MyoArete
Communication

Identification of a Chromosome 6-encoded Dystrophin-related Protein*

(Received for publication, April 11, 1990)
Tejvir S. Khurana, Eric P. Hoffman†, and Louis M. Kunkel‡

High-throughput identification of post-transcriptional utrophin upregulators for Duchenne muscle dystrophy (DMD) therapy

Emmanuel Loro*, Kasthuri Senthoor†, Sabela Bogdanovic‡, Kanopyrya Whigé, David C. Schulte‡, Donna M. Hors** and Tejvir S. Khurana‡

PHARMACOLOGICAL STRATEGIES FOR MUSCULAR DYSTROPHY

Tejvir S. Khurana* and Kay E. Davies‡

MyoArete

Khurana, Hoffman & Kunkel
J. Biol. Chem (1990)


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www.myoarete.com
DMD

Devastating disease caused by deletions in the DMD gene resulting in a loss of Dystrophin protein

Require a wheelchair by 13

Using a ventilator in 20s

Fatal by 3rd-4th decade

No disease-specific treatment available for the vast majority (75%) of patients

Enormous and urgent unmet clinical need
DYSTROPHIN

• 1° lack of Dystrophin beneath the sarcolemma
• Progressive muscle damage due to repeated cycles of contraction and relaxation
UTROPHIN

- Autosomal dystrophin homolog
- When upregulated, can functionally compensate for Dystrophin loss

MyoArete
COMPETITION

**GENE THERAPY**
- Micro-dystrophin
- AAV

**CELL THERAPY**

**EXON SKIPPING**
- 45, 51, 53

**DMD**
- $5.7 B Market

**PHARMACOLOGICAL**
- Steroids

**Dystrophin-dependent**

**Dystrophin-independent**

**MyoArete**
- Utrophin Upregulation
- 1. Small Molecules
- 2. Site-blocking Oligonucleotides
- 3. Gene Editing
ADVANTAGE

UNIVERSAL
Independent of mutations

CURATIVE
Additional benefits as add-on therapy

UTROPHIN UPREGULATION

SAFE
Escapes immune surveillance, no gene delivery

EFFECTIVE
Pharmacologic approach

MyoArete
SMALL MOLECULES
UTROPHIN UPREGULATION

1. NOT a highly inducible gene
2. Ezutromid had poor PK/PD, insufficient utrophin upregulation, and failed in trials.

OPEN THE THROTTLE
Transcriptional

RELEASE THE BRAKES
Post-Transcriptional

1. Majority of muscle utrophin subject to post-transcriptional/translational repression
2. 5’ and 3’ motifs & mechanisms identified
3. Meaningful Utrophin upregulation has been achieved by MyoArete's 'repressing the repressors' approach
HTS PLATFORM

ACTIVATING DRUG

5’UTR Utrophin  
<table>
<thead>
<tr>
<th>luciferase gene</th>
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<tbody>
<tr>
<td>3’UTR Utrophin</td>
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</table>

LIGHT

NIH Innovation Grant

MUSCLE CELL LINE

MyoArete
PILOT SCREEN

Heat Map of 27 Hits

Hits2Lead prioritization algorithm

Orthogonal validation of utrophin upregulation

SELLECK CHEM: 3K
Validation of utrophin upregulation in *mdx* mice

Functional improvement in *mdx* mice
**READY TO LAUNCH**

**Y1**
- SCREENING DEVELOPMENT
  - SelleckChem screen & dose-response
  - 5 plates of OCL library screen and counter

**Y2**
- OCL SCREENING & SAR
  - OCL screen (96,000 compounds) & dose-response
  - Deconvolute, re-screen, counter-screen 50 most promising at SD
  - SAR analysis

**Y3**
- HIT2LEAD & PRECLINICAL STUDIES
  - Re-synthesize 5 top hits
    - MyoAr 6
    - MyoAr 48
    - MyoAr 88
    - MyoAr 100
    - MyoAr 109
  - ADME, luciferase, orthogonal assays

**Y4**
- IND-ENABLING & CLINICAL STUDIES
  - IP, licensing, & infrastructure
  - Lead optimization
  - Preclinical mouse PoC studies
  - Toxicity studies
  - PK/PD studies

**NIH Innovation Grant**

**SELLECK CHEM: 3K**

**OCL: 96K**

**MyoArete**
Seeking $5M in seed funding

DEVELOP BUSINESS INFRASTRUCTURE
CEO, Patent Counsel, & Tech Transfer

ROUND 1:
HITS 2 LEAD
SAR by purchase & In Vitro Validation

ROUND 2:
LEAD OPTIMIZATION
Directed SAR & In Vitro Validation

IN VIVO STUDIES
Safety, PK/PD, & Toxicity

SERIES A: $20M

MyoArete
Patents have all been filed with broad coverage claims

<table>
<thead>
<tr>
<th>Penn Tech ID</th>
<th>Title</th>
<th>Patent Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-7411</td>
<td>DMD Antisense therapeutic approach for up-regulation of utrophin</td>
<td>US utility application 16/319,355</td>
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<td>17-8073</td>
<td>FANA-let7 oligos mediated utrophin upregulation for DMD gene therapy</td>
<td>US utility application 16/982,467</td>
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<td>18-8707</td>
<td>Utrophin Genome editing for treating Duchenne Muscular Dystrophy (DMD)</td>
<td>US provisional application 63/056,397</td>
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<td>21-9570</td>
<td>PMO based Utrophin: let7c miRNA site blocking oligos (SBOs) for treating Duchenne Muscular Dystrophy (DMD)</td>
<td>US provisional application 63/117,419</td>
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<td>U4833</td>
<td>Utrophin upregulation via inhibition of microRNA's</td>
<td>US utility patent 8,916,532</td>
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<td>U4833</td>
<td>Utrophin upregulation via inhibition of microRNA's</td>
<td>Continuation 9,458,459</td>
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<td>20-9100</td>
<td>Utrophin upregulation compounds for muscular dystrophy therapy</td>
<td>US provisional application 62/961,191</td>
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