Progress in gene therapy development for myotubular myopathy

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Gene therapy: How it works?
Gene replacement therapy

- Treatment of a disease by the administration of nucleic acids in cells
- Goal: Replacing or supplementing a mutated gene with a normal copy

Diseased cell
Gene mutation
Gene replacement therapy

- Treatment of a disease by the administration of nucleic acids in cells
- Goal: Replacing or **supplementing** a mutated gene with a normal copy

Diseased cell
Gene mutation

Corrected cell
Vectors for gene therapy

- Derived from viruses, penetrate the cells
- Transport the therapeutic gene

Diseased cell
Gene mutation

Corrected cell
Gene replacement therapy

- Vector choice
- Route of administration
- Therapeutic dose

In humans ~ 640 muscles

Diseased muscle

XLMNTM
Adeno-associated virus (AAV)

Parvoviridae, dependovirus
Non pathogenic for humans
12 serotypes in primates

Genome:
Linear, single stranded DNA
4.7 kb genome
Inverted terminal repetitions (ITR)
**MTM1 vector**

*MTM1* gene (100kb): X chromosome

[Diagram of MTM1 vector with ITR, rep, and cap regions]
MTM1 vector

**MTM1 gene** (100kb): X chromosome

Coding sequence: 1.8 kb
MTM1 vector

MTM1 gene (100kb): X chromosome

- Coding sequence: 1.8 kb

- Recombinant AAV vectors
- Rep–Cap genes replaced by the MTM1 gene
- At Genethon we generated 3 AAV-MTM1 vectors

AAV-Mtm1: Mouse studies
AAV-cMTM1: Dog studies
AAV-hMTM1: Dose-finding studies in mice
Patients
Gene therapy: intramuscular

Viral-mediated expression of myotubularin in muscle corrects myotubular myopathy


- Proof of concept (intramuscular)

Recombinant AAV1-Mtm1
Gene therapy: intramuscular

Viral-mediated expression of myotubularin in muscle corrects myotubular myopathy

- Preclinical development
- Clinical trial in patients
Gene therapy: whole body

- Proof-of-concept
- Preclinical development
- Clinical trial in patients

Intravenous Whole body Mice

Recombinant AAV8-Mtm1


MTM1

ITR ITR
Gene therapy: Proof of concept

AAV8-Mtm1
systemic administration

Group 1: Early stage (3 weeks)
Group 2: Late stage (5 weeks)

At 6 months post-injection
100% survival

Quasi-normalization of body weight

Disease correction by post-symptomatic treatment
Gene therapy: Proof of concept

Wild-type XLMTM + 6 months

Wild-type  XLMNTM  XLMNTM +AAV

5 weeks

6 months after injection

Blue: AAV-treated XLMNTM mouse
Red: wild-type mouse
Gene therapy: Dog model

- Collaboration with MK. Childers
- Translation of GT in a large animal model


Recombinant AAV8-cMTM1
Gene therapy: whole body

Untreated XLMTM dog (17 weeks of age)

AAV-treated XLMTM dog (21 weeks of age)
Development Human Vector

Recombinant AAV8-hMTM1

- Generation of the vector carrying human MTM1
- Test efficacy and dose-finding in mouse model
- Large scale vector production: process development
  (upstream / downstream process)

GMP production
Gene therapy for XLMTM

- AAV8-MTM1 (intravenous): corrects the myopathy of animal models (mice, dogs); the effect persists over time
- Clinical trial started in September 2017, USA
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