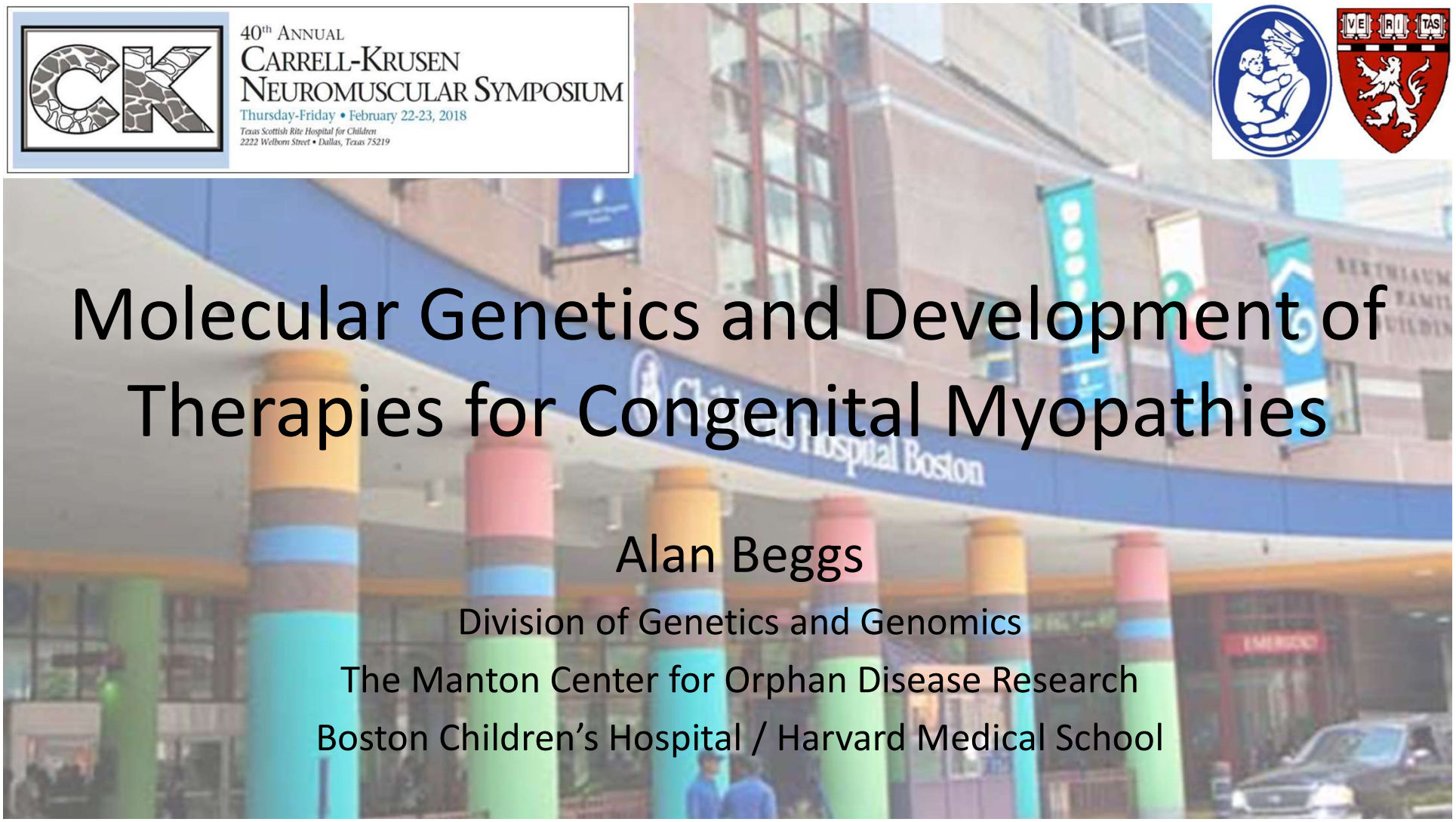


40th Annual
Carrell-Krusen
Neuromuscular Symposium
Thursday-Friday • February 22-23, 2018
Texas Scottish Rite Hospital for Children
2222 Welborn Street • Dallas, Texas 75219

Molecular Genetics and Development of Therapies for Congenital Myopathies

Alan Beggs

Division of Genetics and Genomics

The Manton Center for Orphan Disease Research

Boston Children's Hospital / Harvard Medical School

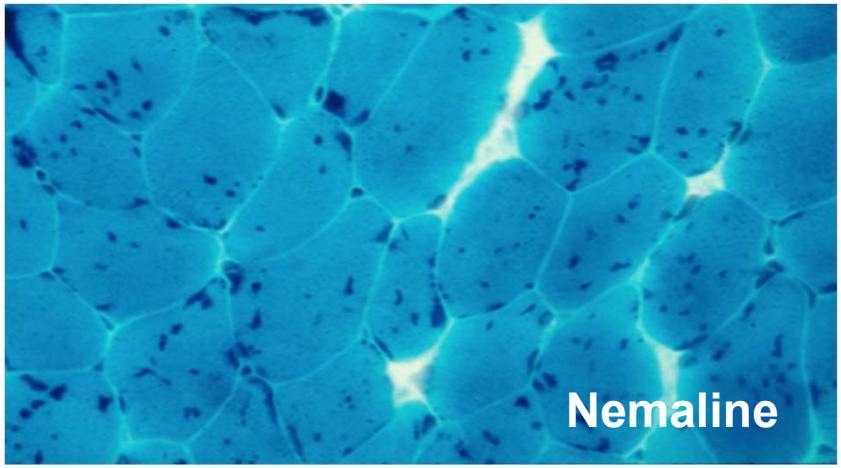
Disclosures

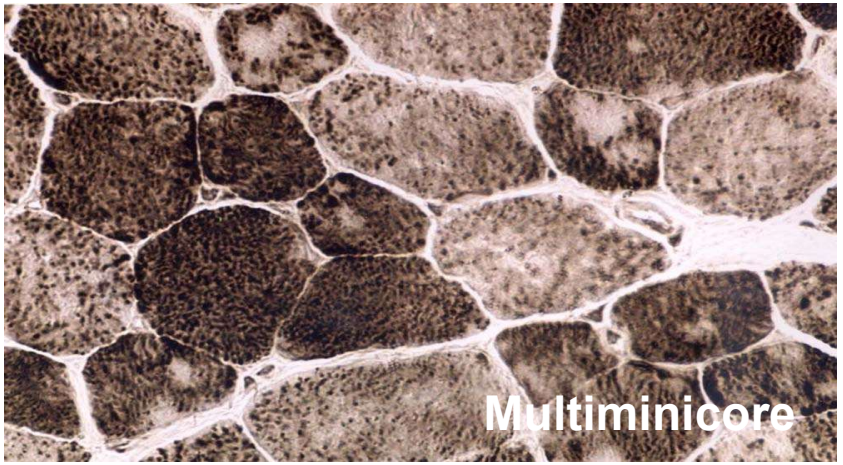
- Alan Beggs is a member of the Scientific Advisory Boards of Audentes Therapeutics Inc.
- This presentation will discuss publically available information on AT132, an investigational stage treatment for X-linked myotubular myopathy

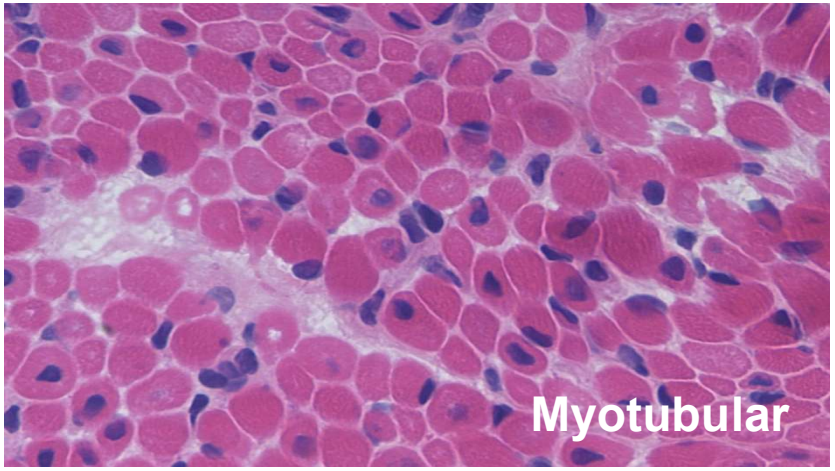
Congenital (nondystrophic) myopathies

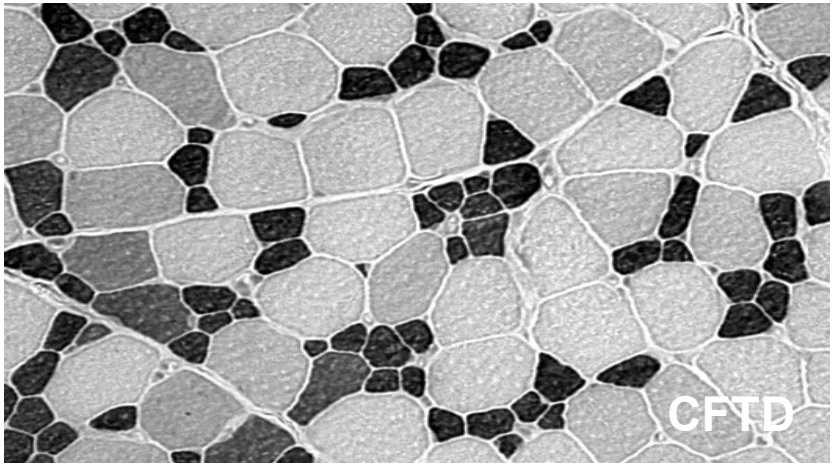
- Primary hypotonia and weakness, typically with onset early in life, and relatively nonprogressive
- Wide variation in clinical severity within each subtype. Later and adult onset forms for each type.
- Rare; genetic basis
  - Incidence roughly 0.06/1,000 live births (~1/16,667)
  - ~ 1/10th of all cases of neuromuscular disorders
- Pathologic changes originate within the myofiber
- Distinctive and specific morphologic abnormalities in skeletal muscle as main pathological feature

Congenital myopathies are defined by muscle pathology

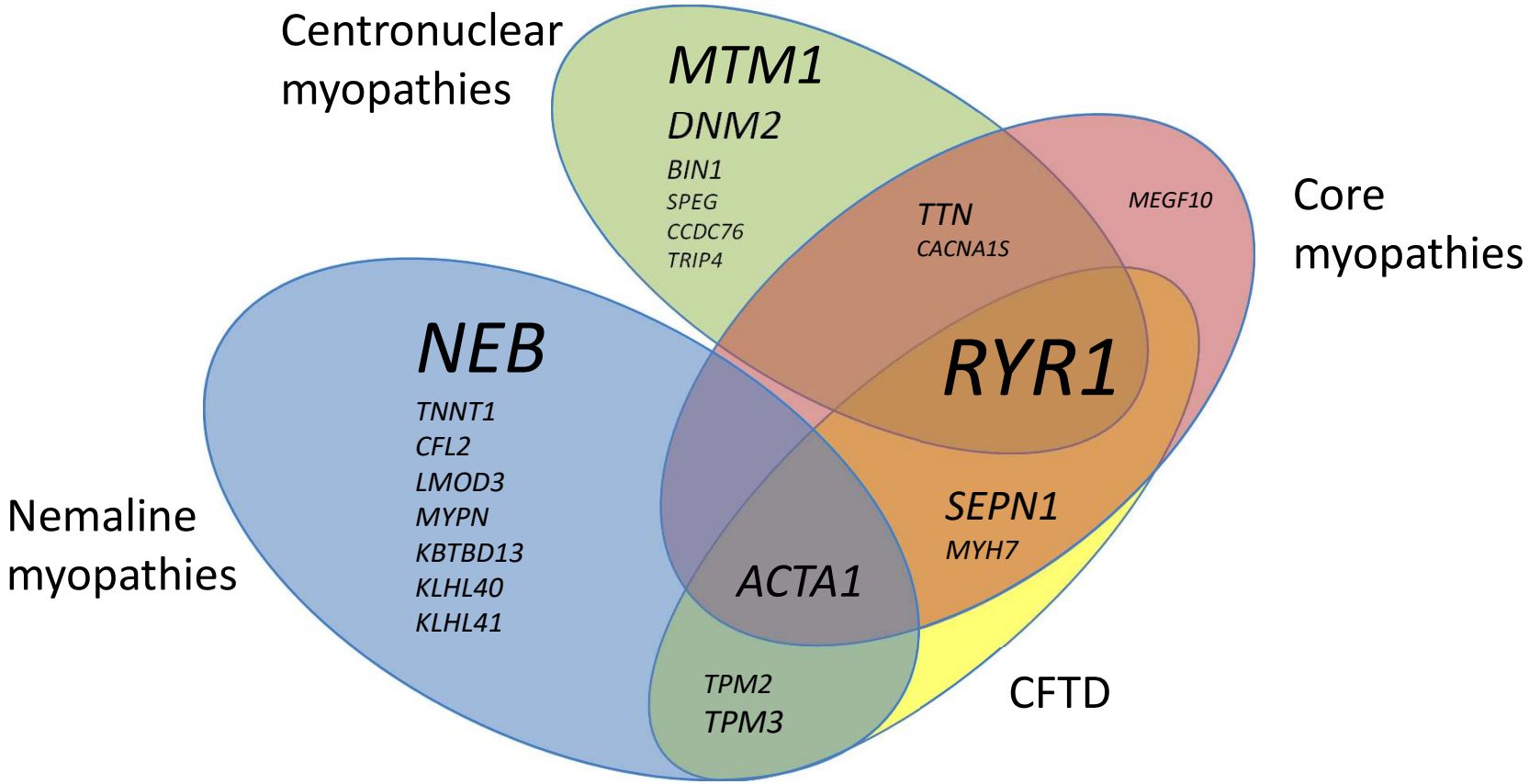




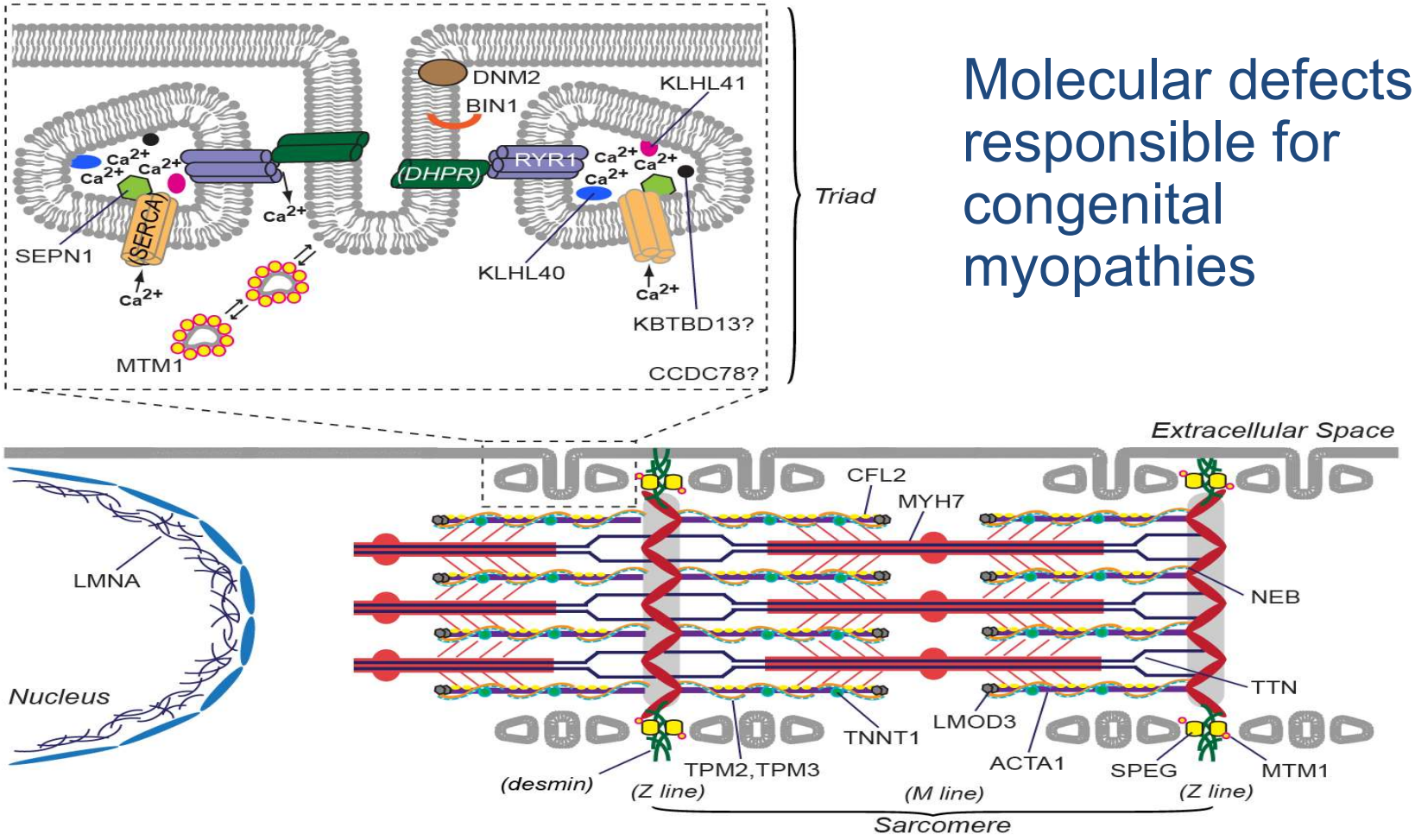




Genetic etiologies of congenital myopathies

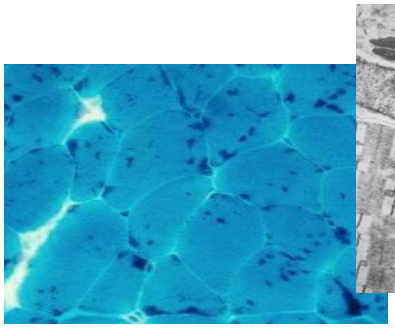


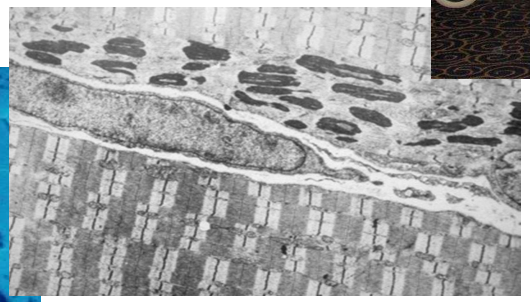
Molecular defects responsible for congenital myopathies

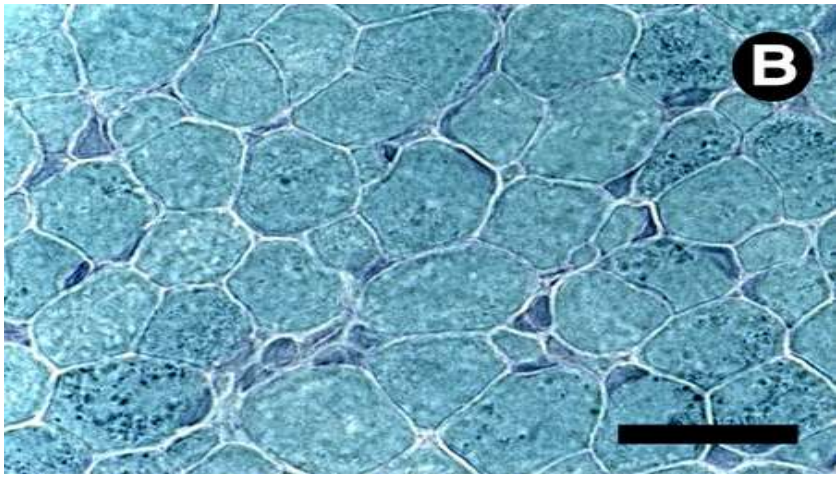


Nemaline Myopathy

- Most common type of congenital myopathy ~1/50,000 incidence
- Non or slowly progressive muscle weakness and hypotonia
- Variable severity: mild weakness in childhood, vent and wheelchair dependence, severe arthrogryposis



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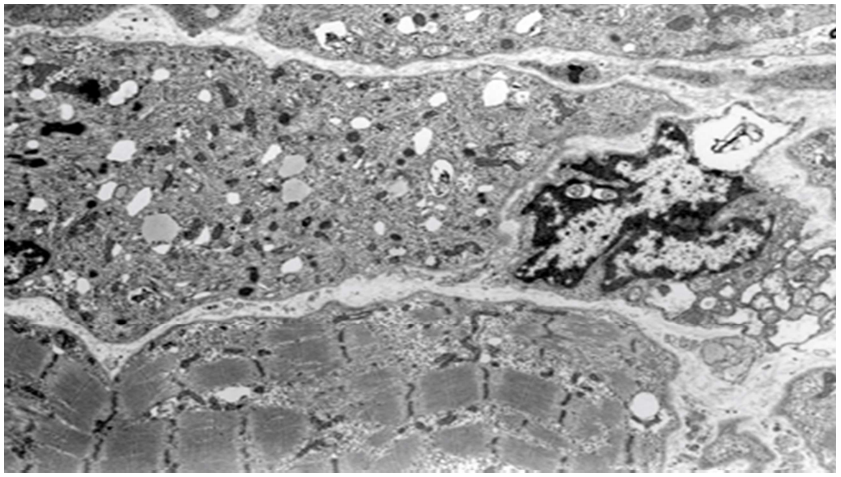

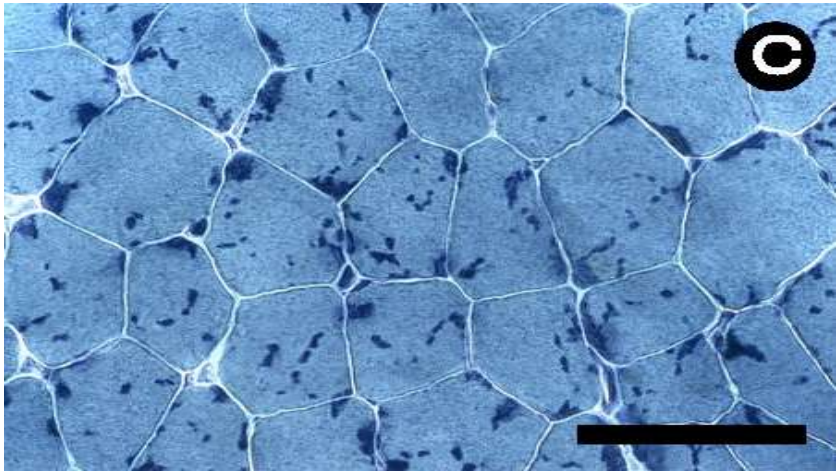
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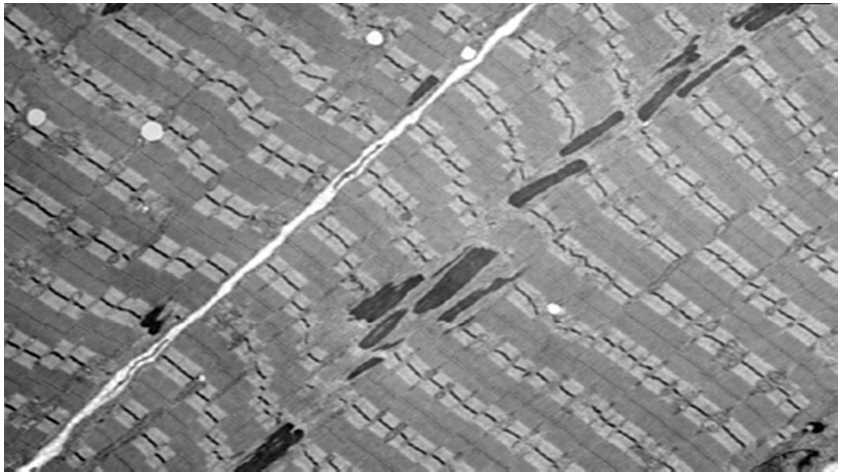


Genetic findings in 170 probands with Nemaline Myopathy

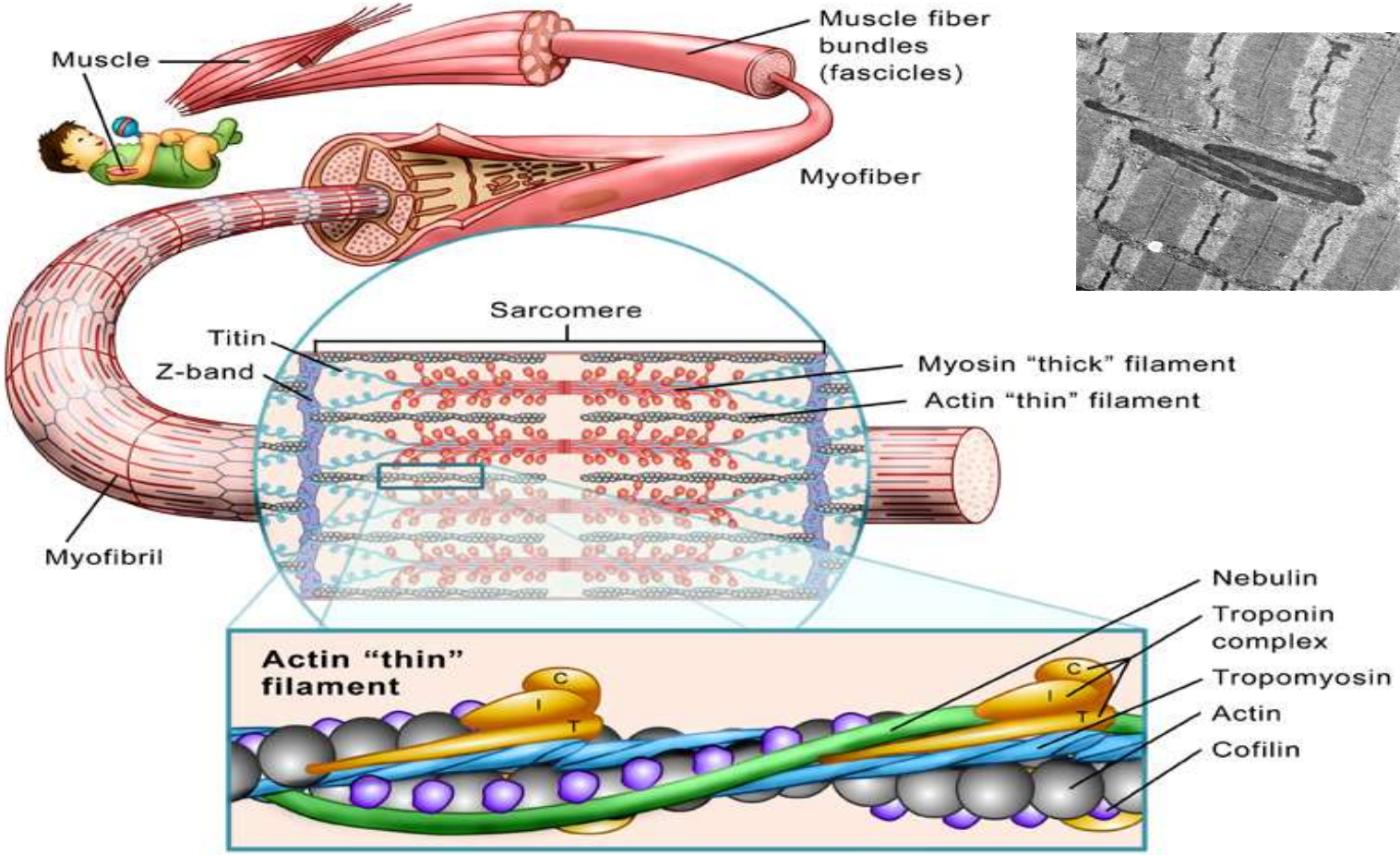
Gene	Candidate gene testing	NGS Panel	WES/WGS	Total	%
NEB	20	2	44	66	39
ACTA1	48	1	5	54	32
TPM3	3		2	5	2.9
TPM2	3	1		4	2.4
TNNT1	1	1	2	4	2.4
CFL2	2			2	1.2
KLHL41			2	2	1.2
KLHL40			1	1	0.6
LMOD3			1	1	0.6
KBTBD13				0	0.0
MYPN				0	0.0
Other	1		1	2	1.2
Unsolved			29	29	17

*85 cases pending, Sept 2017

Nemaline myopathy: Heterogeneity rules the day

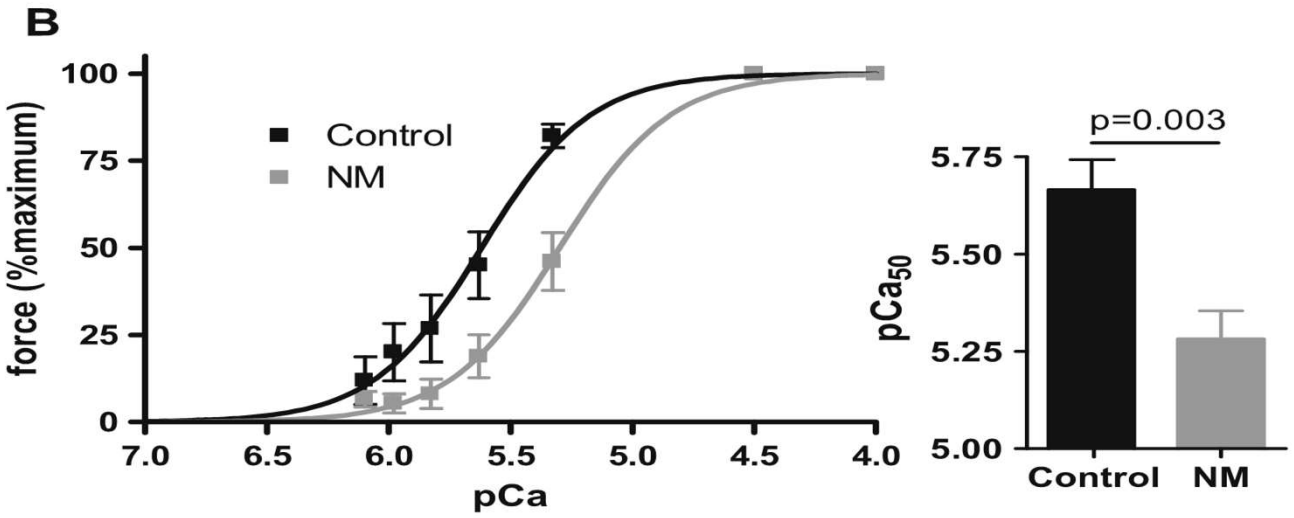
- Clinical heterogeneity (continuum)
- Pathological heterogeneity
- Genetic heterogeneity
  - Multiple inheritance patterns
  - Multiple genes
    - Multiple mutations/gene
  - Multiple inheritance patterns for each gene

Nemaline myopathy is a thin filament disease



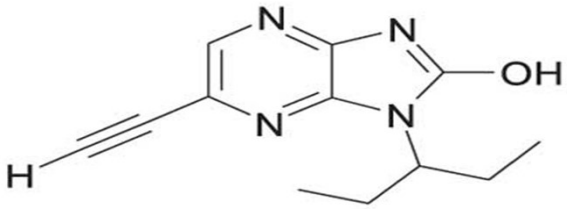
http://www.childrenshospital.org/beggs/nemaline

NM myofibers with NEB mutations exhibit reduced Ca^{2+} sensitivity of force generation



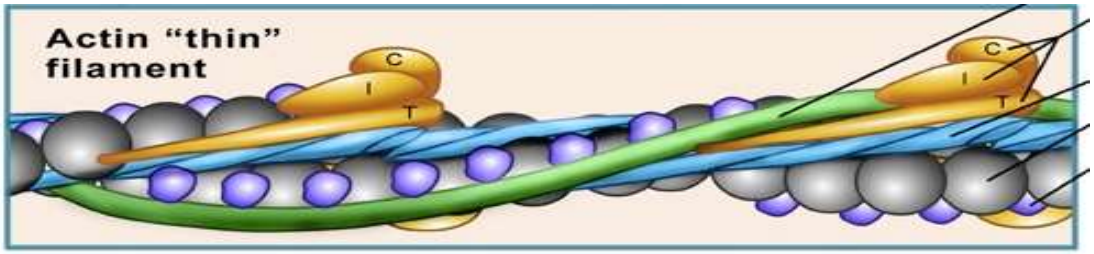
Journal of Structural Biology 170 (2010) 334–343

Troponin activators increase sensitivity of contraction to calcium



CYTOKINETICS

CK-2017357 (tirasemtiv)



Effect of CK-2066260 on calcium-sensitivity of force generation

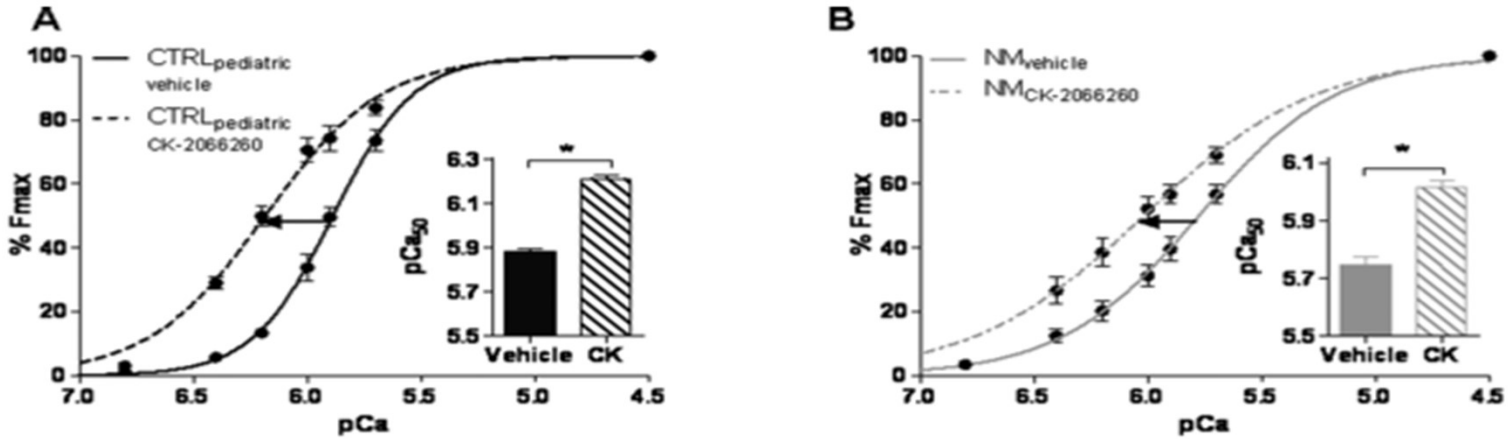


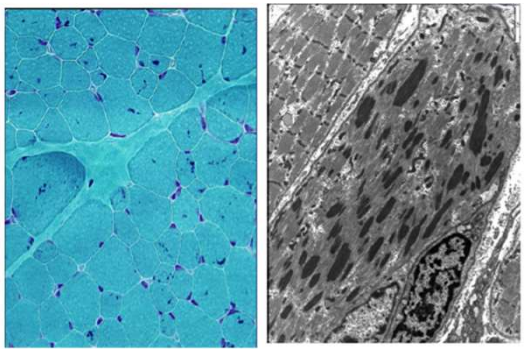
Table 2 Genetic data of nemaline myopathy patients

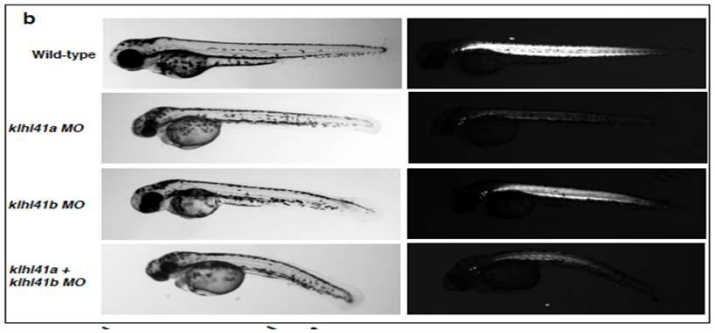
Patient ID	Biopsy ID	*NEB* mutations	Nebulin defects
26–2	T33	c.[7431+1916_7536+372del]+[7431+1916_7536+372del]	p.[Arg2478_Asp2512del]+[Arg2478_Asp2512del]
258–2	T1069	c.[3567+3_3567+7delAAGT]+[18124C>T]	Exon 33 splice defect+p.Gly6041Stop
974–1	T1033	c.[7431+1916_7536+372del]+[24842_24841delAG]	p.[Arg2478_Asp2512del]+[Arg8280SerfsStop2]
988–1	T887	c.[1152+1G>A]+[17013+1G>T]	Exon 13 splice defect+exon 107 splice defect

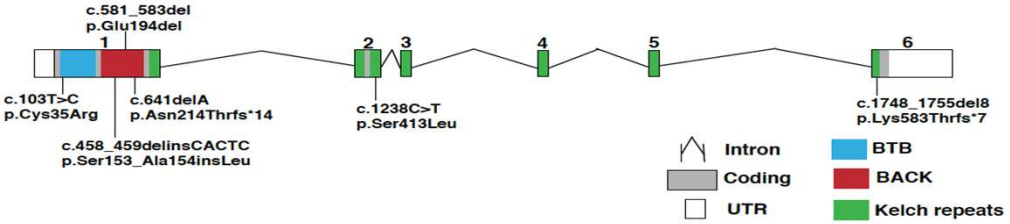
de Winter et al., *Journal of Medical Genetics*, 2013

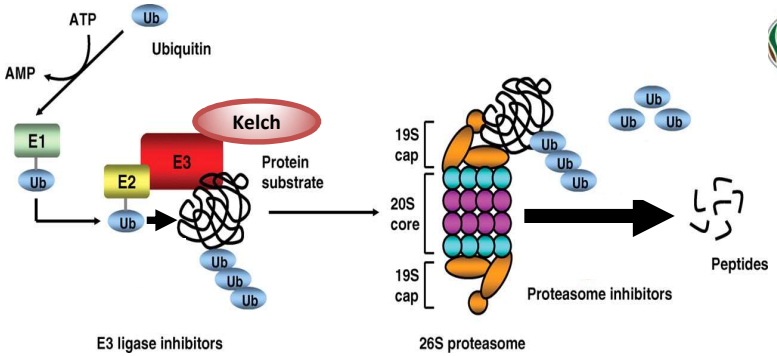
Identification of *KLHL41* Mutations Implicates BTB-Kelch-Mediated Ubiquitination as an Alternate Pathway to Myofibrillar Disruption in Nemaline Myopathy

Vandana A. Gupta,[1] Gianina Ravenscroft,[2] Ranad Shaheen,[3] Emily J. Todd,[2] Lindsay C. Swanson,[1] Masaaki Shiina,[4] Kazuhiro Ogata,[4] Cynthia Hsu,[1] Nigel F. Clarke,[5] Basil T. Darras,[6] Michelle A. Farrar,[7] Amal Hashem,[3] Nicholas D. Manton,[8] Francesco Muntoni,[9] Kathryn N. North,[10] Sarah A. Sandaradura,[5] Ichizo Nishino,[11] Yukiko K. Hayashi,[11] Caroline A. Sewry,[9] Elizabeth M. Thompson,[12,13] Kyle S. Yau,[2] Catherine A. Brownstein,[1] Timothy W. Yu,[1] Richard J.N. Allcock,[14] Mark R. Davis,[15] Carina Wallgren-Pettersson,[16] Naomichi Matsumoto,[17] Fowzan S. Alkuraya,[3] Nigel G. Laing,[2] and Alan H. Beggs[1,*]









eLIFE elifesciences.org
RESEARCH ARTICLE

KLHL41 stabilizes skeletal muscle sarcomeres by nonproteolytic ubiquitination

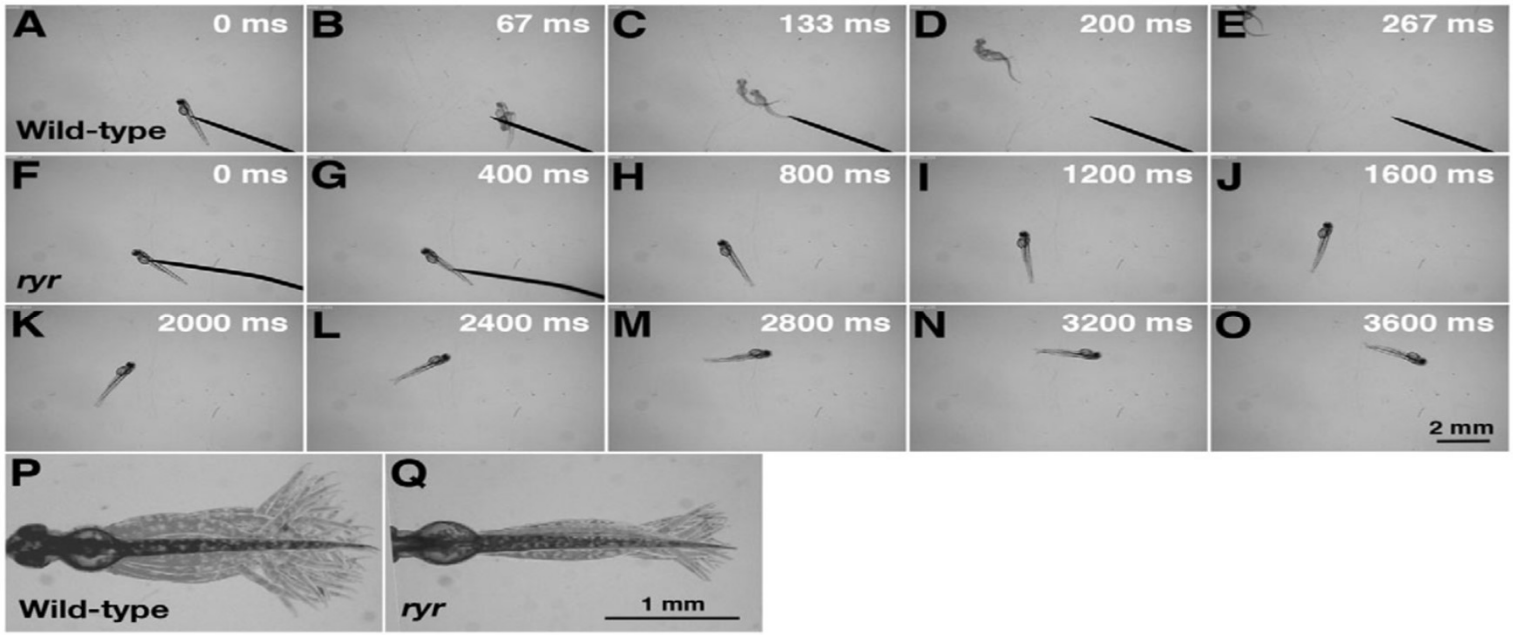
Andres Ramirez-Martinez[1,2,3], Bercin Kutluk Cenik[1,2,3], Svetlana Bezprozvannaya[1,2,3], Beibei Chen[4], Rhonda Bassel-Duby[1,2,3], Ning Liu[1,2,3]*, Eric N Olson[1,2,3]*

Gupta et al., *Am J Hum Genet* 93:1108-17 (2013)

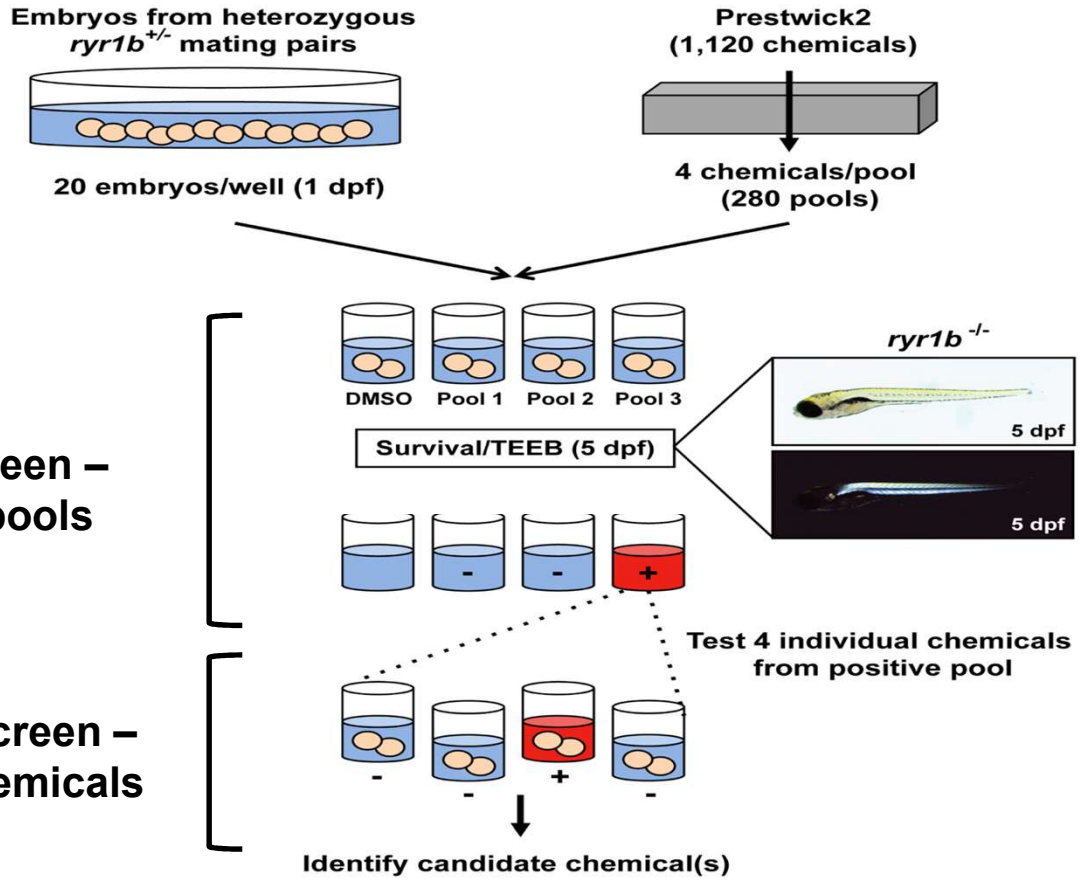
Development 134, 2771-2781 (2007) doi:10.1242/dev.004531

Zebrafish *relatively relaxed* mutants have a ryanodine receptor defect, show slow swimming and provide a model of multi-minicore disease

Hiromi Hirata[1,2,†], Takaki Watanabe[1], Jun Hatakeyama[3], Shawn M. Sprague[2], Louis Saint-Amant[2,*], Ayako Nagashima[2], Wilson W. Cui[2], Weibin Zhou[2] and John Y. Kuwada[2]



Chemical screening strategy



Primary screen – Chemical pools

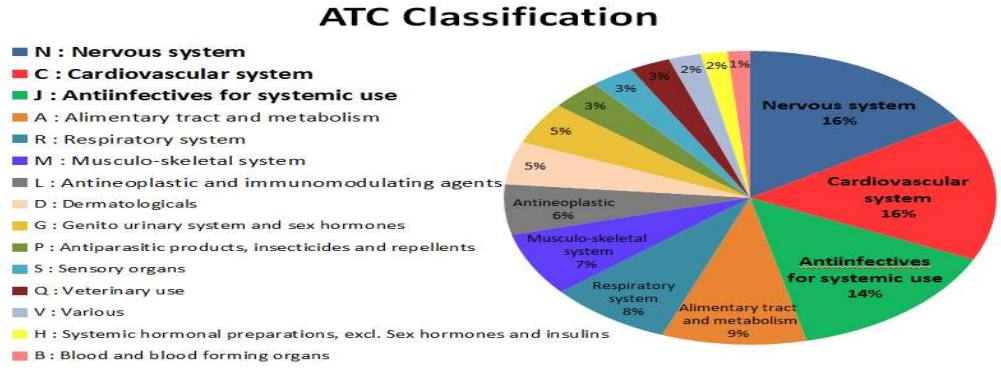
Secondary screen – Individual chemicals

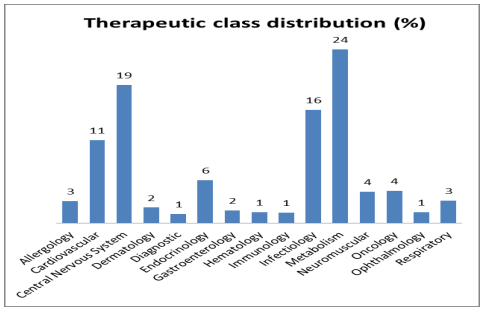
Adapted from Kawahara et al., *PNAS* 2011

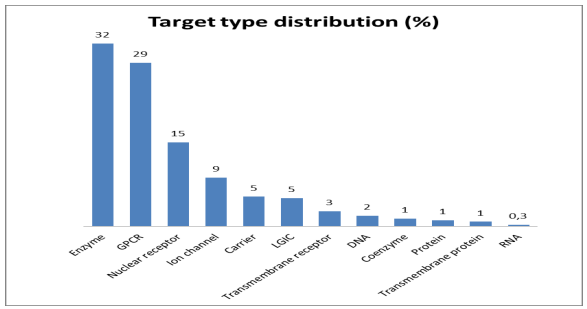
PRESTWICK CHEMICAL
A medicinal chemistry company

Prestwick2 Collection

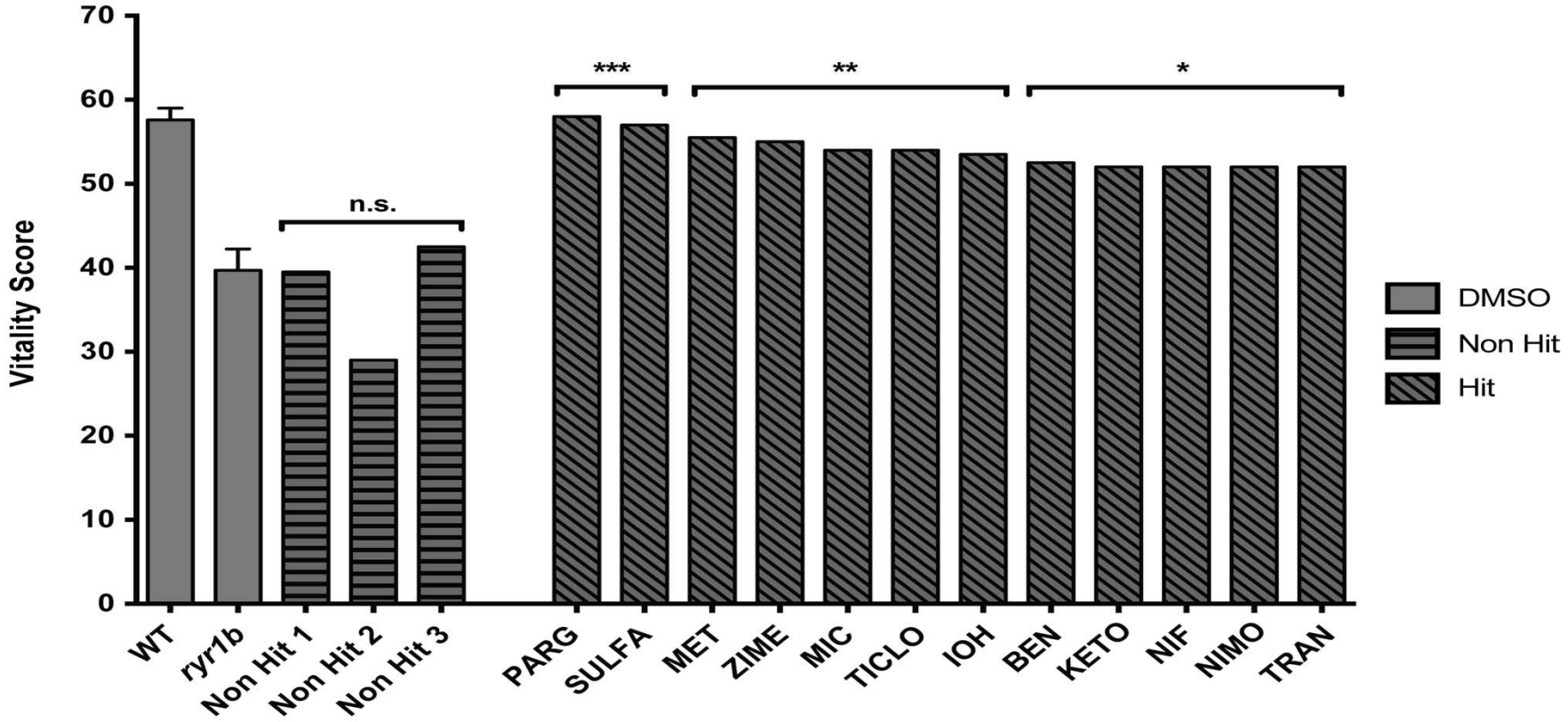
- 1120 off-patent compounds that have been selected for structural diversity, collective coverage of multiple therapeutic areas, and known safety and bioavailability in humans.
- 100% approved drugs. Over 85% of the Prestwick compounds are currently marketed.







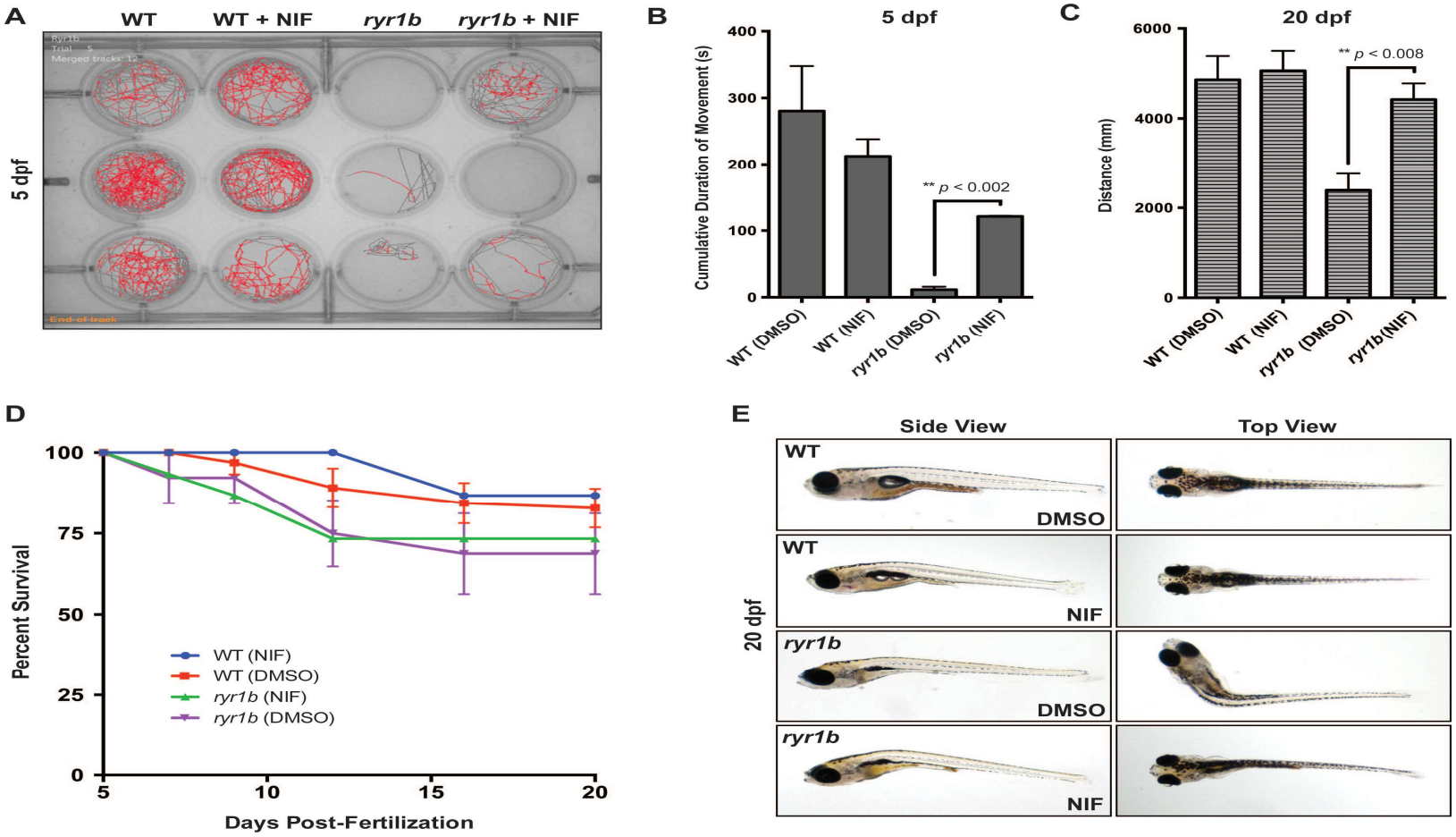
Identifying candidates in the secondary screen



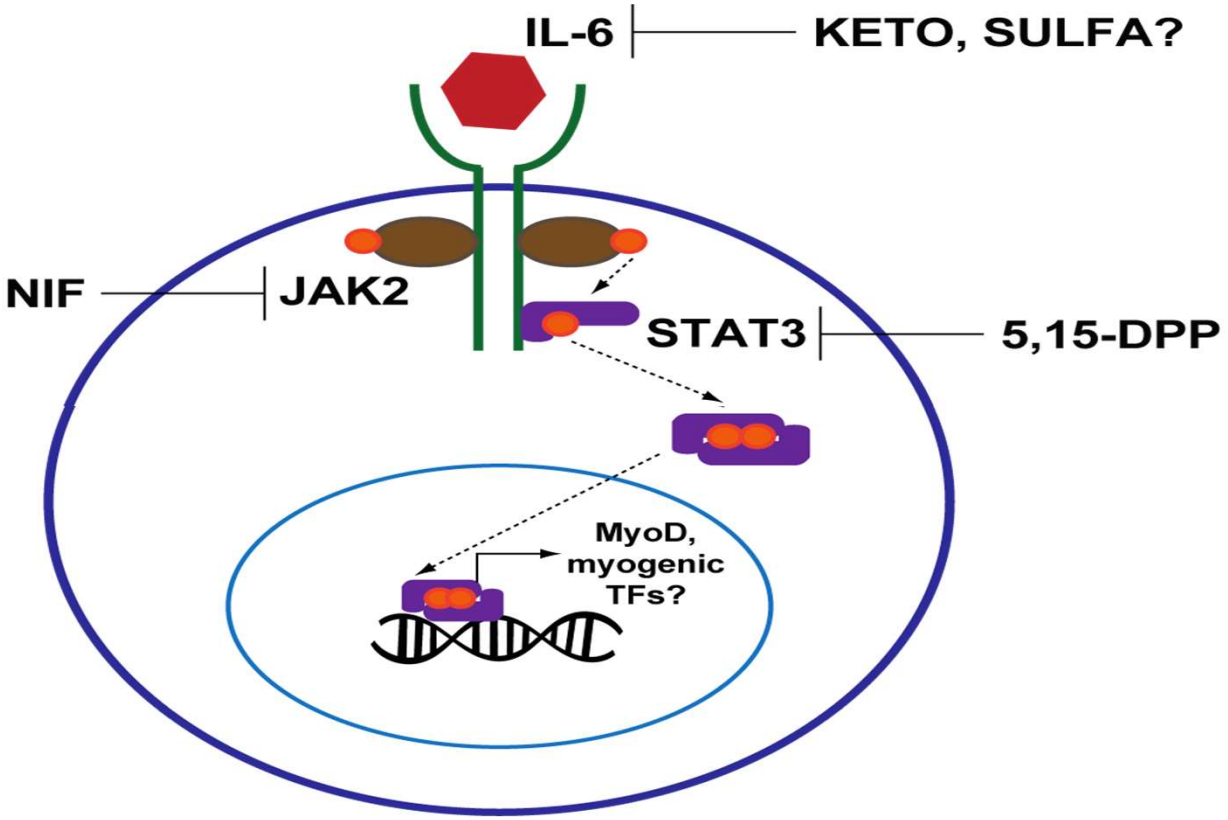
Candidate compounds

Vitality Score	Chemical Name	Formula	MW	Mechanism of Action
58.0	Pargyline hydrochloride *	$C_{11}H_{14}ClN$	195.69	Irreversible monoamine oxidase (MAO) inhibitor
57.0	Sulfasalazine	$C_{18}H_{14}N_4O_5S$	398.39	NF-KB inhibitor; anti-inflammatory
55.5	Metolazone **	$C_{16}H_{16}ClN_3O_3S$	365.83	Sodium-chloride channel inhibitor
55.0	Zimelidine dihydrochloride monohydrate **	$C_{16}H_{21}BrCl_2N_2O$	408.16	Selective serotonin reuptake inhibitor
54.0	Miconazole ***	$C_{18}H_{14}Cl_4N_2O$	416.13	Anti-fungal agent
54.0	Ticlopidine hydrochloride ***	$C_{14}H_{15}Cl_2NS$	300.25	Inhibitor of platelet aggregation
53.5	Iohexol	$C_{19}H_{26}I_3N_3O_9$	821.14	Low-osmolality contrast agent
52.5	Benoxinate hydrochloride ***	$C_{17}H_{29}ClN_2O_3$	344.88	Surface anaesthetic
52.0	Ketoprofen	$C_{16}H_{14}O_3$	254.28	Cyclooxygenase inhibitor; anti-inflammatory
52.0	Nifuroxazide	$C_{12}H_9N_3O_5$	275.22	JAK/STAT signaling inhibitor
52.0	Nimodipine	$C_{21}H_{26}N_2O_7$	418.44	Dihydropyridine calcium channel blocker
52.0	Tranylcypromine hydrochloride *	$C_9H_{12}ClN$	169.65	Irreversible MAO inhibitor

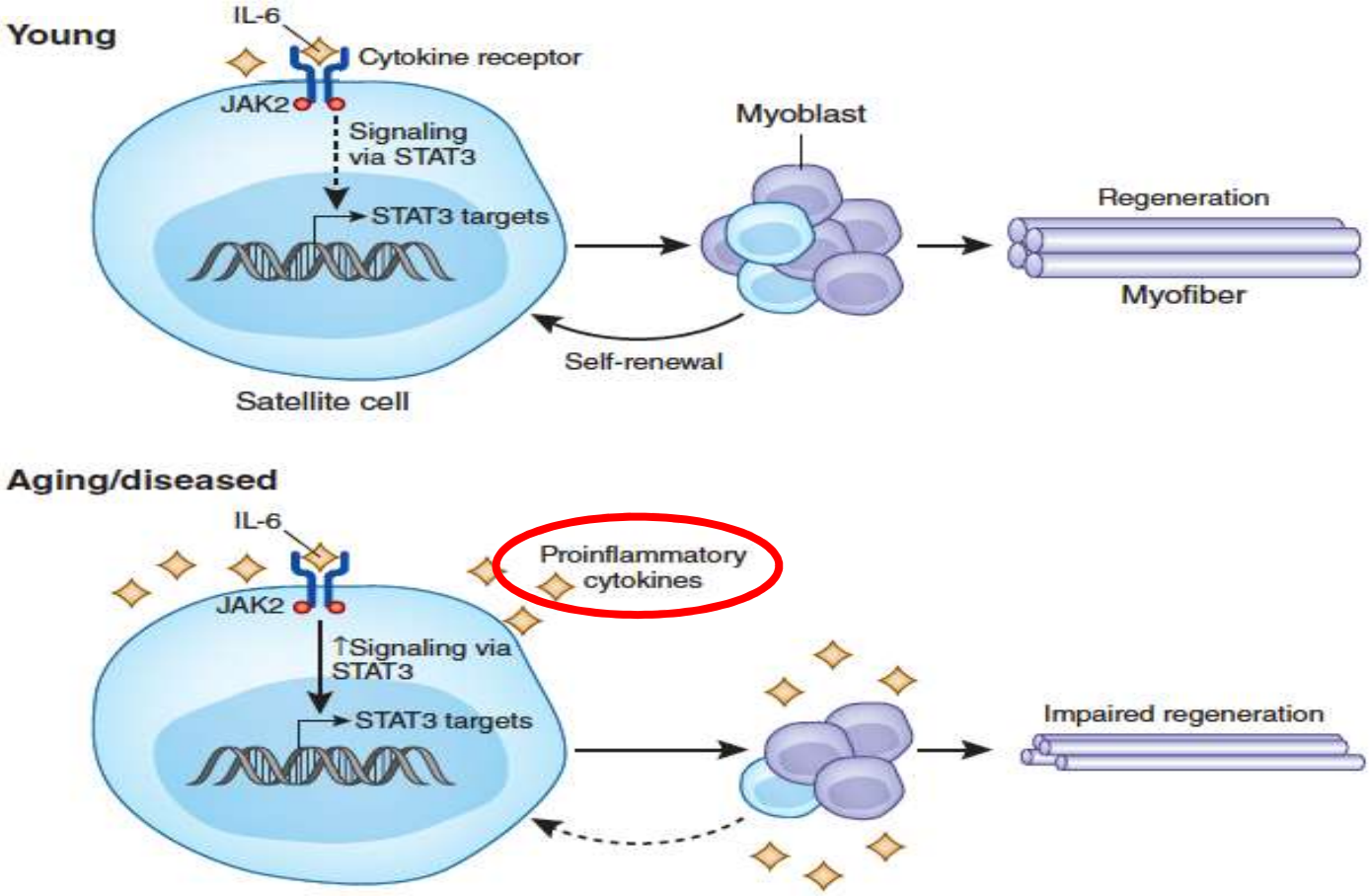
Activity monitoring and survival studies



Inhibiting JAK-STAT as a therapeutic approach for *RYR1*-related congenital myopathy



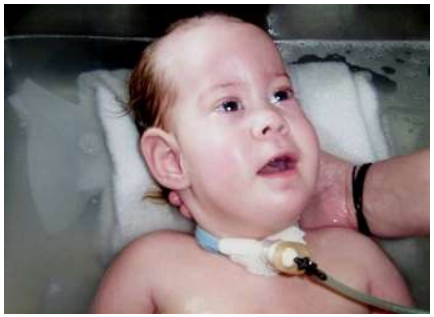
Potential mechanism of JAK-STAT in skeletal muscle

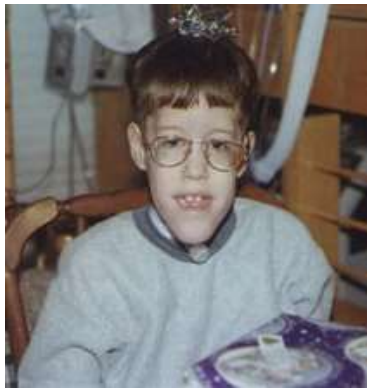


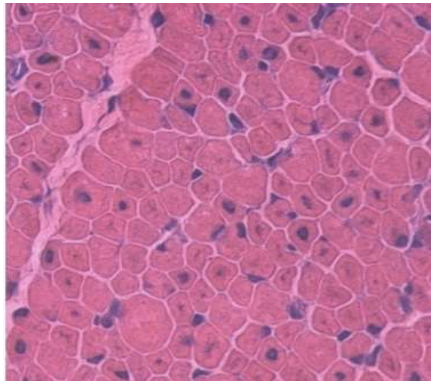
Dole and Olwin, *Nat Med* 2014

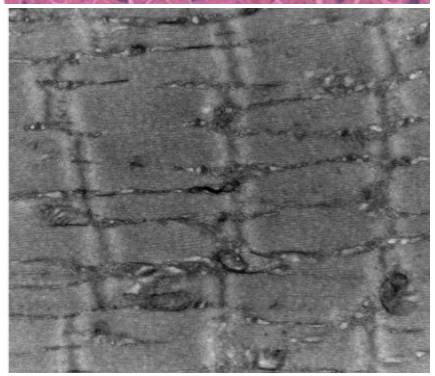
X-Linked Myotubular Myopathy

- Incidence 1:50,000 live-born males
  - Prevalence: 25 in France
- Born floppy with severe global muscle weakness and hypotonia
- Historically defined by pathology
- Mutations of myotubularin gene, *MTM1*
  - lipid phosphatase



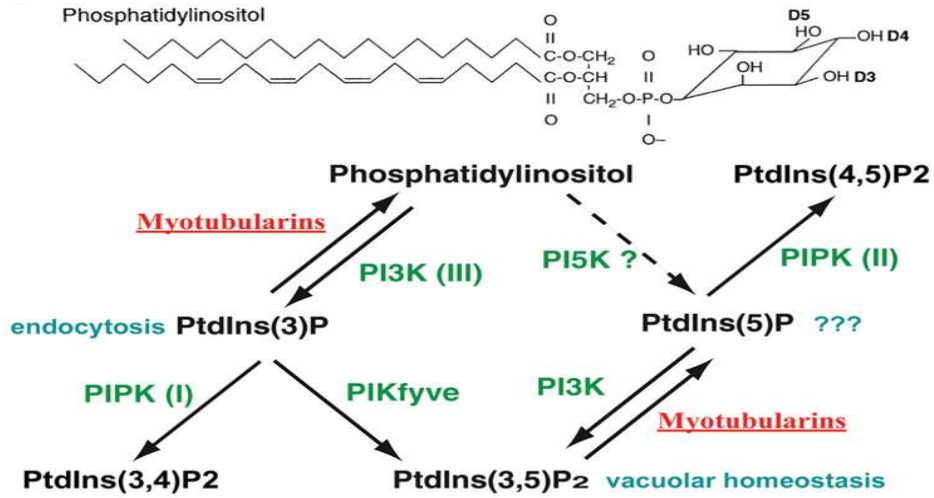




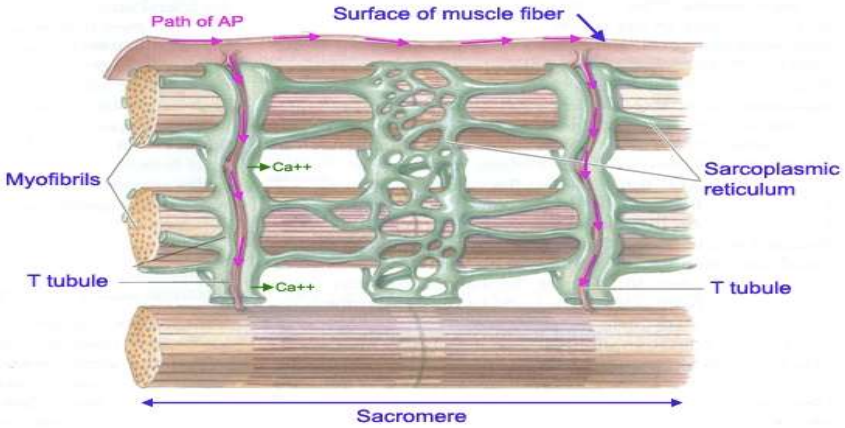


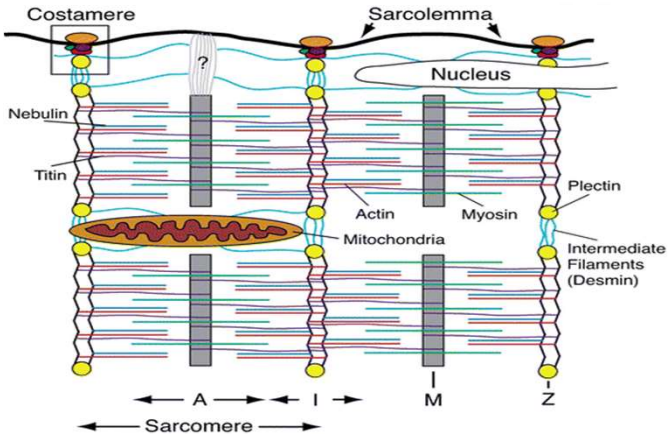
Myotubularin

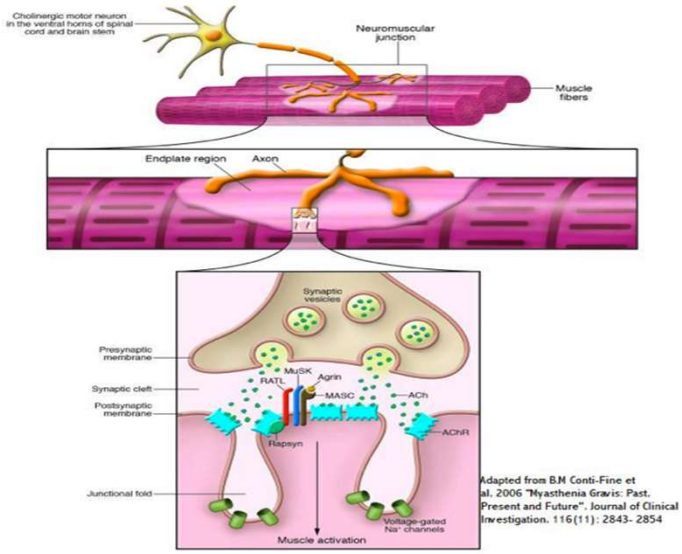
- Gene mutated (*MTM1*) encodes myotubularin (Laporte 1996)
- Ubiquitous transcript (4kb mRNA)
- Biochemically myotubularin is a phosphoinositide lipid phosphatase
- Phosphoinositides involved in:
  - cell proliferation & death
  - growth factor response
  - cell motility
  - regulate cytoskeleton
  - intracellular vesicle trafficking



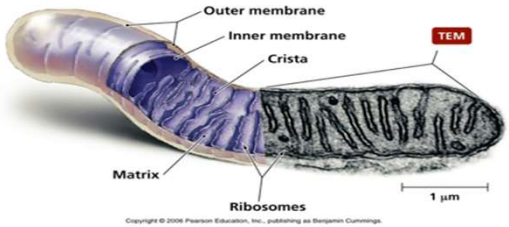
Myotubularin deficiency acts at many levels



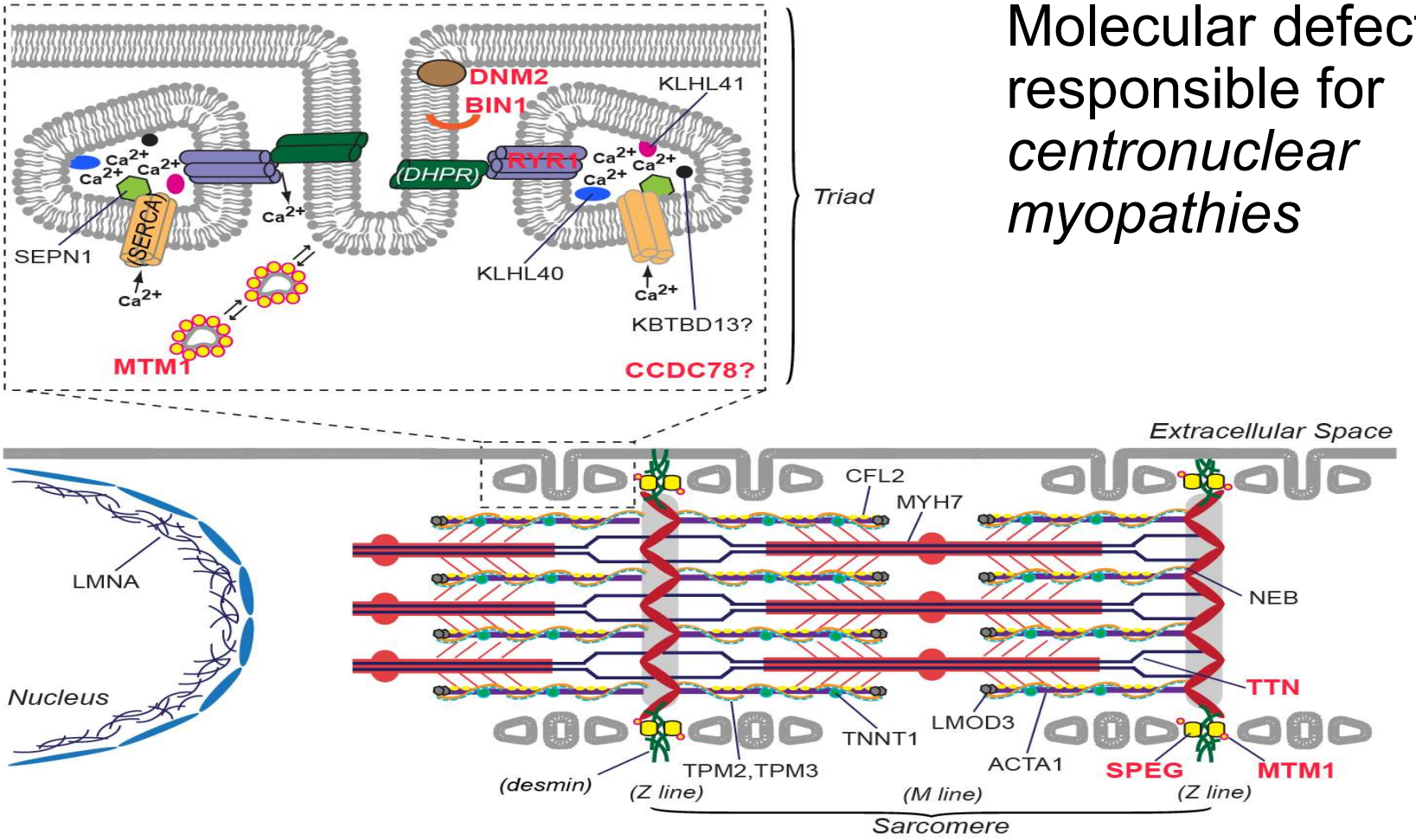




Adapted from B.N Conti-Fine et al. 2006 "Myasthenia Gravis: Past, Present and Future". Journal of Clinical Investigation. 116(11): 2843- 2854



Molecular defects responsible for *centronuclear myopathies*

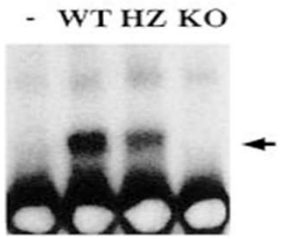


XLMTM as a candidate for gene/protein-replacement therapy

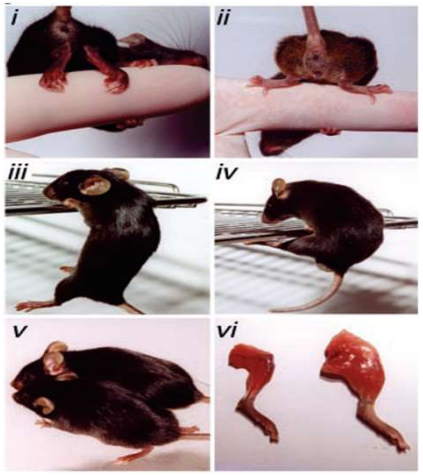
- Clear and straightforward genetic dx
  - Loss of function mutations of *MTM1*
- Early onset and severe disease
  - “CRM-negative” pts relatively uniform
- Myotubularin is an enzyme, and is reasonably sized
- You may not need much myotubularin to improve function dramatically
  - Heterozygote females are generally asymptomatic
- Excellent animal models with clear behavioral and pathological phenotypes

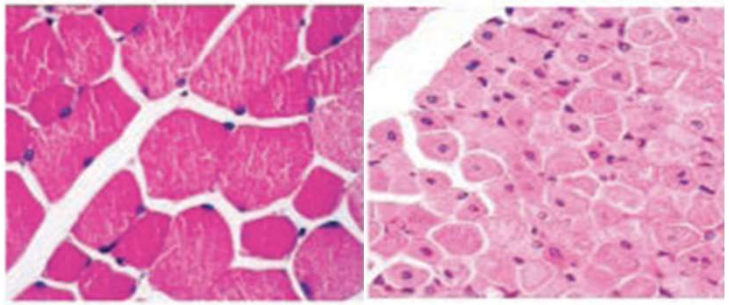
The *Mtm1* KO mouse

- Buj-Bello *et al*., *PNAS, 2002*
  - The animals make no functional myotubularin
  - Onset of generalized weakness after several weeks
  - Weakness and numbers of central nuclei increase over time
  - Animals expire at 8-12 weeks of life



Western Blot

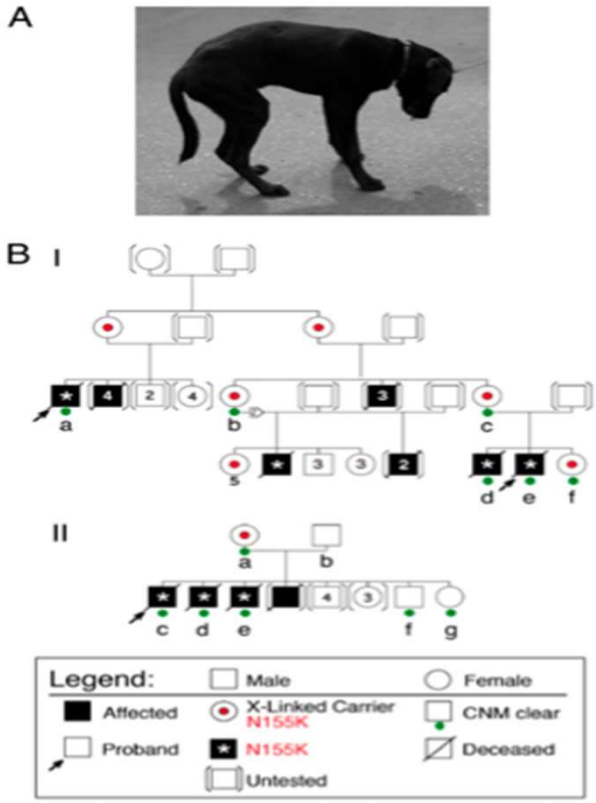


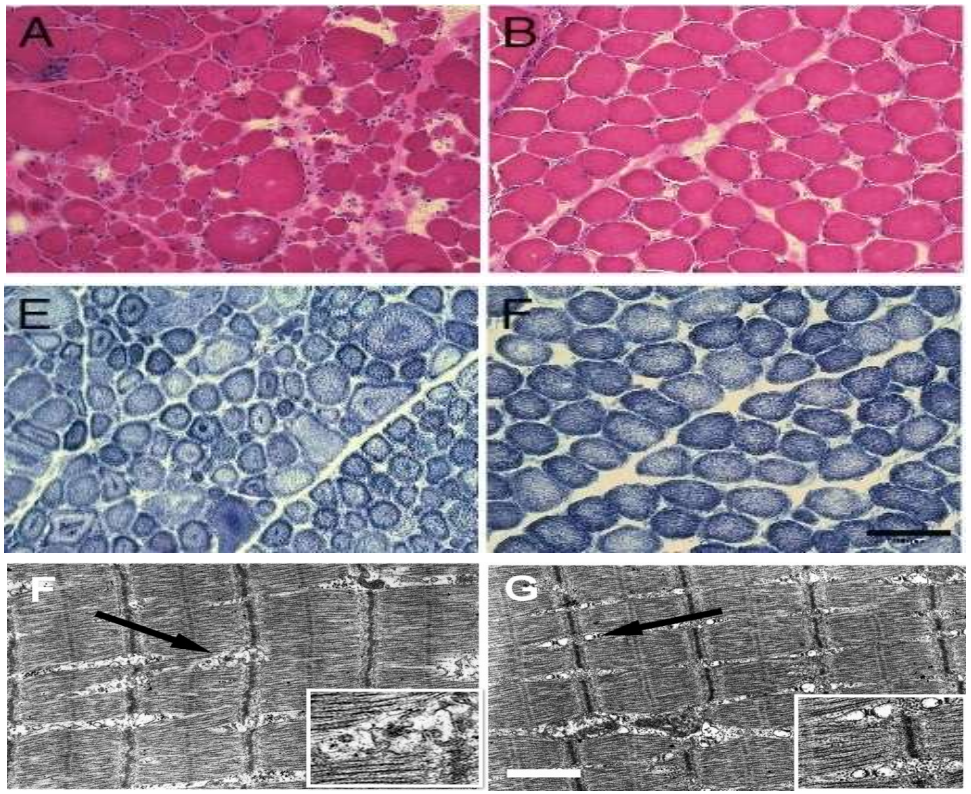


Proc Natl Acad Sci U S A. 2010 Aug 17;107(33):14697-702. Epub 2010 Aug 3.

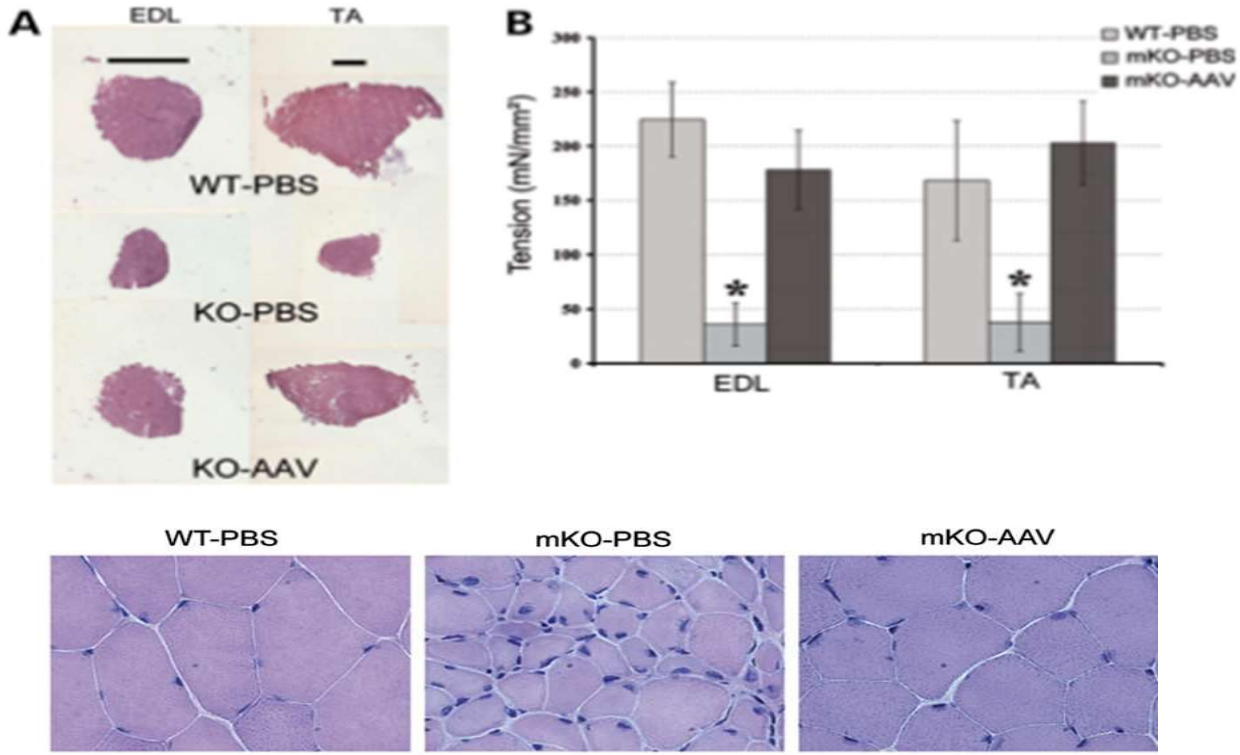
MTM1 mutation associated with X-linked myotubular myopathy in Labrador Retrievers.

Beggs AH, Böhm J, Snead E, Kozlowski M, Maurer M, Minor K, Childers MK, Taylor SM, Hitte C, Mickelson JR, Guo LT, Mizisin AP, Buj-Bello A, Tiret L, Laporte J, Shelton GD.



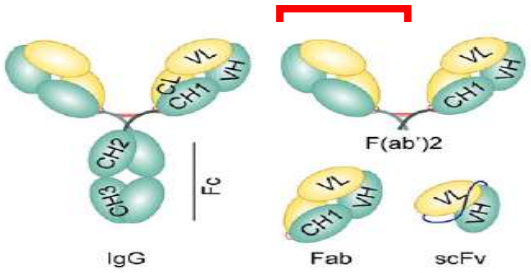


Local administration of rAAV1/2-*Mtm1* can reverse the pathological phenotype in myotubularin deficiency



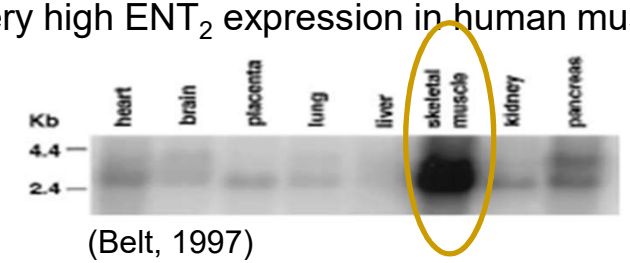
Buj Bello et al. *Human Molecular Genetics*, 2008, 2132-2143.

Muscle targeted enzyme replacement via 3E10Fv



Anti-DNA autoantibody fragment mAb3E10 from MRL/mpi/lpr lupus mouse *Weisbart et al., J. Immunology,* 1996

Very high ENT_2 expression in human muscle

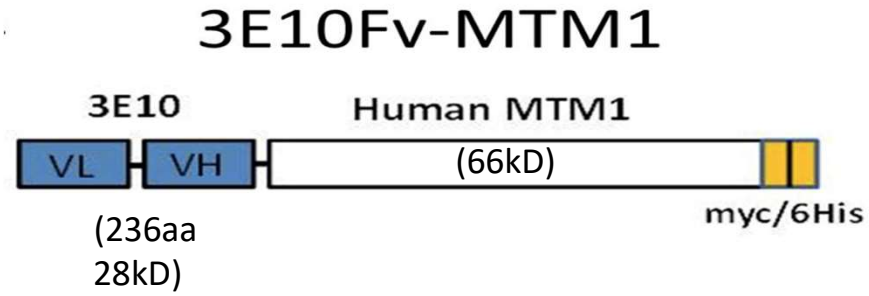


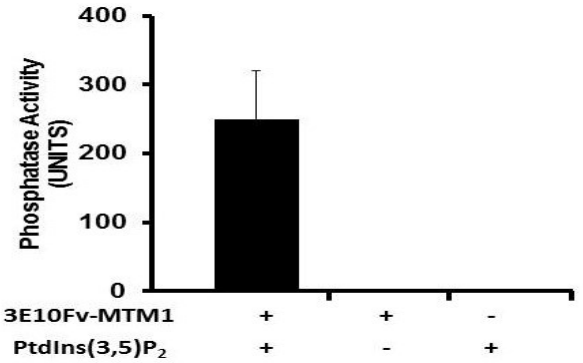
(Belt, 1997)

4s3 Bioscience

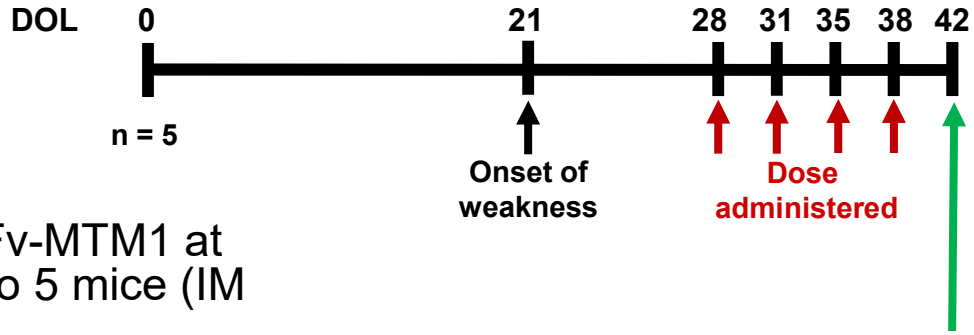
Valerion Therapeutics

3E10Fv-MTM1 protein therapy study design





Malachite green phosphatase activity assay



- 4 doses of 300 mg 3E10Fv-MTM1 at 0.1 mg/mL administered to 5 mice (IM into the TA muscle)
- Control animals received TBS (saline) injections.

Enzyme replacement therapy rescues weakness and improves muscle pathology in mice with X-linked myotubular myopathy

Michael W. Lawlor[1,2], Dustin Armstrong[3], Marissa G. Viola[1], Jeffrey J. Widrick[1,4], Hui Meng[2], Robert W. Grange[5], Martin K. Childers[6], Cynthia P. Hsu[1], Michael O'Callaghan[3], Christopher R. Pierson[7], Anna Buj-Bello[8] and Alan H. Beggs[1,*]

Human Molecular Genetics, 2013, Vol. 22, No. 8 **1525–1538**
doi:10.1093/hmg/ddt003
Advance Access published on January 9, 2013

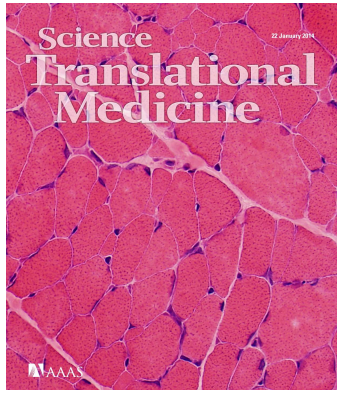
AAV-based gene therapy for XLMTM

1. Systemic (tail vein) administration of rAAV2/9-p*Des-Mtm1* to *Mtm1* KO mice
2. Local IM injection of rAAV2/8 p*Des-MTM1* into canine cranial tibialis muscles
3. Local-regional perfusion of rAAV2/8 p*Des-MTM1* into canine limbs

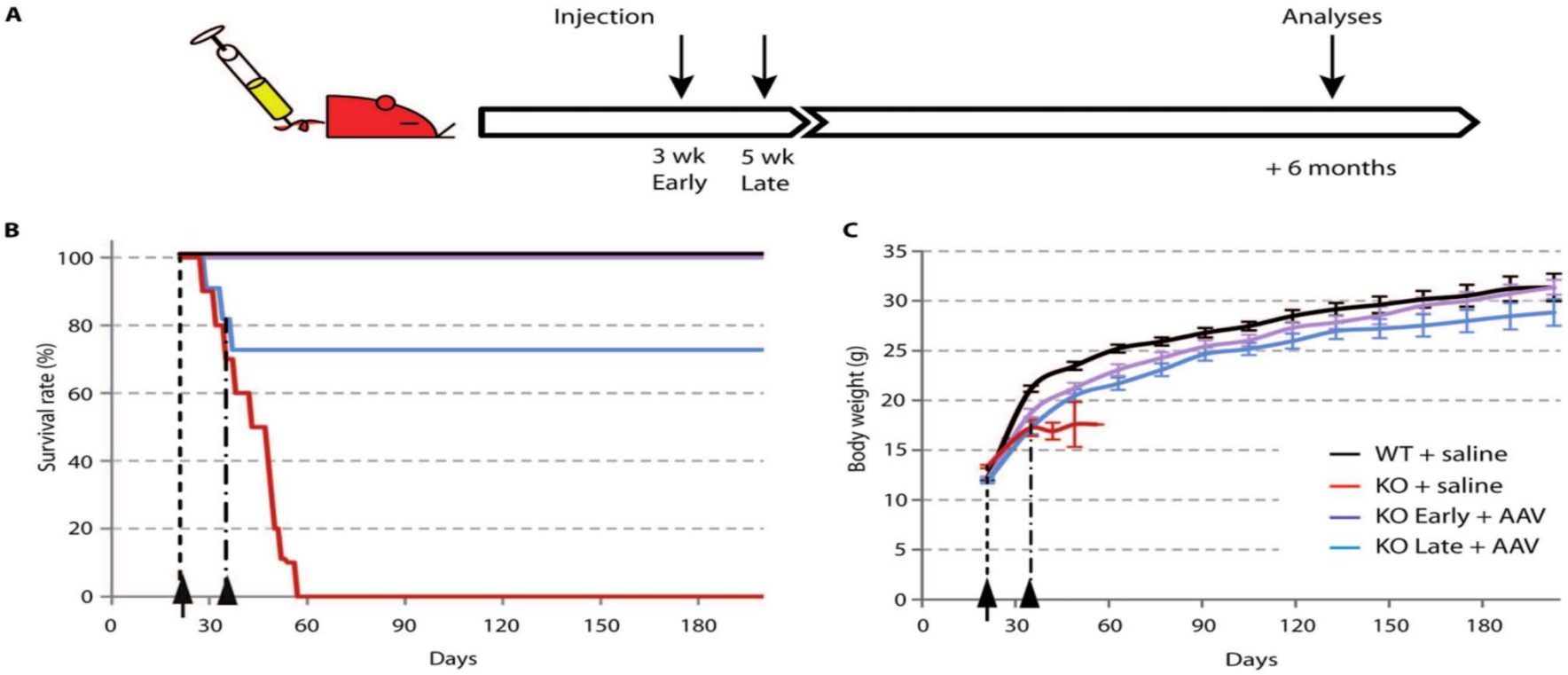
Gene Therapy Prolongs Survival and Restores Function in Murine and Canine Models of Myotubular Myopathy

Martin K. Childers,[1,2]* Romain Joubert,[3] Karine Poulard,[3] Christelle Moal,[3] Robert W. Grange,[4] Jonathan A. Doering,[4] Michael W. Lawlor,[5,6] Branden E. Rider,[5] Thibaud Jamet,[3] Nathalie Danièle,[3] Samia Martin,[3] Christel Rivière,[3] Thomas Soker,[6] Caroline Hammer,[3] Laetitia Van Wittenberghe,[3] Mandy Lockard,[7] Xuan Guan,[7] Melissa Goddard,[7] Erin Mitchell,[7] Jane Barber,[7] J. Koudy Williams,[7] David L. Mack,[1] Mark E. Furth,[8] Alban Vignaud,[3] Carole Masurier,[3] Fulvio Mavilio,[3] Philippe Moullier,[3,9,10] Alan H. Beggs,[5]* Anna Buj-Bello[3]*

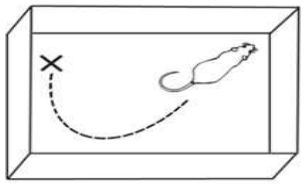
Sci. Transl. Med. **6**, 220ra10 (2014).

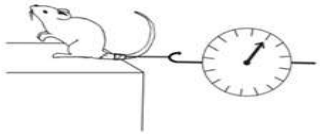


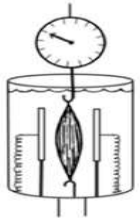
IV rAAV2/9-p*Des-Mtm1* (3.0 x 10^{13} vg/kg) prolongs survival and increases muscle mass in *Mtm1* KO mice

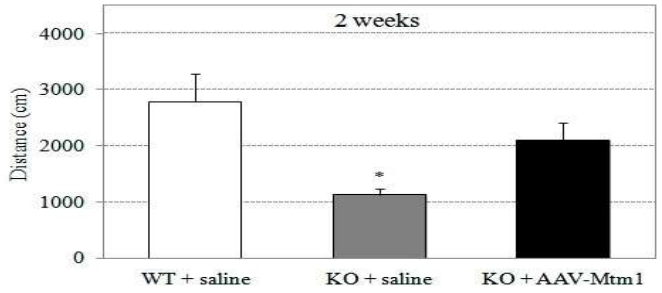


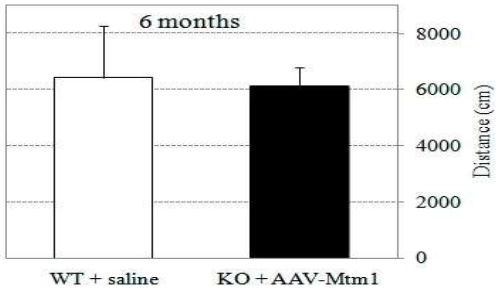
IV rAAV2/9-p*Des-Mtm1* corrects muscle function *in vivo* and *ex vivo*

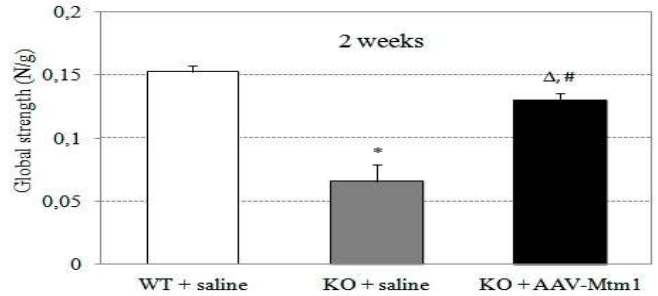


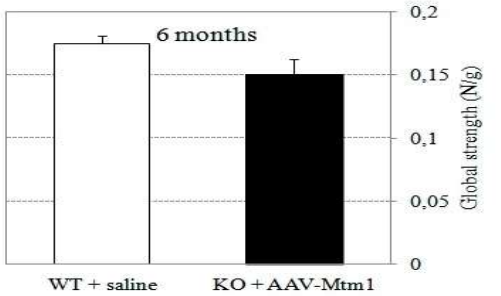


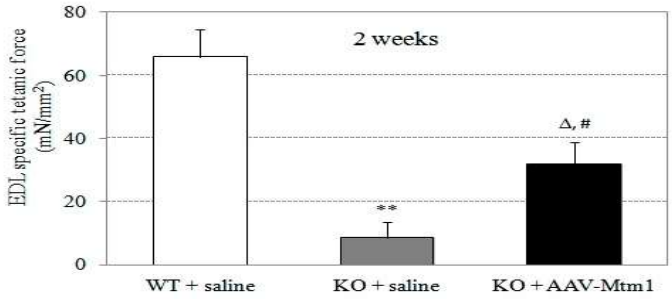


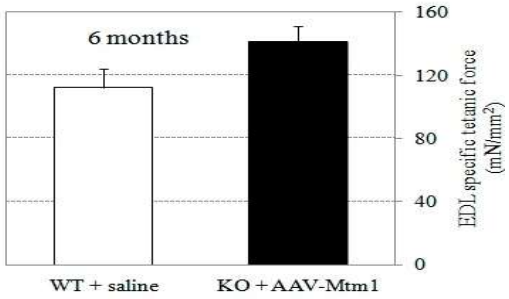




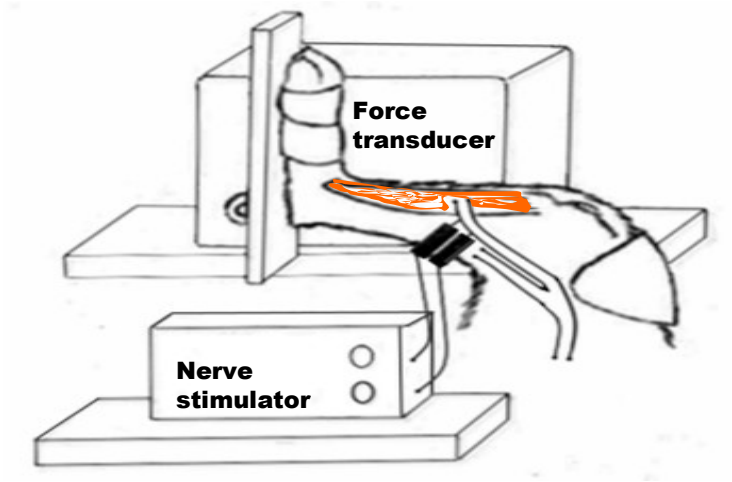


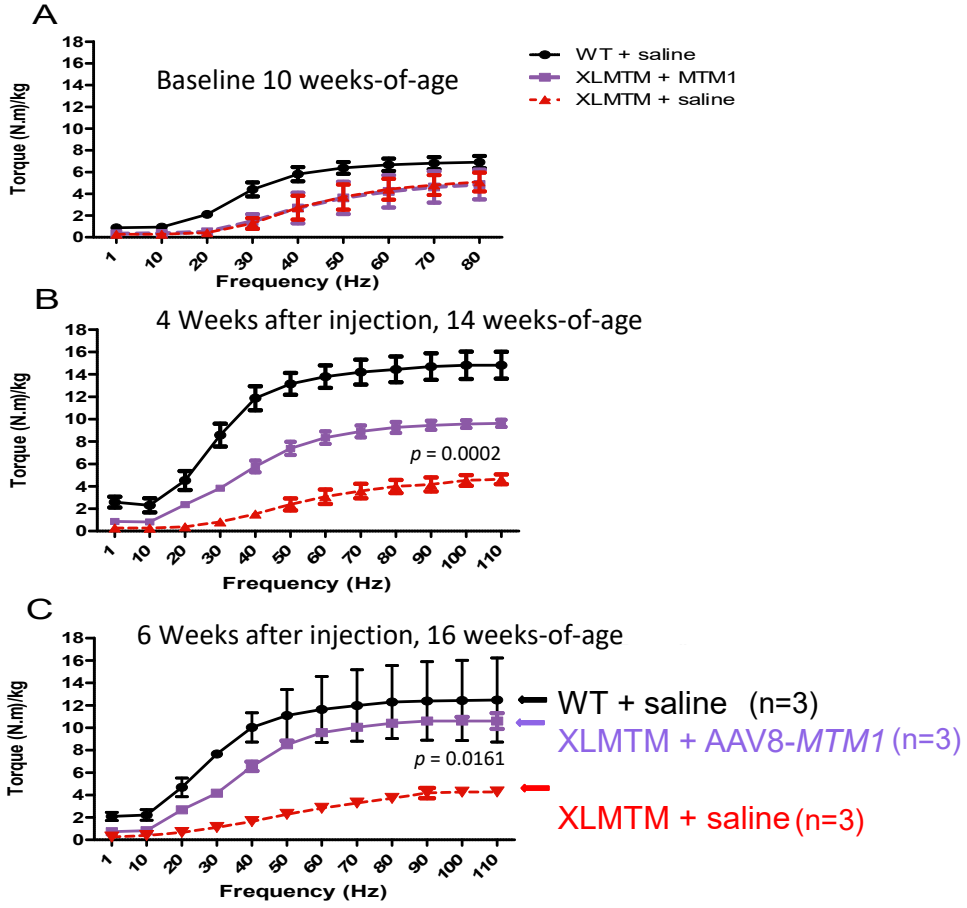






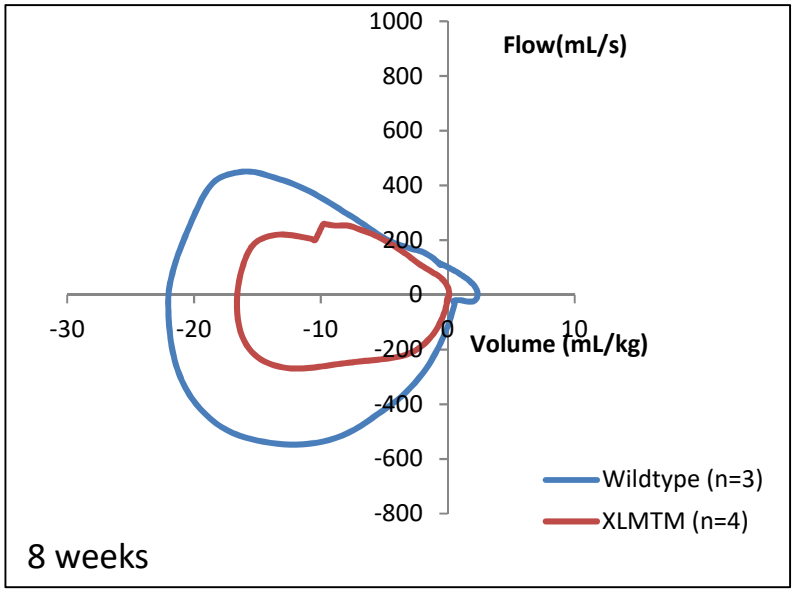
Increased hind limb flexion strength in XLMTM dogs six weeks after IM rAAV2/8-p*DES-MTM1* treatment

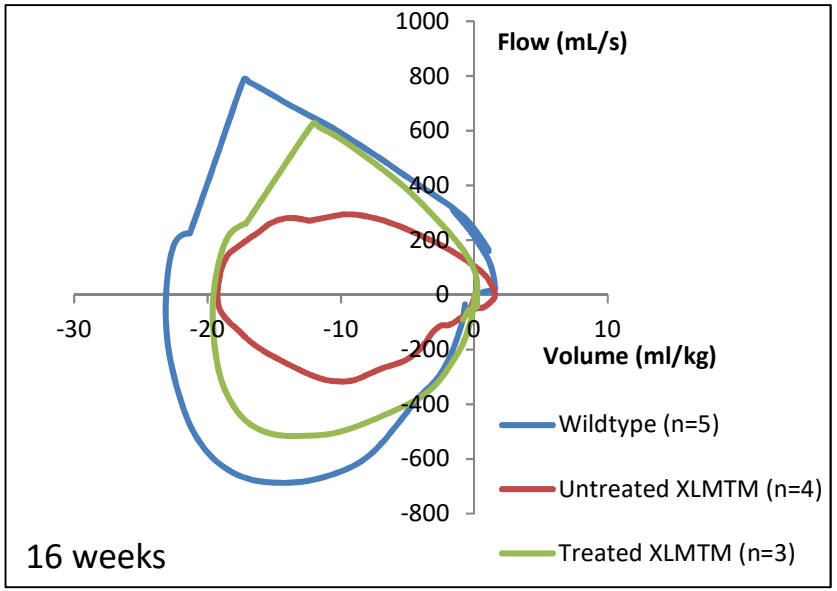




AAV8-MTM1 treatment of XLMTM dogs

Regional limb infusion with rAAV2/8-pDes-MTM1 is associated with improved respiratory function in the XLMTM dog

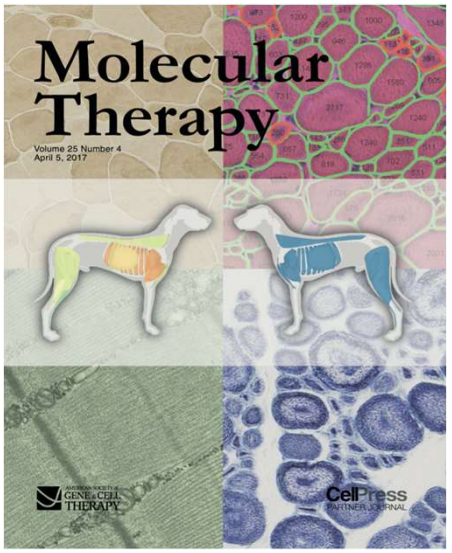




Molecular Therapy
Original Article

Systemic AAV8-Mediated Gene Therapy Drives Whole-Body Correction of Myotubular Myopathy in Dogs

David L. Mack,[1,2] Karine Poulard,[3,4] Melissa A. Goddard,[2] Virginie Latournerie,[3,4] Jessica M. Snyder,[5] Robert W. Grange,[6] Matthew R. Elverman,[2] Jérôme Denard,[3] Philippe Veron,[3,4] Laurine Buscara,[3,4] Christine Le Bec,[3] Jean-Yves Hogrel,[7] Annie G. Brezovec,[6] Hui Meng,[8] Lin Yang,[9] Fujun Liu,[9] Michael O'Callaghan,[10] Nikhil Gopal,[11] Valerie E. Kelly,[1] Barbara K. Smith,[12] Jennifer L. Strande,[13,14,15] Fulvio Mavilio,[3,4] Alan H. Beggs,[16] Federico Mingozzi,[3,4,17] Michael W. Lawlor,[8] Ana Buj-Bello,[3,4,18] and Martin K. Childers[1,2,18]



Muscle Nerve 56: 943–953, 2017

LONG-TERM EFFECTS OF SYSTEMIC GENE THERAPY IN A CANINE MODEL OF MYOTUBULAR MYOPATHY

MATTHEW ELVERMAN, MD,[1] MELISSA A. GODDARD, PhD,[2] DAVID MACK, PhD,[1,3] JESSICA M. SNYDER, DVM,[4] MICHAEL W. LAWLOR, MD, PhD,[5] HUI MENG, MD, PhD,[5] ALAN H. BEGGS, Phd,[6] ANA BUJ-BELLO, MD, PhD,[7] KARINE POULARD, BS,[7] ANTHONY P. MARSH, PhD,[8] ROBERT W. GRANGE, PhD,[9] VALERIE E. KELLY, PhD,[1] and MARTIN K. CHILDERS, DO, PhD[1,3]

ASPIRO Phase 1/2 Clinical Study

Open-label, ascending-dose, safety and preliminary efficacy study

Inclusion Criteria

- Subject is male
- <5 yrs old, or enrolled in INCEPTUS
- Genetically confirmed XLMTM
- Requires ventilator support

Key Efficacy Assessments

Neuromuscular

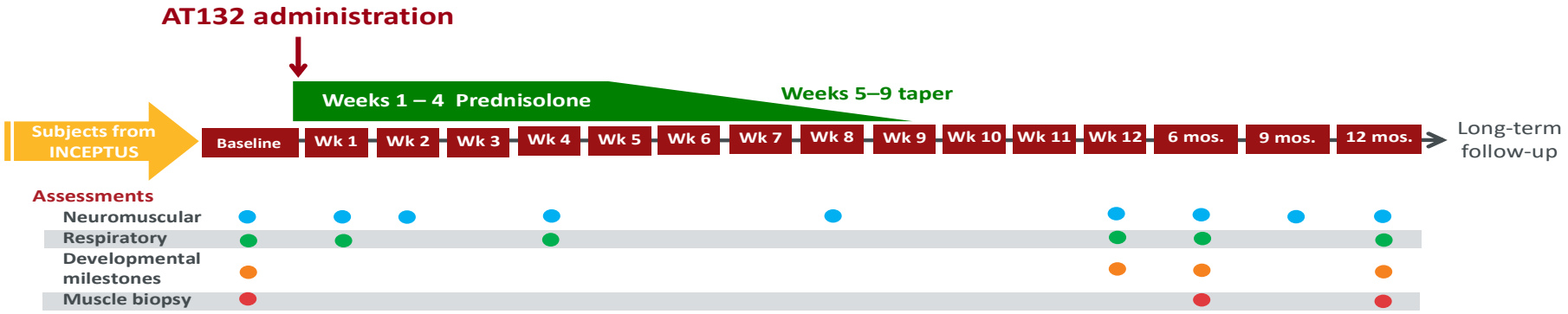
- CHOP INTEND
- MFM-20
- Bayley III
- Muscle biopsy
- Developmental milestones

Respiratory

- Max Inspiratory Pressure (MIP)
- Ventilator use
- Respiratory sprinting

Design

- N=12, roll-over from INCEPTUS
- 3 ascending-dose cohorts (3 active plus a delayed-treatment concurrent control)
- Doses: $1x10^{14}$, $3x10^{14}$, $5x10^{14}$ vg/kg



AUDENTES

https://www.audentestx.com/

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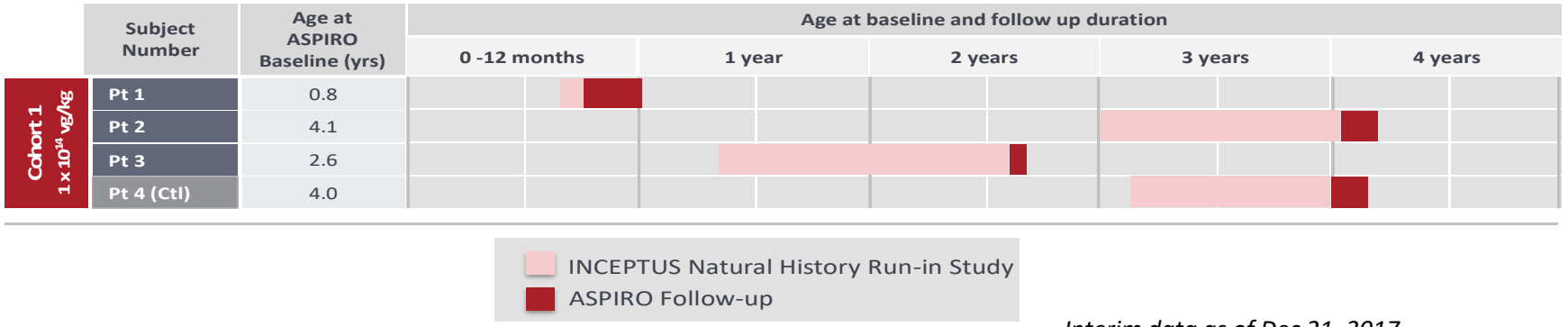


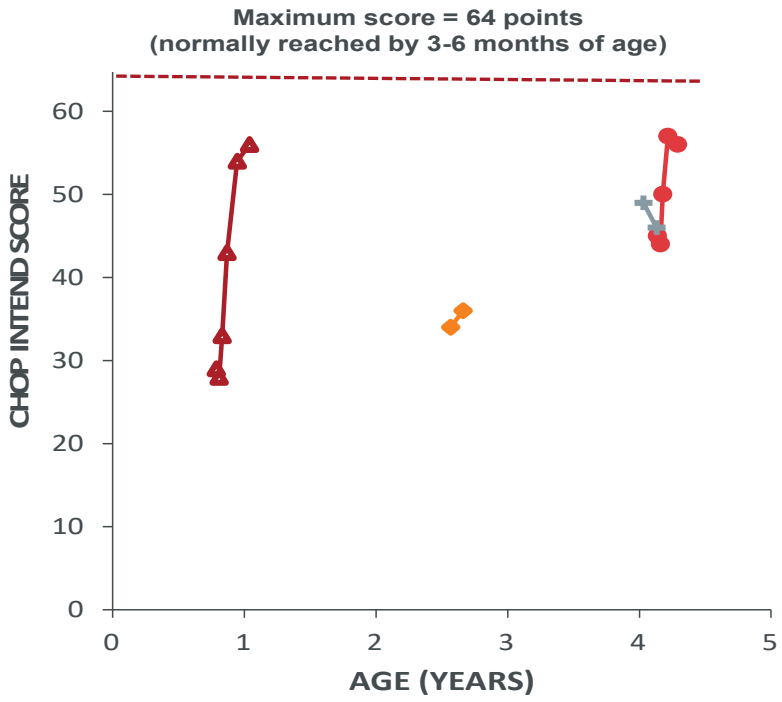
Interim data as of Dec 21, 2017

AT132 Safety and Tolerability Profile at 1 x 10^{14} vg/kg

- No tolerability issues during study drug administration
- Two serious adverse events (SAEs), both in Patient 3
  - Hospitalization for pneumonia (week 2), not treatment-related
  - Hospitalization for GI infection and elevated troponin levels (week 7), is responding to IV steroids and supportive care; probably treatment-related
- Two possibly/probably treatment-related adverse events (AEs)
  - Patient 1
    - Mild, clinically asymptomatic exacerbation of preexisting hyperbilirubinemia, resolved; possibly treatment-related
  - Patient 2
    - Clinically asymptomatic liver enzyme elevation, controlled by extended steroid coverage; probably treatment-related
- Two additional non-treatment related AEs

Interim data as of Dec 21, 2017

Significant Improvements in Neuromuscular Function as Assessed by the CHOP-INTEND Scale



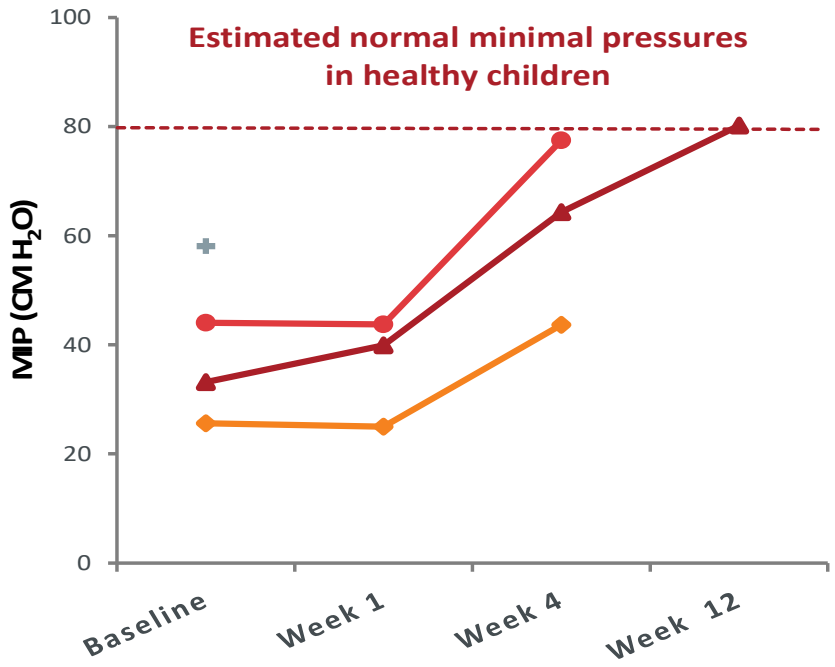
CHOP-INTEND score				
Pt #	Median score in INCEPTUS	Baseline Score in ASPIRO	Most recent score (Wk)	Change from baseline (%)
1	29	29	56 (Wk 12)	27 (93%)
2	45	45	56 (Wk 8)	11 (24%)
3	28	34	36 (Wk 4)	2 (6%)
4 (Control)	49	49	46 (Wk 4)	-3 (-6%)

Interim data as of December 21, 2017

Multiple Motor Milestones Achieved at 12 Weeks in First Treated Patient

First-year developmental milestones in healthy children	Patient 1	
	Baseline	Week 12
Rolling over	–	+
Head Control	–	+
Sitting unassisted >5 sec	–	+

Significant Improvements in Respiratory Function as Assessed by Maximal Inspiratory Pressure (MIP)



Maximum Inspiratory Pressure (cmH_2O)				
Pt #	Median Pressure in INCEPTUS	Baseline Pressure in ASPIRO	Most recent Pressure (Wk)	Change from baseline (%)
1	29	33	80 (Wk 12)	47 (142%)
2	34	44	77 (Wk 4)	33 (76%)
3	24	26	44 (Wk 4)	18 (70%)
4 (Control)	65	58	--	--

Progressive Qualitative Improvements Observed in Disease Severity in All Treated Patients

- Increased trunk and limb strength and activity
  - Early indicator of gross muscle function improvement
  - Velocity and accuracy of movement has also improved
- Reductions in ventilator settings (pressure, rate and volume of mechanical ventilation) Patients 1 and 2
  - First step toward weaning off mechanical ventilation
- Improvements in airway clearance control (swallowing, coughing)
  - Critical for reducing aspiration risk
- Increased vocalization – improved ability to communicate with caregivers
- Initial exposure to oral feeding (Patient 1)

Human Gene Therapy

DOI: 10.1089/hum.2018.015

Severe toxicity in nonhuman primates and piglets following high-dose intravenous administration of an AAV vector expressing human SMN

Christian Hinderer[1], Nathan Katz[1], Elizabeth L. Buza[1], Cecilia Dyer[1], Tamara Goode[1], Peter Bell[1], Laura K. Richman[1] and James M. Wilson[1].

XLMTM as a candidate for gene/protein-replacement therapy – open questions

- Consider potential toxicity of AAV-based therapeutics
  - Hepatotoxicity at high AAV doses?
  - DRG toxicity – real? species/serotype/cargo dependent?
- Immune responses
  - Anti-capsid responses?
  - Anti-cargo (myotubularin) related?
    - Patient genotype – null vs missense mutations
  - T cell mediated? Develop appropriate immunosuppression regimens
- Longevity of therapeutic response
  - Will retreatment be possible?

Thanks to…

More than 1000 children and adults with CM and their families

Collaborators:

ENMC NM & CNM Consortia
- Carina Wallgren-Pettersson
- Nigel Laing
- Carsten Bonnemann

Susan Iannaccone
Mike Lawlor
Jim Dowling
Casey Childers
Ana Buj Bello
Nigel Clarke/Kathy North

The Manton Center for Orphan Disease Research

NIH NICHD

NIAMS

A Foundation BUILDING STRENGTH For Nemaline Myopathy

MDA

CURE CMD Congenital Muscular Dystrophy

EXTRA SLIDES

RECENSUS Objectives

- Overarching goals of RECENSUS (NCT02231697)
  - Serve as a historical control for the interventional trial
  - Map out the natural history of the disease and inform the medical and patient community about XLMTM
- Primary objective of RECENSUS (as per protocol)
  - Describe disease burden and unmet medical need in patients with XLMTM from one of the world's largest XLMTM datasets
- Secondary objectives of RECENSUS (as per protocol)
  - Secondary objectives are to identify prognostic variables of the disease, potential outcome measures for therapeutic intervention studies, and clinical features of the disease that warrant monitoring during therapeutic intervention

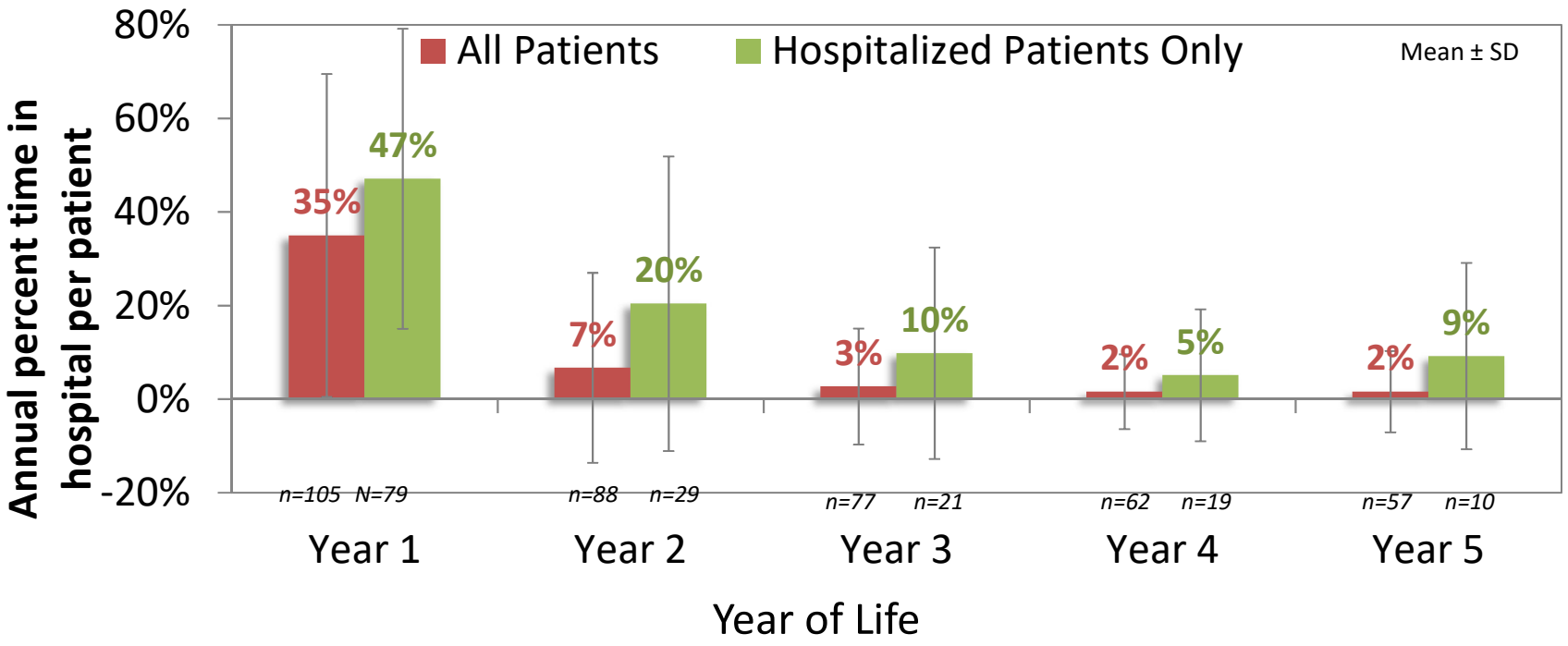
RECENSUS Methods

- Retrospective, multicenter medical chart review of male patients with XLMTM
  - Inclusion criteria – males with confirmed pathogenic *MTM1* variant or with a clinicopathological diagnosis of XLMTM/CNM and a genetically confirmed family history
- Data extracted from patient records between September 10, 2014 and June 16, 2016

Demographics	Method(s) of diagnosis	Gestation/birth
Pulmonary function/support	Hospitalizations	Surgeries
Motor function	Comorbidities	Cognitive function
Muscle strength	Cardiac structure/function	Hepatic structure/function
Ophthalmology	Musculoskeletal assessments	

RECENSUS

Annual percentage time in the hospital per patient



"All patients" = all study patients

"Hospitalized patients only" = patients with recorded hospitalization start and end dates

ASPIRO Clinical Study Sites

Same study sites as INCEPTUS natural history run-in study

ASPIRO Study
Interim data as of December 21, 2017

Congenital myopathies are defined by muscle pathology