MAHIDOL UNIVERSITY
Wisdom of the Land

Update on Spinal Muscular Atrophy (SMA)

Chaiyos Khongkhatithum, MD

Neurology Division

Department of Pediatrics

ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

Spinal Muscular Atrophy (SMA)

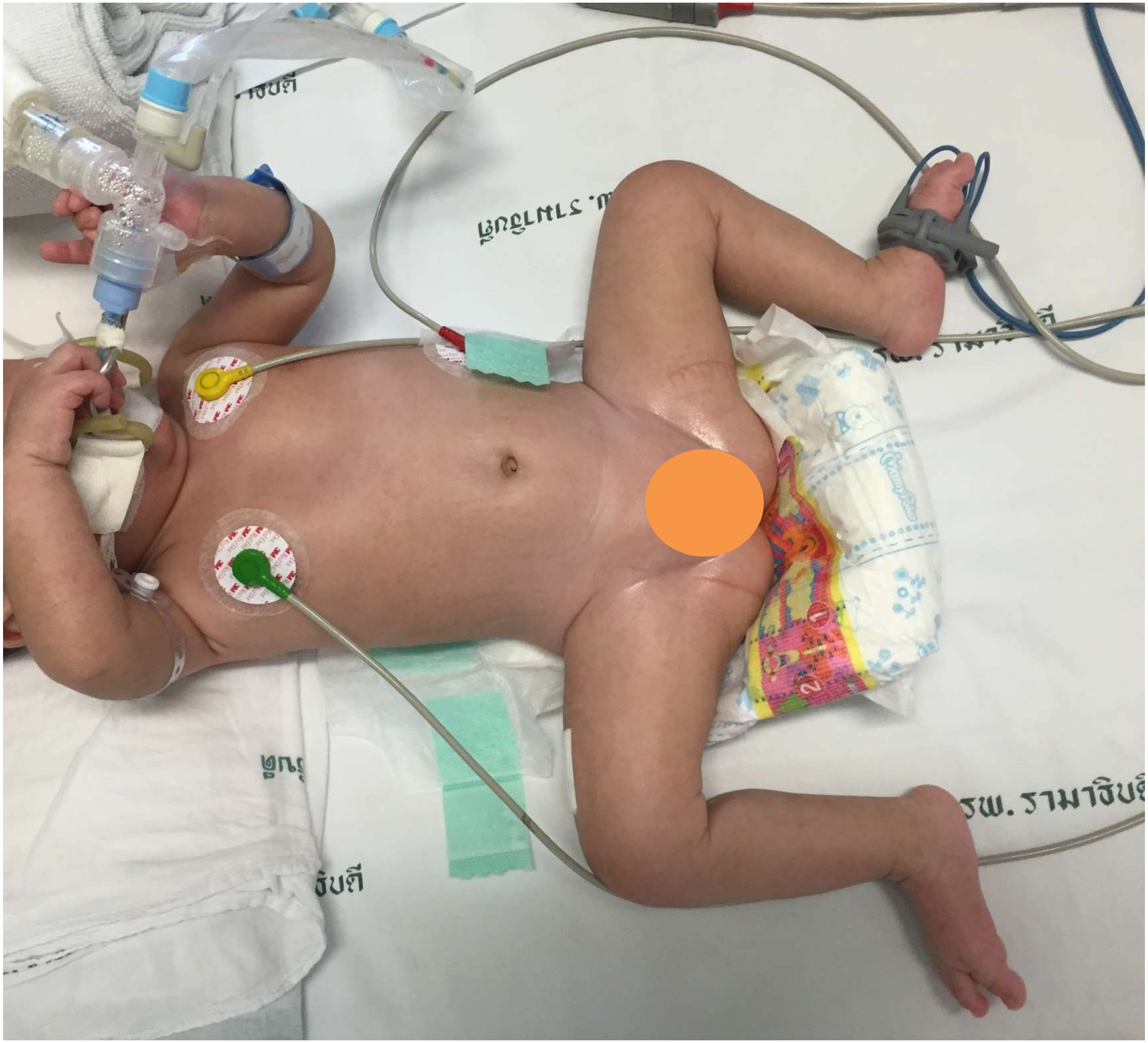
- Clinical features & subtypes
- Genetic diagnosis
- Basic science of SMN gene
- Current management
- Recent advanced treatment
- Late-onset & SMN1-negative SMA

Characteristic Features in Neuromuscular Diseases

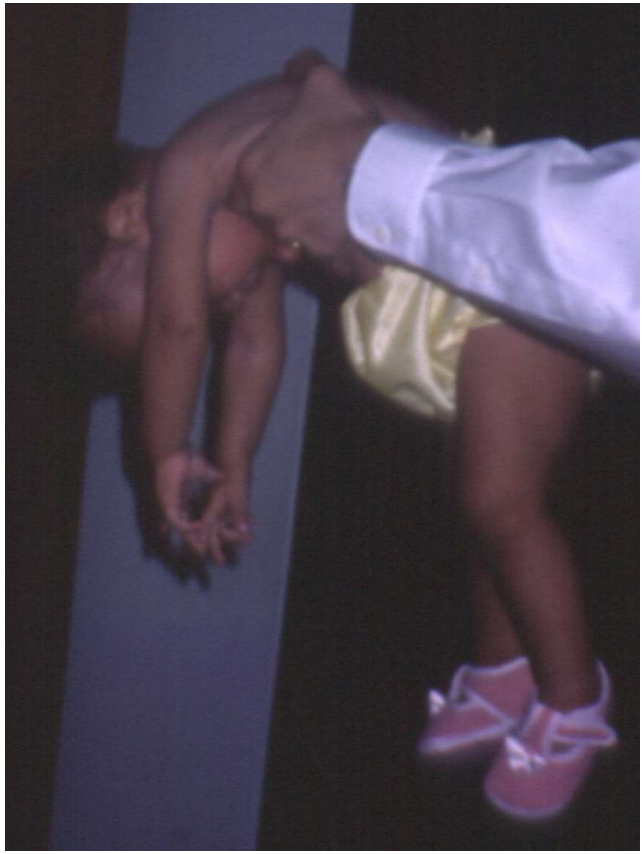
	Motor neurons	Neuropathy	NMJ	Muscle
Muscle tone	Decreased	Decreased	Normal	Decreased
Weakness	Generalized, Fasciculation, Tremor	Distal>Prox.	Fatigue, Generalized Prox>Distal, Bulbar	Prox>Distal
DTRs	Absent	Decreased	Normal	Normal/ Decreased
CK	Normal, 2-4X	Normal	Normal	Elevated
NCS/EMG	Fasciculation	Neuropathic	Rep. Stim	Small units

Spinal Muscular Atrophy (SMA)

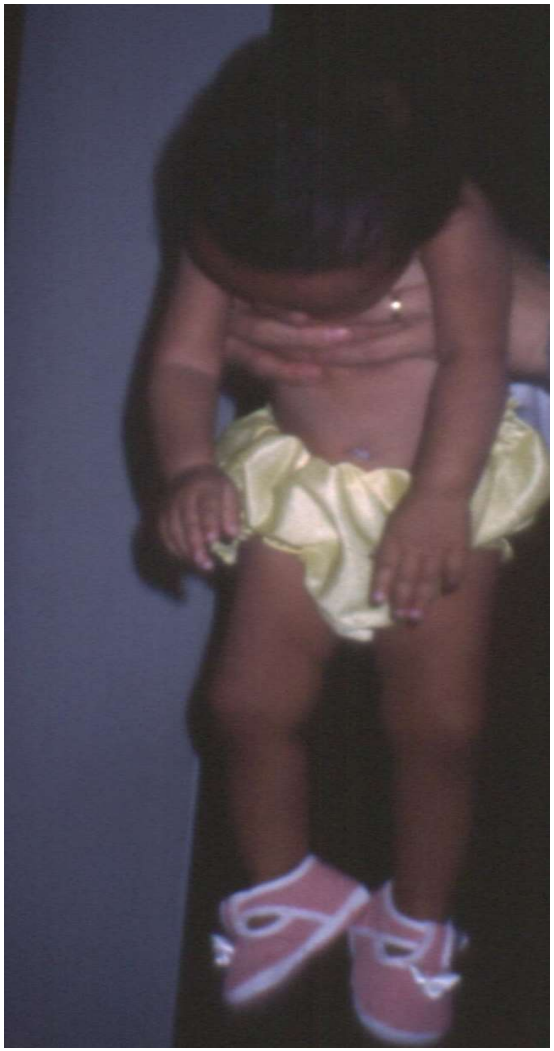
- AR, chromosome 5q12.2-13.3
- SMN1, SMN2 gene
- Progressive loss of anterior horn cells and motor nuclei
- Hypotonia, generalized weakness
- Tongue fasciculation and hand tremor
- Respiratory & skeletal problems
- CK; normal or slightly elevated



Horizontal suspension



Vertical suspension



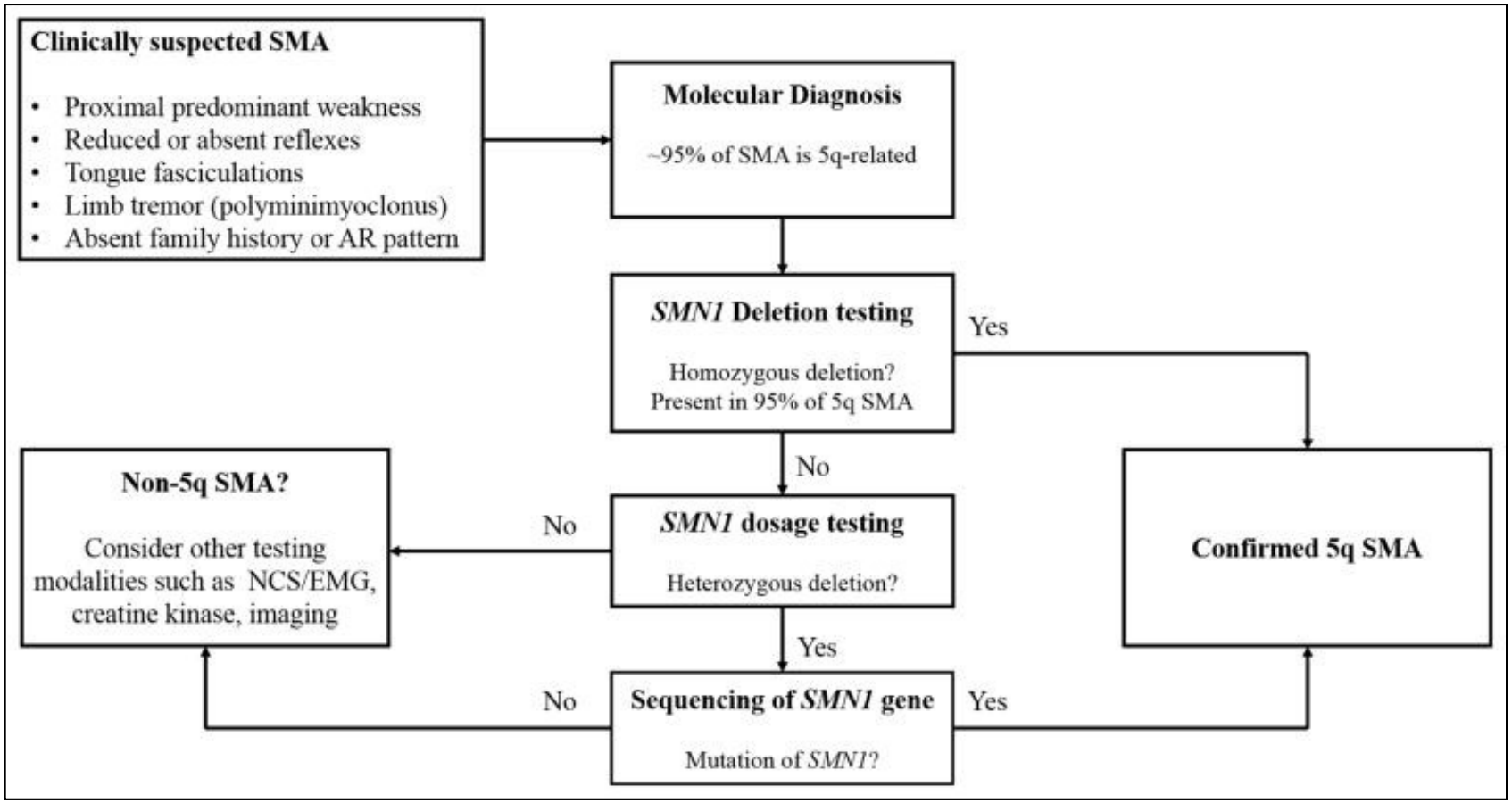
Classification and Subtypes of SMA

Type	Frequency (%)	SMN2 copy	Age of Onset	Maximal Motor Milestone	Motor Ability and Additional Features	Prognosis[c]
SMA 0	<1	1	Before birth	None	Severe hypotonia; unable to sit or roll[a]	Respiratory insufficiency at birth; death within weeks
SMA I	50-60	2, 3	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit or roll[b]	Death/ventilation by 2 years
SMA II	30	2, 3, 4	6 to 18 months	Sitting	Proximal weakness; unable to walk independently	Survival into adulthood
SMA III	10	3, 4	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
SMA IV	1	4+	>30 years or 10 to 30 years	Normal	Mild motor Impairment	Normal life span

a: Need for respiratory support at birth; contractures at birth, reduced fetal movements.
b: Ia joint contractures present at birth; Ic may achieve head control.
c: Prognosis varies with phenotype and supportive care interventions.

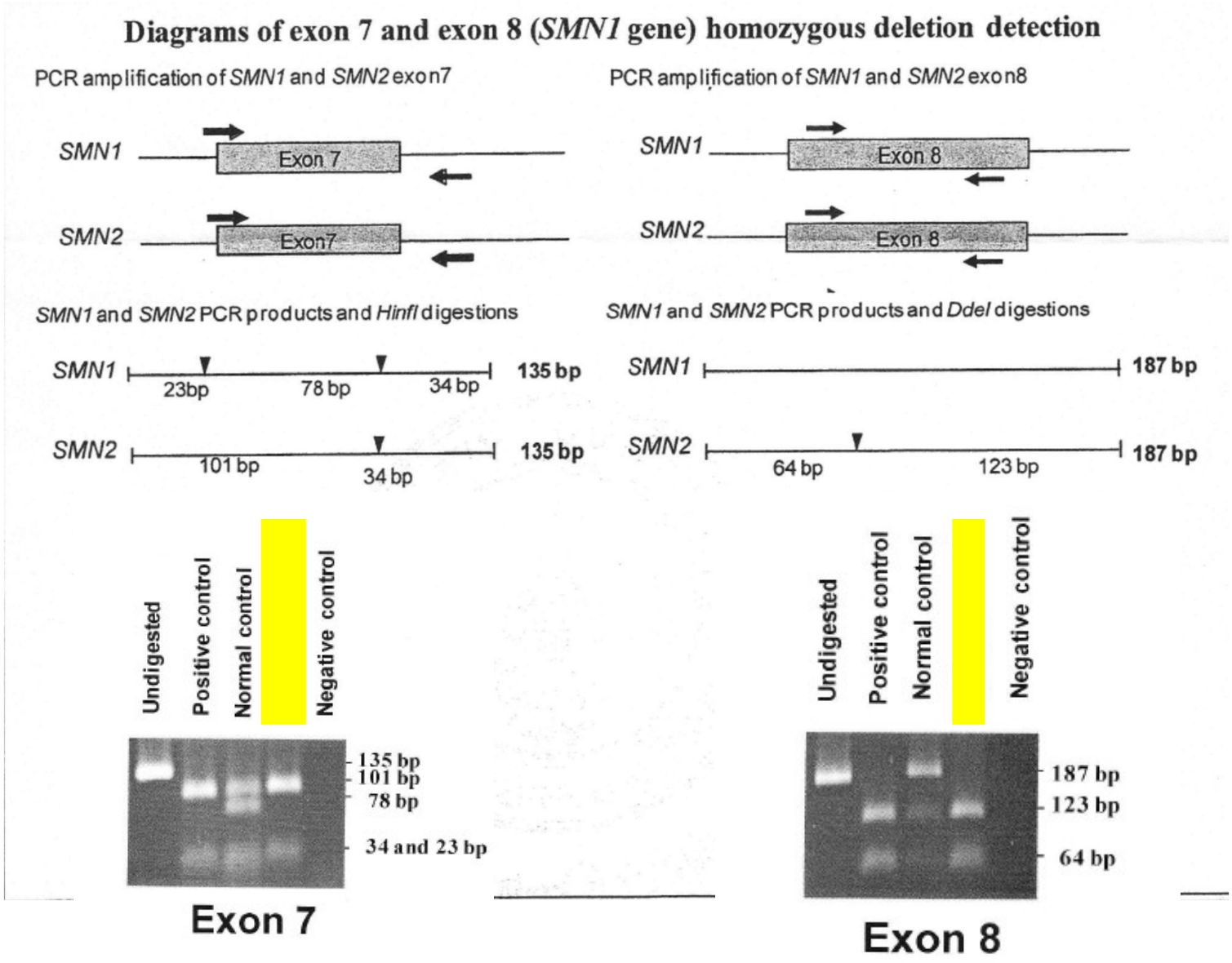
Farrar Ma, et al. Ann Neurol. 2017;81:355–368
Bharucha-Goebel D. Curr Neurol Neurosci Rep. 2017;17: 91

Approach to Molecular Diagnosis of SMA

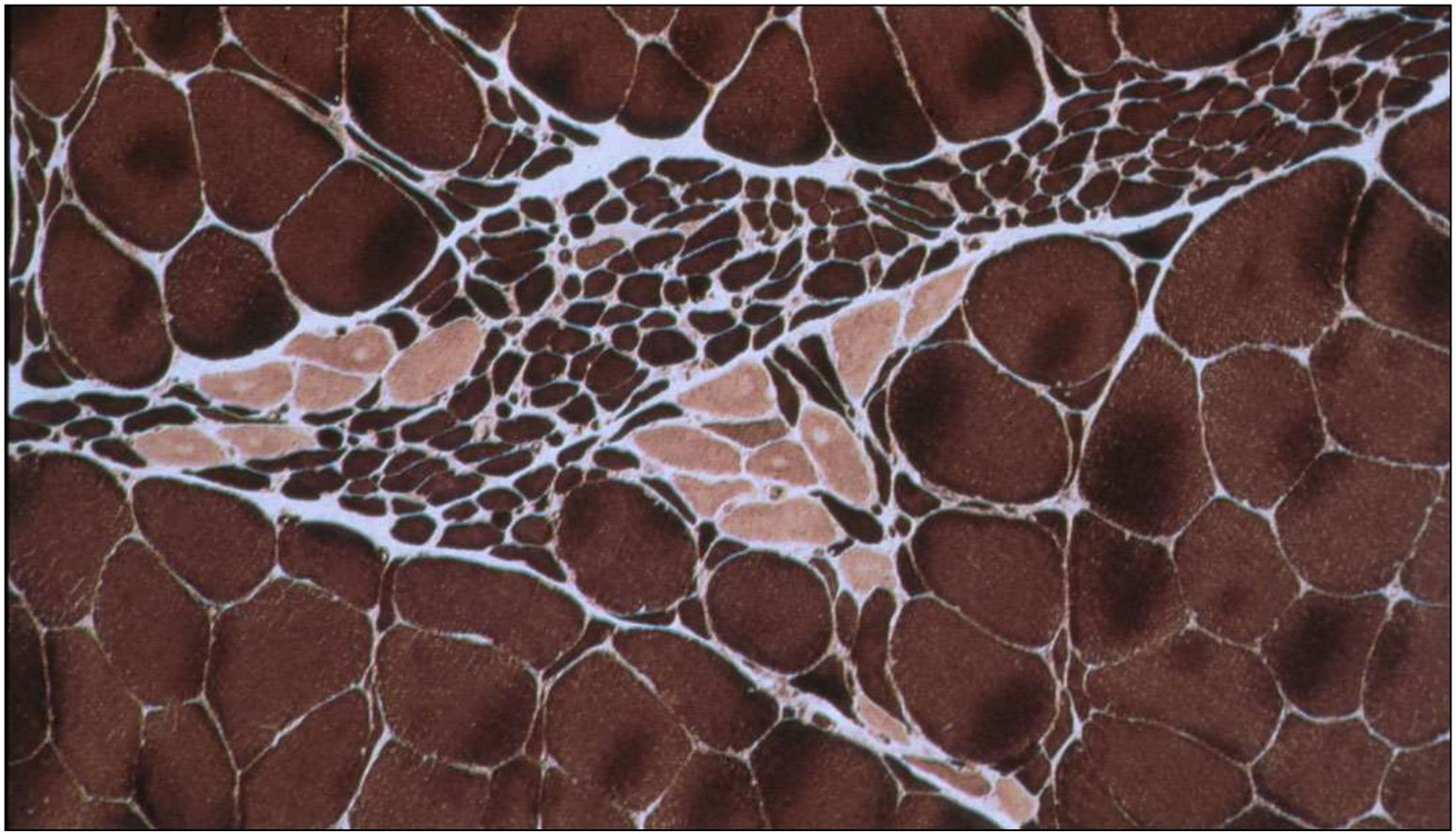


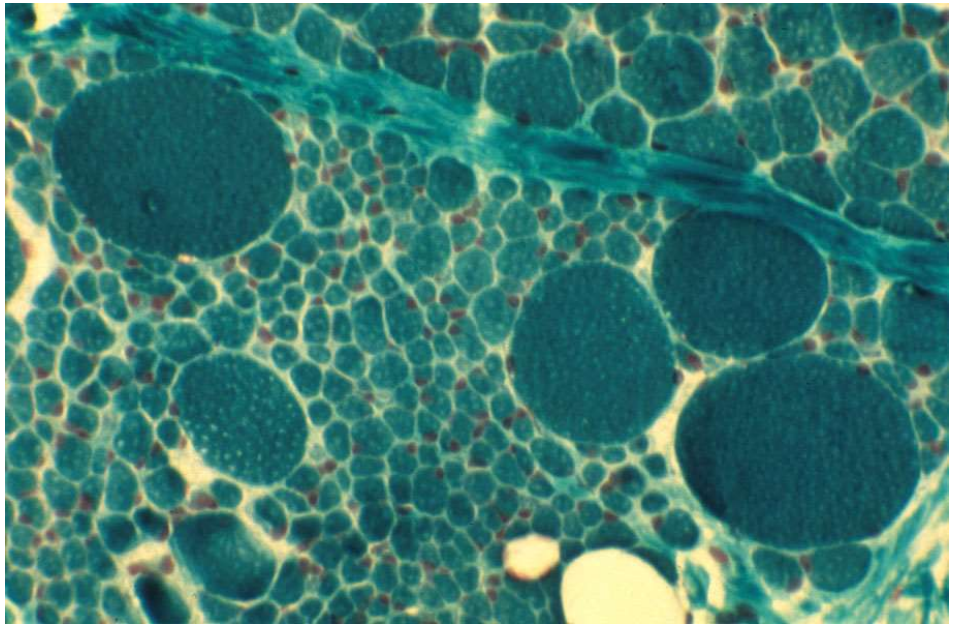
Arnold WD. Muscle Nerve. 2015; 51(2):157–167

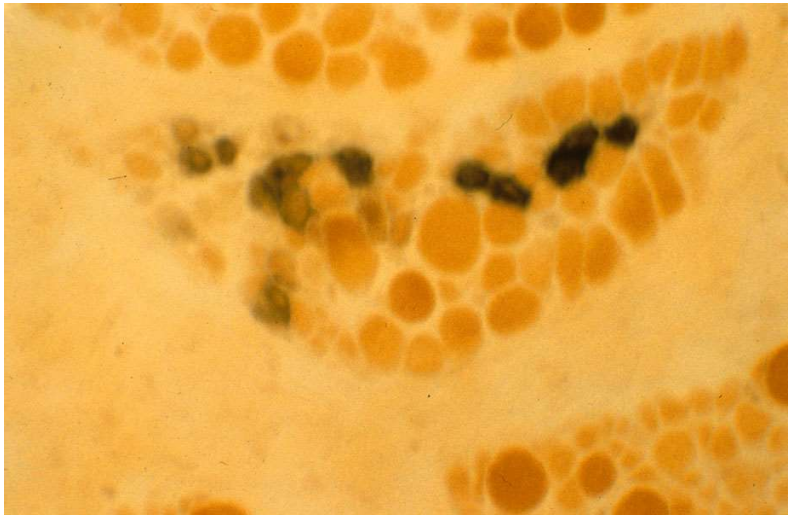
11-year-old girl with SMA type III



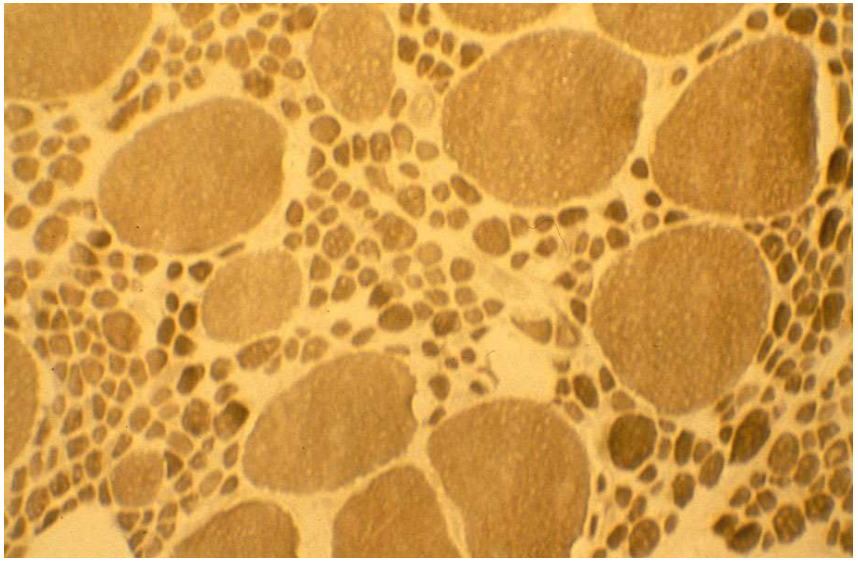
Muscle biopsy:
Denervation atrophy
Group/Fascicular atrophy

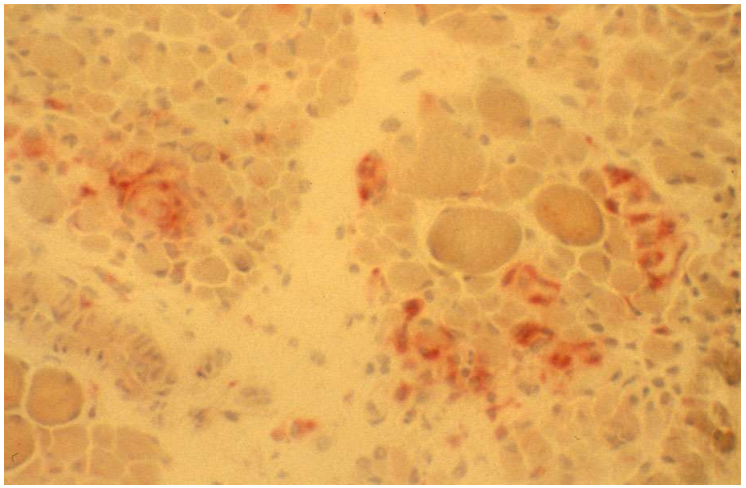






SMA
Infantile pattern of denervation





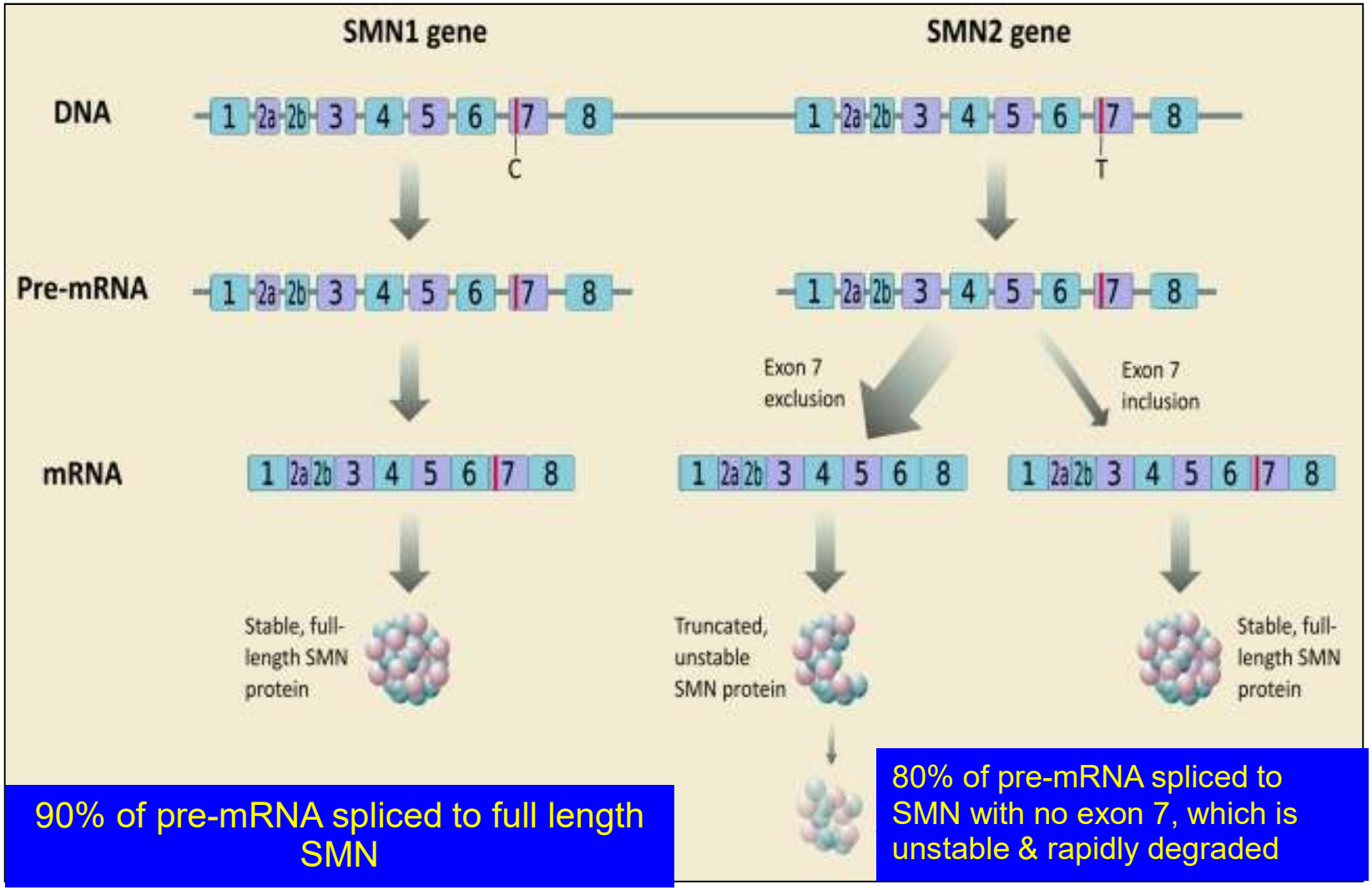
Carrier Frequencies for SMA

Ethnicity	Number of identified carriers	Number of study participants	Carrier frequency	95% CI
Arab	152	9058	0.017	0.014–0.019
Asian	2492	119,718	0.021	0.020–0.022
Asian Indian	20	1465	0.014	0.008-0.020
Black (Sub-Saharan ancestry)	80	8012	0.010	0.008–0.012
Caucasian	680	31,549	0.022	0.020–0.023
Hispanic	127	9649	0.013	0.011–0.015
Jewish	1059	59,196	0.018	0.017–0.019

Thai population about 1:50

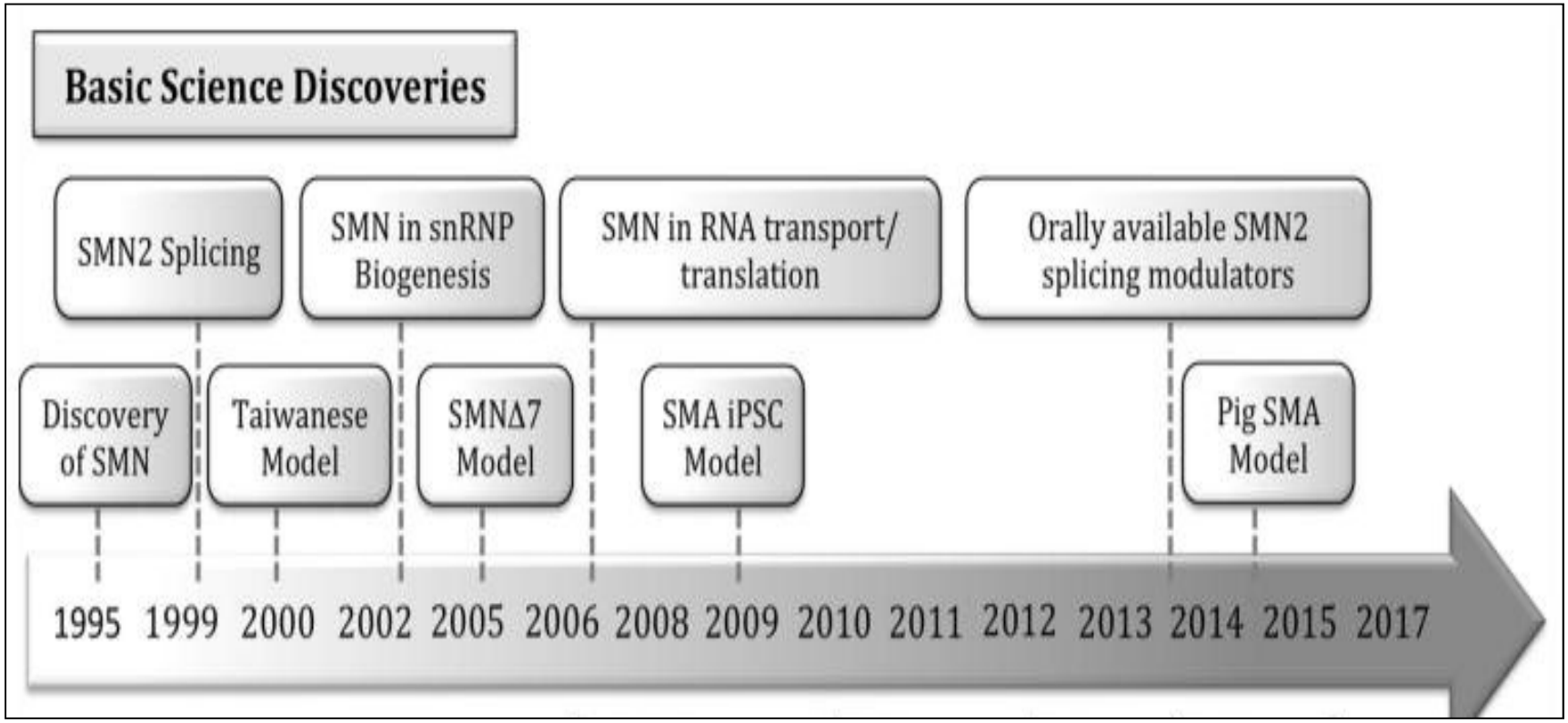
e Diseases. 2017;12:124

Genetics of SMA



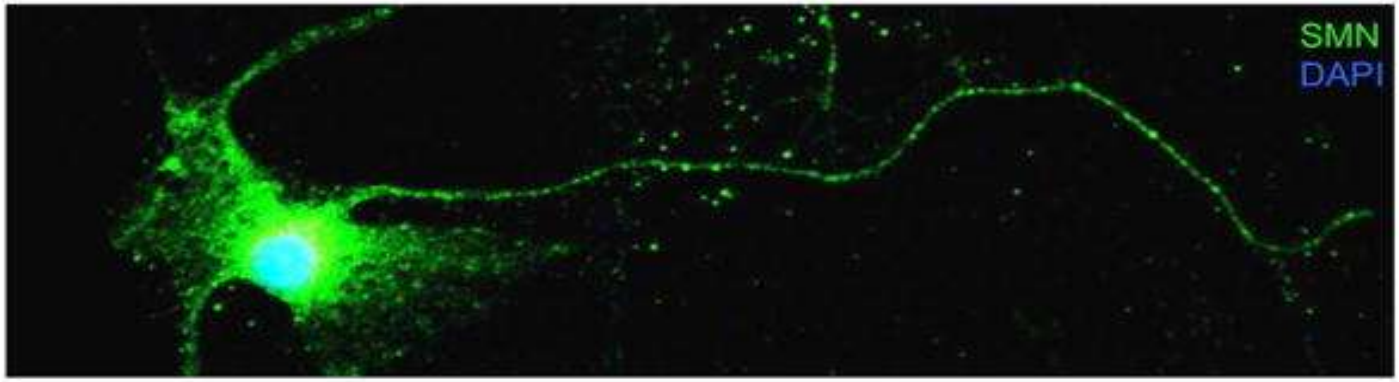
Farrar Ma, et al. Ann Neurol. 2017;81:355–368

Important Milestones in SMA Basic Science and Clinical Development



Wertz MH. Ann. N.Y. Acad. Sci. 2016;1366:5–19

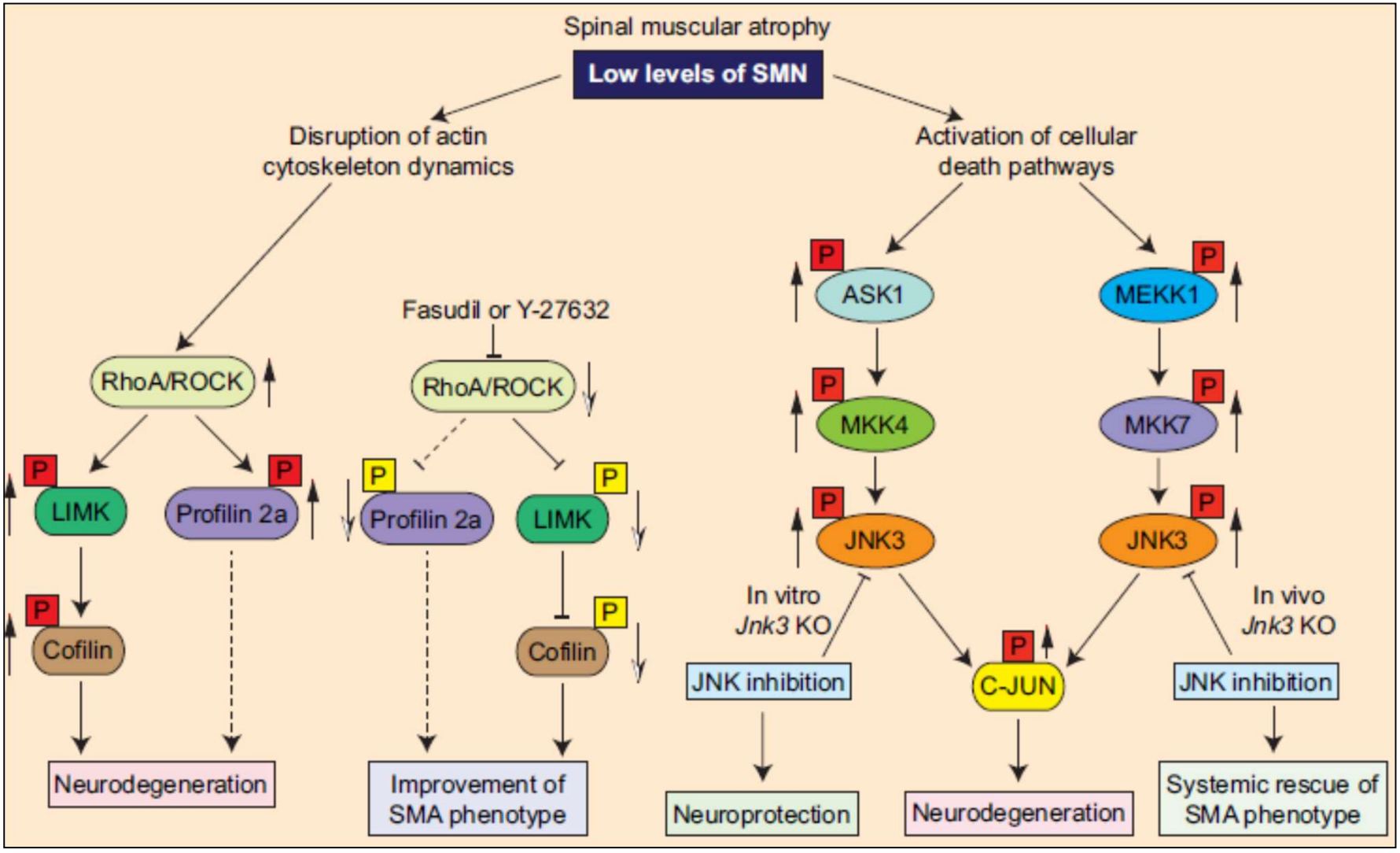
Subcellular Localization of SMN Function in Motor Neurons



Cell Body	Neurites (Axon/Dendrites)
Functions • Forms SMN-complex with gemins and sm core proteins • snRNP biogenesis • Splicing and alternative splicing	**Functions** • Binding RNA-binding proteins • Trafficking axonal mRNA • Interacting with COPI vesicles
Phenotypes • Aberrant mRNA splicing • Cellular stress • Motor neuron cell death	**Phenotypes** • Impaired neurite outgrowth/ morphology • Altered growth cone dynamics • Aberrant local translation

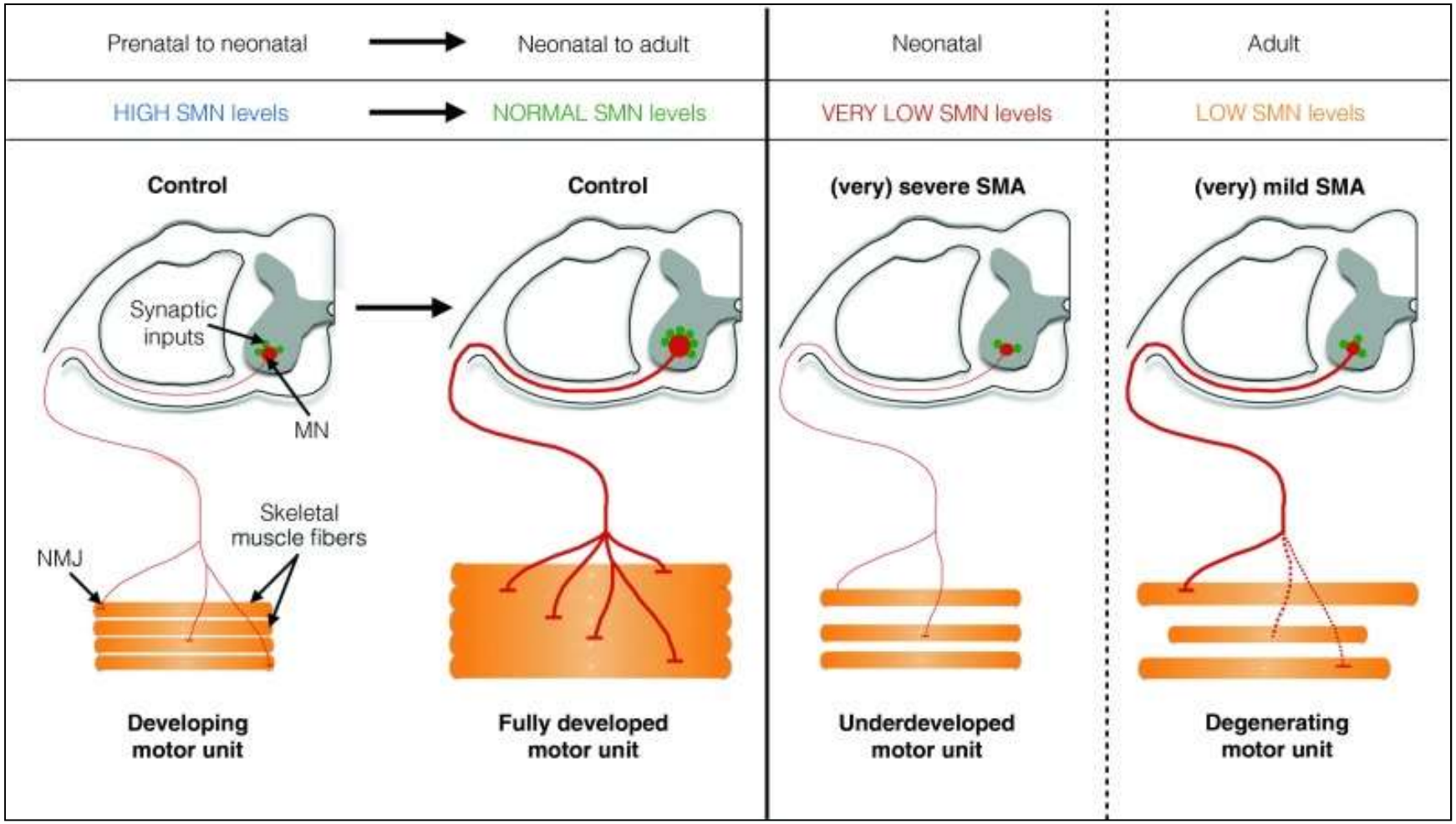
Wertz MH. Ann. N.Y. Acad. Sci. 2016;1366:5–19

Molecular Mechanisms Mediated Neurodegeneration in SMA



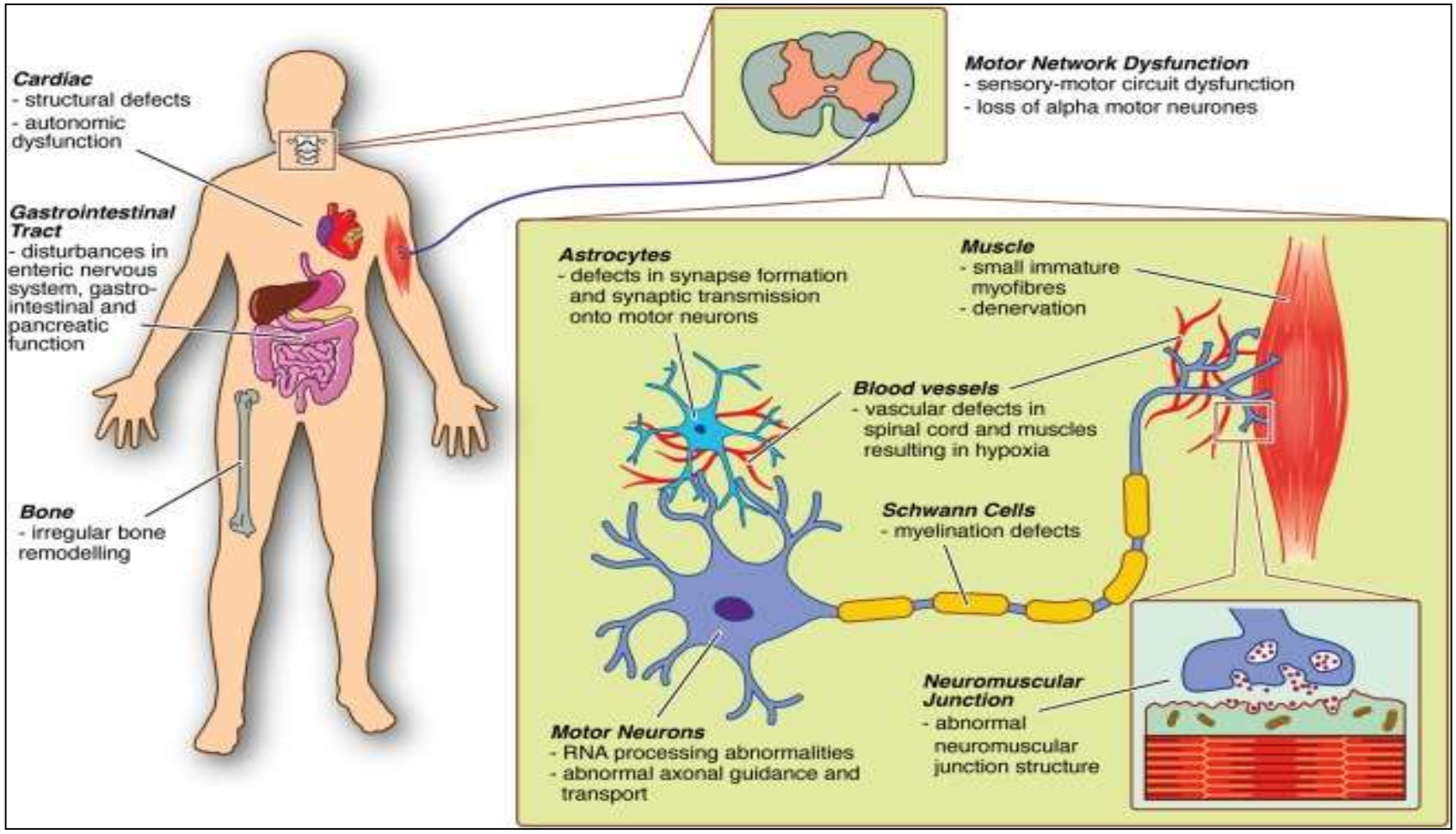
Journal of Experimental Neuroscience 2016:10

Development and Postnatal Maintenance of the Motor Unit



d'Ydewalle C. Neurotherapeutics. 2015;12:303–316

Multiple Functional Abnormalities in SMA



Farrar Ma, et al. Ann Neurol. 2017;81:355–368

Current Management of SMA

	Assessments	Interventions
Respiratory	Cough effectiveness; respiratory muscle function tests; overnight oximetry; forced vital capacity (>6 years) Overnight polysomnography if disordered breathing suspected Acute respiratory infections	Referral to respiratory specialist Routine immunizations Annual influenza vaccination Airway clearance techniques and cough assistance-chest physiotherapy, postural drainage, mechanical or manual cough assistance Noninvasive ventilation (nocturnal and/or daytime if indicated) Antibiotics intensified airway clearance, increased ventilation support
Gastrointestinal and nutritional	Feeding and swallowing assessment Assess caloric intake Assess for signs of reflux or aspiration Assess for constipation	Nutritional supplementation, modifying food consistency, optimizing oral intake, positioning and seating alterations Nasogastric, nasojejunal, or percutaneous gastronomy-as soon as reduced oral intake is recognized Nissen fundoplication (if indicated) Hydration, regular oral aperients

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Current Management of SMA

	Assessments	Interventions
Orthopedic and rehabilitation	Posture, mobility, function Contractures Scoliosis Hip subluxation/dislocation	Equipment to assist with mobility, self-care, and function Physiotherapy, standing frames, orthoses Spinal surgery
Psychological	Assess for depression/anxiety (patient & family)	Counseling, pharmacotherapy

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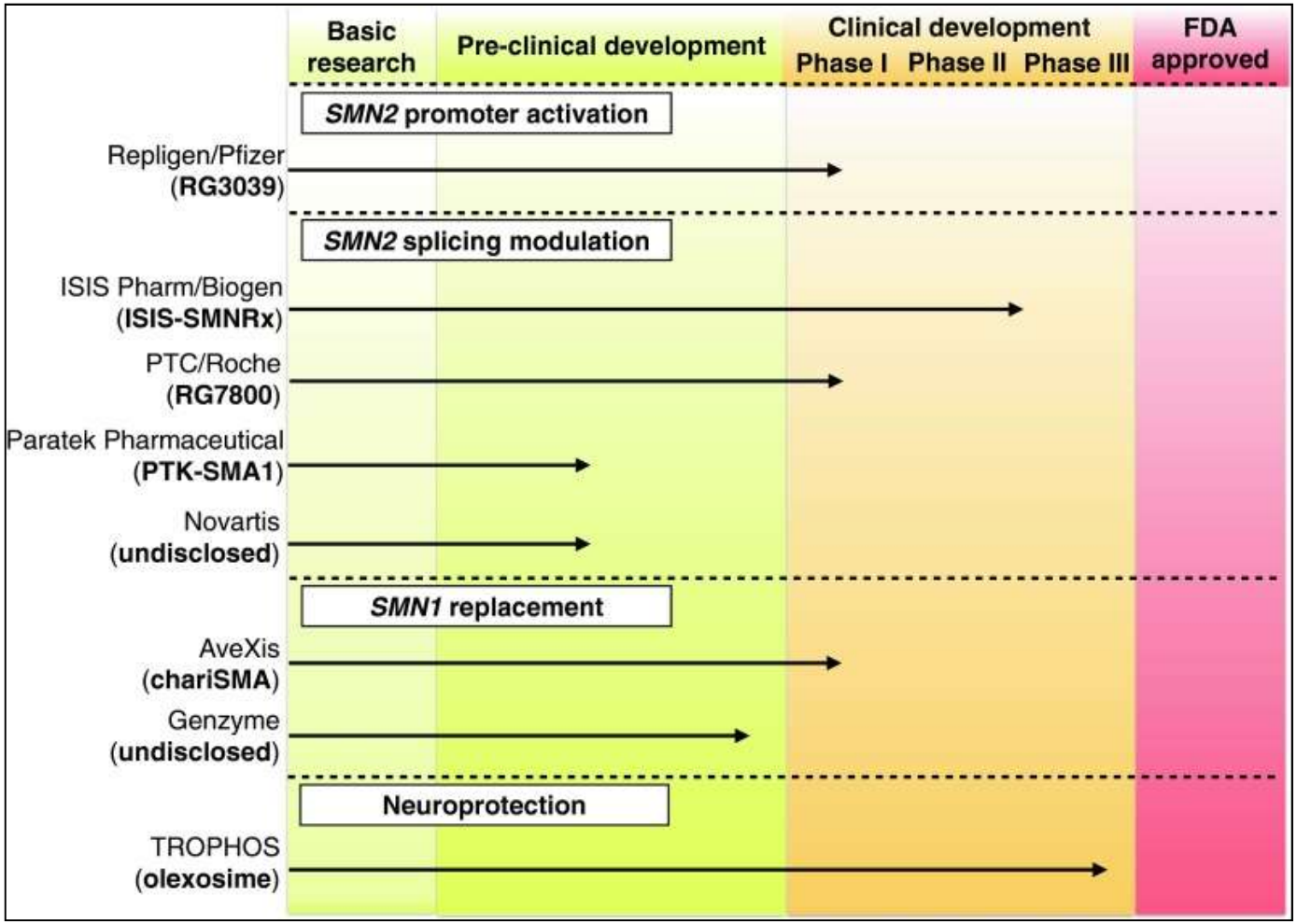
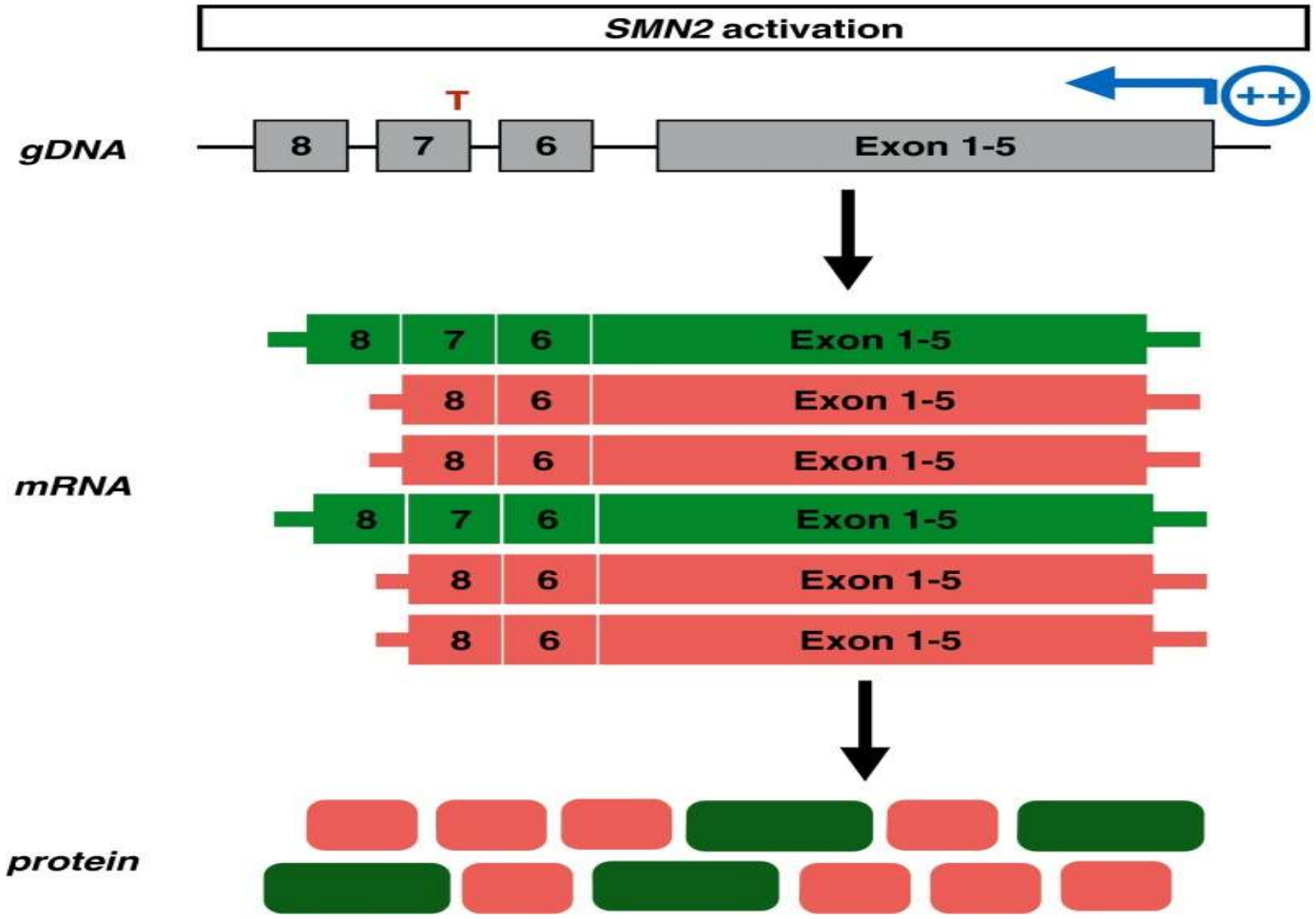
Pipeline of SMA Drugs Development



d'Ydewalle C. Neurotherapeutics. 2015;12:303–316

SMN2 Promoter Activating Strategies aim to Induce SMN2 Expression



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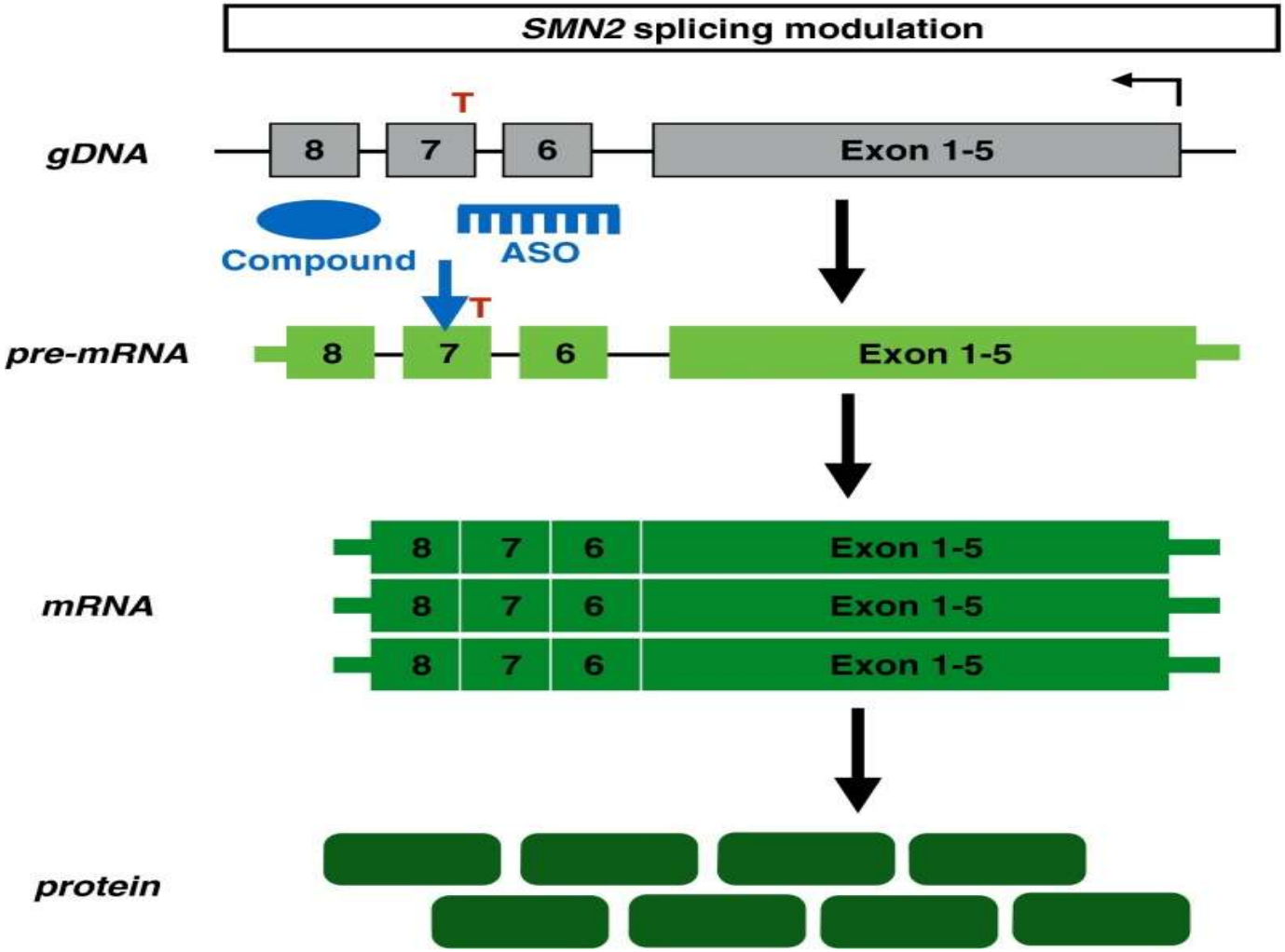
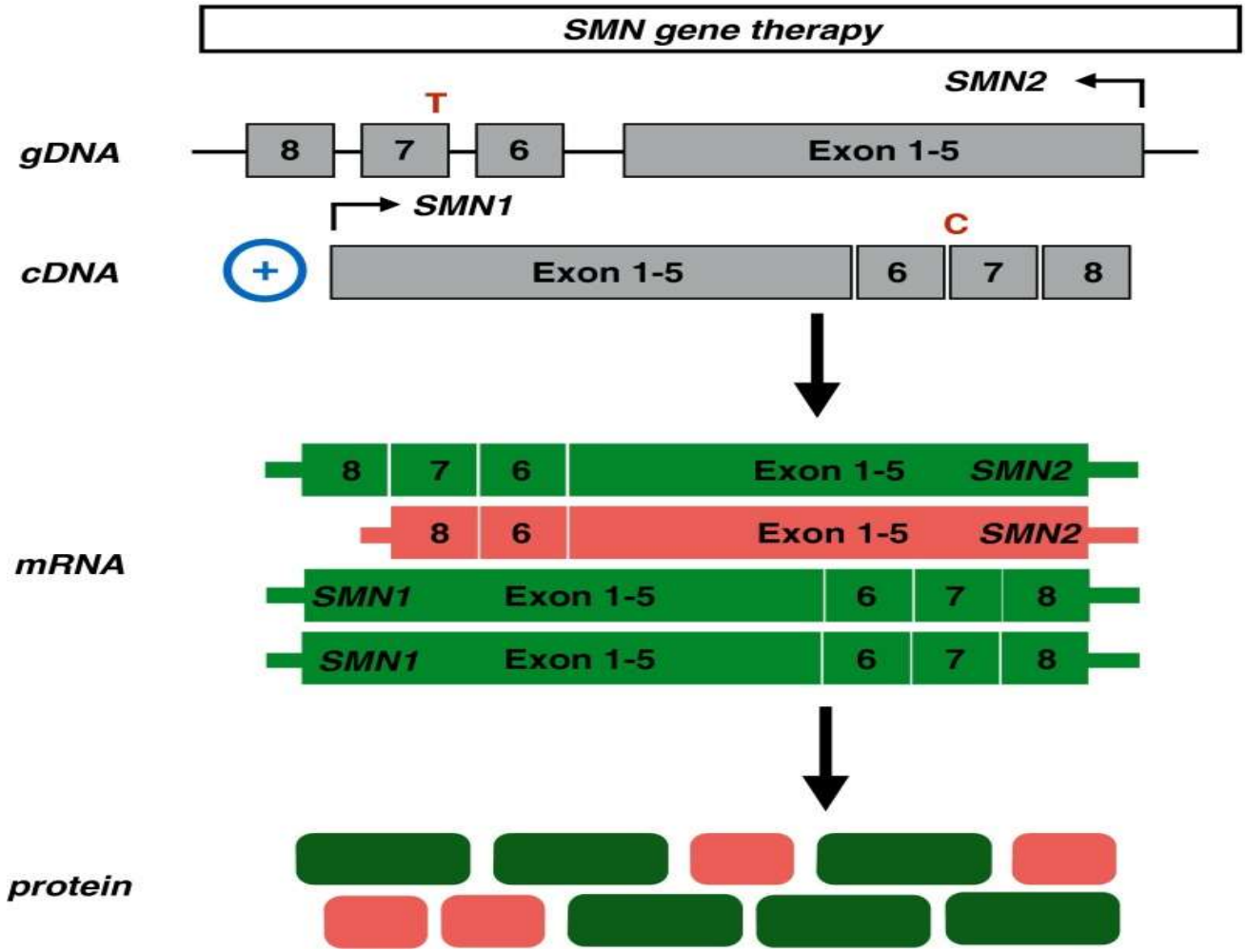
SMN2 Splicing Modulation Drugs; Antisense oligonucleotides (ASOs)



d'Ydewalle C. Neurotherapeutics. 2015;12:303–316

Gene Therapy by Using Adenovirus-associated SMN1 cDNA incorporated in the Human Genome



d'Ydewalle C. Neurotherapeutics. 2015;12:303–316

Mechanisms of Action of SMA Therapeutics

Name	Mechanism of action	SMN Expression
Antisense Oligonucleotide	↑ Exon 7 inclusion in SMN2	↑ Full-length SMN from SMN2
Gene Therapy	AAV delivery for exogenous SMN	↑ SMN expression
Olesoxime	⊣ Cell death	N/A
Quinazoline	⊣ DcpS ↓ RNA turnover	↑ Full-length SMN from SMN2
HDAC Inhibitors	↑ Promotor acetylation ↑ SF2/ASF ↓ hnRNPA1	↑ Full-length SMN expression
IGF-1	↓ Motor neuron cell death	N/A
mTOR	↑ Protein Synthesis	N/A
Stem Cell Replacement	↑ Wildtype motor neuron number	↑ Full-length SMN expression

Wertz MH. Ann. N.Y. Acad. Sci. 2016;1366:5–19

Multidisciplinary Care for SMA

- Neurologist
- Geneticist
- Pulmonologist
- GI/Nutritionist
- Orthopedic
- Rehabilitation
- Pain specialist
- Ambulator/palliative care nurses
- Social worker

SMN1-Negative SMA

Type (OMIM #)	Gene	Locus	Inheritance	Phenotype
Early onset				
SPSMA (181405)	*TRPV4*	12q24.11	AD	Scapuloperoneal spinal muscular atrophy
SMALED1 (158600)	*DYNC1H1*	14q32.31	AD	Lower extremity-predominant spinal muscular atrophy-1
SMALED2 (615290)	*BICD2*	9q22.31	AD	Lower extremity-predominant spinal muscular atrophy-2
LAAHD (611890)	*GLE1*	9q34.11	AR	Arthrogryposis with anterior horn cell disease
SMAX2 (301830)	*UBA1*	Xp11.23	XR	Lethal infantile spinal muscular atrophy, with arthrogryposis
SMAPME (159950)	*ASAH1*	8p22	AR	Spinal muscular atrophy with progressive myoclonic epilepsy
PCH1A (607596)	*VRK1*	14q32.2	AR	Pontocerebellar hypoplasia with infantile spinal muscular atrophy
PCH1B (614678)	*EXOSC3*	9p13.2	AR	Pontocerebellar hypoplasia with infantile spinal muscular atrophy
BVVLS1 (211530)	*SLC52A3*	20p13	AR	Brown-Vialetto-Van Laere syndrome 1
BVVLS2 (614707)	*SCL52A2*	8q24.3	AR	Brown-Vialetto-Van Laere syndrome 2

Peeters K. Brain 2014: 137; 2879–2896

SMN1-Negative SMA

Late onset				
SMAFK (182980)	*VAPB*	20q13.32	AD	Late-onset spinal muscular atrophy, Finkel type
–	*HEXB*	5q13.3	AR	Late adult-onset pure spinal muscular atrophy
SMAJ (615048)	–	22q11.2-q13.2	AD	Spinal muscular atrophy, Jokela type
ALS4 (602433)	*SETX*	9q34	AD	Juvenile to adult onset SMA with pyramidal features
LGMD1B (159001)	*LMNA*	1q22	AD	Adult-onset proximal spinal muscular atrophy followed by cardiac involvement
HMSNP (604484)	*TFG*	3q12.2	AD	Proximal hereditary motor and sensory neuropathy, Okinawa type
SMAX1 (313200)	*AR*	Xq12	XR	Kennedy disease, spinal and bulbar muscular atrophy

Peeters K. Brain 2014: 137; 2879–2896

ขอบคุณครับ

คำถามและข้อคิดเห็น