Proposal to establish a cooperative research centre

Presenter: Professor Steve Wilton

Affiliation: Centre for Neuromuscular and Neurological Disorders
Australian Neuro-muscular Research Institute
Details of the Centre

• Title:

Personalized genetic medicines for inherited disorders

• Purpose:

• Address unmet needs in providing therapies for genetic diseases previously considered intractable

• Establish new therapeutic platform.

• Distinction: A unique opportunity to become a national/international focal point for the personalized genetic therapies

By-passing gene lesion by splice switching was first demonstrated in Perth

History of innovation and involvement

- impetus for current DMD clinical trials and choice of chemistry

- compelling pre-clinical studies for other conditions
Personalized genetic medicines for inherited disorders

• Duchenne muscular dystrophy: proof-of-concept
  – Most common serious, form of childhood muscle wasting
  – X-linked recessive
    • males affected, females may be carriers/manifesting
  – 1 in 3 cases are *de novo*

  – Near complete inactivation of the dystrophin gene
    • Protein truncating defects (indels, nonsense)

• Symptoms present 1-5 years
  – muscle degeneration overwhelms regenerative capacity

• Restricted to wheelchair by age 12

• Death from cardiac and respiratory complications
Molecular surgery

• Splice switching antisense oligomers redirect gene transcript processing
  – DMD pre-mRNA > BMD-like mRNA > functional protein
    • Remove an exon(s) carrying early stop codon
    • Restore the reading frame

...17.18.19.20.21.22.23.24.25.26.27.28......

...17.18.19.20.21.22.23.24.25.26.27.28......
Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study

Maria Kinali*, Virginia Arechavala-Gomez*, Lucy Feng, Sebahattin Cirak, David Hunt, Carl Adkin, Michela Guglieri, Emma Ashton, Stephen Abbs, Petros Nihoyannopoulos, Maria Elena Garralda, Mary Rutherford, Caroline McCulley, Linda Popplewell, Ian R Graham, George Dickson, Matthew JA Wood, Dominic JWells, Steve D Wilton, Ryszard Kole, Volker Straub, Kate Bushby, Caroline Sewry, Jennifer E Morgan, Francesco Muntoni
Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study


Summary

Background We report clinical safety and biochemical efficacy from a dose-ranging study of intravenously administered AVI-4658 phosphorodiamidate morpholino oligomer (PMO) in patients with Duchenne muscular dystrophy.

Method We undertook an open-label, phase 2, dose-escalation study (0.5, 1.0, 2.0, 4.0, 10.0, and 20.0 mg/kg bodyweight) in ambulant patients with Duchenne muscular dystrophy aged 5–15 years with amenable deletions in DMD. Participants had a muscle biopsy before starting treatment and after 12 weekly intravenous infusions of AVI-4658. The primary study objective was to assess safety and tolerability of AVI-4658. The secondary objectives were pharmacokinetic properties and the ability of AVI-4658 to induce exon 51 skipping and dystrophin restoration by RT-PCR, immunohistochemistry, and immunoblotting. The study is registered, number NCT00844597.

Findings 19 patients took part in the study. AVI-4658 was well tolerated with no drug-related serious adverse events. AVI-4658 induced exon 51 skipping in all cohorts and new dystrophin protein expression in a significant dose-dependent (p=0.0203), but variable, manner in boys from cohort 3 (dose 2 mg/kg) onwards. Seven patients responded to treatment, in whom mean dystrophin fluorescence intensity increased from 8.9% (95% CI 7.1–10.6) to 16.4% (10.8–22.0) of normal control after treatment (p=0.0287). The three patients with the greatest responses to treatment had 21%, 15%, and 55% dystrophin-positive fibres after treatment and these findings were confirmed with western blot, which showed an increase after treatment of protein levels from 2% to 18%, from 0.9% to 17%, and from 0% to 7.7% of normal muscle, respectively. The dystrophin-associated proteins α-sarcoglycan and neuronal nitric oxide synthase were also restored at the sarcolemma. Analysis of the inflammatory infiltrate indicated a reduction of cytotoxic T cells in the post-treatment muscle biopsies in the two high-dose cohorts.

Interpretation The safety and biochemical efficacy that we present show the potential of AVI-4658 to become a disease-modifying drug for Duchenne muscular dystrophy.
Induction of dystrophin
Other applications

- Spinal muscular atrophy
- Leading genetic cause of death in children < 2 years
- Loss of SMN1 gene with abnormal SMN2 splicing
- SMN protein involved in RNA metabolism
- Carrier frequency about 1/40.
SMA

compelling in vivo results

• Splice switching to promote exon retention

Day 15

Day 40

average survival 100+ days, longest 165 days
Details of the Centre

• Strategies to value-add

Big Pharma now investing in rare disorders

Australia has world class diagnostic and health-support facilities for neuromuscular and other genetic disorders.

Splice switching for DMD was pioneered in Perth

- established track record
- member of MDEX (UK consortium)
- member of iDESC steering committee

Extensive experience in SS oligo design and implementation

AVI-4658 (developed in Perth) now in Phase 2 trials in USA/UK (and Australia?), others under evaluation
Details of the Centre

• Strategies to achieve national/international outcomes
  – demonstrate effectiveness of DMD exon skipping
    • addressing different mutations
  – initiate SMA trials
  – application to other conditions (genetic/acquired)

• Strategies for education and training
  – PhD student programs
  – Workshops
  – Public seminars (school, Rotary etc)
  – International researcher exchange
**Details of the Centre**

- **Strategies to translate into policy & practice**
  - Australian regulatory frame-work could be engaged to pioneer personalized medicine
    - awaiting conclusive results from DMD phase 2 trials
  - WA has engaged with Treat-NMD patient registries
  - Special interest groups support and lobbying

- **Strategies for collaboration**
  - extensive track record of collaboration (mainly overseas)
  - open and honest interactions
  - joint publications (in press, submitted, in preparation) on DMD, SMA, FSH, Utrophin, Cystic Fibrosis, asthma genes
  - Special interest groups support and lobbying
# Participants & Skills

<table>
<thead>
<tr>
<th>Local</th>
<th>Available</th>
<th>Sought</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Professors Steve Wilton, Sue Fletcher, Frank Mastaglia, Nigel Laing, Phillipa Lamont, Phil Thompson</td>
<td>Dr Anthony Akkari, ex GSK. North Carolina, USA</td>
</tr>
<tr>
<td>National</td>
<td>Professors Kathy North (Sydney) and Andrew Kornberg (Melbourne)</td>
<td>??</td>
</tr>
</tbody>
</table>
## Participants & Skills

<table>
<thead>
<tr>
<th>International</th>
<th>Available</th>
<th>Sought</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK/USA-DMD: Dame Professor Kay Davies, Professors Francesco Muntoni, Matthew Wood, Mike Gait, Volker Straub, Kate Bushby, Jerry Mendell, Eric Hoffman and Kevin Flanigan, Teji Khurana USA-SMA: Professor Arthur Burghes, Israel-PD and CF: Professors Hermona Soreq and Batsheva Kerem Belgium-FSHMD: Professor Alexandra Belayew</td>
<td></td>
</tr>
</tbody>
</table>
Progress to date

• DMD
  – Proof-of-concept demonstrated (Kinali et al, Lancet Neurology, 2009)
  – Phase 2a systemic trial completed (Cirak et al, Lancet, 2011)
  – Extended trials underway in USA
  – Clinical significance still to be demonstrated
  – Academic and Industry consortia being established

• Companies currently involved
  – AVI Biopharma, (competing interests GSK, Prosensa)

• Interest from Pfizer, GSK, Wellcome Trust, confidential.
Future Plans

• Crystallize application scope

• Identify collaborating research facilities in Australia
  – identify amenable target genes/conditions
  – application to gene down-regulation
  – modify miRNA expression

• Future discussions with Pharma

• Establishment of oligomer production facility?
  – source from USA and prepare to clinical grade
What is needed now

• To achieve competitive application in the next year
  – a very focused effort!
    • establish scope of centre and collaborators
  – funding for feasibility secured
  – legal and commercial advice
    • Social return on investment vs commercial viability or sustainability

• To achieve competitive application in the next two years
  – clinically significant results from current DMD trials
  – engage TGA
  – recruiting enthusiastic and motivated clinicians
  – me to stay in Perth!
    • Gan-bei!