Development of therapy for GNE myopathy

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Disclosure

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  – Sanofi

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  – Japan Blood Products Organization
  – Nihon Seiyaku
  – Sanofi
  – Teijin Pharma

• SAB/RAB
  – Nobel Pharma
  – PTC Therapeutics
  – Ultragenyx
GNE myopathy
DMRV/Nonaka myopathy
QSM/hIBM/IBM2

• AR - GNE mutations
  ↓Sialic acid production

• Adult onset, progressive
  Onset: 15-40y (av. 28y)
  wheelchair: 26-57y (av. 37y)

• Symptoms:
  Tibialis anterior (TA) muscle atrophy
  Quadriceps femoris (QF) muscle sparing
  Neck weakness

• Creatine kinase: up to 1,000 IU/L
• No cure
FAMILIAL DISTAL MYOPATHY WITH RIMMED VACUOLE AND LAMELLAR (MYELOID) BODY FORMATION

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“RIMMED VACUOLE MYOPATHY” SPARING THE QUADRICEPS

A Unique Disorder in Iranian Jews

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GNE myopathy
Normal

GNE myopathy

Autophagic vacuoles

Rimmed vacuole
Protein aggregates

- β-Amyloid
- p-Tau
- TDP-43
- α-Synuclein
- poly-ubiquitinated proteins
Genetic cause:
Recessive mutations in *GNE* gene

The UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy

Iris Eisenberg¹, Nili Avidan³*, Tamara Potikha¹*, Hagit Hochner¹, Miriam Chen³, Tsviya Olender³, Mark Barash¹, Moshe Shemesh¹, Menachem Sadeh⁴, Gil Grabov-Nardini¹, Inna Shmilevich¹, Adam Friedmann¹, George Karpati⁵, Walter G. Bradley⁶, Lisa Baumbach⁷, Doron Lancet³, Edna Ben Asher³, Jacques S. Beckmann³, Zohar Argov² & Stella Mitrani-Rosenbaum¹

* These authors contributed equally to this work.
GNE gene

190 mutations reported (HGMD 2016.4)

Huizing et al. Neuromuscul Disord. 2014 May;24(5):387-9
GNE myopathy – globally distributed

Modified from Nishino et al. J Neurol Neurosurg Psychiatry. 2015 Apr;86(4):385-92
Sialic acid Biosynthesis

GNE

UDP-GlcNAc

ManNAc

GlcNAc-6-P

GlcNAc-1-P

GlcNAc

Glucose

ManNAc kinase

GlcNAc 2-epimerase

ManNAc-6-P

NeuAc-9-P-synthase
NeuAc-9-P-phosphatase

NeuAc (sialic acid)

CMP NeuAc synthetase

CMP: NeuAc

GnlAc: N-acetylglucosamine
ManNAc: N-acetylmannosamine
NeuAc: N-acetylneuraminic acid
Sialic acid

- Cell-cell interaction
- Receptor/agonist interaction
- Protein turnover
- ROS scavenger

Glycolipid

Sialic acid

CELL MEMBRANE

Glycoprotein

Membrane protein

Secreted protein

Ser/Thr

N Asn

O Ser/Thr

O N
Human GM myotubes

Control

WGA

Hyposialylation can be recovered

SBA

GNE myopathy is treatable?

Lectins
WGA: Sialic acid
SBA: GalNAc

Gne\(^{+/+}\) × hGNE D207V-Tg

Gne\(^{+/+}\)hGNE D207V-Tg × Gne\(^{+/+}\)

Gne\(^{+/+}\) 177 (22%)
Gne\(^{+/+}\) 225 (28%)
Gne\(^{-/-}\)hGNE D207V-Tg 72 (9%)
Gne\(^{+/+}\) 136 (17%)
Gne\(^{+/+}\) 193 (24%)

**Gne-/-hGNE D207V-Tg recapitulates features of GNE myopathy**

- **Clinical**
  - Muscle weakness/atrophy: 21wks~

- **Pathological**
  - β-Amyloid deposition: 31wks ~
  - Rimmed vacuoles: 41wks ~
  - p-Tau: 41wks ~

- **Biochemical**
  - Hyposialylation: birth~
  - Mild CK elevation: 21 wks~

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*Hum Mol Genet* 2007
*Physiol Genomics* 2008
Muscle weakness
Muscle atrophy
Rimmed vacuoles
p-Tau
Amyloid deposition
Muscle weakness
Muscle atrophy

Treatment with low dose agents

GNE-/- hGNE D207V-Tg

Littermate

ManNAc
20 mg/kg/day

20 wks
30 wks
40 wks
50 wks
60 wks

NeuAc
20 mg/kg/day

SiaLac
20 mg/kg/day

GM: N=7
Littermate: N=7

Nat Med 2009
Survival

Treatment with low dose agents

Treatment with low dose agents

Muscle weight
56 weeks

Treatment with low dose agents

Motor performance
56 weeks

![Graph showing distance run (m) for different treatments.](image)

Treated  Non-treated

Littermate  GNE myop.  Littermate  GNE myop.
Treatment with low dose agents

Contractile force
56 weeks

Treatment with low dose agents

Creatine kinase
56 weeks

Treatment with low dose agents

Sialic acid levels in muscle
56 weeks

GNE myopathy

• Due to decreased sialic acid level in muscle
  = Sialic acid deficiency

• GNE metabolites efficacious in model mice
  → Clinical trial
SA-ER phase 2 study

Jul 2012 - Nov 2013

ClinicalTrials.gov NCT01517880

• Design
  – 4 sites (3US and 1 Israel)
  – Ambulatory

• Endpoints
  – PD
    • Sialylation
  – Muscle strength
  – Clinical
    • 6MWT
  – QOL scales
  – Biomarkers

Upper Extremity Composite by HHD

24 week evaluation

* +2.33 kg (5.5%), p = 0.040

Lower Extremity Composite by HHD

24 week evaluation

Mean Kg change from baseline

SA-ER phase 3 study

May 2015 – Jul 2017

ClinicalTrials.gov NCT02377921

• Design
  – 13 sites (4 US, 1 Canada, 7 EU and 1 Israel)
  – 6MWT > 200 m

• Primary endpoints
  – Upper extremity muscle strength

• Secondary endpoints
  – Lower extremity muscle strength
  – 6MWT
  – Mobility scores
SA-ER phase 2/3 study in Japan

Feb 2016 – Sep 2017

• Design
  – 5 sites
  – 6MWT > 200 m

• Primary endpoints
  – Upper extremity muscle strength

• Secondary endpoints
  – Lower extremity muscle strength
  – 6MWT
  – Mobility scores

n=20
6g/day
48 weeks
Placebo

UMIN-CTR UMIN000020683
Phase 1 Clinical Trial of ManNAc for GNE Myopathy

NIH study: 12-HG-0207
ClinicalTrials.gov: NCT01634750

- First in-human study - COMPLETED
- Randomized, placebo-controlled (3:1), double-blind
- Single ascending dose of ManNAc (3, 6 and 10 g)
- Developed validated LC-MS/MS method plasma ManNAc and sialic acid

Quantitative hydrophilic interaction chromatography–mass spectrometry analysis of N-acetylneuraminic acid and N-acetylmannosamine in human plasma

Yifan Shi, Xin Xu, Meng Fang, Michael Zhang, Yinghe Li, Brad Gillespie, Selwyn Yorke, Nora Yang, John C. McKew, William A. Gahl, Marjan Huizing, Nuria Carrillo-Carrasco, Amy Qiu Wang

Contents lists available at ScienceDirect

Journal of Chromatography B
journal homepage: www.elsevier.com/locate/chromb

Courtesy of Dr. Nuria Carrillo-Carrasco, NIH
Increase plasma sialic acid (Neu5Ac) after ManNAC

- Sustained increase in plasma Neu5Ac after a single dose of oral ManNAC.
- T\text{MAX} of Neu5Ac: 8-11 h
- Neu5Ac levels remained above baseline 48 hours post-dose in subjects who received a dose of 6 or 10 grams

Courtesy of Dr. Nuria Carrillo-Carrasco, NIH
Phase 2 Open Label ManNAc Trial
NIH study: 15-HG-0068
ClinicalTrials.gov: NCT02346461

Jan 2015 – Aug 2017

• Phase 2, open-label, single-center study at the NIH
• Ongoing, recruitment complete
• ManNAc 6 grams twice daily (12 grams/day) for 24 months.
• Safety: No SAEs. Grade 1 and 2 gastrointestinal AEs reported
• Preliminary analysis at 12 months showed 39% slowing in the rate of progression ($\gamma = 0.61 \ (95\% \ CI \ 0.09, \ 1.27)$)
• Analysis at 18 and 24 months pending.
Beyond simple sialic acid supplementation

• Add-on
  – Modulation of molecular pathway
    • Muscle atrophy
    • Muscle degeneration
  – Modulation of sialic acid metabolic pathway

• Alternative therapy
  – Better sialic acid compounds
  – Bone marrow transplantation
  – Gene therapy
Sialyllactose is more efficacious than NeuAc

Body weight (mg)

Isometric force (mN)

Tetanic force (mN)

Yonekawa T et al. Brain 2014
Natural history after sialic acid supplementation

http://www.gnem-dmp.com/

http://www.remudy.jp/
Summary

• GNE myopathy
  – Sialic acid deficiency
  – GNE metabolites / sialic acid effective

• Clinical trials
  – SA-ER Global phase 3 (Ultragenyx)
  – SA-ER Phase 2/3 (Japan)
  – ManNAc Open-label phase 2 (NIH)

• Patient organization
  – Wonderful job!
## Key Factors driving success

### Internal factors

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<th>Strengths</th>
<th>Opportunities</th>
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<td>Myology in NCNP</td>
<td>Patients</td>
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<td>– Disease discovery</td>
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<td>– History of muscle disease research</td>
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<tr>
<td>Strategy, idea</td>
<td>– Patient’s association</td>
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<td>– Demonstration of hyposialylation</td>
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<tr>
<td>Luck</td>
<td>– Support from society, government</td>
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<tr>
<td>– Successful establishment of animal model</td>
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<td>– Efficacy by simple supplementation</td>
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<tr>
<td>Hard work</td>
<td>– Collaboration</td>
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<td>– Enthusiastic post-docs</td>
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### External factors

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<th>Opportunity</th>
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<tr>
<td>Patients</td>
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<td>– Support from society, government</td>
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<tr>
<td>Collaboration</td>
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<tr>
<td>– Domestic, with clinicians</td>
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<td>– International, among myologists</td>
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<td>– With patients</td>
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<td>Pharmaceutical venture</td>
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<td>– Early contact</td>
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### Key success factors

- Successful establishment of animal model
- Efficacy of supplementation therapy
- Patient’s activity
- Collaboration
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• Companies

• Patient Organization

• Funding Source