated mild human type I SMA. Injection of scAAV9-SMN into the facial vein of day-old SMA pups results in SMN expression in ~40% of motor neurons, normalization of synaptic electrophysiology and an extension of life span to >250 days, albeit at half the size of unaffected mice (right).

Estrategias terapéuticas AME

Sustituir las neuronas motoras o ayudarlas por medio de la terapia celular (células troncales).

- La inyección de células madres de la estirpe neuronal es capaz de generar neuronas
- Produce factores en el ambiente de las motoneuronas que puede ser de beneficio.
- No migran a otros sectores de la médula (Wyatt et al., 2011)

Stem cells in severe infantile spinal muscular atrophy (SMA1)

Carrozzi et al., Neuromuscular Disorders, 2012.

- 5 type I children (1m, 4 f) 3-20 months age range
- Mesenchymal stem cells administered on a monthly basis for 6 months.
- Outcome measures:
 - general clinical assessment (weight, respiratory function, feeding),
 - motor function using the CHOP Intend Scale
 - video recording
 - cerebrospinal fluid collected before each injection concentration of 48 proteins (Bio-Rad human cytokine and growth factors set 27plex and 21plex

One of the five patients enrolled at the age of 13 months, died from respiratory failure at the age of 18 months, 1 month after the second injection.

The family of another patient asked to stop the treatment after the 5th injection, at 8 months of age, and the child died at the age of 12 months of respiratory failure.

The other three patients completed the 6 month treatment course. During this period in all three there was the need to initiate supportive therapy with nutritional and respiratory aids. In all three patients there was **a progressive decline of motor function** as demonstrated by the reduction of the CHOP Intend scale total score and **no clinical evidence of any improvement.**

There were no reproducible changes in concentration of the proteins dosed in the cerebrospinal fluids before, during or after treatment.

The Hospital asked an external Scientific Board including experts in stem cells and SMA to review the results of the study. The clinical course of the treated patients showed no improvement and did not differ from the recent natural history data available in infants with SMA1. Because of the lack of efficacy, in December 2011 the hospital, in accordance with the local Ethical Committee, decided to stop recruitment.



HOME CHI SIAMO POLITICA CRONACA SPORT EVENTI VIDEO CI N'È PI TUTTI

Staminali. Migliorano i tre piccoli che hanno ripreso le cure del pediatra Andolina con le cellule della Onlus Stamina Foundation

Home - Scienza - Salute - Staminali per terapie compassionevoli: cura miracolosa o bufala?

■ Staminali per terapie compassionevoli: cura miracolosa o bufala?

Un'ordinanza dell'Agenzia del farmaco ha bloccato le cure dell'équipe di Davide Vannoni e della **Stamina Foundation**. Sebbene i risultati diano speranza. L'inchiesta di *Panorama*

Le cure per le piccole Celeste e Smeralda? «Pericolose per la salute»

 Mi piace 9

 Tweet 1



Novembre 5, 2012 Redazione

Per gli esperti del ministero le cure con staminali per le due bambine al centro di un caso giudiziario sono nocive. Eppure nei video i ballerini affetti da Parkinson tornavano a danzare

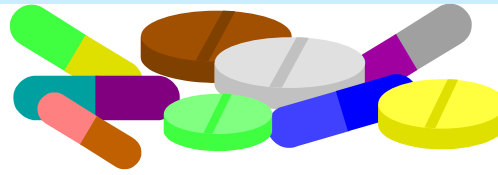
IL BALLERINO COL PARKINSON. Non solo.

Come scrive oggi *Repubblica*, «per convincere ad accettare il loro metodo, gli esperti della Stamina, onlus senza fine di lucro (che, però, si faceva pagare dai 7 ai 50 mila euro), mostravano ai familiari dei malati i video “di un ballerino russo affetto da Parkinson che si alzava dalla carrozzella e tornava a ballare”. “Di una giovane paralizzata dalla Sla che riprendeva a camminare”. “Di un uomo che guariva da una grave forma di psoriasi alle mani”. Ma si trattava solo di un inganno: di qui, la contestazione da parte del procuratore torinese del reato di associazione per delinquere e truffa»

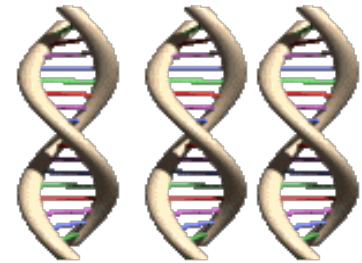
More generally, our findings highlight the risk that the combination of newspaper ‘hype’ and parental ‘hope’, with the support of courts that are sympathetic to families with children with severe disorders, may produce shortcuts in the design of clinical studies that would need more rigorous preclinical information and more accurate safety and efficacy measures and may actually put patients at risk of potential side effects of therapy.

Carrozzi et al., NMD, 2012

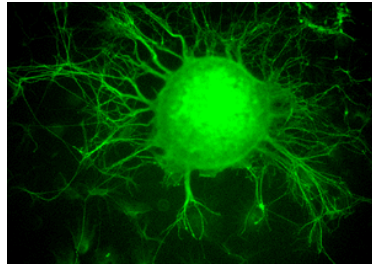
EL FUTURO: TERAPIA COMBINADA DE LA AME



Fármaco que active SMN2



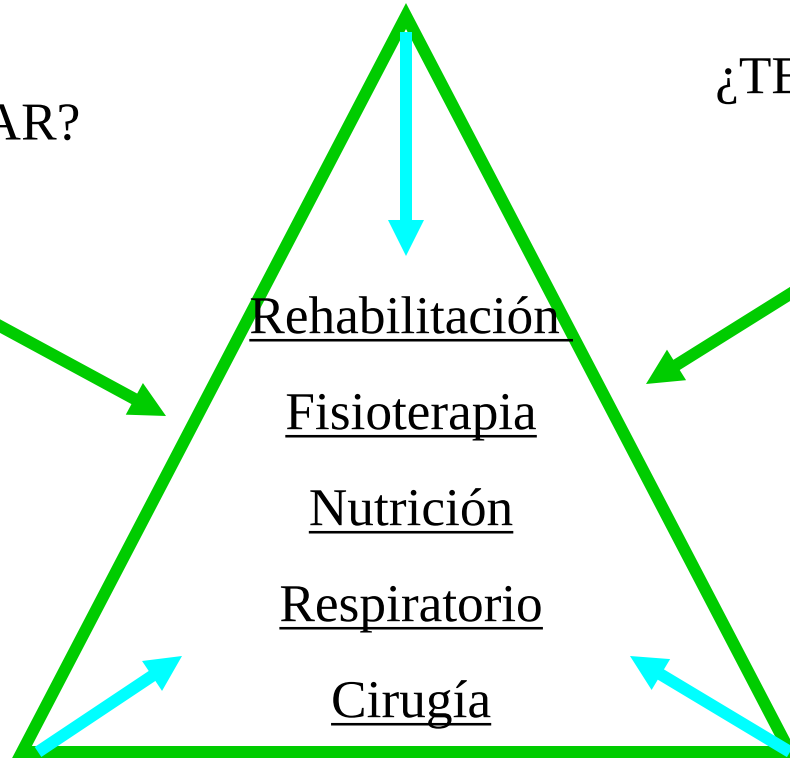
¿TERAPIA GENICA?



¿TERAPIA CELULAR?



Neuroprotector



**Estimulante fuerza
muscular**

Es poco probable que una sola acción farmacológica suponga una completa solución terapéutica.

Conclusiones y perspectivas

- Estratificación pacientes, historia natural y ventana terapéutica tiene que ser considerados en el diseño de los ensayos clínicos en AME.
- Es posible que no solo las neuronas motoras sean dianas de la enfermedad. Existe evidencia que dianas periféricas como músculo, la unión neuromuscular, aparato cardiovascular, y a lo mejor hígado puedan ser necesarios considerar para el tratamiento.
- Una vez demostrada su eficacia, la terapia combinada farmacológica y genética permitirá la aplicación de protocolos de tratamiento en un futuro próximo.

SMA

SMA overview >

About SMA >

SMA care standards >

SMA patient registries >

SMA research overview ✓



Overview of therapeutic approaches for SMA

The problem

The splicing process

Therapeutic strategies for SMA

SMA clinical research and trials >

SMA patient organizations >

SMA meetings and events >

Overview of therapeutic approaches for spinal muscular atrophy

Information on current best practice in care for people with spinal muscular atrophy (SMA) is provided in the **SMA care standards** section of this website. This research overview section aims to inform patients and their families about the approaches currently being investigated for the possible future treatment of SMA - therapies that are currently still at the laboratory or clinical trial stage. It discusses the strengths and limitations of each approach. These factors need to be carefully assessed before the alternatives described here can be implemented clinically.

Many developments are taking place in the therapeutic approaches in SMA. This is a dynamic and promising field but as a detailed account of progress is outside the scope of this short review we provide a general overview of present investigation into SMA.



<http://www.treat-nmd.eu/sma/research-overview/introduction/>

GENAME Project (Genoma España- FUNDAME)

Intramural CIBERER U705.3

FIS 05-2416/ 08-0729/11-2606

SMA group

Laura Alias

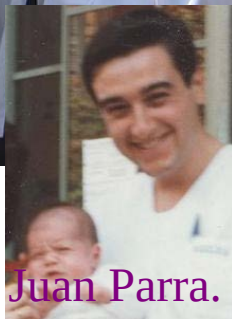
Eva Also

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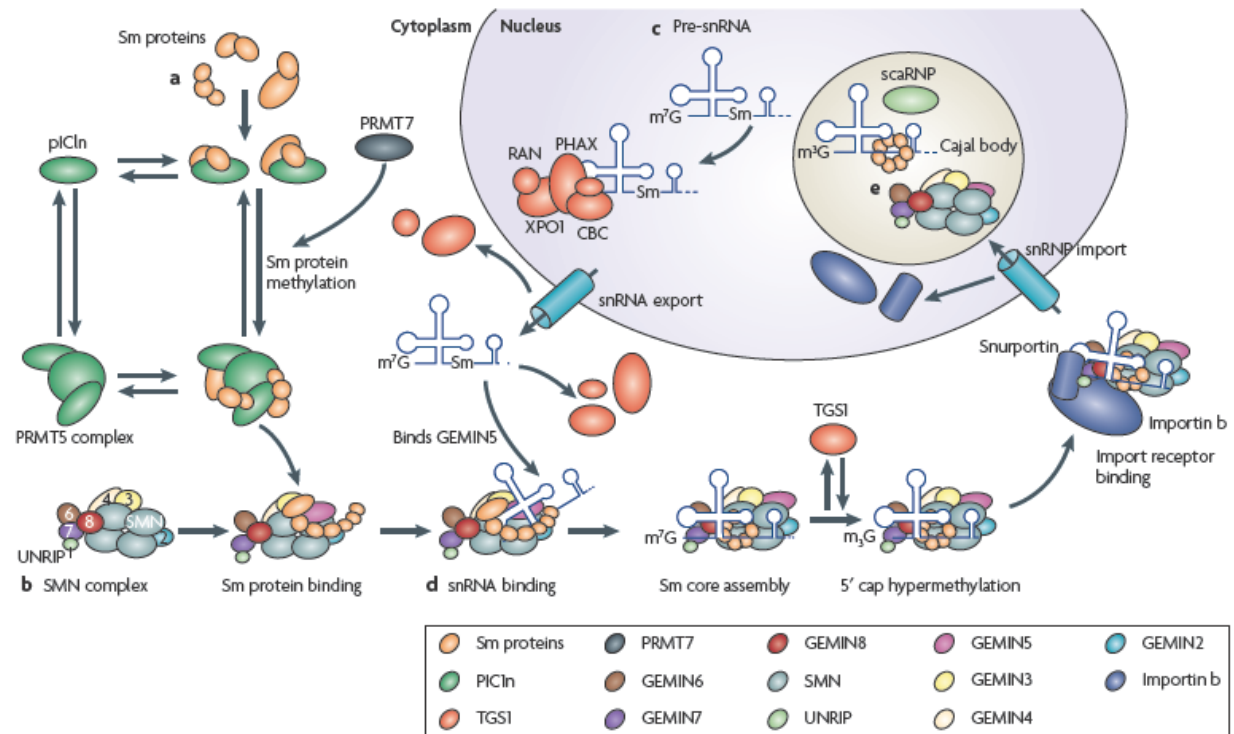
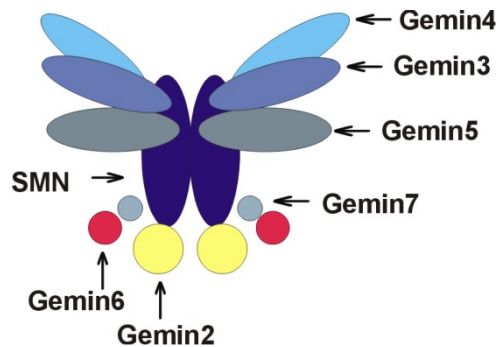
Funciones

•Generales?

- Biogénesis y ensamblaje de las partículas snRNPs
- *Splicing* del pre-mRNA
- Transcripción génica
- Metabolismo del RNA ribosómico

• Neuronales?

- Apoptosis
- Transporte axonal mRNA
- Formación de las neuritas y uniones neuromusculares



Lining up against a genetic killer: The SMA drug pipeline.

Mechanism	Developer	Drug type (name)	Phase
SMN splicing	Isis Pharmaceuticals & Biogen Idec	Antisense oligonucleotide (ISIS-SMNRx)	1
	Roche & PTC Therapeutics	Small molecule	Preclinical
	Novartis	Small molecule	Preclinical
	Paratek Pharmaceuticals	Small molecule	Preclinical
SMN translation	Repligen	Small molecule (RG3039)	1
SMN stabilization	NINDS	Small molecule (ALB-111)	Preclinical
SMN gene therapy	Genzyme	Viral vector	Preclinical
	Généthon & INSERM	Viral vector	Preclinical
	Nationwide Children's Hospital	Viral vector	Preclinical
Neuroprotection ^a	Trophos	Small molecule (olesoxime)	2

INSERM, Institut National de la Santé et de la Recherche Médicale; NINDS, National Institute of Neurological Disorders and Stroke.

^aOlesoxime, a mitochondrial pore modulator, is designed to protect neurons but does not affect SMN levels.

Letter to the Editor
Stem cells in severe infantile spinal muscular atrophy
(SMA1)
Carrozzi et al., Neuromuscular Disorders, 2012.

Between December 2010 and December 2011 five type I SMA children (1 m, 4 f, age range: 3–20 months) were enrolled. Mesenchymal stem cells were supplied by the Stem Cell Facility of the San Gerardo Hospital, Monza, Italy. Cells were administered on a monthly basis for 6 months. At each admission, the following evaluations were performed: a general clinical assessment (weight, respiratory function, feeding), assessment of motor function, using the CHOP Intend Scale, a functional scale specifically developed for children with type I SMA [11], and video recording of the assessment and of spontaneous movements. The cerebrospinal fluid collected before each injection was analyzed by measuring the concentration of 48 proteins (Bio-Rad human cytokine and growth factors set 27plex and 21plex).