

# Exon skipping trials in DMD- the beginning

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# The pathway

- Verify efficient exon skipping with specific AOs (cell culture)
  - Different chemistries, different sequences, different exons
- Verify that protein production is significant (cells and animals)
- Toxicology (defined by legislation)
- Regulatory issues
- Limited local injections (?proof of principle)
- Systemic delivery

# Specific aims of the initial trials

- To work with the regulatory authorities to improve understanding of this area
  - "Special treatment" for an orphan disease
  - Gene therapy? Medicine?
- To verify if local administration of AON in a single muscle of DMD boys is
  - Safe
  - Effective at restoring dystrophin production
  - BUT is local administration at all logical?
- To collaborate with preclinical studies of systemic delivery
- To prepare to gear up for larger scale trials

# Issues in selecting the target population?

- Could we get the "wrong answer" if we look at older children?
- Consent from minors for procedures that will not benefit them
- Views of the regulatory authorities vary in different countries
- In UK likely age will be 14+
- PhD underway on issues of consent in minors

# Local administration (UK strategy)

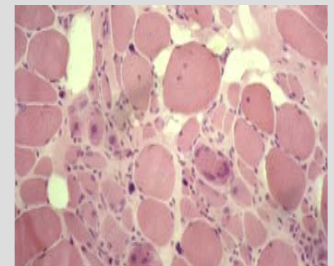
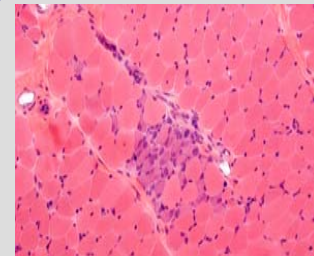
- Single target exon
  - 51
- One chemistry
  - morpholino
- Single muscle delivery
  - EDB
- Endpoints
  - Safety
  - Dystrophin production

# Preparatory work

- Selection of muscle to be targeted
  - Damage will not be a functional problem
  - Easy to biopsy
  - Pathology not end stage
  - Requires a close look (pathology, level of revertants, MRI) at small muscles we usually ignore

# Muscle assessment

- MRI scanning (future projects)
- Biopsy of target muscles during surgery for other procedures (spinal surgery, TA lengthening)



# Preparatory work

- Genetics
- We “know” the deletions of all our patients.....
  - Deletion endpoints?
  - Intronic polymorphisms
  - Cell culture models of all relevant deletions
- Far greater precision is needed than is usually provided

# At the end of the preparatory work:

- Be better informed in discussion with regulatory authorities to define a realistic age group for the study
- Understand the likely pathology in the target age group more precisely
- Correlate this with non invasive methods of assessment
- Understand the genetic and protein production profile of possible participants
- Be ready for systemic delivery

# Getting it right

- “Proof of principle” studies are high risk
- We want to avoid getting a negative result for the wrong reasons
  - “killing an innocent oligo”

# What we wish we already knew

- An "atlas" of muscle pathology in easily biopsied muscles at different ages
  - Is there a point where damage is irreversible?
- An "atlas" of non-invasive monitoring methods
- An idea of how revertant fibres change with age
- A comprehensive registry of patients
- A more productive discussion before now about phase 1 studies in these patients at an early age

# Attempting a collaborative effort

- UK consortium (MDEX)
- Dutch consortium
  - European consortium
- GSK initiative (Australia)
  
- International AO consortium
  - Safely take the most promising routes from cells and animals to people
  - Move as smoothly as possible from step to step
  - Reduce duplication of effort

# Opportunity for further collaboration: EU call

- This network of excellence will aim at sharing expertise between **basic and clinical academics** and **industrial partners** in order to develop **technological and methodological tools** with a view to **accelerate the elaboration of new therapies for rare neuromuscular diseases**. Important tools include animal models, databases, biobanks, well defined patient cohorts, methods for efficacy assessment. The participation of SMEs is highly encouraged

# The underlying concepts

- Change in working practice is the goal of an NoE so that integration on this topic is total and permanent
- Focus on addressing areas where fragmentation is hindering the competitiveness of European researchers in the field
- Application to be led from Newcastle (TREAT-NMD) with support of AFM, ENMC

# Aims and objectives of TREAT-NMD

- to work towards the establishment of a durable entity (European NM Institute)
- to deliver innovative treatments for rare NMD
- to bring together the top EU researchers, clinicians and industry working in NMD
- to address the fragmentation currently hindering the progress of promising therapies
- to educate clinicians and researchers in these processes

# Work packages illustrate the passage from lab to clinic

- Animal/ cell studies
- Getting enough safe product
- Targeting to muscle
- Databases, registries and biobanks
- Standardisation of diagnosis and care
- Standardising outcome measures
- Running trials
- Defining the ethical environment

# Disease groups will "test out" the roadmap

- DMD (antisense oligos, gene transfer, stem cells)
- SMA (promising drugs from cell studies)
- CMD (cyclosporin in UCMD, alteration of glycosylation, upregulation strategies)
  - But the map must also be "future proof"

# Additional workpackages will address

- Integration
- Education
- Management
- Establishment of a durable structure for the future
  
- Additional international interactions, need to reduce duplication of effort