DMD program
Utrophin modulation

Next Generation Compounds

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Utrophin modulation programme

- **Utrophin:**
  - Foetal form and a paralogue of dystrophin,
  - Express at specialized sites in normal mature muscle fibers,
  - Expression the full-length utrophin prevents muscular dystrophy in *mdx* mice (J. Tinsley, Nature. 1998).

- **Benefits to use utrophin**
  - Applicable to all DMD patients, regardless of their dystrophin mutation
  - Not toxic
  - Systemic strategy
  - No immune response
Utrophin modulation programme

- SMT C1100 is the first oral bioavailable utrophin modulator (Phase 1b) = lead compound,

- **Objective**: Develop the next generation utrophin modulator molecules.

**UtroDMD Alliance**: a multi-year strategic collaboration that combines the extensive biology, chemistry and drug discovery expertise of the University of Oxford, Summit plc.
Utrophin modulation programme

- Screening assays

Original screen (based on utrophin A)

New screen (encompasses all known utrophin isoforms)

- New screen assay:
  - Screen utrophin in its genomic context,
  - Better mimicking the \textit{in vivo} situation,
  - Enabling identification of compounds which modulate utrophin through additional regulatory pathways.
Utrophin modulation programme

- Improved screening cascade

- Compound pre-selection criteria

25,000-member drug-like compound collection

In silico searching

7,000 compounds selected

Luciferase assay

Target family-directed selection:
  e.g. Epigenetic modulators

In vitro ADME
Solubility, MLM Stability, Caco-2

DMD Patient Muscle cell Utrophin Assay

In vivo PK (po)

MTD d4

In vivo mdx

Representative examples of 4 structurally distinct hit series

Compound A

Compound B

Compound C

Compound D
New drug candidates demonstrate promising *in vitro* levels of activity

- SMT C1100 increased the utrophin expression by **1.2x** fold at 0.1 µM,
- SMT1 and 2 treatment resulted in a **1.6x** and **1.3x** fold increase in utrophin expression at 3 µM.
New drug candidates demonstrate promising *in vitro* levels of activity

**Utrophin protein expression - Western Blots**

- SMT1 (1 µM) and SMT 2 (10 µM) result respectively in a **2.1x** and **2.5x** fold increase of the utrophin protein expression in murin myoblasts,

- SMT C1100 (1 µM) = **2.0x** fold.
Benefits of daily dosing of sedentary *mdx* mice with new drug candidates

- New SMT compounds improved systemic exposure *in vivo* compared to SMT C1100

![Graph showing systemic exposure](chart)

- *In Vivo* Trial in the *mdx* mouse

  - Group 1: Vehicle
  - Group 2: SMT1 - 30mg/kg/day
  - Group 3: SMT2 - 30mg/kg/day

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Benefits of daily dosing of sedentary *mdx* mice with new drug candidates

- **SMT compounds prevent the muscular dystrophy in skeletal muscle**

A 5 weeks treatment with SMT1/2 in the *mdx* mouse resulted in a **decrease in muscle pathology**:

- Regeneration: SMT2: -21% (p=0.03)
- Necrosis: SMT2: 65% reduction (p=0.018)
Benefits of daily dosing of sedentary mdx mice with new drug candidates

- SMT compounds increase in the utrophin and β-dystroglycan expression

A five weeks treatment with SMT1 and 2 (30 mg/kg/day) in the mdx mouse resulted in:

- An increase of the utrophin at the sarcolemma: SMT1 (x1.3); SMT2 (x1.8, \( p=0.006 \)),

- A restoration of β-dystroglycan, a component of the dystrophin protein complex linking to the extracellular matrix: SMT1: (x1.3); SMT2: (x1.7, \( p=0.019 \)).
Benefits of daily dosing of sedentary \textit{mdx} mice with new drug candidates

- \textbf{SMT compounds modulate utrophin in the \textit{mdx} diaphragm and heart}

- \textbf{SMT treatments:}
  - decrease fibre regeneration: SMT1: (-38%, \textit{p}<0.001); SMT2: (-36%, \textit{p}<0.001),
  - prevent the accumulation of these deposits demonstrating a significant decrease in membrane damage,
  - lead to an increase of utrophin protein in the diaphragm: SMT1: 1.5x, \textit{p}=0.05; SMT2: 1.2x,
  - result in an increase of the utrophin protein level in the heart: SMT2: 1.6x fold.
Benefits of daily dosing of sedentary *mdx* mice with new drug candidates

- **SMT compounds treatments protects muscle**

  - SMT1 results in a **40% decrease** in force drop after five eccentric contractions ($p=0.036$),
  - SMT2 results in a **50% decrease** in force drop ($p=0.003$).

  - Increased utrophin levels after SMT1 and 2 treatments result in a **significant improvement in membrane stability and resistance to damage.**
Utrophin next generation programme

Development of the next generations utrophin modulator molecules:

- Base on a new screening cascade, **new utrophin modulators being identified with exciting activities.**

- New compounds **improved systemic exposure in vivo** compared to SMT C1100.

- Oral administration of small molecule modulators of utrophin expression significantly **prevents pathology in the mdx mouse.** In particular administration of SMT C1100 or SMT 1 and 2 modulate utrophin expression in **key muscle types including the heart and the diaphragm.**

- **Others Utrophin modulators are currently being studied in the mdx mouse**
Third generation drug candidates

- **Third generation** compounds show promising potential to increase utrophin level ($O$$X$$2 = 2.43x$ at 10 µM)
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