Developing new therapies for children with neuromuscular diseases

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Disclaimer

- I work at Newcastle University and my post is funded by a UK charity Duchenne UK
- I receive no funding or honorarium from industry
Who We Are

- **TREAT-NMD**: a global network of excellence in neuromuscular disease
  - FP6 EU-funded global network of excellence in 2007; sustained as TREAT-NMD Alliance since 2011
  - Infrastructure project not research project
  - Supports translation of neuromuscular research from lab to patient
  - Developing “tools” for trial-readiness in neuromuscular disease (NMD)
  - Advancing diagnosis, care and treatment for NMD
Many Areas of Activity

- Outcome measures
- Training and education
- Clinical Trial Coordination Centre
- Global patient registries
- Communication infrastructure
- Advisory committee for therapeutics
- Regulatory information
- Care and trial site registry
- Standards for animal assessment
- Care standards
- Ethical framework
- EuroBioBank
Who We Are

• **TACT**: TREAT-NMD Advisory Committee for Therapeutics

  - Established in 2009 to provide guidance on the translation and development path of therapeutic programs in rare neuromuscular diseases with large unmet need
Need for TACT was Identified Because of:

- A fragmented and subjective approach to funding translational research in NMD
- A lack of comprehensive reviews of both science and development potential in therapy development
- Variability in the rigor of assessments across funders and researchers
- Compounds moving to clinic despite non-compelling pre-clinical data leading to (predictable) failure in the clinic
- A frequent lack of realistic development perspectives
- Poor selection of inclusion criteria and outcome measures for trials
- A lack of patient input and perspectives in research planning
Remit of TACT is to:

- Provide applicants with transparent and consistent guidance, in an educational and directional context for therapy development
- Facilitate the preparation of funding and regulatory applications
- Publish a non-confidential summary to inform the neuromuscular community
TACT does NOT:

- Provide on-going advice following review
- Make funding decisions
TACT is

- **Expert:** members of the committee are leaders in their field
- **Global:** applications are from around the world and meetings are held in Europe and the US
- **Multidisciplinary:** the committee comprises experts covering all areas of therapy development
- **Confidential:** reviews are not shared with 3rd parties
- **Credible:** valued by industry and funders
- **Collaborative:** eliminating historical barriers between academia, industry, patient organizations
- **Unique:** There is no duplication of existing efforts
How TACT Works

- **Core committee** (10)
- **Wider committee** of international experts selected depending on the nature of each application (70)
  - preclinical assessment of animal and cellular models
  - pharmacology and drug development
  - statistical considerations of trial design
  - regulatory in both the US and the EU
  - clinical trials, ethics and patient representation
- **TREAT-NMD Secretariat** based in Newcastle, UK
- Members sign **confidentiality agreement** and disclose potential conflict of interest
  - Transparency is key to TACT’s credibility
Patient representation
Nick Catlin
Pat Furlong
Sharon Hesterlee
Jane Larkin
Robert McDonald
Debra Miller
Beatrice de Montleau
Marie-Christine Ouillade
Marita Pohlschmidt
Anne Rutkowski

Drug development
Cristina Csimma
Donald Kirsch

Cardiology
Hugh Allen
John Bourke

Preclinical
Arthur Burghes
Gunnar Buyse
Annamaria De Luca
Kenneth Fishbeck
Miranda Grounds
Eric Hoffman
Jill Jarecki
Kanneboyina Nagaraju
Lee Sweeney
Meg Winberg
Dominic Wells
Annemieke Aartsma-Rus

Physiotherapist
Michelle Eagle
Anna Mayhew
Linda Lowes
Richard Lovering

Ethics
Joseph Irwin
Shaun Pattinson
C Rehmann-Sutter
Lars Sandman

Regulatory
Didier Caizergues
Simon Day
Tracey Zoetis

Statistics
Avital Cnaan
Oliver King
Dieter Hauschke

Toxicology & Pharmacology
John McCall
Paul Pearson
Mike Pleiss
Urs Ruegg
Jon Tinsley
Michael Kelly
Donald Cairns

Clinical
Edward Connor
Alberto Dubrovsky
Paula Clemens
Sven Dittrich
Kevin Flanagan
Pascal La Forêt
Mike Hanna
Petra Kauffman
Rudolf Korinthenberg
Oscar Henry Mayer
Elizabeth McNally
Elizabeth McNeil
Jerry Mendell
Kathryn North
Monique Ryan
Anita Simonds
Jeff Towbin
Mar Tulinius
Jan Verschuuren
Kathryn Wagner
Maggie Walters
Marianne de Visser
Jeremy Shefner (ALS)
Ulrika Schara
Diane Escolar
Nathalie Goemans
Francesco Mutoni

Kathryn Wagner
Current Chair
of TACT
Wider TACT Committee

- **Total of 70 additional expert members**
- **12 countries represented:**
  - Argentina
  - Australia
  - Belgium
  - Canada
  - Denmark
  - France
  - Germany
  - Italy
  - Sweden
  - Netherlands
  - UK
  - USA
TACT Review Process

Meeting convened
Review 2-4 applications - half a day per application
Applicant to participate in a 1 1/2 hour face-to-face discussion

Collate reviews and circulate to all reviewers involved in the review of a specific application

Distribute completed applications to selected reviewers

Receive completed full application

Confirmed proposals invited to submit a full application

Receive expression of interest and completed pre-application forms

Confidential report sent to applicant

General non-confidential report available via TREAT-NMD website www.treat-nmd.eu/tact

- 4 months
- 3 months
- 2 months
- 1 month
+ 1 months
+ 2 months
How TACT Works

- 2 meetings per year (USA/Europe), 4 applications per meeting
- Brief pre-application establishes the suitability of a TACT review for particular compound at a specific point in time
- Full application is submitted
- Each review is coordinated and summarised by a lead reviewer with a highly relevant area of expertise
- Significant review process occurs before the meeting
- Applicants participate in part of the meeting to answer additional questions or provide clarification
- Meeting integrates and aligns reviews from the multidisciplinary committee into one comprehensive report for the applicant
40 Programs Reviewed to Date

- Applications from USA, Europe, Australia
- 70% industry, 30% academia
- Multiple neuromuscular diseases (9)
  - DMD, BMD, CMD, IBM, SMA, MTM, NMD, MNGIE, DM1
- 19 novel, 20 repurposed and 1 no identified lead compound
- 23 small molecule and 17 biologics
- 20 pre-clinical and 20 clinical stage programs
Costs of TACT

- Half-time project manager, travel, accommodation, meeting room hire and meals
- Honorarium of $400 for attending experts
- ~ $40-50,000 per meeting
- Funding: EU, then US DoD, EHAC, PPMD, CureDuchenne, Myotubular Trust, Foundation to Eradicate Duchenne

Since 2012 applicants contribute to meeting costs:
  - no cost for academia
  - $5,000 for industry with <10 employees
  - $10,000 for industry with >10 employees
Recurrent Themes

- Need to use gold standard operating procedures for animal studies (e.g. SOPs available on the TREAT-NMD website)
- Importance of ensuring reproducibility in preclinical studies
- Molecule intended for development should be the one tested pre-clinically
- Re-purposing – efficacy results from other populations may not be relevant in target population or in paediatric use; additional work may be needed
- Clinical trial design – suboptimal design seen e.g. plans to get “results” quickly using small numbers, use of inappropriate outcome measures, reliance on untested “biomarker”; thinking one trial at a time
- Insufficient consideration of drug development complexity (i.e. what will happen following clinical trial - manufacture, scale-up, further funding, partnership, etc.)
What Is the Impact?

- High industry engagement: 70% of programs
- Patient foundations fund and use TACT reviews
- Higher quality applications over time
- Applicants
  - Feedback (e.g. Wall Street Journal)
  - Returning for further review
- Guidance immediately actionable
- Other non-NMD foundations emulating model
- Directly addresses IRDiRC goals
- TACT model no longer novel but remains unique!
- Future funding remains critical
In Summary: Elevator Pitch

- “The strength of TACT is its broad scientific and development expertise coupled with the rigour and independence of its review process, performed in a truly global context. This committee can provide objective and constructive guidance from world experts in the field that will both help researchers focus on areas for development and ensure the wider community is better informed about the readiness of new therapies for the next step.”

Cristina Csimma, previous TACT chair
For more info: TACT Publication

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The TREAT-NMD advisory committee for therapeutics (TACT): an innovative de-risking model to foster orphan drug development

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