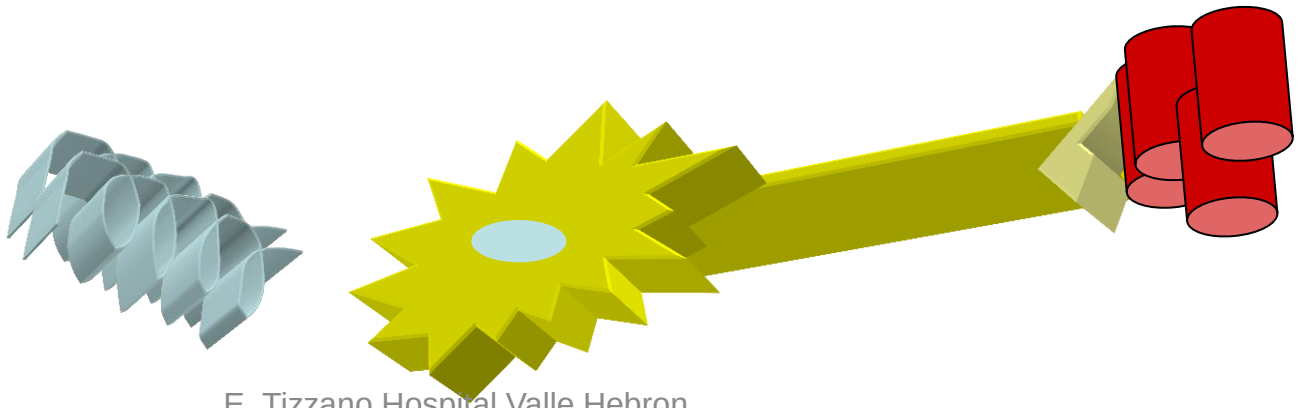
- Porque ocurre la AME
- Correlación genotipo fenotipo
- Discordancias fenotipicas
- Terapias avanzadas
- Perspectivas mas allá de los ensayos clínicos

Porqué ocurre la AME

- Ausencia o mutación de las dos copias del gen SMN1 entonces hay menos proteína SMN
- Pérdida y degeneración neuronas motoras del asta anterior de la medula espinal
- Falla en la unión neuromuscular y contacto con el músculo
- Denervación y debilidad muscular

SMN 1

SMN 1



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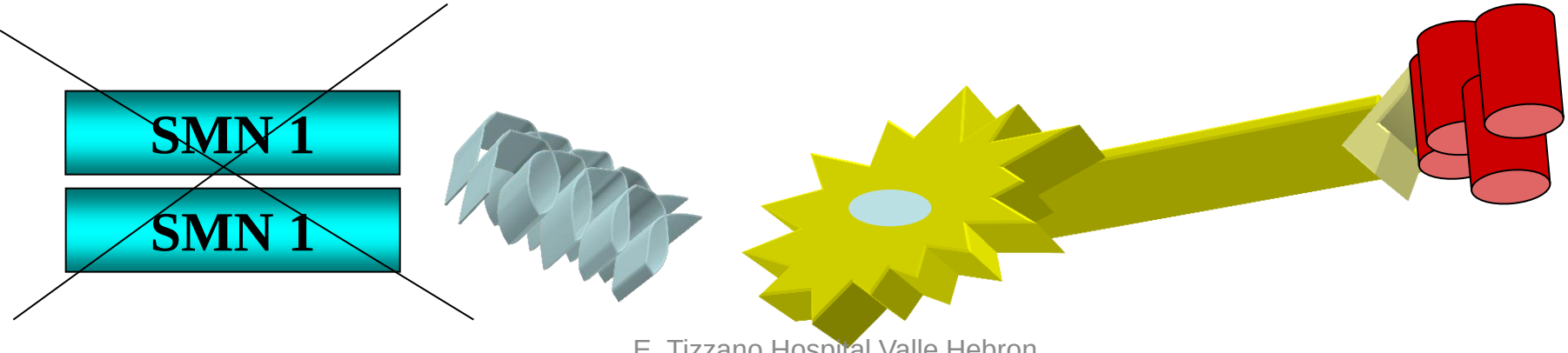

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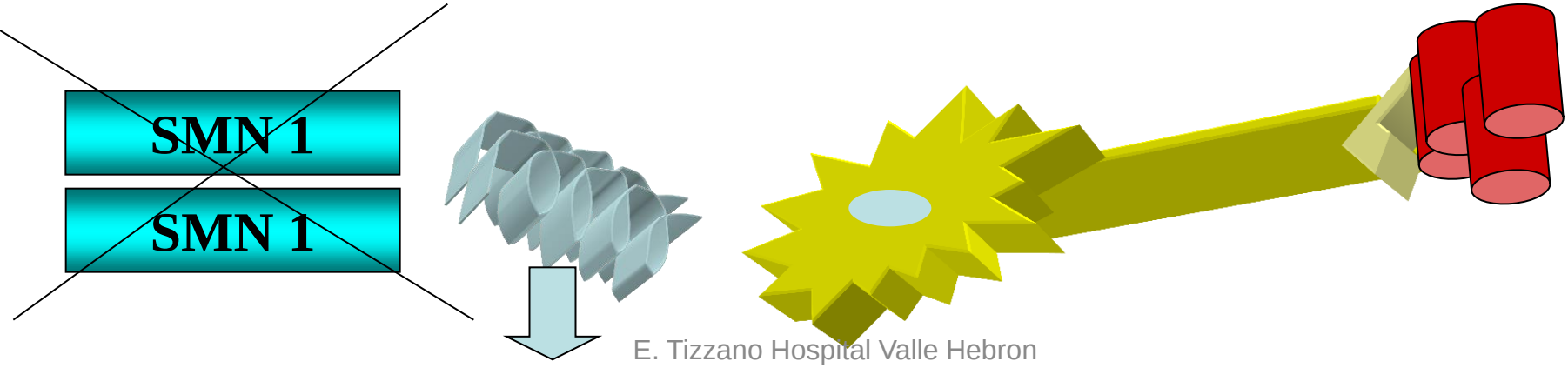

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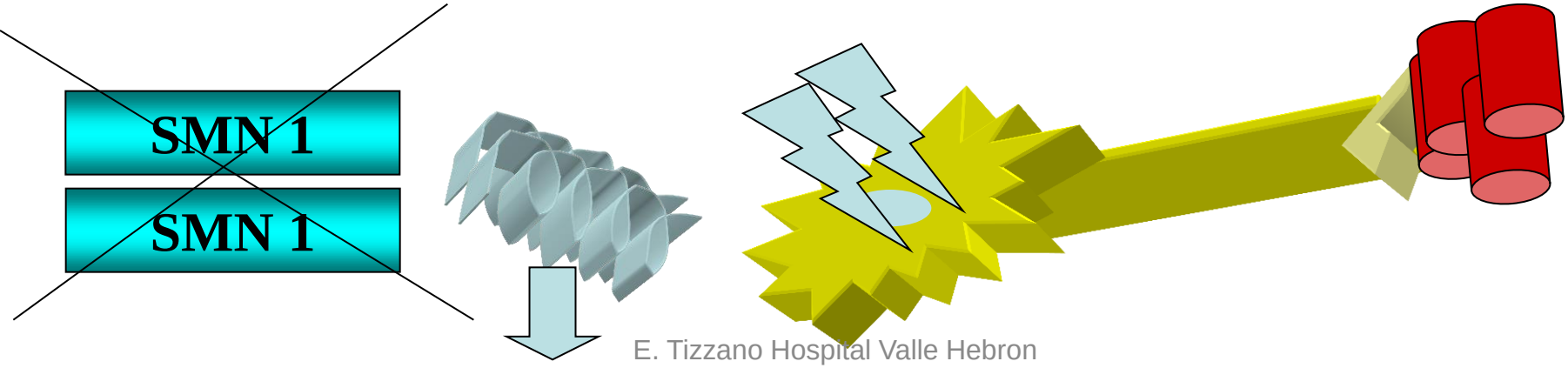

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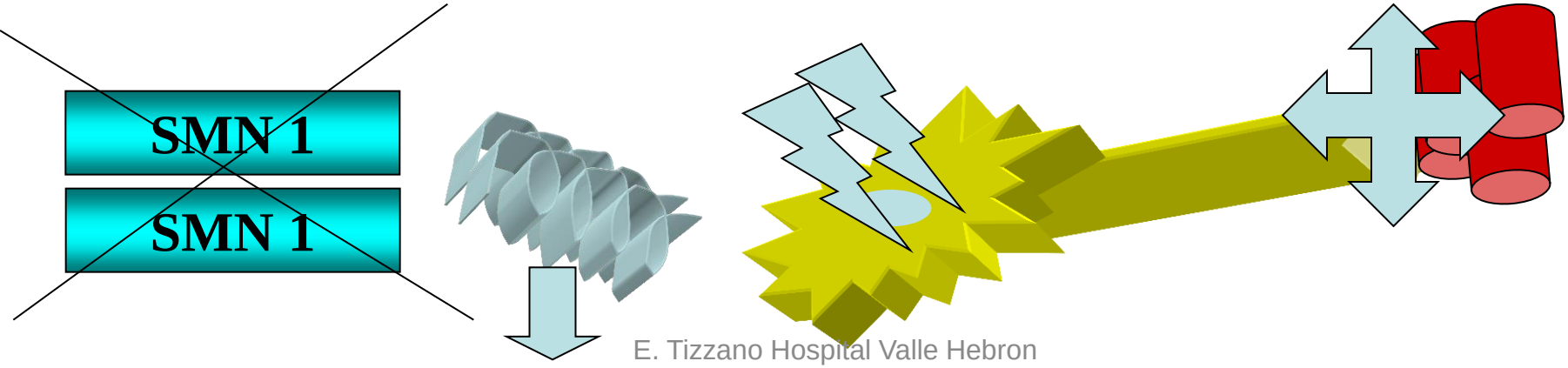

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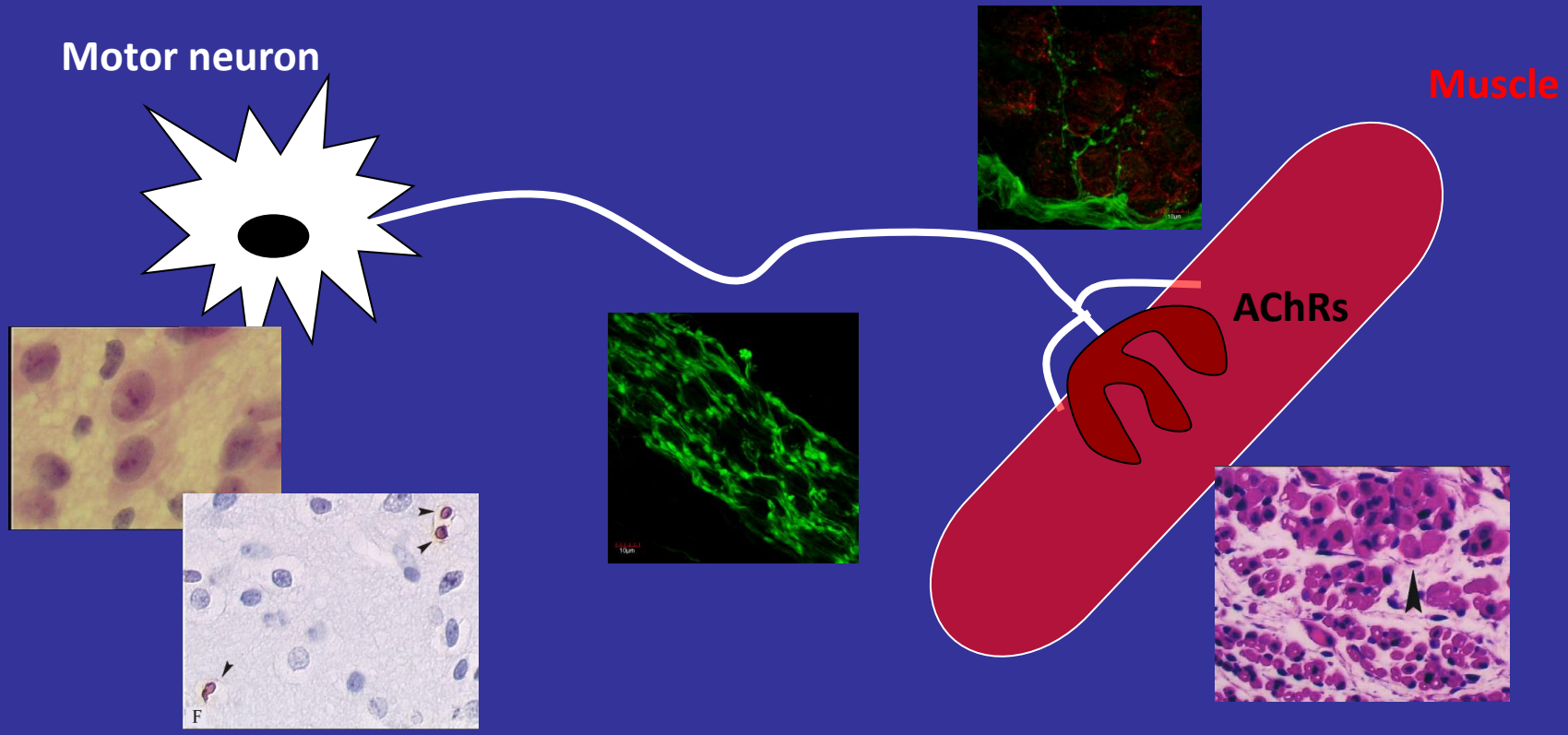
- Denervación y debilidad muscular

Summary of developmental findings

Soler-Botija et al., Brain, 2002,

Martínez-Hernandez et al., JNEN 2009

Martínez-Hernandez et al., J Pathol 2013



Pathological findings are present at early stages of the disease along the neuromuscular unit

Summary of postnatal findings

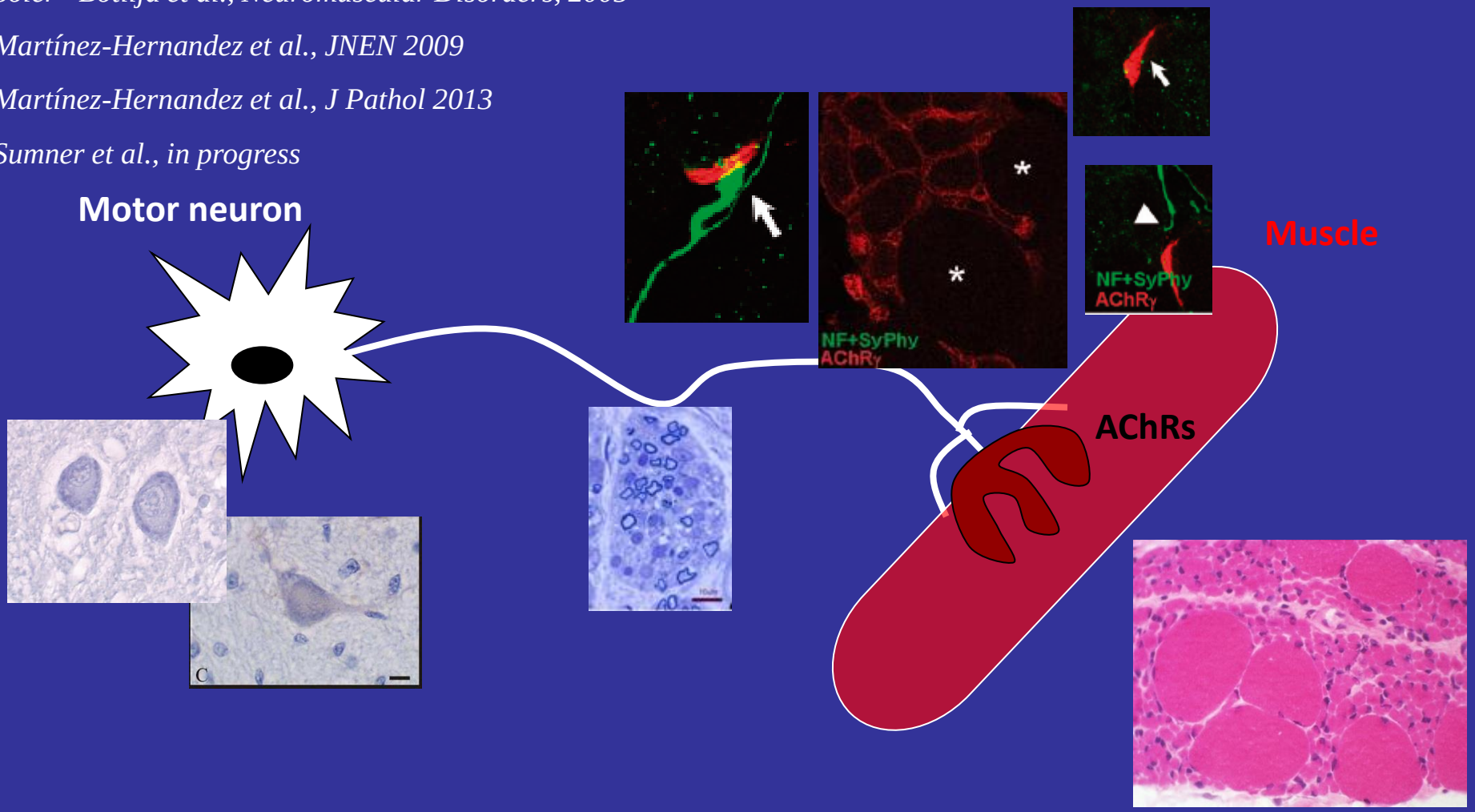
Soler-Botija et al., Brain, 2002

Soler –Botilja et al., Neuromuscular Disorders, 2005

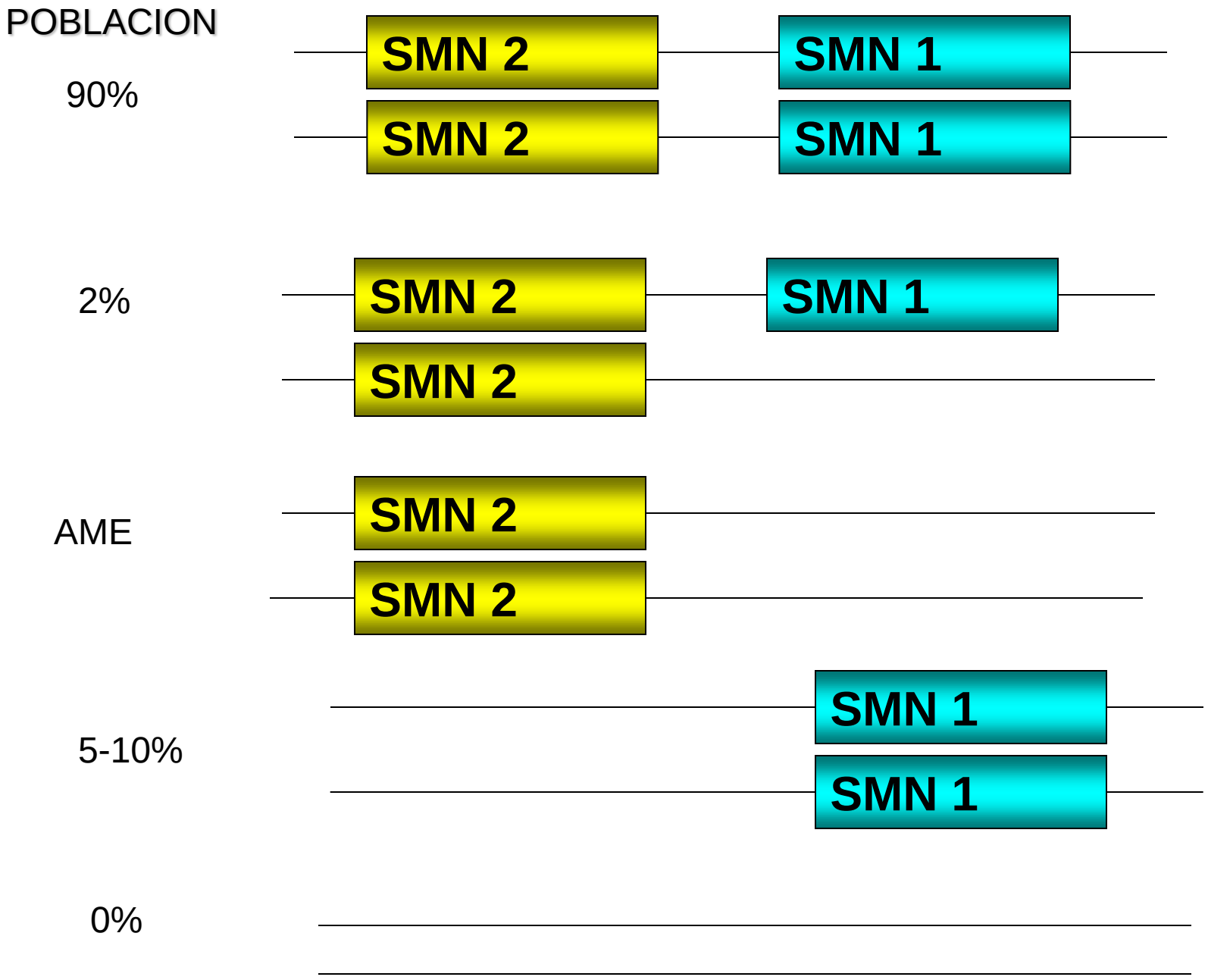
Martínez-Hernandez et al., JNEN 2009

Martínez-Hernandez et al., J Pathol 2013

Sumner et al., in progress



Pathological findings are present postnatally in the neuromuscular unit


POBLACION
90%
SMN 2
SMN 1
SMN 2
SMN 1
2%
SMN 2
SMN 1
SMN 2
AME
SMN 2
SMN 2
5-10%
SMN 1
SMN 1
0%

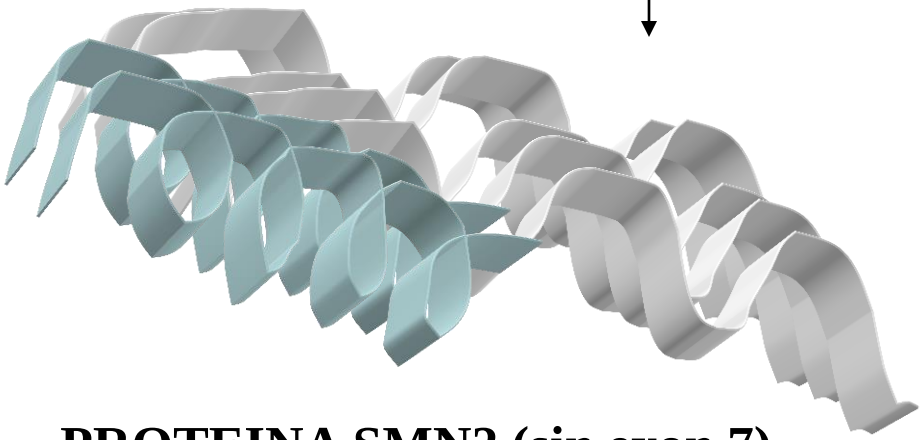
ADN

SMN 2

SMN 1

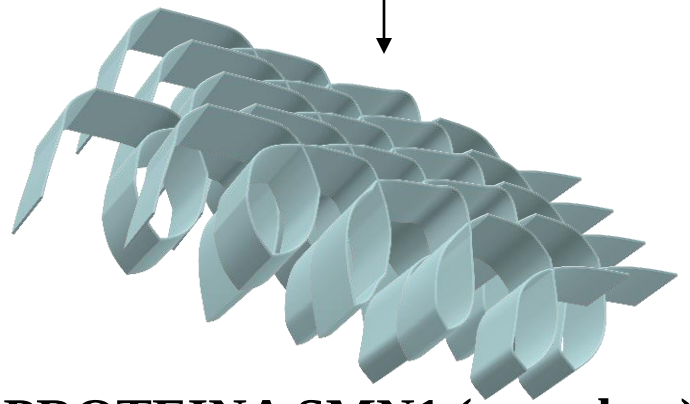
EXONES

ARN mensajero



PROTEINA SMN2 (sin exon 7)

inestable y parcialmente funcionante



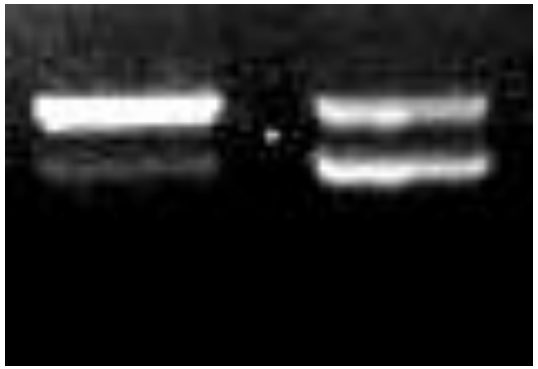
PROTEINA SMN1 (completa)

totalmente funcionante

A decrease of SMN protein in spinal cord causes SMA

Control SMA

SMN1+SMN2 SMN2



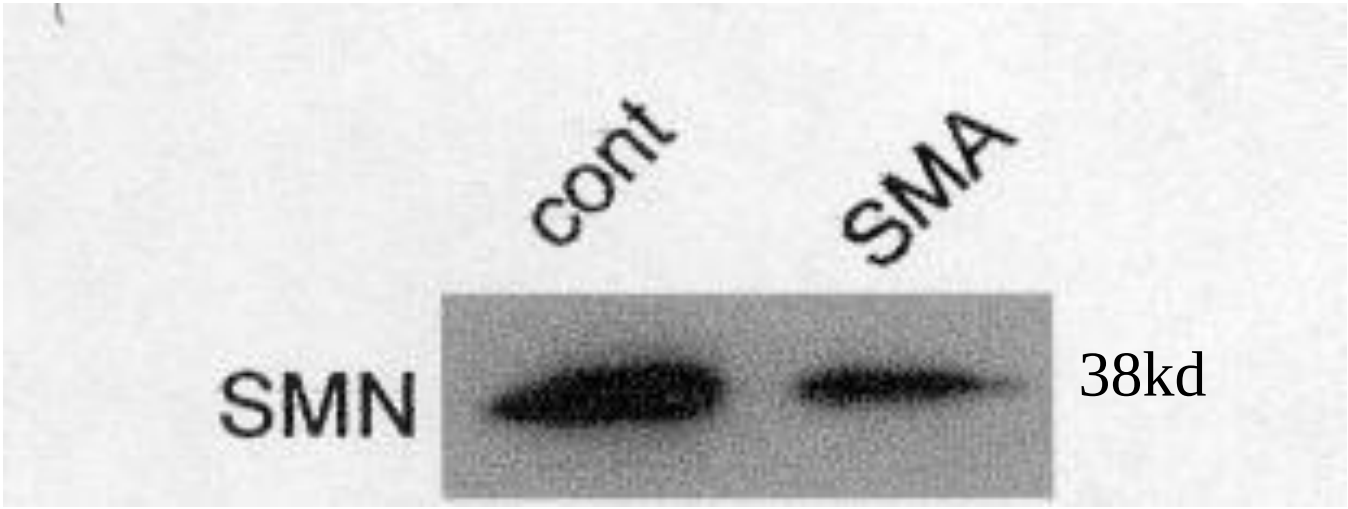
SMN transcripts Ex7

FL SMN (COMPLETE)

delta 7 SMN (INCOMPLETE)

SMN mRNA and protein in fetal SPINAL CORD

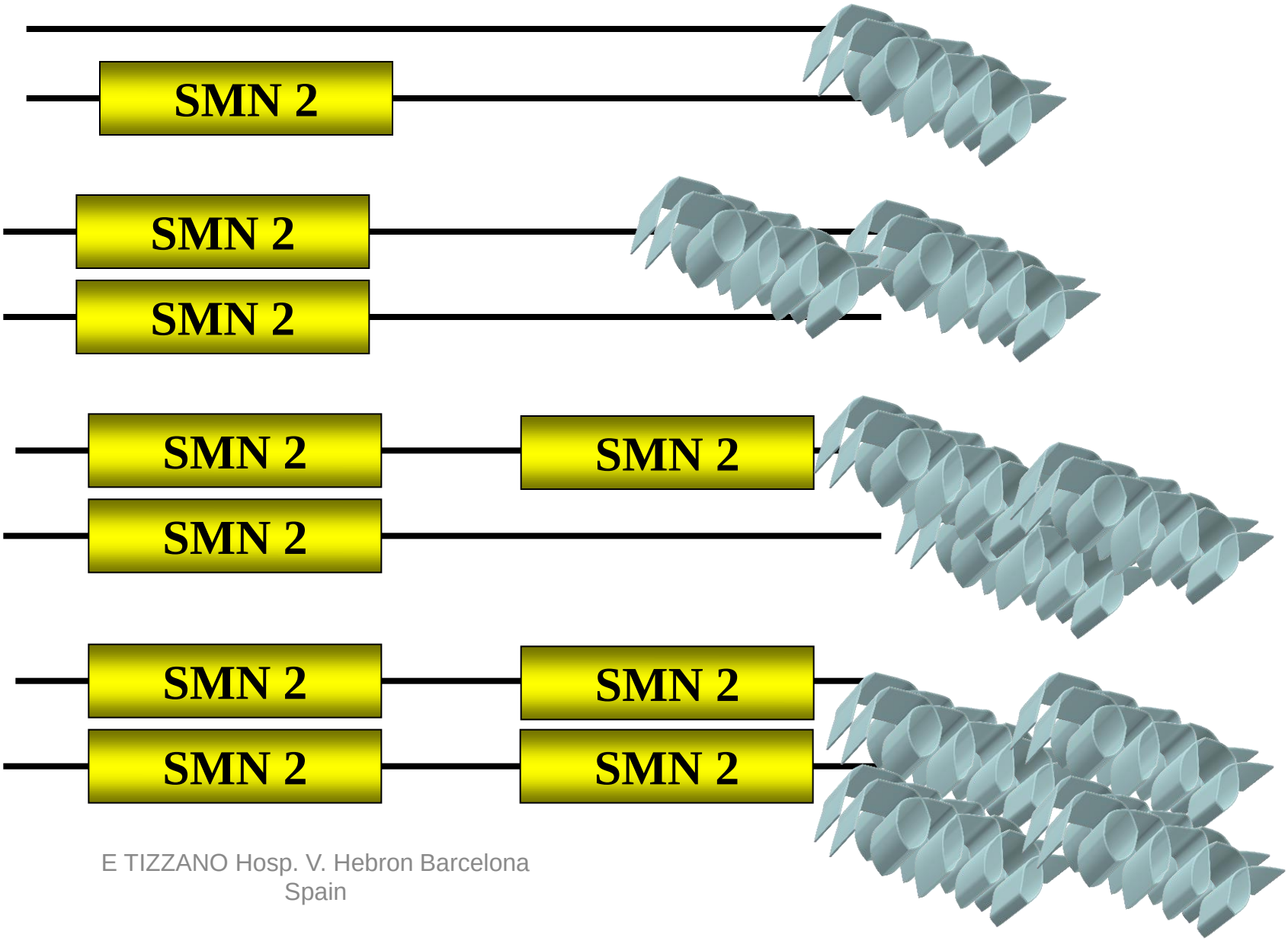
(15 weeks)

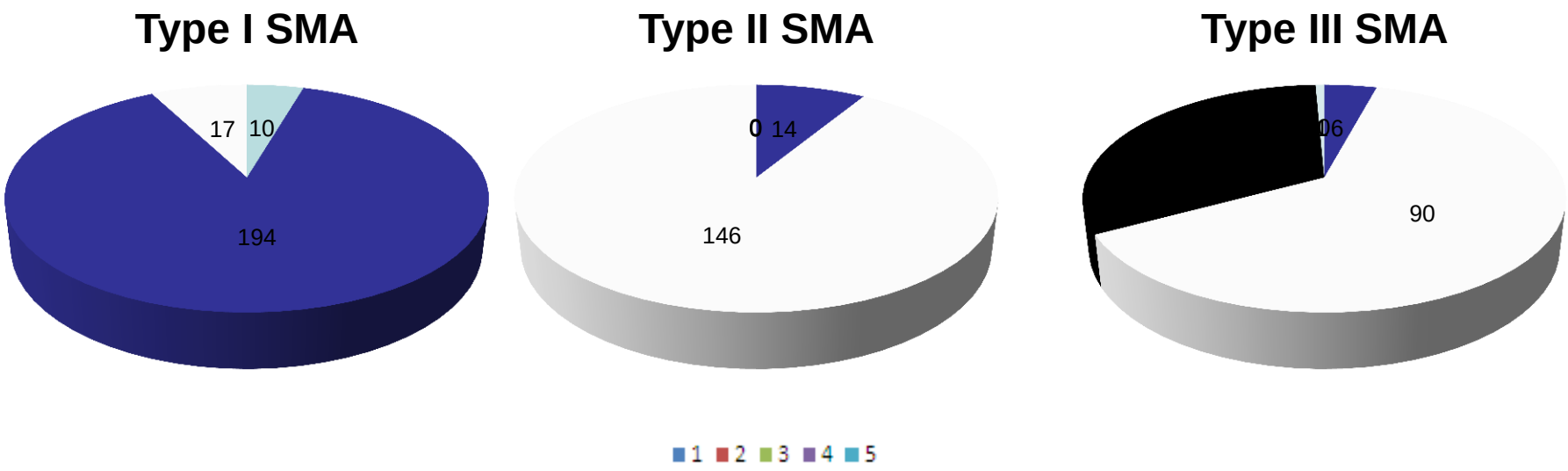


SMN1+SMN2 SMN2

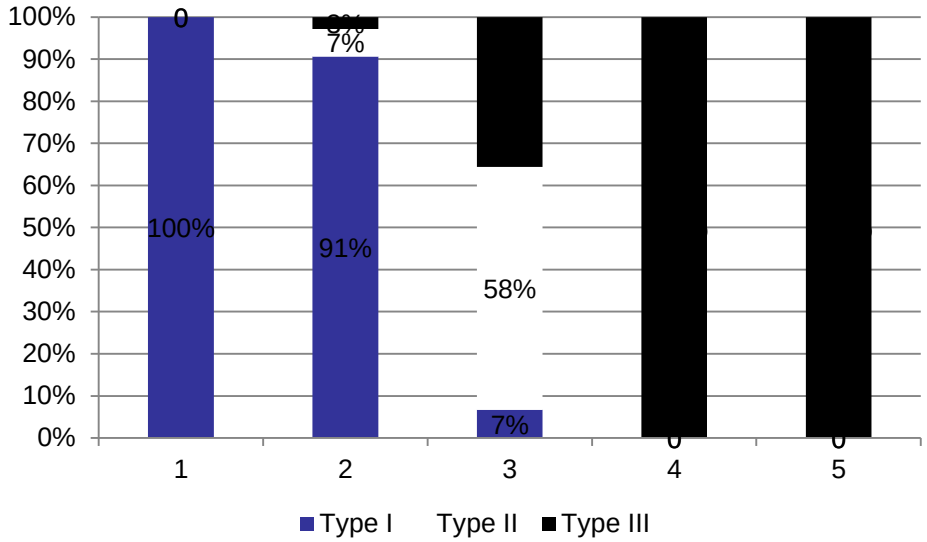
Soler-Botija et al., JNEN, 2005

SMN2 copies in SMA patients





	1 SMN2	2 SMN2	3 SMN2	4 SMN2	5 SMN2	
Type I SMA	10	194	17	0	0	221
Type II SMA	0	14	146	0	0	160
Type III SMA	0	6	90	46	1	139
	5	138	162	35	0	524



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	5	138	162	35	0	524

Disease severity typically depends on the number of copies of the SMN2 gene

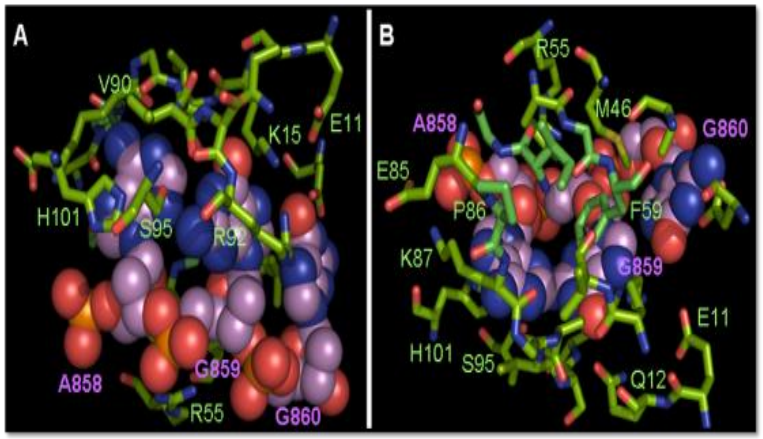
+ AGE OF ONSET + MOTOR MILESTONES

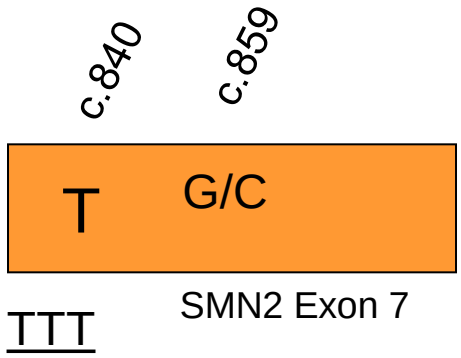
Phenotypic discordances

Moderate-mild patients (type II-III) with 2 SMN2 copies (variants in SMN2, i.e. c.859G>C)

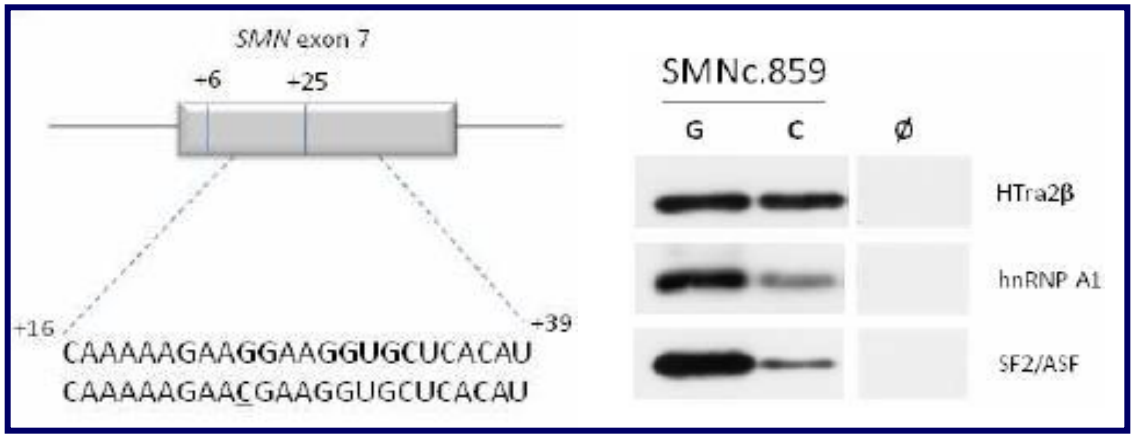
Phenotypic discordances in SMA

- **Moderate-mild patients (type II-III) with 2 SMN2 copies[5]**
  - variants in SMN2, i.e. c.859G>C in exon 7[2,3]



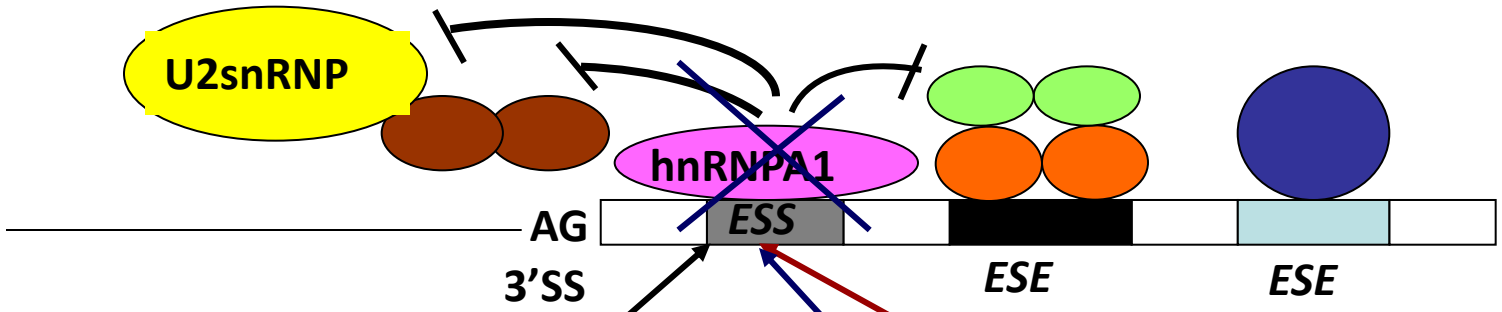


1. Hauke J, et al. Hum Mol Genet. 2009;18:304-17.
2. Prior TW, et al. Am J Hum Genet. 2009; 85: 408-13.
3. Vezain M, et al. Human Mut. 2010;31:E1110-25.
4. Oprea GE, et al. Science. 2008;320:524-7.
5. Bernal S, et al. J Med Genet. 2010;74:640-2.
6. Bernal S, et al. Neuromuscul Disord. 2011;21:413-9.



Vezain 2010

Inclusion exon 7 **(SMN2)** / exclusion exon 7 **(SMN2)**



Htra2-β1

SF2/ASF

SRp30

U2AF

TAGACA….GGAAGG (SMN2 WT) → **ESS**

TAGACA….CGAAGG (SMN2 mut) → **ESE**

ESE: Exonic Sequence Enhanced

ESS: Exonic Sequence Silencer

Distribution of the c.859G>C variant among SMA patients with 2 copies of the *SMN2* gene

SMA	Type I	Type II	Type III
Patients with the c.859G>C variant	0	4 (36%)	4 (80%)
Patients negative for the variant	126 (100%)	7 (64%)	1 (20%)
Total	**126**	**11**	**5**

Bernal S, et al. J Med Genet. 2010;74:640-2.

E TIZZANO Hosp. V. Hebron Barcelona Spain

Patient	1	2	3	4	5	6	7	8	9	10
Gender	Male	Male	Male	Male	Male	Male	Male	Male	Male	Female
Age (years)	65	36	22	59	34	18	30	12	5	3
SMA type	IIIb	IIIb	IIIb	IIIb	IIIb	IIIa	II	II	II	II
Age at onset of weakness (mths / yrs)	15 yrs	14 yrs	4 yrs	14 yrs	13 yrs	< 3 yrs	7 mths	8-9 mths	12 mths	14 mths
Walked unaided	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No
Wheelchair bound (age)	Yes (59 yrs)	No	No	Recently*	Recently*	Yes (6 yrs)	Yes**	Yes**	Yes**	-***
***SMN2* copies**	2	2	2	3	3	2	2	2	2	2
c.859G>C in *SMN2*	Homoz.	Homoz	Homoz	Hetz.	Hetz.	Hetz.	Hetz.	Hetz.	Hetz.	Hetz.
Telomeric *NAIP*	+	-	-	+	-	-	-	-	-	-
Parental inheritance	NA	Both	NA	NA	NA	M	P	NA	P	M
C272 alleles	**193**	**193**	**193**	189 191 **193**	181 189 **193**	181 **193**	183 **193**	181 **193**	183 **193**	181 **193**
C212 alleles	**225**	**227**	**227**	**225** **227** 233	219 221 **225**	217 **227**	217 **225**	215 **227**	217 **227**	215 **227**

Protocolos sobre terapia en la AME

- ESTRATEGIAS
- Eficacia terapéutica versus realidad biológica enfermedad
- Terapia Central versus periferica
- Ventana terapéutica
- Combinación Terapias

- EFECTOS
- Curación, detener el proceso, cambiar de tipo de AME
- Manifestaciones de la enfermedad con las nuevas terapias

- CONTEXTO
- Trasfondo biosicosocial
- Modelo seguimiento y atencion multidisicplinar
- Uniformidad Standard of Care

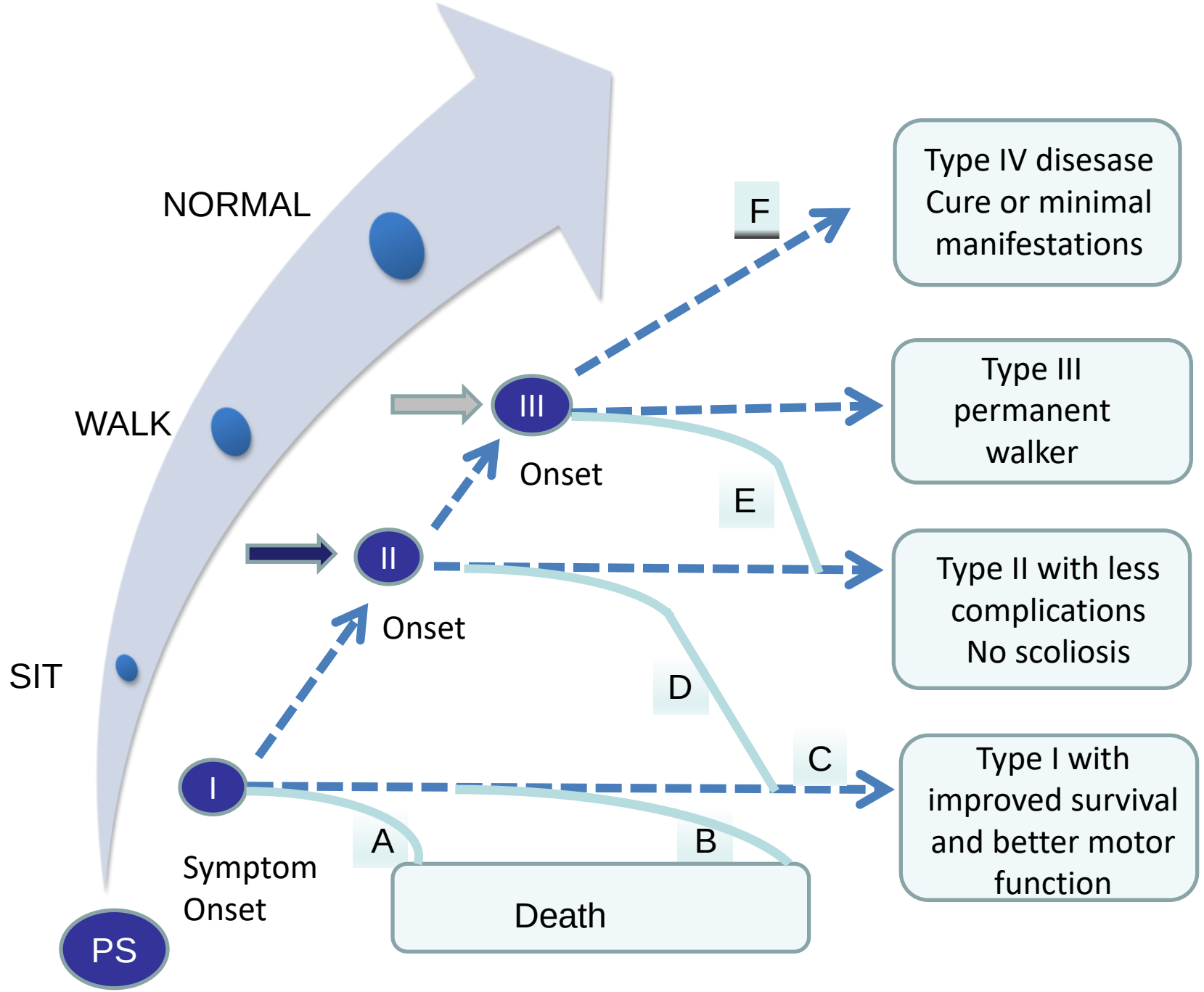
Issues on therapy in SMA: whom, what, where and when (w.w.w.w.)

Whom

- 1. **All SMA patients?**
- Severe Type 1 SMA and chronic Type 2 and III.
- Type 1A (or 0) may be beyond rescue at the time of birth.
- Adults with type IV need to be considered as well, with attention to the burden of the therapy versus the potential benefit to be accrued.
- 2. **Presymptomatic patients?**
- This raises the topic of newborn screening. Feasibility has already been demonstrated.

- *Expected changes in predicted natural histories*

(Tizzano and Finkel under revision)



(Tizzano and Finkel under revision)

Issues on therapy in SMA: whom, what, where and when (w.w.w.w.)

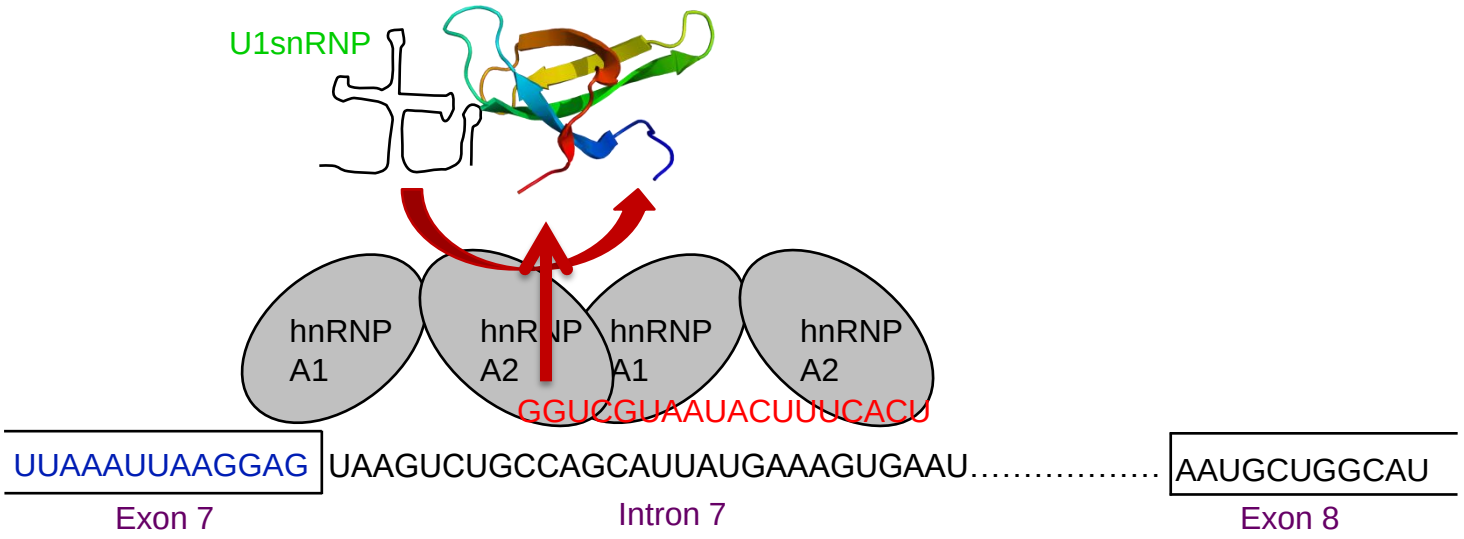
What

- 1. **SMN dependent**: SMN1 replacement, SMN2 splicing modulation
- 2. **SMN independent**: Neuroprotection, enhancement of neuromuscular transmission, myoactivation/muscle trophic agents.
- *Current measures for standard of care would continue to be part of the following-up strategies and interventional measures*

(Tizzano and Finkel under revision)

Modulation of *SMN2*

Ionis/Biogen program (1)



- 2’-*O*-methoxyethyl (MOE) modified antisense drug
- Displaces negative splicing factors on pre-mRNA, promoting inclusion of mis-spliced exon 7
- Promotes synthesis of fully functional SMN protein

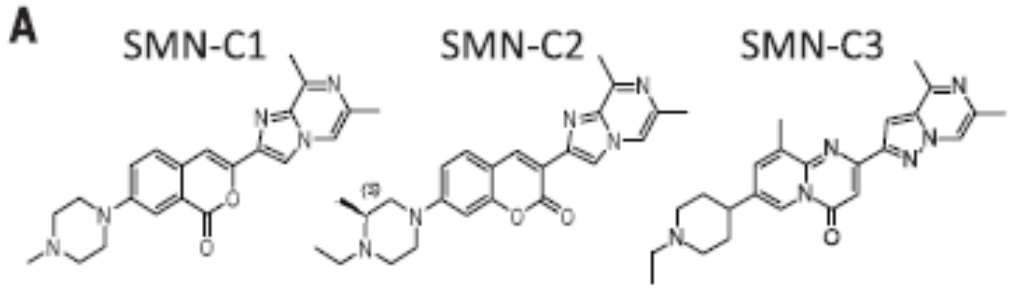
Farmacos orales que afectan la inclusión del exon 7 pero no se sabe su mecanismo de acción

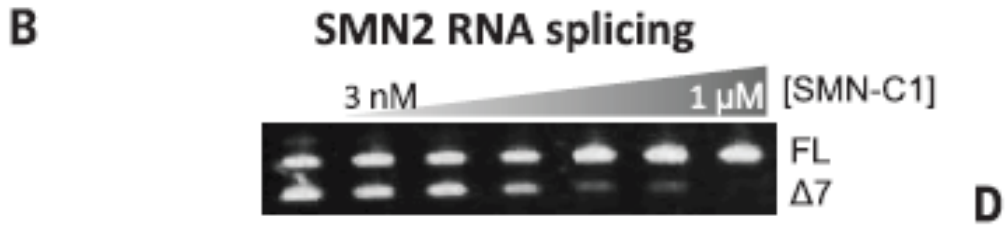
Science
AAAS

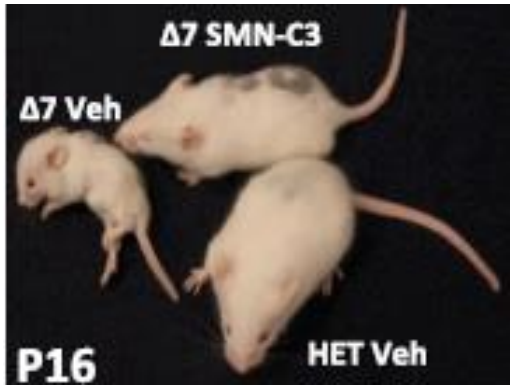
***SMN2* splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy**

Nikolai A. Naryshkin *et al.*

Science **345**, 688 (2014);
DOI: 10.1126/science.1250127





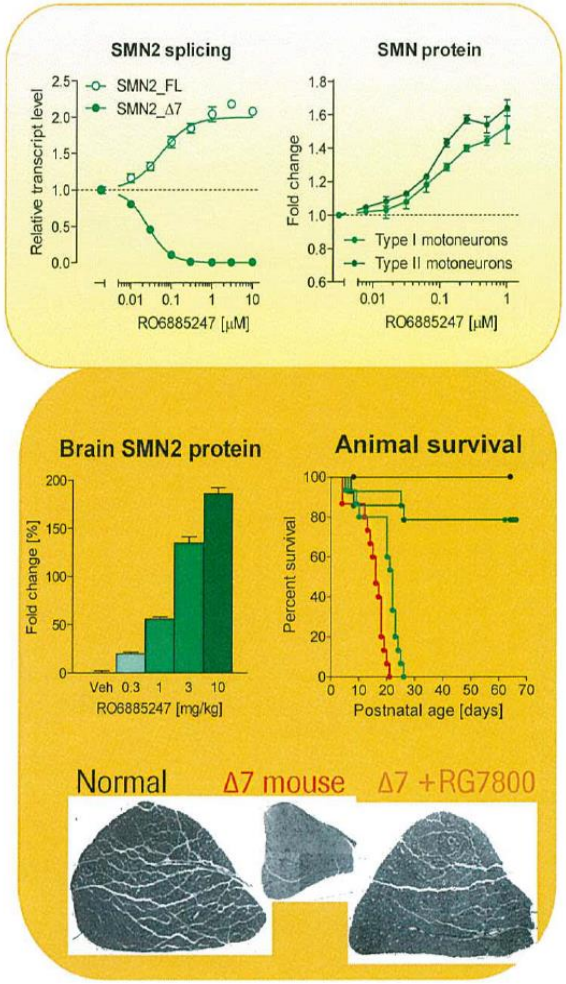


SMN2 splicing modifier for SMA

Preclinical summary

- In SMA patient fibroblasts
  - Modifies SMN2 splicing (ratio full length to Δ7 mRNA)
  - Increases SMN protein levels

- Highly active in SMA animal models
  - Modifies SMN2 splicing
  - Restores deficient SMN protein levels
  - Rescues motor neurons
  - Increases muscle mass
  - Increases body weight
  - Prolongs survival



PTC/ROCHE Program

✓ **R06885247/RG7800**

➢ **Moonfish trial (suspended)**

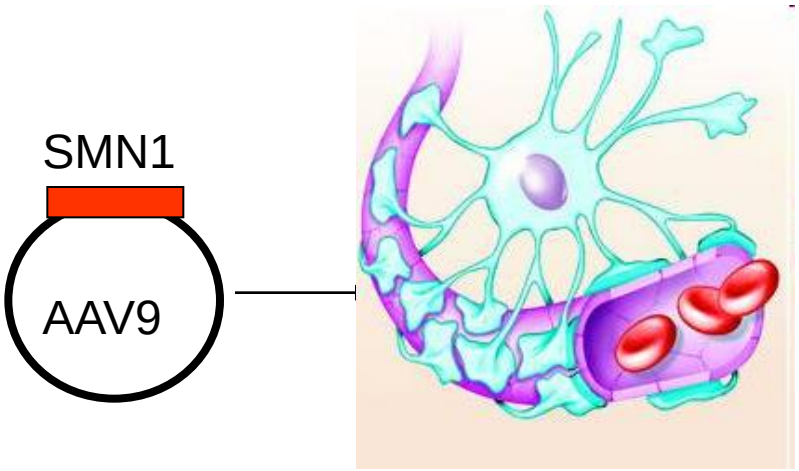
- Phase Ib, double-blind, randomized, placebo controlled, multiple dose
- Investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of RO6885247 following 12 Weeks of treatment
- adult and pediatric patients with spinal muscular atrophy (2 to 55 years old)

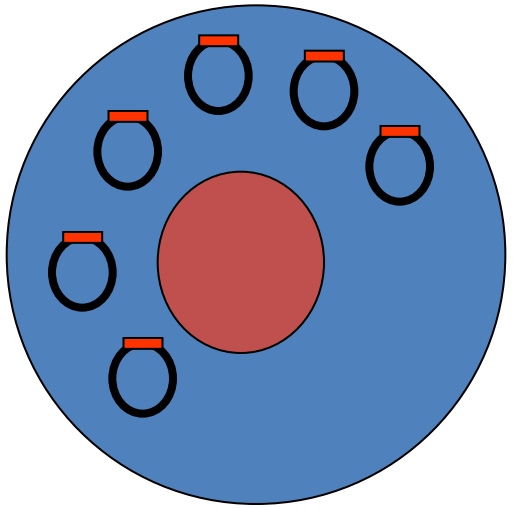
✓ **RO7034067/RG7916 (SUNFISH/ FIREFISH)**

- Phase I (2016) adaptive single-ascending-dose, placebo-controlled study
- Investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of RO7034067 given by mouth in **Healthy Volunteers**
- **End of 2016/Beginning of 2017 started dose studies in SMA patients** www.clinicaltrials.gov

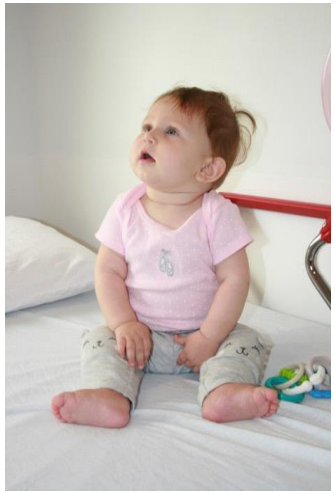
Transferir copias normales del gen SMN1 a la médula espinal (terapia génica).

- AAV9 que pasa la barrera hematoencefálica
- Aumenta la supervivencia cuando se administra muy precozmente al ratón SMA.
- Se estudió su eficacia ademas en un modelo de cerdo con SMA y se aprobó en 2014 el protocolo para tipo I en humanos por la FDA



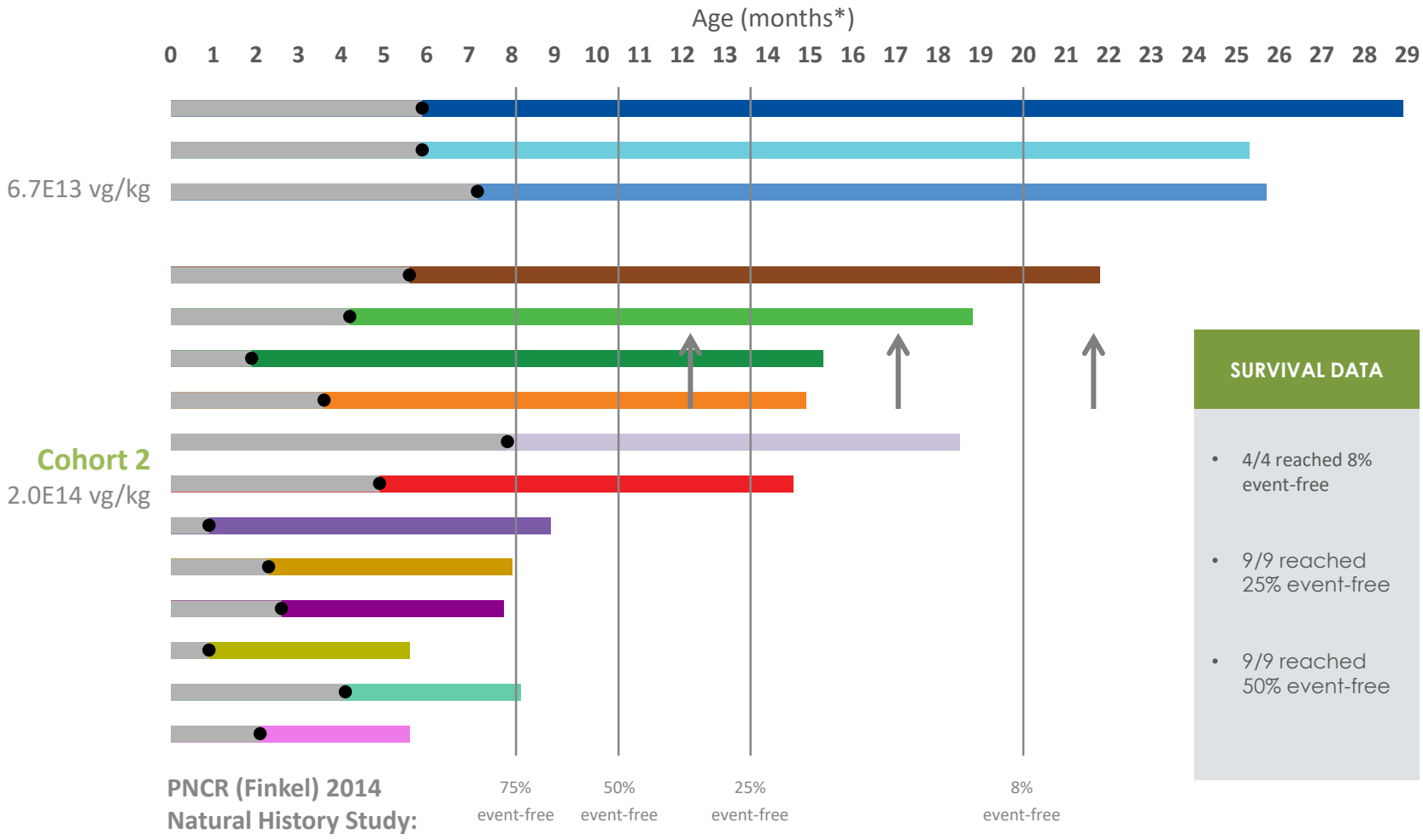


SMA Type 1 treated at 2 mo and picture 6 mo post GT



Courtesy Dr. J. Mandell /B. Kaspar

Survival Data – Ongoing Phase 1 Trial

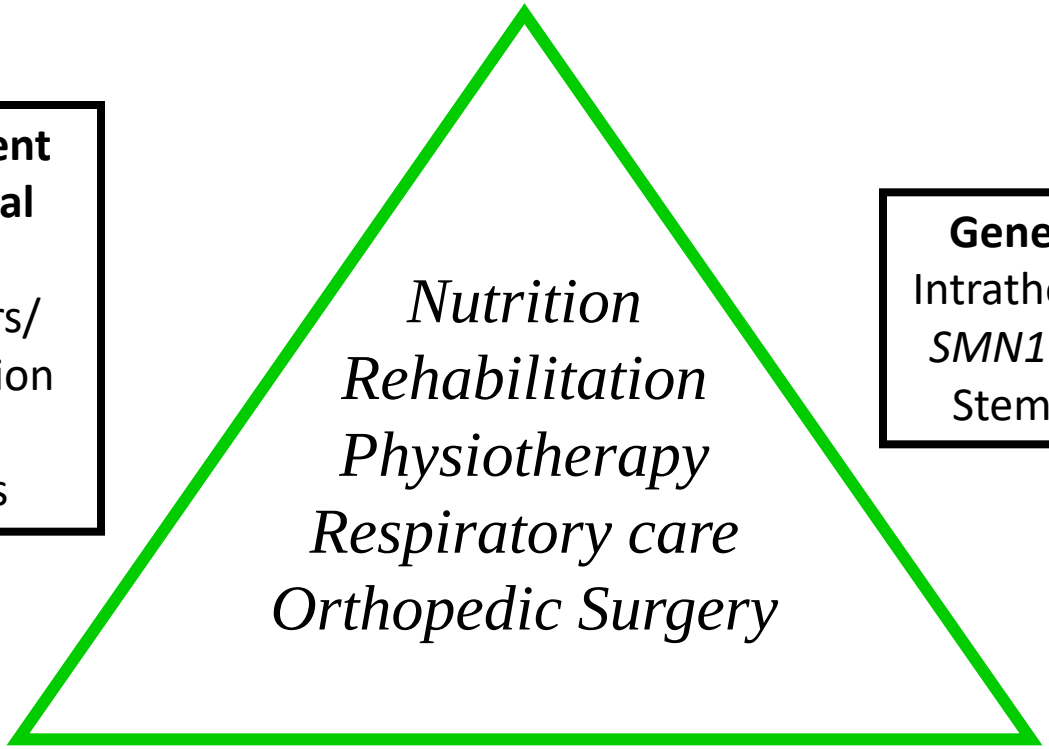


* A month is defined as 30 days

Courtesy Dr. J. Mandell /B. Kaspar

SMN2 splicing modifier approach
Antisense oligonucleotides molecules
Oral small molecules
(Oral [systemic] and/or intrathecal delivery; increased expression of full-length *SMN2* transcript)

SMN independent pharmacological approach
Neuroprotectors/
Neurotransmission enhancers /
Myoactivators



Gene replacement
Intrathecal or systemic
SMN1 gene transfer/
Stem cell therapy?

(Tizzano and Finkel under revision)

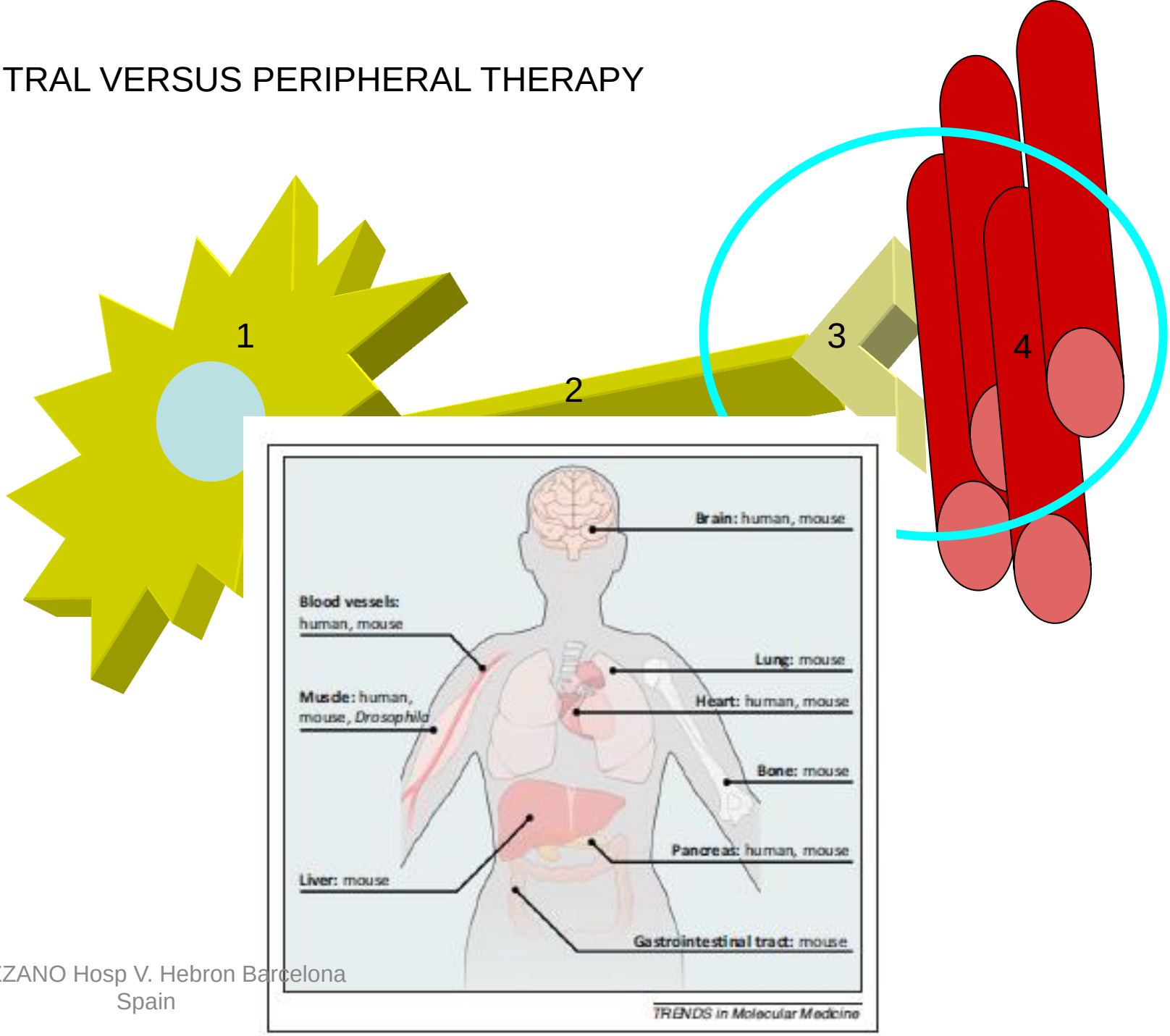
Issues on therapy in SMA: whom, what, where and when (w.w.w.w.)

Where

- 1. **Central therapy.**
- Clearly motor neurons need to be targeted. This can be accomplished with intrathecal antisense oligos, systemic neurotrophic vectors or oral small molecule drugs. Other neuronal types may be targeted.
- 2. **Peripheral therapy**.
- There is evidence from research in animal models and patient observations that peripheral therapy including neuromuscular junction and muscle would be necessary.
- *Combined central and peripheral therapy seems reasonable*

(Tizzano and Finkel under revision)

CENTRAL VERSUS PERIPHERAL THERAPY



Issues on therapy in SMA: whom, what, where and when (w.w.w.w.)

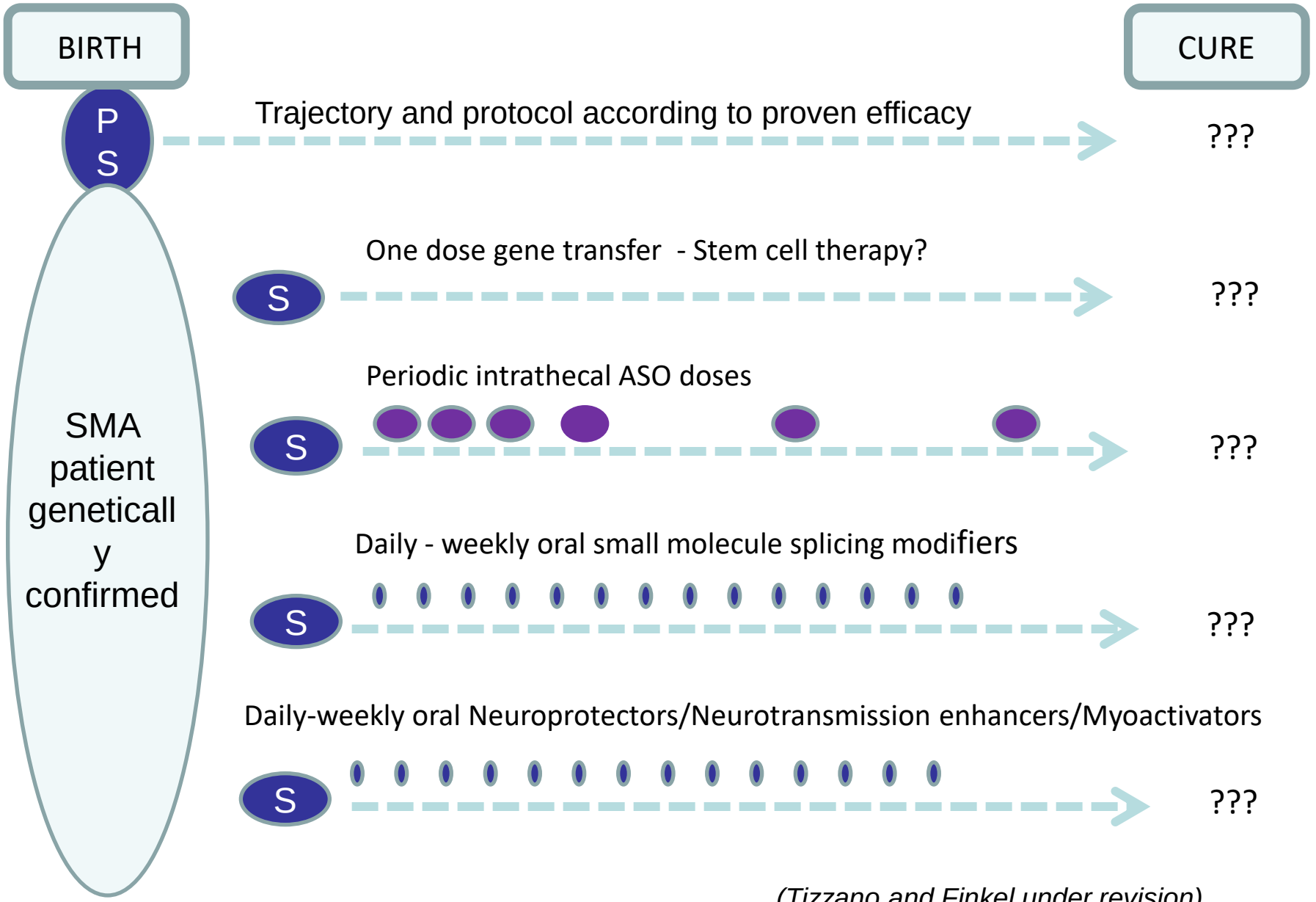
When

- 1. **Therapeutic window:**
- There is an interval of time in which dysfunctional MN and NMJ determine part of symptoms followed by MN death.
- An argument can be made for neonatal treatment in early detected cases, at least for those individuals with a SMN2 copy number of 2 or 3, and not to wait until the patient becomes symptomatic.

- 2. **Frequency of administration**:
- Gene transfer therapy may be a single dose treatment with life-long benefit. It is unclear if retreatment will be needed or is possible.

- *Other strategies such as antisense oligos or small molecule splicing modifiers are envisaged to be administered life-long to the patient*

(Tizzano and Finkel under revision)



(Tizzano and Finkel under revision)

Spinal Muscular Atrophy: a changing phenotype beyond the clinical trials

- SMA has evolving phenotypes due to improved standard of care and new treatments.
- The clinician should be alert to identify new patterns of motor development in SMA.
- Cognitive development in patients with SMA type 1 warrants further study.
- Other organ systems may develop signs of dysfunction as these patients live longer.
- Early diagnosis and intervention including presymptomatic newborn screening have to be considered
- Combined therapeutic strategies targeting central nervous system and peripheral tissues are envisaged.

(Tizzano and Finkel under revision)

ORGANISMO

Modelo

Biopsicoosocial

SOCIAL

PSIQUIS

Concepto: En muchas enfermedades raras, nos enfrentamos por primera vez a un tratamiento de las causas genéticas o de las alteraciones que éstas producen y por lo tanto no sabemos como responderá el paciente ni como se modificará su historia natural

Nos enfrentamos a un "nuevo" paciente.

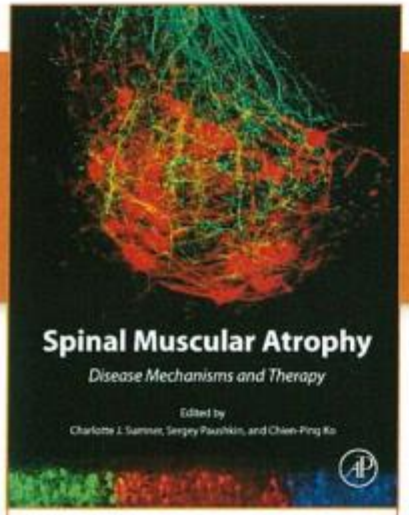
PACIENTES Y ORGANIZACIONES

DISPONIBILIDAD TERAPIA PARA PACIENTES

LABORATORIOS FARMACEUTICOS

MINISTERIOS

MUTUAS



Spinal Muscular Atrophy

Disease Mechanisms and Therapy

Edited by: *Charlotte J Sumner* Neurology and Neuroscience, Johns Hopkins University School of Medicine, USA
Sergey Paushkin Research, Spinal Muscular Atrophy (SMA) Foundation, USA
Chien-Ping Ko Neurobiology, Department of Biological Sciences, University of Southern California, USA

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FORMAT: Hardback
PAGES: c. 505
TRIM: 8.5w x 10.875h

AUDIENCE

Neuroscientists, biomedical researchers, grad students, postdocs, academic/biotech researchers, clinicians

A comprehensive reference on the entire spinal muscular atrophy field including disease mechanisms, pathology, standards of care, and therapeutic development

KEY FEATURES

- Provides comprehensive up-to-date reviews by leading investigators on diverse topics of SMA including clinical features and patient care, SMN genetics and protein functions, animal models, disease pathology and mechanisms, biomarkers, current therapeutic development, as well as the role of non-profit organizations in therapeutic development
- Written to bridge multiple disciplines and promote better communications among basic scientists, clinical researchers and health care providers on the latest development in SMA
- Chapters include outstanding questions/perspectives for future investigations and key references for additional detailed study

DESCRIPTION

Spinal Muscular Atrophy (SMA), characterized by motoneuron loss and muscle atrophy, is the leading genetic cause of infant mortality. Since the identification of the gene responsible for SMA in 1995, there have been important advances in basic understanding of disease mechanisms as well as in therapeutic development. **Spinal Muscular Atrophy: Disease Mechanisms and Therapy** is a comprehensive reading of recent advances in basic and clinical research. The book covers SMA clinical features and standards of care, multifaceted aspects of SMN protein functions and SMA disease pathology, various animal models, biomarkers, as well as current therapeutic development.

This title is ideal for graduate students/postdocs and principal investigators who are already in the SMA field and need to keep updated of recent findings and approaches, and also those who are new to, or would like to join, the field. Likewise, **Spinal Muscular Atrophy: Disease Mechanisms and Therapy** provides an excellent source of readings for biotech/pharma scientists, clinical researchers and practitioners, regulators, as well as patients and their advocacy organizations. Furthermore, this book is a handy reference for researchers and clinicians who may want to apply the research strategies and therapeutic approaches in SMA to other rare diseases.

CHAPTER

2

Developmental Aspects and Pathological Findings in Spinal Muscular Atrophy

M.J. Pérez-García[1], *L. Kong*[2], *C.J. Sumner*[1,2], *E. Tizzano*[1,3]

[1]Vall d'Hebron Hospital, Barcelona, Spain; [2]Johns Hopkins University School of Medicine, Baltimore, MD, United States; [3]Vall d'Hebrón Research Institute, Barcelona, Spain

OUTLINE


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Menthol


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Vall d'Hebron
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FUNDACIÓ PRIVADA
DANIEL BRAVO ANDREU

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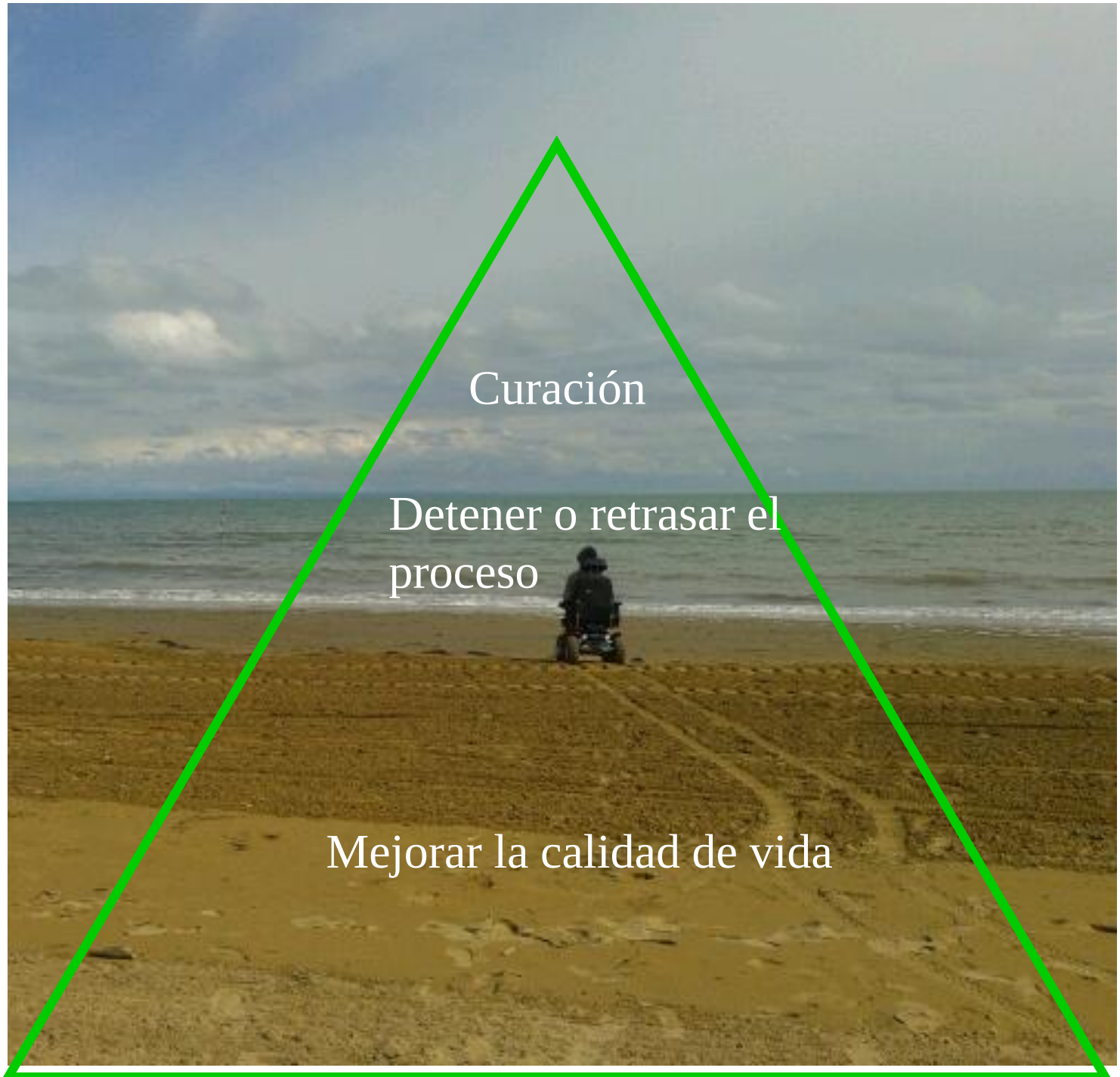
Fundación Atrofia Muscular Espinal

SMA Europe

Institut sant pau


Curación
Detener o retrasar el proceso
Mejorar la calidad de vida

Vall d'Hebron Hospital

Institut sant pau

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Instituto de Salud Carlos III

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SMA Europe

Historia natural tipo I

AME tipo I tiene un curso variable							
Subtipo AME I	**Edad comienzo**	**Contracturas**	**Control cefalico**	**Alimentación**	**Función respiratoria**	**Evolución**	**SMN2**
IA	**Prenatal**	**+al nacer**	**Ausente**	**Mala**	**Mala**	**Semanas Cardio-patías**	**1**
IB	**<3M**	**-**	**Pobre**	**Suficiente**	**Suficiente**	**Declinación linear**	**2**
IC	**>3M**	**-**	**Presente**	**Adecuada**	**Adecuada**	**Plateau**	**3**

Bertini et al., 2005, Rudnik-Schöneborn et al., 2009

Ionis/Biogen program (3)
Ionis-SMNrx (Nusinersen)

✓ **EMBRACE Trial (2015-2017: ongoing)**

- Phase II, double-blind, randomized, sham-procedure controlled study
- 21 infants and childrens who was not eligible to participate Endear and Cherish study
- Assess the safety and tolerability and explore the efficacy of nusinersen
- US study

✓ **NURTURE trial (2015-2020: ongoing)**

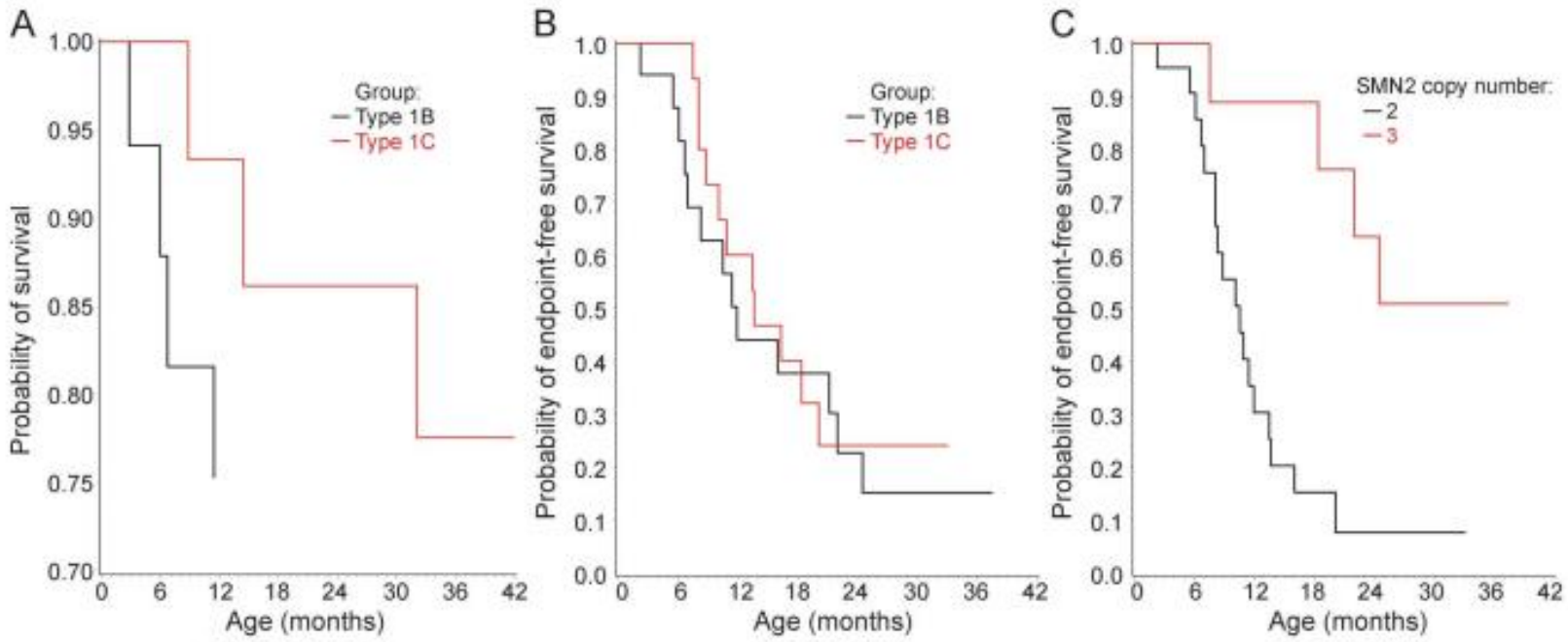
- Phase II, open label, multidose study (intrathecal injection)
- 25 presymptomatic SMA infants (up to 6 weeks)
- Evaluate the efficacy of multiple doses of nusinersen in preventing or delaying the need for respiratory intervention or death in infants
- International study

Actualization	cherish **Recruitment finalized** endear **Recruitment finalized**
Future steps	• **EAP ongoing** • **Approval FDA and EMA** • **Accelerate process of commercialization**

www.clinical trials.gov

IONIS PHARMACEUTICALS

Figure 1 **Time-to-event curves for SMA-I**



Kaplan-Meier curves for SMA-I. (A) Probability of survival with advancing age by SMA-I subtype (type IB, n = 18; type IC, n = 16). (B) Probability of not reaching the combined endpoint of death or the need for a minimum of 16 hours/day of noninvasive ventilation support for a minimum of 14 continuous days, in the absence of an acute reversible illness or perioperatively, with advancing age by SMA-I subtype. (C) Probability of not reaching the combined endpoint with advancing age by *SMN2* copy number (2 copies, n = 23; 3 copies, n = 9). SMA-I = spinal muscular atrophy type I.

The median age at reaching the combined endpoint of death or requiring at least 16 hours/day of ventilation support was **13.5 months** (interquartile range 8.1–22.0 months)

Infants with SMA-I can be effectively enrolled and retained in a 12-month natural history study until a majority reach the combined endpoint

Finkel et al., 2014

Discordancias fenotípicas

Pacientes graves (tipo I) con 3 copias de SMN2

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

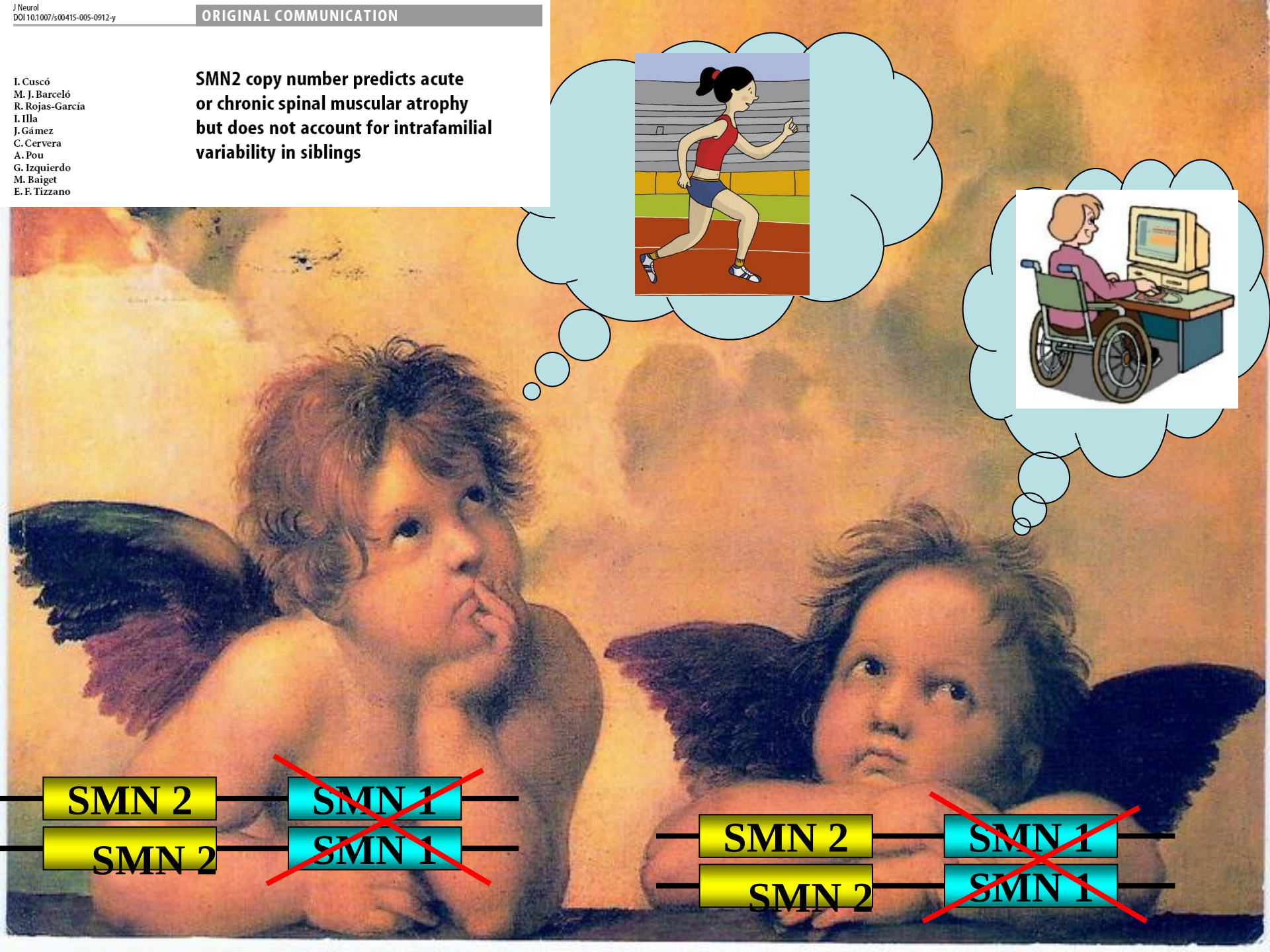
Hermanos haploidenticos pero con evolución diferente

J Neurol
DOI 10.1007/s00415-005-0912-y

ORIGINAL COMMUNICATION

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

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



Correlación genotipo fenotipo

- Todos pacientes tienen ausencia o mutaciones en el gen SMN1
- Todos los pacientes tienen al menos una copia del gen SMN2
- No se ha descrito ausencia total de ambos genes
- El número de copias del gen SMN2 puede definir con una alta probabilidad el tipo de AME aunque no es absoluto cuando hay dos o tres copias
- En los hermanos con fenotipo diferente, el número de copias de SMN2 es igual

AME en España

- 745 pacientes no relacionados con mutaciones en SMN1
  - 377 varones (50.6%)
  - 368 mujeres (49.4%)
- 367 tipo I (49.2%) 165 var 202 muj
- 225 tipo II (30.2%) 123 v 102 m
- 153 tipo III (20.5%) 89 v 64 m

(Alias et al., 2009)

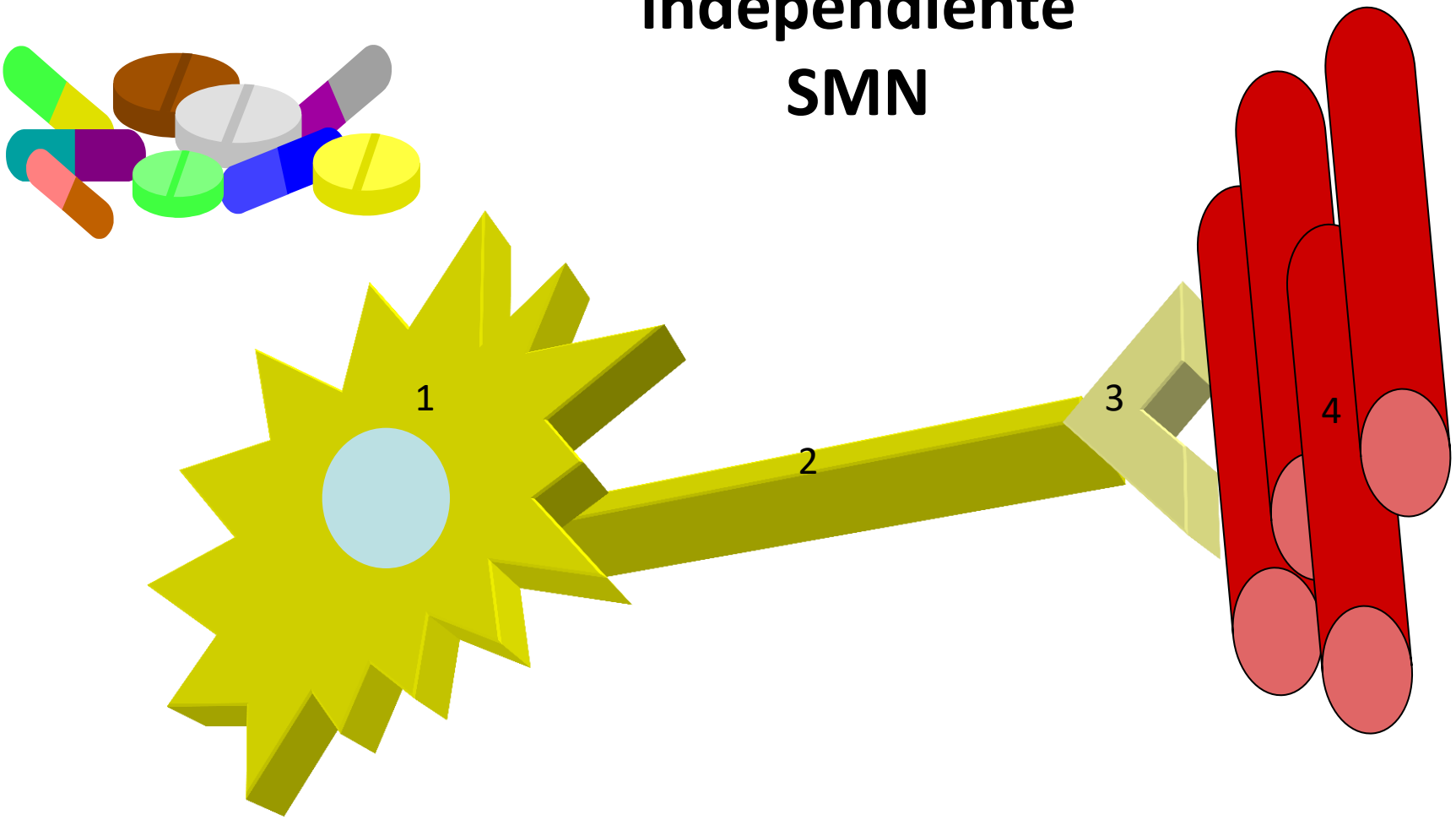
($p<0.008$)

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)

Estrategia independiente SMN



NEUROPROTECTION

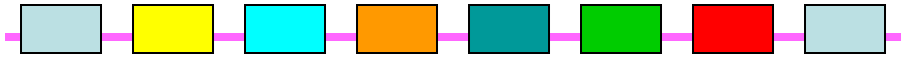
Riluzol, Olesoxime, Cardiotrophin

MYOPROTECTION-IMPROVEMENT

Salbutamol, Follistatin, Tirasemtiv

Targeting SMN genes

SMN2 upregulation



VPA, Phenylbutyrate, Hydroxyurea, , Salbutamol

Including exon 7 in SMN2 transcripts.

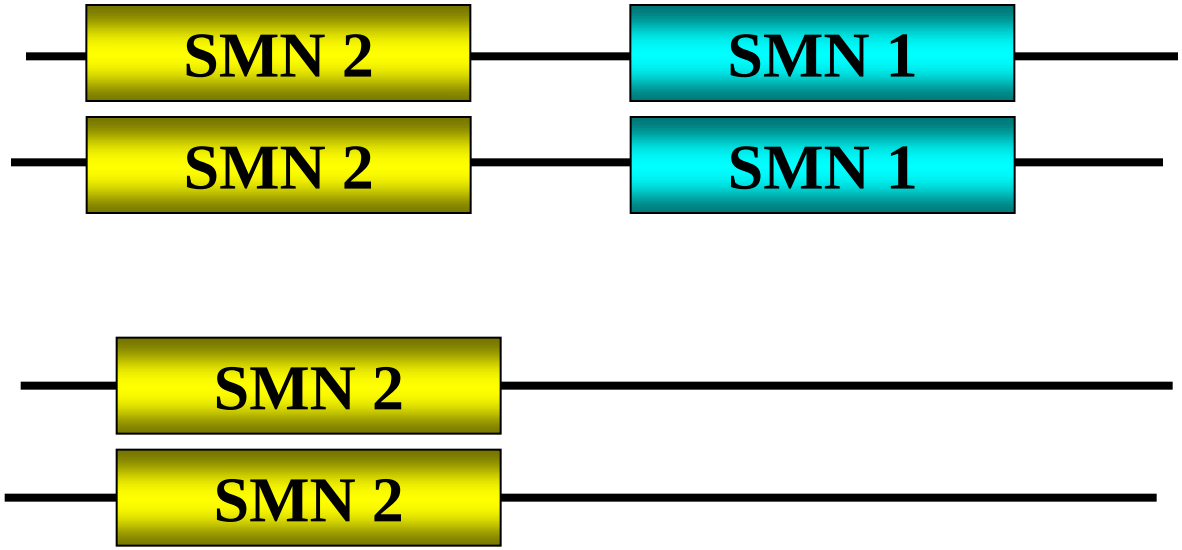
SMN RX (antisense)
RO6885247 (MOONFISH)

PAUTAS MOTORAS EN LA AME

NUNCA SE SIENTAN

NUNCA CAMINAN

PERDIDA DEAMBULACION



SMN 2

SMN 2

I

SMN 2

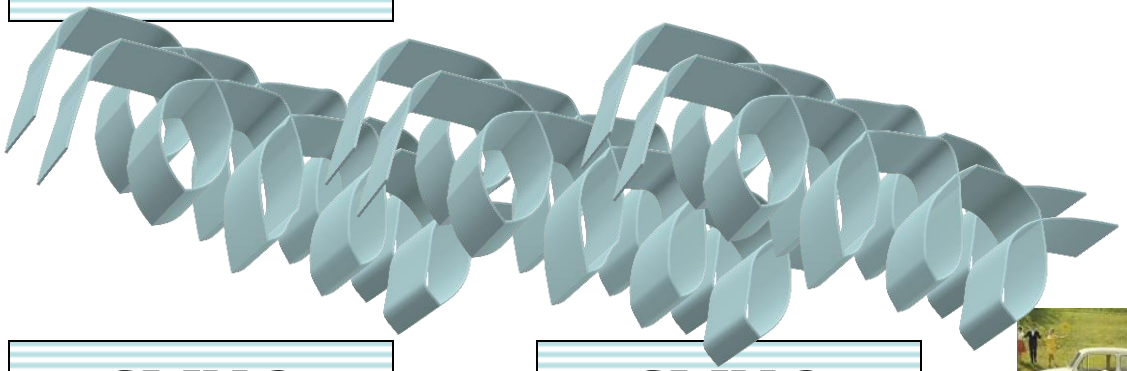
Ningún paciente se ha descrito con ausencia de los dos genes SMN

II / III

SMN 2

SMN 2

SMN 2

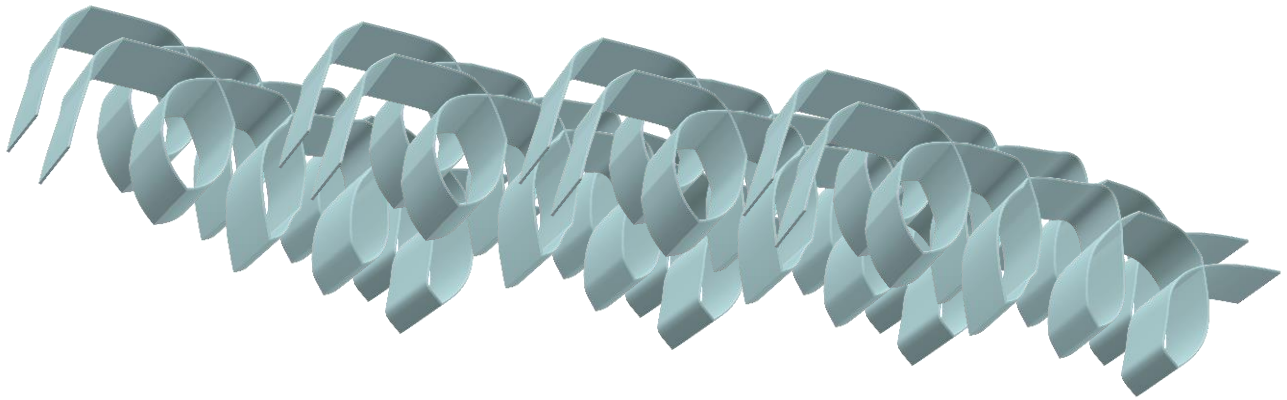


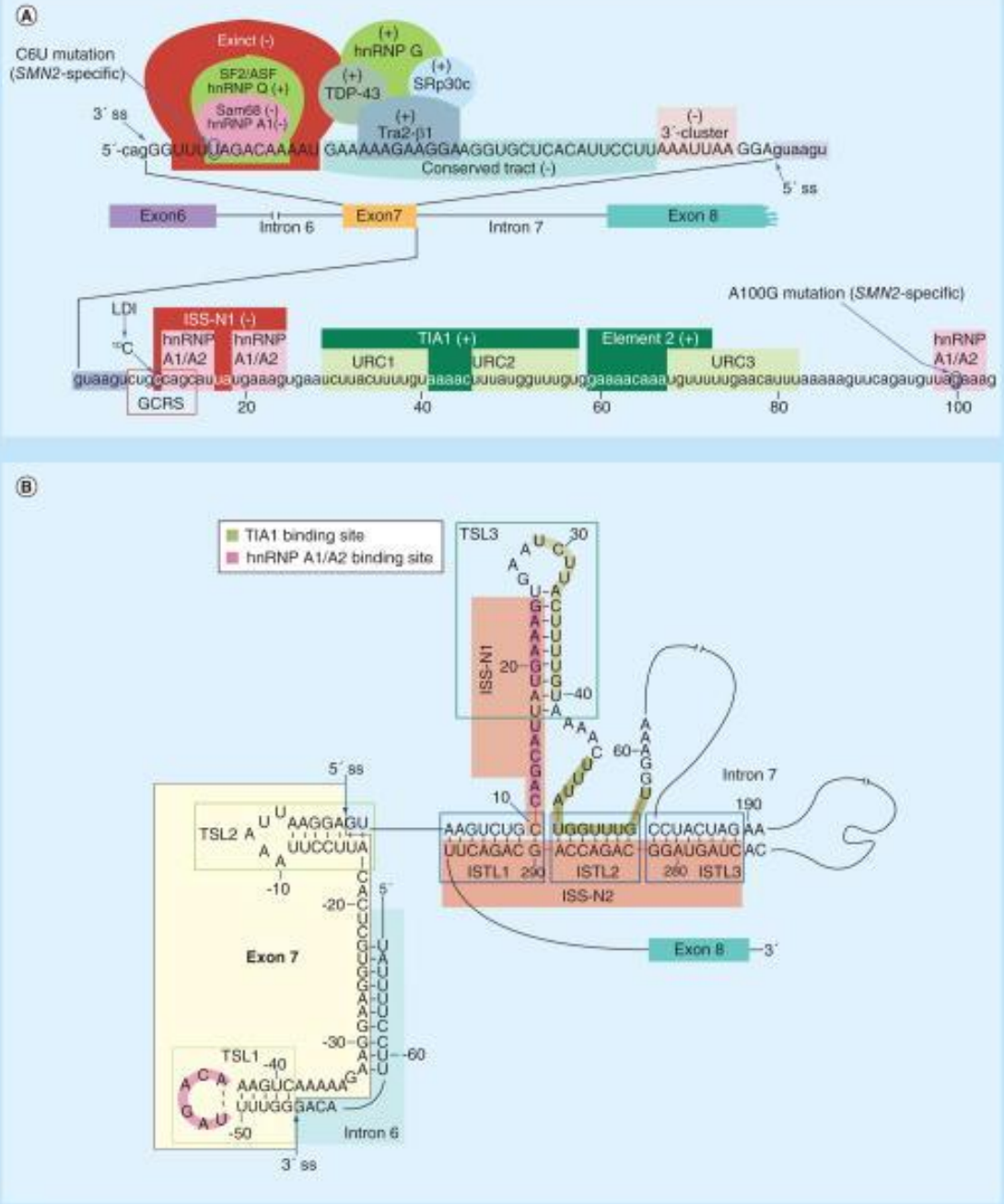
SMN 2

SMN 2

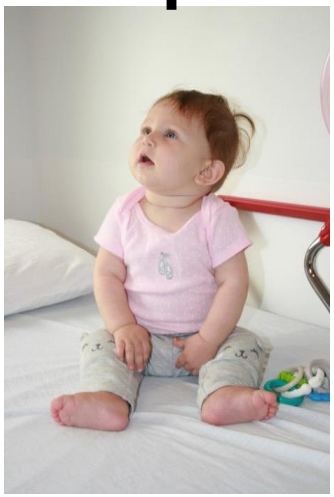
SMN 2

SMN 2

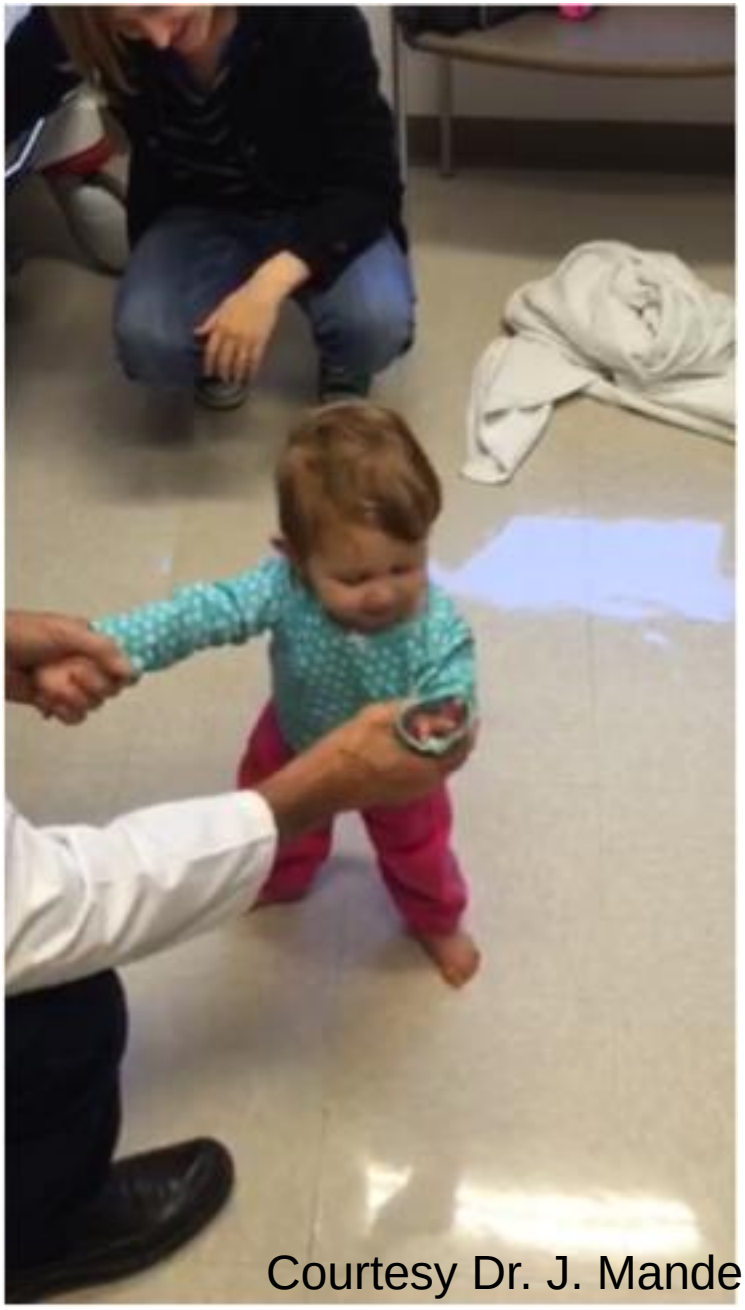


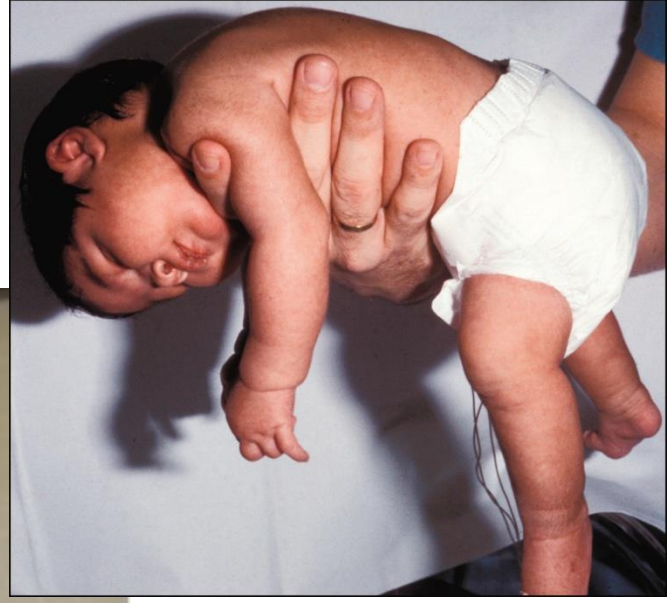

A
C6U mutation (SMN2-specific)
Exinct (-)
SF2/ASF hnRNP Q (+)
Sam68 (-) hnRNP A1(-)
(+) hnRNP G
(+) TDP-43
(+) SRp30c
(+) Tra2-β1
(-) 3´-cluster
3´ ss
5´-cagGGUUUUAGACAAAAU GAAAAAGAAGGAAGGUGCUCACAUUCCUUAAAUUAA GGAguaagu
Conserved tract (-)
5´ ss
Exon6
Intron 6
Exon7
Intron 7
Exon 8
LDI
ISS-N1 (-)
hnRNP A1/A2
hnRNP A1/A2
TIA1 (+)
Element 2 (+)
URC1
URC2
URC3
A100G mutation (SMN2-specific)
hnRNP A1/A2
GCRS
20
40
60
80
100
B
TIA1 binding site
hnRNP A1/A2 binding site
TSL3
ISS-N1
Intron 7
TSL2
5´ ss
Exon 7
ISTL1
ISTL2
ISTL3
ISS-N2
Exon 8
TSL1
Intron 6
3´ ss

SMA Type 1 treated at 2 mo and picture 6 mo post GT



Courtesy Dr. J. Mandell /B. Kaspar





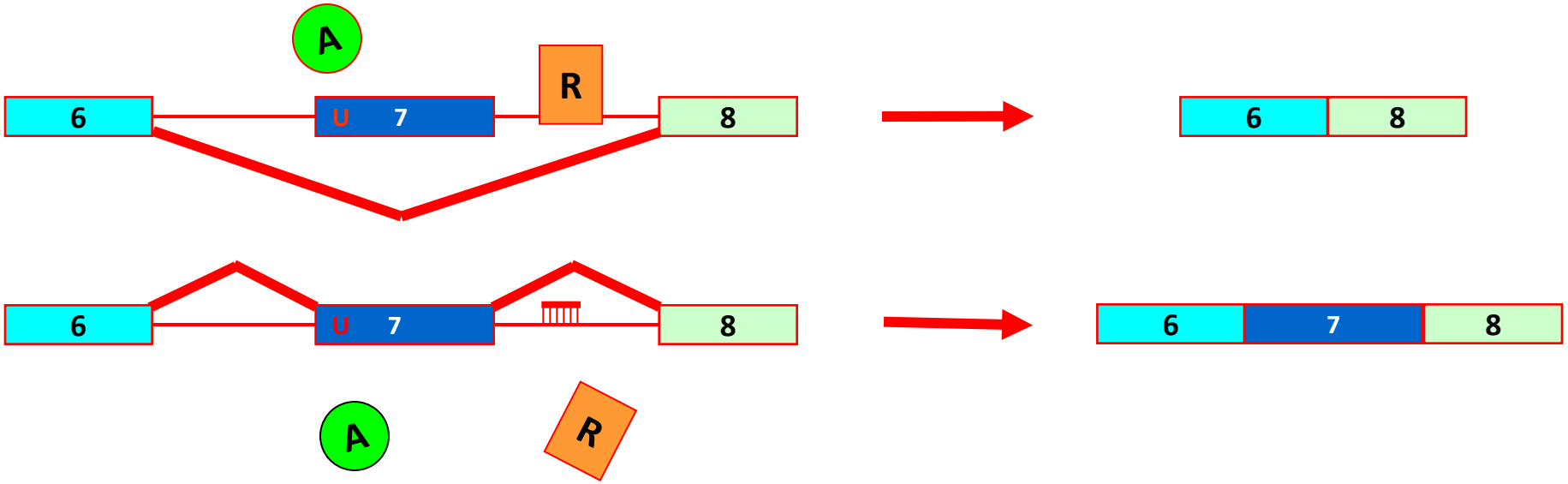
Courtesy Dr. J. Mandell /B. Kaspar

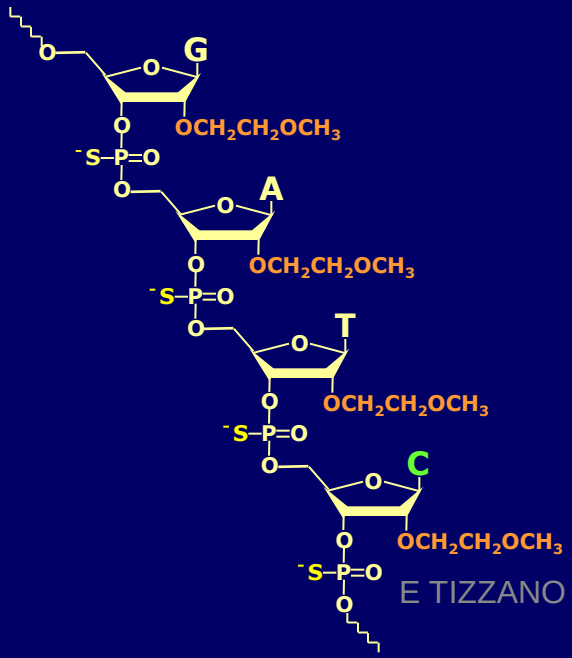

FLUJO DEL LÍQUIDO CEFALORRAQUÍDEO
Glot-Up
www.glot-up.com

SMA: Incidence and Prevalence

- Frequency of types of SMA
  - Type I ~ 50%
  - Type II ~ 30%
  - Type III ~ 20%
- Prevalence of carrier (based on direct carrier testing):
  - **Europe: 1:35 (2.7%)**
  - Asian population: 1 : 56 (1.8%)
  - African population: 1 : 91 (1.1%)
- Incidence: **~1 : 5,000/6,000** Europe
- Prevalence of SMA: **~25,000** Europe (~40% under 20 yrs)

(Feldkötter et al. AJHG 2002; Cuscon et al EJHG 2002, Alias et al, 2009; Alias et al, 2013, Hendrickson et al JMG 2009; Sugarman et al 2012)





2'-*O*-(2-methoxyethyl) ribose

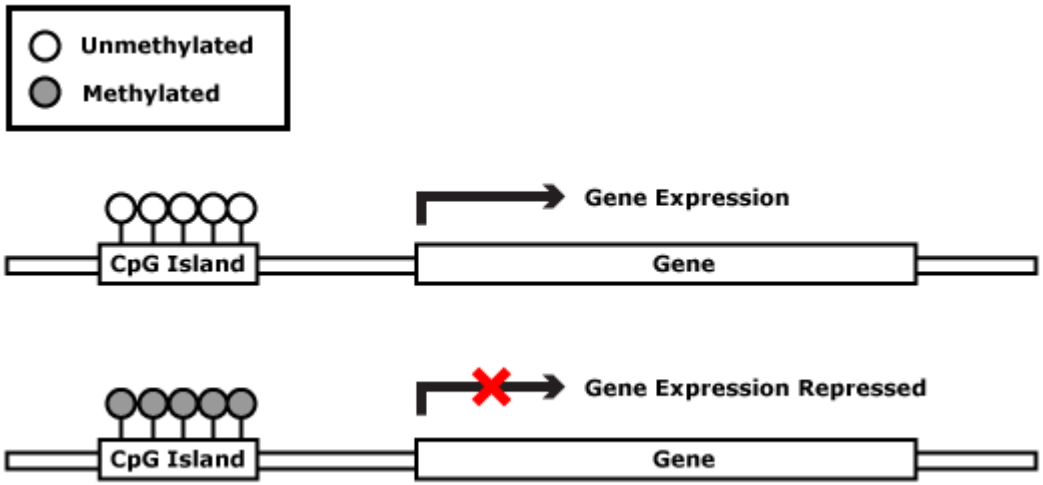
phosphorothioate

5-methyl cytosine

ISIS PHARMACEUTICALS

Phenotypic discordances

Severe patients (type I) with 3 SMN2 copies (methylation?)



Phenotypic discordances

Patients with 3 SMN2 copies may be type II (sitters) or type III (walkers)

Patients with 3 SMN2 copies may be type II and some may be weak sitters (that may after loss this capacity) or others may stand and walk with help

Need for biomarkers that predict standing-walk

Phenotypic discordances

Haploidentical siblings with different clinical evolution

(Modifier genes cis or trans, PLS3?)

J Neurol
DOI 10.1007/s00415-005-0912-y

ORIGINAL COMMUNICATION

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

I. Cuscó
M. J. Barceló
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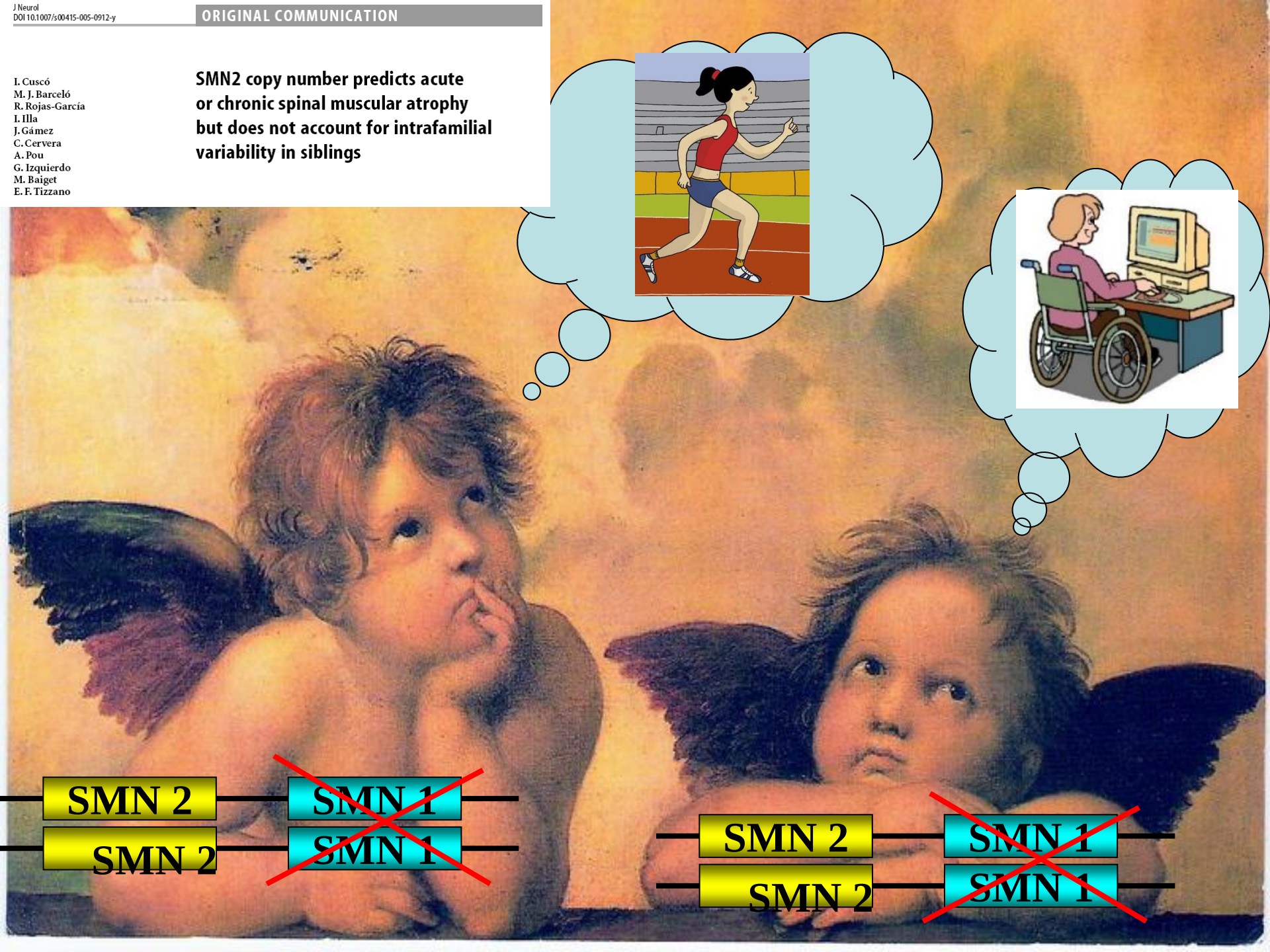
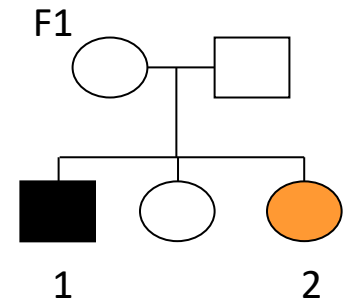
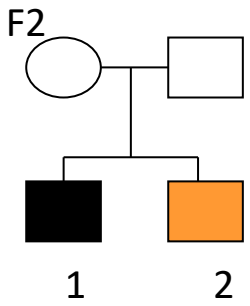
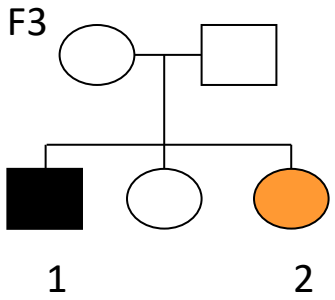
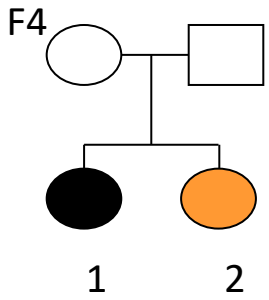




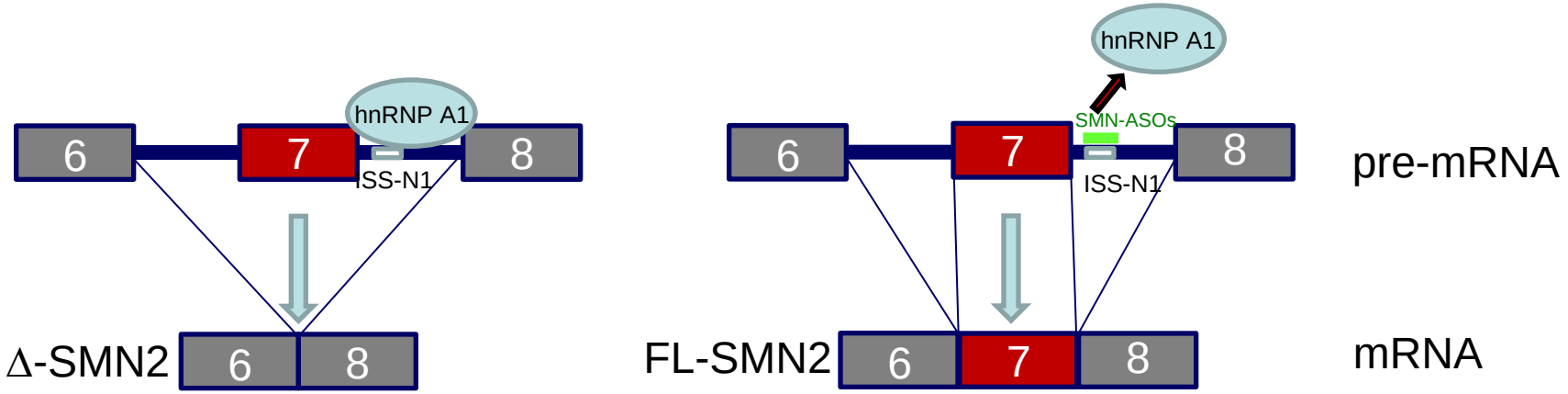


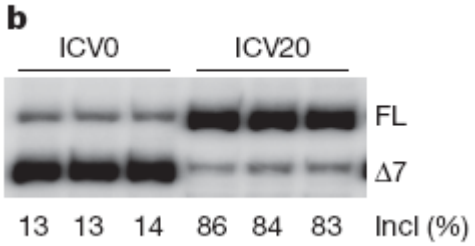


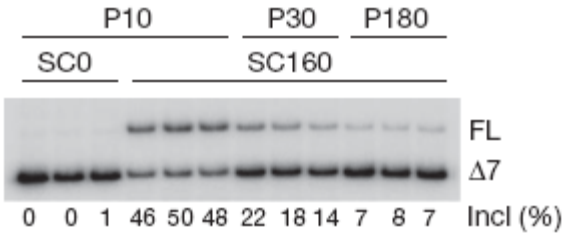


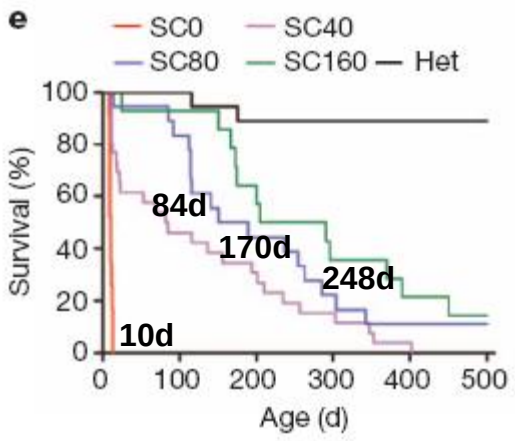
Family	Nº	Phenotype	Onset	Wheelchair	Symptoms	EMG	NAIP	SMN2 copies
F1	1	Type III	2	17	+++	D	+	4
	2	A	-	-	-	MUP	+	4
F2	1	Type III	8	12	+++	D	+	4
	2	Type IV	32	-	+	D	+	4
F3	1	Type III	2	12	+++	D	+	3
	2	Type III	2	-	+/++	D	+	3
F4	1	Type II	<1	2	++++	D	+	3
	2	Type III	12	20	++/+++	D	+	3

SMN2 splice correction by antisense oligonucleotides (ASOs), morpholinos (MOs) or peptide-mediated oligonucleotides (PMOs)





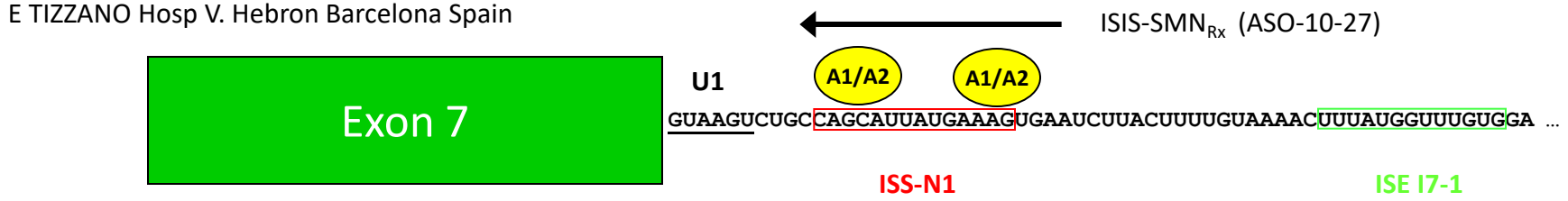


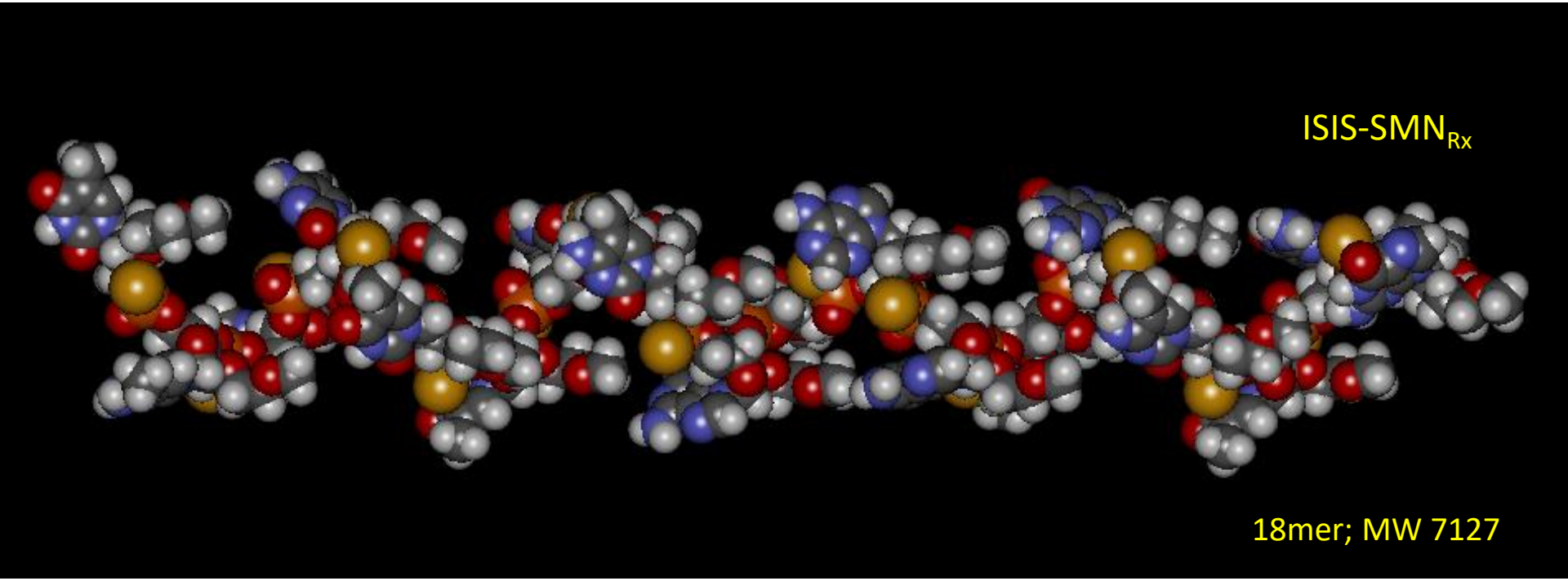


(Hua et al. Nature 2011; Porensky et al. HMG 2012; Hammond et al. PNAS 2016)

ANTISENSE THERAPY

E TIZZANO Hosp V. Hebron Barcelona Spain





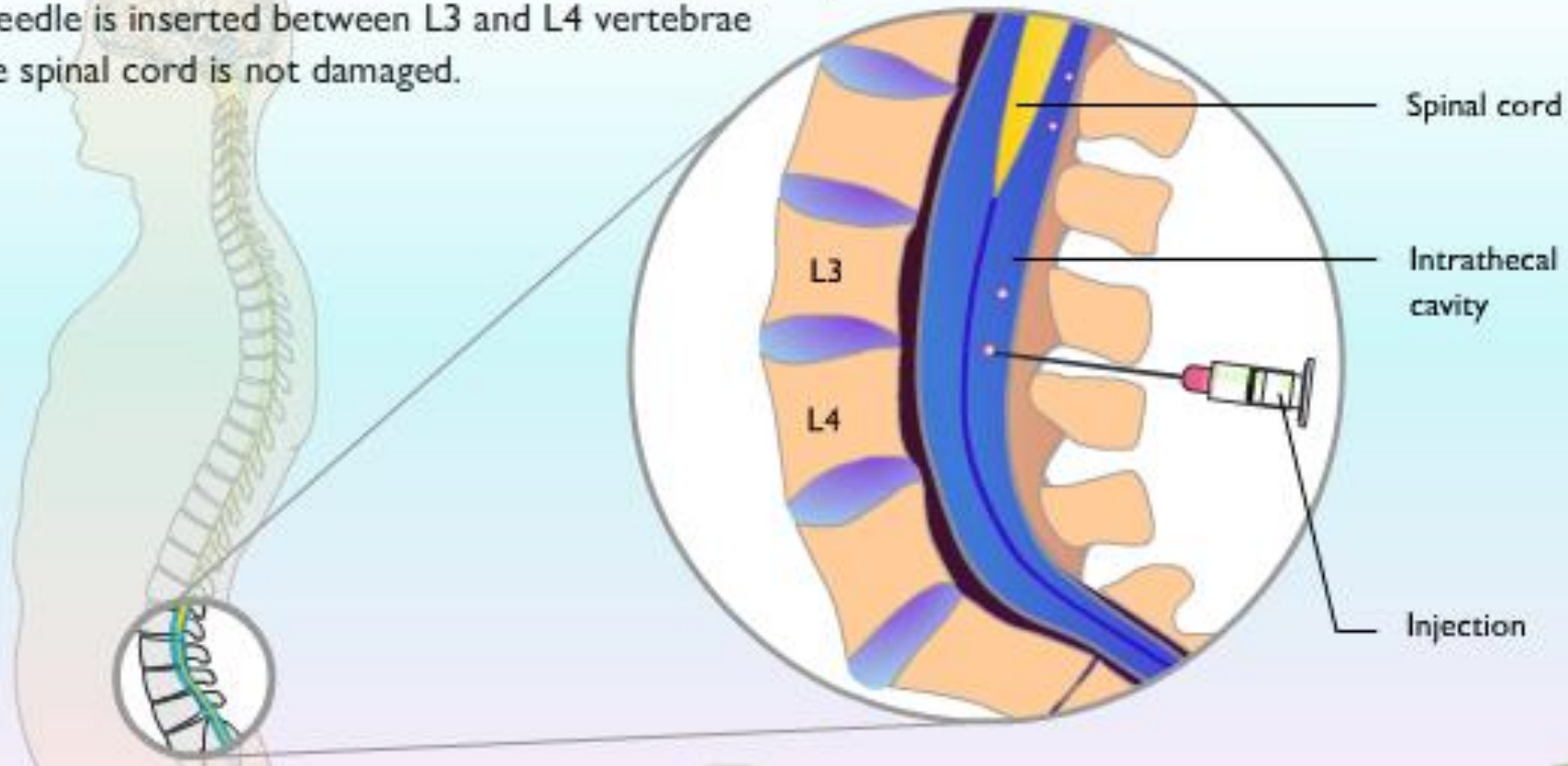
Hua et al (2007) *PLoS Biol* 5: e73
Hua et al (2008) *Am J Hum Genet* 82: 834
Hua et al (2010) *Genes Dev* 24: 1634
Passini et al (2011) *Science Transl Med* 3: 72ra18
Hua et al (2011) *Nature* 478: 123

Courtesy Dr. A. Krainer

see https://**clinicaltrials.gov/**

Intrathecal drug delivery

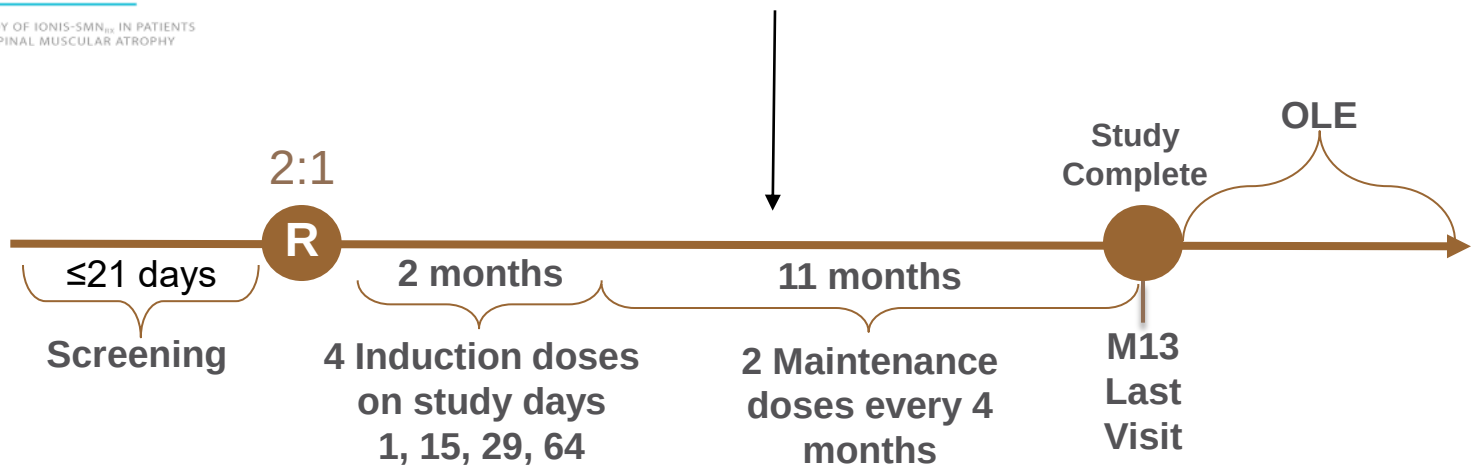
In a technique called intrathecal drug delivery, a drug can be injected into the CSF, where it flows through the intrathecal cavity between the vertebrae of the lower back. The injection is similar to a lumbar puncture procedure where a needle is inserted between L3 and L4 vertebrae so that the spinal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



endear

A PHASE 3 CLINICAL STUDY OF IONIS-SMN$_{Rx}$ IN PATIENTS WITH INFANT-ONSET SPINAL MUSCULAR ATROPHY

INTERIM ANALISIS July 2016



Comunicado 1 de agosto de 2016. El análisis muestra que los niños que han estado recibiendo Nusinersen experimentan una mejora estadísticamente significativa en la consecución de los hitos motores en comparación con aquellos que no recibieron tratamiento

Nusinersen pasa la primera prueba: perspectivas y esperanza para los pacientes con AME tipo I

http://www.fundame.net/investigacion-ame/ultimas-noticias/

Ionis/Biogen program (2)
Ionis-SMNrx (Nusinersen)

✓ **ENDEAR Trial (2014-2017: ongoing)**

endear
A PHASE 3 CLINICAL STUDY OF IONIS-SMN$_{Rx}$ IN PATIENTS WITH INFANT-ONSET SPINAL MUSCULAR ATROPHY

- Phase III, randomized, double-blind, sham procedure (2:1) controlled study
- 13 months study
- 110 SMA type I Infants (up to 7 months years old)
- Evaluate the efficacy and safety of a 12 mg dose of nusinersen (primary endpoint : survival)
- International study – Enrollment completed

✓ **CHERISH trial (2014-2017 : ongoing)**

cherish
A PHASE 3 CLINICAL STUDY OF IONIS-SMN$_{Rx}$ IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY

- Phase III, randomized, double-blind, sham procedure (2:1) controlled study
- 15 months study
- 117 Children with SMA type II (2 to 12 years old)
- Evaluate the efficacy of nusinersen by measuring changes in muscle function score
- International study
- Enrollment completed

✓ **SHINE trial (2015-2020: ongoing)**

- open label extension for patients who have completed Endear and Cherish International studies

endear

A PHASE 3 CLINICAL STUDY OF IONIS-SMN$_{Rx}$ IN PATIENTS WITH INFANT-ONSET SPINAL MUSCULAR ATROPHY

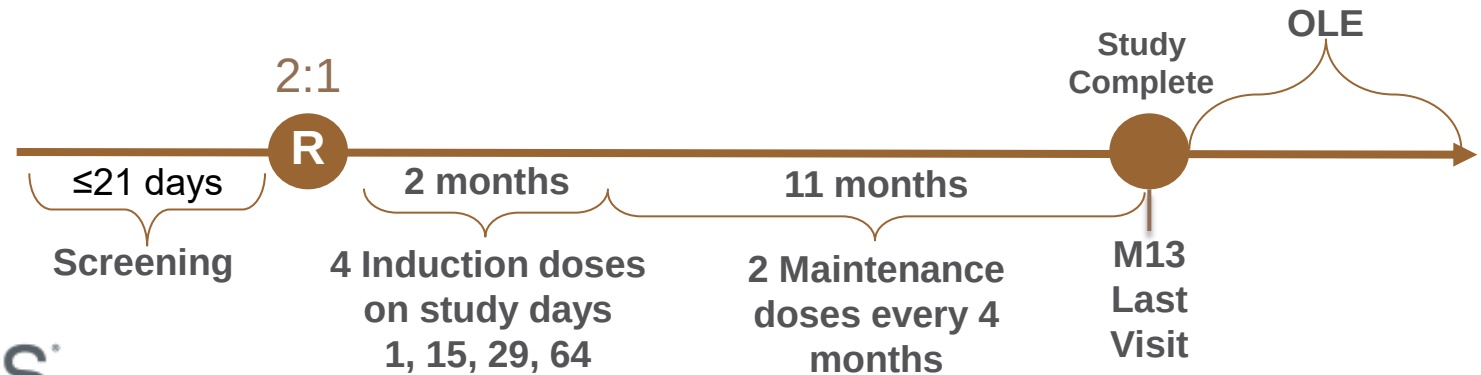
ENDEAR diseño del estudio

Phase 3 2:1 randomized in type I patient less than 7 months

USA, Canada, Europe, AsiaPac, Japan (~30 centres)

- **~111 pacientes . Recrutiment completed**
- **Open label extension SHINE**

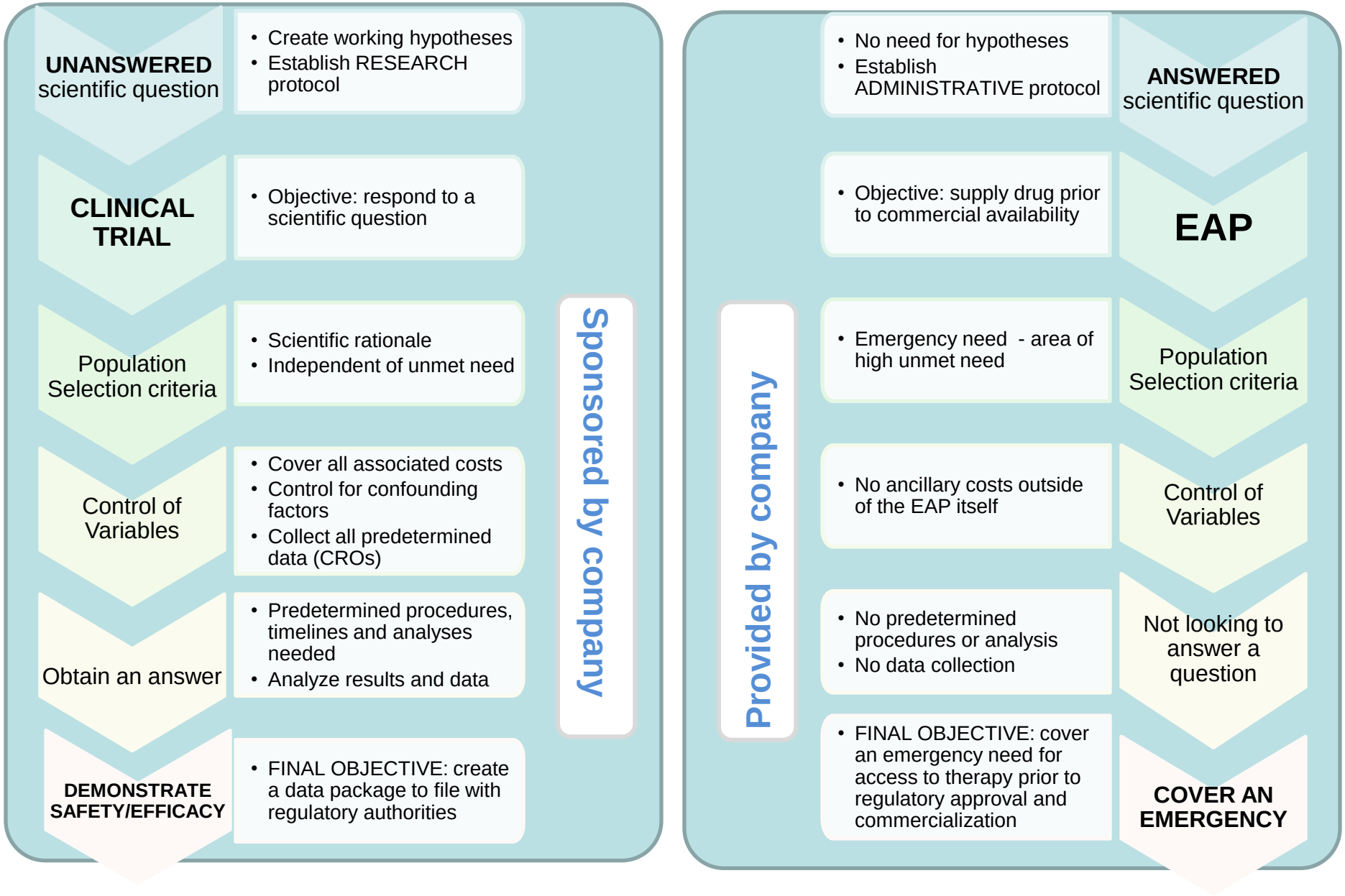
Cohort 2:1
12 mg
Sham



IONIS PHARMACEUTICALS

www.clinicaltrial.gov

Clinical Trial vs. EAP



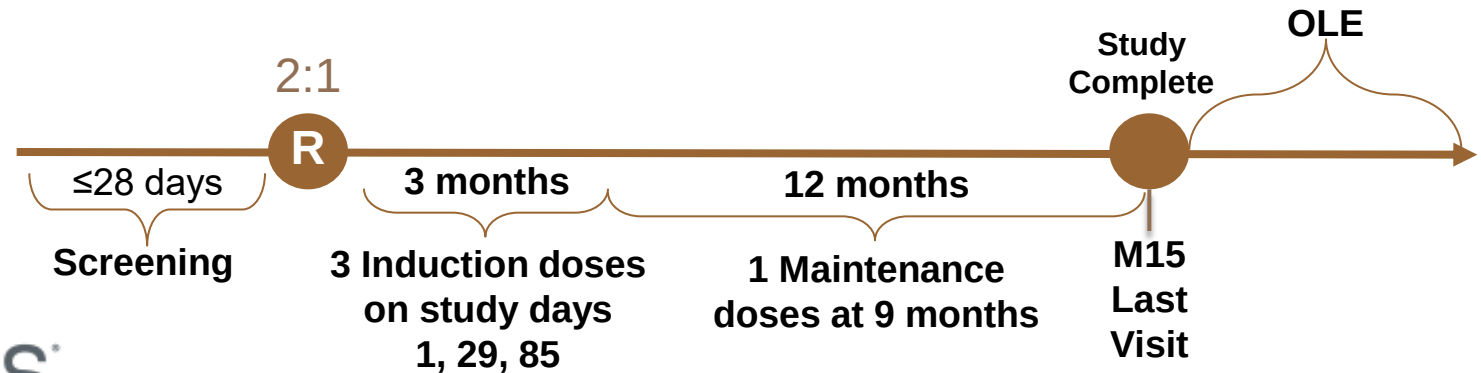
cherish

A PHASE 3 CLINICAL STUDY OF IONIS-SMN$_{Rx}$ IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY

CHERISH diseño del estudio

- Phase 3 in SMA patients type II and III non ambulant aged 2-12
- **USA, Canada, Europa, AsiaPac, Japan (~24 centres)**
- **~117 patients . Recruitment completed .**
- **Open label extension shine**

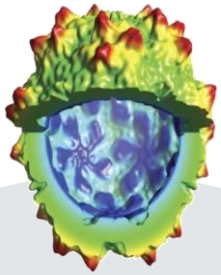
Cohort 2:1
12 mg
Sham



IONIS PHARMACEUTICALS

Gene therapy is the right approach for SMA: Monogenic mutation that drives the pathology

Recombinant AAV9 Capsid Shell



scAAV ITR	Continuous Promoter	Human SMN Transgene	scAAV ITR

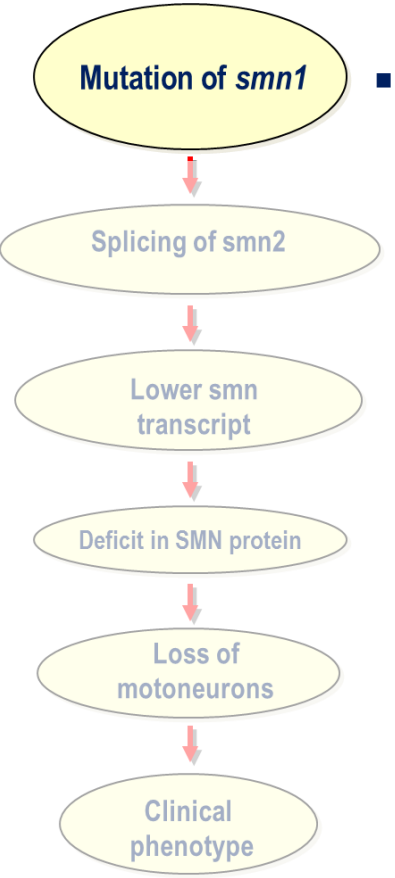
KEY COMPONENTS	PURPOSE
Recombinant AAV9 Capsid Shell	• Ability to deliver across the blood brain barrier (BBB) and into the spinal cord - Avoids the need for intrathecal delivery when treating infants • Non-replicating virus does not modify the existing DNA of the patient.
scAAV ITR (Self-complementary DNA technology)	• Enables rapid onset of effect which is key in a quickly deteriorating population
Continuous Promoter	• Activates the transgene to allow for continuous and sustained SMN expression
Human SMN Transgene	• Full copy of a stable, functioning SMN gene that is introduced into the cell's nucleus

Rendering adapted from DiMattia et al. Structural Insight into the Unique Properties of Adeno-Associated Virus Serotype 9 J. Virol. June 2012.

Courtesy Dr. J. Mandell /B. Kaspar

Replacement or correction of SMN1
Gene Therapy

Avexis Program



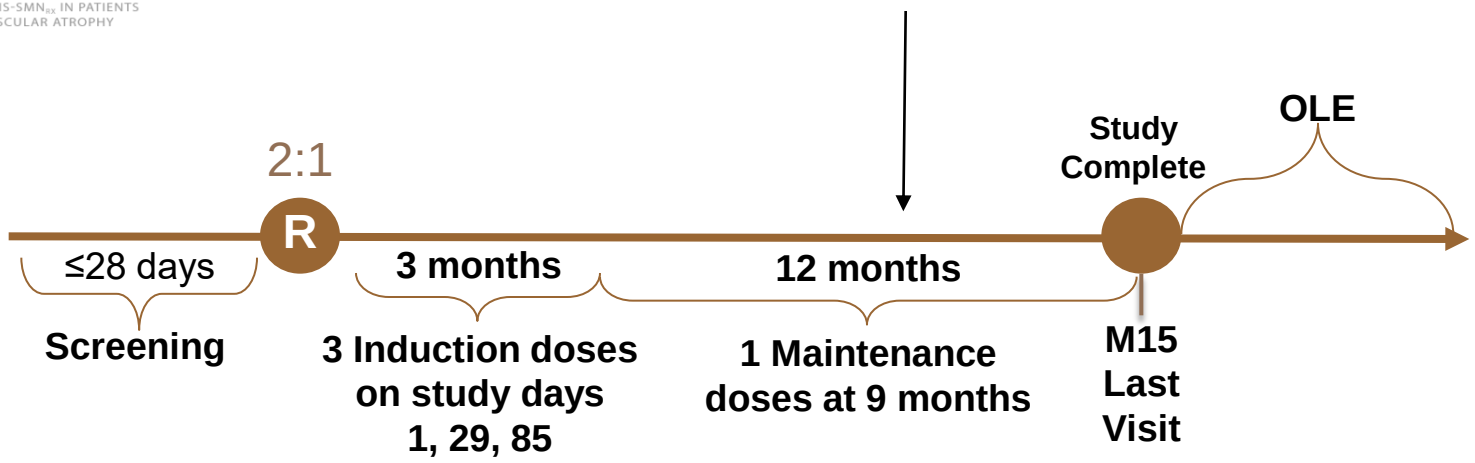
- **Phase I/II clinical trial (2014-2017)**
  - Nationwide Children's Hospital in Columbus, Ohio
  - Systemic delivery of AVXS-101 (scAAV9-SMN)
  - Open-label, dose-escalation study
  - SMA type I before 6 months of age
  - Aims: safety and preliminary indications of efficacy
  - Enrollment **completed**:
    - ✓ Cohort 1 includes three patients dosed at (6.7 $X10^{13}$ vg/kg), aged six to seven months at time of dosing
    - ✓ Cohort 2 includes 12 patients dosed at (2.0 $X10^{14}$ vg/kg), aged one to eight months at time of dosing
  - Appears to be generally safe and well tolerated in the patients studied to date

Courtesy Dr. J. Mandell /B. Kaspar

cherish

A PHASE 3 CLINICAL STUDY OF IONIS-SMN$_{Rx}$ IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY

INTERIM ANALISIS October 2016



Comunicado 7 noviembre de 2016. El análisis muestra que los niños que han estado recibiendo Nusinersen experimentan una mejora estadísticamente significativa en la consecución de los hitos motores en comparación con aquellos que no recibieron tratamiento (15 meses, Escala funcional Hammersmith 5 puntos en comparación con placebo). También se prepara un EAP. SPINRAZA

http://www.fundame.net/investigacion-ame/ultimas-noticias/

Results from compilation data emerged from our Spanish cohort of 556 patients and 2,469 SMA patients worldwide from the review of the most complete published articles from 1999 to nowadays

	Type I (n=1,095)	**Type II** (n=1,003)	**Type III** (n=925)
One *SMN2* copy	7% (74/1,095)	<1% (4/1,003)	0%
Two *SMN2* copies	75% (825/1,095)	17% (175/1,003)	5% (49/925)
Three *SMN2* copies	17% (193/1,095)	77% (774/1,003)	51% (473/925)
Four *SMN2* copies	<1% (2/1,095)	5% (47/1,003)	42% (389/925)
Five *SMN2* copies	<1% (1/1,095)	<1% (3/1,003)	1% (12/925)
Six *SMN2* copies	0%	0%	<1% (2/912)

(Calucho et al, under revision)