Dr. Belinda Cowling, Dynacure, France

ASO-mediated DNM2 knockdown for Myotubular and Centronuclear Myopathies

Family Myotubular & Myotubular

Trust ZNM Conference–ZNM

July 13-15th, 2018
Frédéric Legros
PhD. Msc
Chief Operating Officer
Formerly Vice President and Head of Business Development
Valneva
Head of TTO Institut Pasteur Paris

Stephane van Rooijen
MD MBA
Chief Executive Officer
Formerly CEO ConfoTherapeutics
Formerly Head of Genzyme's European Cardiovascular Business
ViroPharma

Chris Freitag
MD
Chief Medical Officer
Formerly head of clinical development Debiopharm, Shire, Roche

Belinda Cowling
PhD
Head of Research
Former Project Leader
INSERM, Department of NeuroMuscular Disease

Leen Theleman
MD
Chief Operating Officer
Frederic Legros

Stephane van Rooijen
MD MBA
Chief Executive Officer
Attending

Attending talk tomorrow

Attending
Molecular diagnosis (Find the gene)

Understand disease (in vitro and in vivo)

Therapeutic Approaches (Treat animal model)

IGBMC-LAPORTE team

Patients
Can we treat several forms of centronuclear myopathies?

Reducing DNM2

Myotubularin

MTM1

Dynamin 2

Myotubular myopathy

Dominant CNM

Cross therapy: potential to treat all forms
Balance between MTM1 and DNM2 essential for normal muscle function.

Myotubular myopathy: Less MTM1 → DNM2 overactive

The idea behind this approach: Cross therapy

Imbalance
Reduces DNM2

Rebalance
Cross therapy: DNM2
In mice we removed DNM2 genetically.

3 mice in cage:
- Normal mouse
- No MTM1
- No MTM1/Less DNM2

Myotubular myopathy (X-linked): mutations in MTM1

Mtm1 knockout mice: severe myopathic phenotype, survive 5-10 weeks

The first proof-of-principle to target DNM2

Myotubular myopathy (X-linked): mutations in MTM1

Genetic cross with mice

J Clin Invest 2014

50% DNM2 x MTM1

Which is which?
Goal – to go to clinic

How can we reduce DNM2?

'TRANSLATED' therapy

Next step – develop translated approach

J Clin Invest 2014

'PROOF-OF-PRINCIPLE'

Genetic cross with mice

50% DNM2 x DNM1

MTM1
How can we reduce DNM2 in patients?

At the protein level: block dynamin 2
At the genetic level: produce less dynamin

Two possibilities to reduce DNM2

Dynamin 2 is the car in the cell
A protein has an activity in
A gene is a fragment of a chromosome
It carries the information for a protein

Antisense Drug
Prevents Formation of All Types of Protein

How can we reduce DNM2 in patients?
Next step – develop translated approach

Antisense oligonucleotides targeting DNM2 (and reversible) treatment

Genetic cross with mice

Research team

Dynacure (project and startup)

'PROOF-OF-PRINCIPLE'

J Clin Invest 2014

'TRANSLATED'

Dynacure (project and startup)
Myotubular Myopathy - Disease Reversion

The model...

Reducing DNM2 = Less DNM2
No MTM1 + Reduced life expectancy
No MTM1

The question...

Reducing DNM2 
RESCUED?
Reversion of disease observed after treatment

Let's put the mice in the gym...

No MTM1/ Less DNM2

Same mouse 2w after treatment (7w old)

Myotubular myopathy - Disease Reversion

Mtm1 KO (5w old) before treatment

Weeks 1 and revert after 2

STOP progression after 1

Disease normalization might be sufficient

STOP progression after 1

Weeks 1 and revert after 2

Reversion of DNM2 level normalization
Can we treat several forms of centronuclear myopathies?

Reducing DNM2
Summary

Myotubular myopathy

Imbalance in muscle

Reduce DNM2 = therapy?

Aromosomal dominant centronuclear myopathy:

Similar DNM2 imbalance in muscle?

Almost the same force as normal mice

Normal life span

Mice without MTM1 and less DNM2:

Same therapeutic approach for MTM / CNM?

Cross therapy ideas and applications
Dominant Centronuclear Myopathy

Autosomal dominant - neonatal or adult onset mutations in DNM2

The question...

Reducing DNM2

Rescue?

Very mild myopathy

Dnm2 knockin mice

Dominant Centronuclear Myopathy

The model...

Reducing DNM2

Rescue?

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Dnm2 knockin mice

Dominant Centronuclear Myopathy

Very mild myopathy

Dnm2 knockin mice

Reducing DNM2

Rescue?
Dominant Centronuclear Myopathy

- Muscle strength is improved
- Muscle fiber size is rescued

Let's have a look at muscles under the microscope.
Dominant Centronuclear Myopathy

Rescued histology

Untreated %

0%

Treated %

3.8%

ASO-1

ASO-C

Dynacure
Can we treat several forms of centronuclear myopathies?

Reducing DNM2
**Goal – to go to clinic**

Dynacure

Chris Freitag - CMO

Next step – Dynacure to develop to clinic

Treatment
- Repeated (and reversible)
- Antisense oligonucleotides
- RNAi targeting DNM2

Genetic cross with mice
- PROOF-OF-PRINCIPLE

Research team

Dynacure and IGBMC

Translational therapy
Confidential

MESSAGE UNDERSTOOD

DYNACURE SAS

Module 2 du bio-incubateur de l'ESBS, Pôle API.

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