Molecular Genetics and Development of Therapies for Congenital Myopathies

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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)
  - ~1/10\(^{\text{th}}\) 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

Nemaline

Multiminicores

Myotubular

CFTD
Genetic etiologies of congenital myopathies

Centronuclear myopathies
- MTM1
- DNM2
- BIN1
- SPEG
- CCDC76
- TRIP4

Core myopathies
- MEGF10
- SEPN1
- MYH7
- RYR1
- TTN
- CACNA1S

Nemaline myopathies
- NEB
- TNNT1
- CFL2
- LMOD3
- MYPN
- KBTBD13
- KLHL40
- KLHL41

CFTD
- TPM2
- TPM3
- ACTA1
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
Genetic findings in 170 probands with Nemaline Myopathy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Candidate gene testing</th>
<th>NGS Panel</th>
<th>WES/WGS</th>
<th>Total</th>
<th>%</th>
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<tbody>
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<td>20</td>
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<td>44</td>
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<td>ACTA1</td>
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<td>0.6</td>
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<td>0.6</td>
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<tr>
<td>KBTBD13</td>
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<td>29</td>
<td>29</td>
<td></td>
<td>17</td>
</tr>
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</table>

*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 Ca²⁺ sensitivity of force generation
Troponin activators increase sensitivity of contraction to calcium

CK-2017357 (tirasemtiv)
Effect of CK-2066260 on calcium-sensitivity of force generation

![Graphs showing the effect of CK-2066260 on calcium-sensitivity of force generation.](Image)

**Table 2** Genetic data of nemaline myopathy patients

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Biopsy ID</th>
<th>NEB mutations</th>
<th>Nebulin defects</th>
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</thead>
<tbody>
<tr>
<td>26–2</td>
<td>T33</td>
<td>c.[7431+1916_7536+372del]+[7431+1916_7536+372del]</td>
<td>p.[Arg2478_Asp2512del]+[Arg2478_Asp2512del]</td>
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<tr>
<td>258–2</td>
<td>T1069</td>
<td>c.[3567+3_3567+7del[AAGT]+[18124C&gt;T]</td>
<td>Exon 33 splice defect+p.Gly6041Stop</td>
</tr>
<tr>
<td>974–1</td>
<td>T1033</td>
<td>c.[7431+1916_7536+372del]+[24842_24841delAG]</td>
<td>p.[Arg2478_Asp2512del]+[Arg8280SerfsStop2]</td>
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<tr>
<td>988–1</td>
<td>T887</td>
<td>c.[1152+1G&gt;A]+[17013+1G&gt;T]</td>
<td>Exon 13 splice defect+exon 107 splice defect</td>
</tr>
</tbody>
</table>

*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 Shilina,4 Kazuhiro Ogata,4 Cynthia Hsu,1 Nigel F. Clarke,5 Basil T. Darras,6 Michelle A. Farrar,7 Amal Hashem,8 Nicholas D. Manton,9 Francesco Muntoni,9 Kathryn N. North,10 Sarah A. Sandradura,1 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. Alcock,14 Mark R. Davis,15 Carina Wallgren-Pettersson,16 Naomichi Matsumoto,17 Fowzan S. Alkuraya,3 Nigel G. Laing,2 and Alan H. Beggs1,*

KLHL41 stabilizes skeletal muscle sarcomeres by nonproteolytic ubiquitination

Andrés Ramirez-Martínez1,2,3, Bercin Kutluğ Canik1,2,3, Svetlana Bezpazovannaya1,2,3, Beiwei Chen4, Rhonda Bassel-Duby1,2,3, Ning Liu4,5,6, Eric N Olson1,2,3

Gupta et al., Am J Hum Genet 93:1108-17 (2013)
Zebrfish relatively relaxed mutants have a ryanodine receptor defect, show slow swimming and provide a model of multi-minicore disease

Hiromi Hirata\textsuperscript{1,2,*}, Takaki Watanabe\textsuperscript{1}, Jun Hatakeyama\textsuperscript{3}, Shawn M. Sprague\textsuperscript{2}, Louis Saint-Amant\textsuperscript{2,*}, Ayako Nagashima\textsuperscript{2}, Wilson W. Cui\textsuperscript{2}, Weibin Zhou\textsuperscript{2} and John Y. Kuwada\textsuperscript{2}
Chemical screening strategy

Embryos from heterozygous ryr1b<sup>+-</sup> mating pairs

20 embryos/well (1 dpf)

Prestwick2 (1,120 chemicals)

4 chemicals/pool (280 pools)

Primary screen – Chemical pools

Secondary screen – Individual chemicals

Test 4 individual chemicals from positive pool

Identify candidate chemical(s)

Adapted from Kawahara et al., PNAS 2011
• 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

<table>
<thead>
<tr>
<th>Vitality Score</th>
<th>Chemical Name</th>
<th>Formula</th>
<th>MW</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>58.0</td>
<td>Pargyline hydrochloride /*</td>
<td>C₁₁H₁₄ClIN</td>
<td>195.69</td>
<td>Irreversible monoamine oxidase (MAO) inhibitor</td>
</tr>
<tr>
<td>57.0</td>
<td>Sulfasalazine</td>
<td>C₁₈H₁₄N₄O₅S</td>
<td>398.39</td>
<td>NF-KB inhibitor; anti-inflammatory</td>
</tr>
<tr>
<td>55.5</td>
<td>Metolazone **</td>
<td>C₁₆H₁₆ClIN₃O₃S</td>
<td>365.83</td>
<td>Sodium-chloride channel inhibitor</td>
</tr>
<tr>
<td>55.0</td>
<td>Zimelidine dihydrochloride monohydrate **</td>
<td>C₁₆H₂₁BrCl₂N₂O</td>
<td>408.16</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>54.0</td>
<td>Miconazole ***</td>
<td>C₁₉H₁₄Cl₄N₂O</td>
<td>416.13</td>
<td>Anti-fungal agent</td>
</tr>
<tr>
<td>54.0</td>
<td>Ticlopidine hydrochloride ***</td>
<td>C₁₄H₁₅Cl₂NS</td>
<td>300.25</td>
<td>Inhibitor of platelet aggregation</td>
</tr>
<tr>
<td>53.5</td>
<td>Iohexol</td>
<td>C₁₉H₂₆I₃N₃O₉</td>
<td>821.14</td>
<td>Low-osmolality contrast agent</td>
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<tr>
<td>52.5</td>
<td>Benoxinate hydrochloride ***</td>
<td>C₁₇H₂₇ClIN₂O₃</td>
<td>344.88</td>
<td>Surface anaesthetic</td>
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<tr>
<td>52.0</td>
<td>Ketoprofen</td>
<td>C₁₆H₁₄O₃</td>
<td>254.28</td>
<td>Cyclooxygenase inhibitor; anti-inflammatory</td>
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<tr>
<td>52.0</td>
<td>Nifuroxazide</td>
<td>C₁₂H₆N₃O₅</td>
<td>275.22</td>
<td>JAK/STAT signaling inhibitor</td>
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<tr>
<td>52.0</td>
<td>Nimodipine</td>
<td>C₂₁H₂₆N₂O₇</td>
<td>418.44</td>
<td>Dihydropyridine calcium channel blocker</td>
</tr>
<tr>
<td>52.0</td>
<td>Tranylcypromine hydrochloride /*</td>
<td>C₉H₁₂ClIN</td>
<td>169.65</td>
<td>Irreversible MAO inhibitor</td>
</tr>
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</table>
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

```
Phosphatidylinositol

PI3K (III)  PI5K ?  PIPK (II)
endocytosis PtdIns(3)P

PtdIns(3,4)P2  PtdIns(3,5)P2

PIPK (I)  PIKfyve  PI3K

Myotubularins

Phosphatidylinositol  PtdIns(4,5)P2

vacuolar homeostasis
```
Myotubularin deficiency acts at many levels
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 \textit{Mtm1} KO mouse

- Buj-Bello \textit{et al.,} \textit{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
MTM1 mutation associated with X-linked myotubular myopathy in Labrador Retrievers.

Local administration of rAAV1/2-Mtm1 can reverse the pathological phenotype in myotubularin deficiency
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)
3E10Fv-MTM1 protein therapy study design

- 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. Lawlor¹,², Dustin Armstrong³, Marissa G. Viola¹, Jeffrey J. Widrick¹,⁴, Hui Meng³, Robert W. Grange⁵, Martin K. Childers⁶, Cynthia P. Hau¹, Michael O’Callaghan³, Christopher R. Pierson⁷, Anna Buj-Bello⁸ and Alan H. Beggs¹,⁹

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-pDes-Mtm1 to Mtm1 KO mice
2. Local IM injection of rAAV2/8 pDes-MTM1 into canine cranial tibialis muscles
3. Local-regional perfusion of rAAV2/8 pDes-MTM1 into canine limbs

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


IV rAAV2/9-pDes-Mtm1 (3.0 x 10^{13} vg/kg) prolongs survival and increases muscle mass in Mtm1 KO mice.
IV rAAV2/9-pDes-Mtm1 corrects muscle function \textit{in vivo} and \textit{ex vivo}
Increased hind limb flexion strength in XLMTM dogs six weeks after IM rAAV2/8-pDES-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
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,5,6 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. Strand,13,14,15 Fulvio Mavilio,3,4 Alan H. Beggs,16 Federico Mingoazzi,3,6,17 Michael W. Lawlor,8 Ana Buj-Bello,3,6,18 and Martin K. Childers1,2,18

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. LAWLER, 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, PhD1,3
# 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: \(1 \times 10^{14}, 3 \times 10^{14}, 5 \times 10^{14}\) vg/kg

## AT132 administration

Subjects from INCEPTUS

- **Weeks 1 – 4** Prednisolone
- **Weeks 5–9** taper

## Assessments

<table>
<thead>
<tr>
<th>Neuromuscular</th>
<th>Respiratory</th>
<th>Developmental milestones</th>
<th>Muscle biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>Wk 1</td>
<td>Wk 2</td>
<td>Wk 3</td>
</tr>
<tr>
<td>Wk 4</td>
<td>Wk 5</td>
<td>Wk 6</td>
<td>Wk 7</td>
</tr>
<tr>
<td>Wk 8</td>
<td>Wk 9</td>
<td>Wk 10</td>
<td>Wk 11</td>
</tr>
<tr>
<td>Wk 12</td>
<td>6 mos.</td>
<td>9 mos.</td>
<td>12 mos.</td>
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</tbody>
</table>

Long-term follow-up

https://www.audentestx.com/
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
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**Key Efficacy Assessments**

<table>
<thead>
<tr>
<th>Neuromuscular</th>
<th>Respiratory</th>
</tr>
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<tbody>
<tr>
<td>• CHOP INTEND</td>
<td>• Max Inspiratory Pressure (MIP)</td>
</tr>
<tr>
<td>• MFM-20</td>
<td>• Ventilator use</td>
</tr>
<tr>
<td>• Bayley III</td>
<td>• Respiratory sprinting</td>
</tr>
<tr>
<td>• Muscle biopsy</td>
<td></td>
</tr>
<tr>
<td>• Developmental milestones</td>
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</table>

**Design**
- N=12, roll-over from INCEPTUS
- 3 ascending-dose cohorts (3 active plus a delayed-treatment concurrent control)
- Doses: $1 \times 10^{14}$, $3 \times 10^{14}$, $5 \times 10^{14}$ vg/kg

### Age at baseline and follow up duration

<table>
<thead>
<tr>
<th>Cohort 1 1 x 10^{14} vg/kg</th>
<th>Subject Number</th>
<th>Age at ASPIRO Baseline (yrs)</th>
<th>0 -12 months</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
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<tr>
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<td>0.8</td>
<td></td>
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<td>Pt 3</td>
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<td>2.6</td>
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<tr>
<td>Pt 4 (Ctl)</td>
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<td>4.0</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

Interim data as of Dec 21, 2017

https://www.audentestx.com/
AT132 Safety and Tolerability Profile at 1 x 10^{14} \text{ 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

Maximum score = 64 points (normally reached by 3-6 months of age)

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Median score in INCEPTUS</th>
<th>Baseline Score in ASPIRO</th>
<th>Most recent score (Wk)</th>
<th>Change from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>29</td>
<td>56 (Wk 12)</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>45</td>
<td>56 (Wk 8)</td>
<td>11 (24%)</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>34</td>
<td>36 (Wk 4)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>4 (Control)</td>
<td>49</td>
<td>49</td>
<td>46 (Wk 4)</td>
<td>-3 (-6%)</td>
</tr>
</tbody>
</table>

Interim data as of December 21, 2017
**Multiple Motor Milestones Achieved at 12 Weeks in First Treated Patient**

<table>
<thead>
<tr>
<th>First-year developmental milestones in healthy children</th>
<th>Patient 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rolling over</td>
<td>Baseline</td>
</tr>
<tr>
<td>Head Control</td>
<td>-</td>
</tr>
<tr>
<td>Sitting unassisted &gt;5 sec</td>
<td>-</td>
</tr>
</tbody>
</table>

https://www.audentestx.com/
Significant Improvements in Respiratory Function as Assessed by Maximal Inspiratory Pressure (MIP)

Estimated normal minimal pressures in healthy children

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Median Pressure in INCEPTUS</th>
<th>Baseline Pressure in ASPIRO</th>
<th>Most recent Pressure (Wk)</th>
<th>Change from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>33</td>
<td>80 (Wk 12)</td>
<td>47 (142%)</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>44</td>
<td>77 (Wk 4)</td>
<td>33 (76%)</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>26</td>
<td>44 (Wk 4)</td>
<td>18 (70%)</td>
</tr>
<tr>
<td>4 (Control)</td>
<td>65</td>
<td>58</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Maximum Inspiratory Pressure (cmH\textsubscript{2}O)

https://www.audentestx.com/
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)

https://www.audentestx.com/
Severe toxicity in nonhuman primates and piglets following high-dose intravenous administration of an AAV vector expressing human SMN

Christian Hinderer¹, Nathan Katz¹, Elizabeth L. Buza¹, Cecilia Dyer¹, Tamara Goode¹, Peter Bell¹, Laura K. Richman¹ and James M. Wilson¹.
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
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

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Method(s) of diagnosis</th>
<th>Gestation/birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function/support</td>
<td>Hospitalizations</td>
<td>Surgeries</td>
</tr>
<tr>
<td>Motor function</td>
<td>Comorbidities</td>
<td>Cognitive function</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>Cardiac structure/function</td>
<td>Hepatic structure/function</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Musculoskeletal assessments</td>
<td></td>
</tr>
</tbody>
</table>
RECENSUS
Annual percentage time in the hospital per patient

```
Year of Life
```

```
<table>
<thead>
<tr>
<th>Year</th>
<th>All Patients</th>
<th>Hospitalized Patients Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>35%</td>
<td>47%</td>
</tr>
<tr>
<td>Year 2</td>
<td>7%</td>
<td>20%</td>
</tr>
<tr>
<td>Year 3</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>Year 4</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Year 5</td>
<td>2%</td>
<td>9%</td>
</tr>
</tbody>
</table>

```

“All patients” = all study patients

“Hospitalized patients only” = patients with recorded hospitalization start and end dates

Mean ± SD
ASPIRO Clinical Study Sites
Same study sites as INCEPTUS natural history run-in study

ASPIRO Study
Interim data as of December 21, 2017

UCLA Health
California, USA

NIH
Maryland, USA

Ann & Robert H. Lurie
Children's Hospital of Chicago
Illinois, USA

London, UK

Paris, France

München, Germany

https://www.audentestx.com/
Congenital myopathies are defined by muscle pathology