A decade of optimizing drug development for rare neuromuscular disorders through TACT

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This year marks the tenth anniversary of the TREAT-NMD Advisory Committee for Therapeutics (TACT), a group of multidisciplinary experts that evaluates drug development programmes for rare neuromuscular diseases and identifies pitfalls. Here, we discuss the experience with TACT based on its reviews of more than 50 applications and its potential as a model for other rare disorders.

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The TREAT-NMD Advisory Committee for Therapeutics (TACT) was initiated in 2009 to address the issue that most drug development programmes targeting neuromuscular disorders failed to bridge the gap between preclinical and clinical studies or failed in early-stage clinical trials[1]. This was due in part to a lack of knowledge of drug development processes in general and in part to specific challenges for conducting clinical trials in rare neuromuscular disorders, including the degree of specialization required and the extremely limited number of patients available for clinical trials.

TACT is composed of multidisciplinary, independent, key opinion leaders in preclinical studies, clinical trials, outcome measures, drug development, pharmacology, toxicology, regulatory affairs, statistics and ethics from across the world. The committee also includes patient representatives. Originally funded by the European Union Framework Programme 6, TACT is currently supported by patient foundations and contributions from industry applicants. TACT is a non-profit organization and does not provide funding for clinical trials, but advice and guidance is offered to applicants in a professional, interactive forum for a nominal contribution, the cost of which is on a sliding scale that depends on the size of the applicant company, with no cost for academic applications.

In order to submit a TACT application, applicants need to have at least identified a lead compound. However, applications can also be reviewed during later clinical phases of a development programme. Final recommendations come in the form of a confidential written report within 6 weeks of a face-to-face meeting between the applicant and the committee. Non-confidential brief summaries of TACT reports are posted on the website (see Related links).

There are common pitfalls that applicants encounter that can be avoided with proper guidance. For example, academic applications and those from smaller companies may underestimate the quality and quantity of data needed to make a decision to advance a lead compound or a programme. This can be from lack of funds or lack of experience in the drug development process. These applications generally miss key experiments and critical data. Quite often, important preclinical studies are underpowered or not independently verified. To avoid such pitfalls, it is important to choose the most relevant cell or animal models and rigorously conduct experiments so that comparable and reproducible results are obtained within the same or in different labs and, whenever feasible, in an independent and capable contract research organization. TREAT-NMD has held workshops with key scientists with expertise in animal models to reach consensus on standard operating procedures (SOPs) for preclinical efficacy studies[2] (see Related links). Use of these SOPs is recommended by TACT to minimize the risk of false-positives that then fail in later development.

Established drug developers typically have substantial human and financial resources, and their applications usually have a plethora of data. Nevertheless, they still face the challenge of translating novel targets to the clinic to treat less well understood diseases. In such cases, TACT can provide an understanding of the diseases, natural history, outcome measures and the patient community that can be invaluable. If data are not available on the natural history or appropriate outcome measures for a specific disease entity, TACT may recommend de-risking activities prior to proof-of-concept trials. Patient representatives are always included on the panels and will advise on the burden of trial protocols as well as the relevance and significance of the expected outcomes.

Impact of TACT

TACT meets twice yearly and has reviewed a total of 56 applications since its inception: 32% originated from academia, 45% from small companies (50 employees or fewer), 7% from middle-sized companies (51–250 employees) and 16% from large companies (more than 250 employees). Geographically, 48% of applications were from the USA, 46% from Europe, 4% from Australia and 2% from Asia. The programmes were at various stages of development, ranging from those that had only recently identified their lead compound and required assistance in designing their preclinical studies to those that had proof-of-concept clinical data and required advice in designing their pivotal study and regulatory route.

Various diseases were targeted, including Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), facioscapulohumeral muscular dystrophy, Pompe disease, Becker muscular dystrophy, myotonic muscular dystrophy, congenital muscular dystrophy, limb girdle muscular dystrophy, inclusion body myositis, X-linked myotubular myopathy and mitochondrial neurogastointestinal encephalomyopathy. The most common indication was DMD. This reflects in part the prevalence of the disease, its comparably well understood pathology and natural history, and the strong pipeline in DMD.

Small molecules were the most common class of therapeutic agent reviewed (38%), followed by biologics and advanced therapy medicinal products (ATMPs) (25%), repurposed drugs (32%) and nutritional supplements (5%). The field of rare neuromuscular disorders has seen rapid expansion of biologics and ATMPs, with the FDA and European Medicines Agency (EMA) approvals of antisense oligonucleotides for SMA and DMD and gene therapy for SMA among the first approved therapies for these disorders. TACT has reviewed several ATMP programmes including gene therapies and anticipates that this class will grow over the next few years.

The applicants used the TACT review process for a variety of purposes, including to enable additional funding, to revise their preclinical or clinical study plans, to modify their milestones, to prepare for regulatory meetings and in some cases to re-evaluate whether to continue development of their lead compound. Programmes previously reviewed by TACT are currently in all stages of development, with several in phase III trials. The status of compounds in development following TACT review is shown in Supplementary Fig. 1.

Recommendations made by TACT are tailored to the specific questions the applicants address to the committee as well as the stage of development, but commonly include additional rigour for preclinical studies, issues related to good laboratory practice (GLP) and good manufacturing practice (GMP), appropriate disease-specific outcome measures in clinical trial design, quality of life measures, patient feedback and early regulatory interactions. With these recommendations, applicants can avoid common pitfalls, which can be very costly in time, resources and patients. In the DMD field in particular, the landscape is very competitive and the number of patients of specific ages and disease severity is extremely limited.

Expansion of the TACT model

Although the indication targeted by the majority of applications was DMD, TACT advice can be appropriate for all neuromuscular diseases. TACT selects each review committee of approximately 15 individuals from more than 70 key opinion leaders worldwide and frequently welcomes new members to provide expertise tailored to the application. TACT is also a model for other rare diseases. To promote the TACT model for other indications, a limited number of observers from other rare disease fields, patient advocacy groups and specialty networks can participate in TACT meetings. All participants sign confidentiality agreements and are required to submit disclosure statements before they can see an application or attend a meeting. Transparency about potential conflicts of interest is of utmost importance as it ensures total independence of panellists during the review process.

The TACT committee aims to apply the TACT model to other disease areas. This will be explored through two projects — conect4children (c4c) and the European Joint Programme for Rare Diseases (see Related links). The aim of the pan-European project c4c, which is funded by the Innovative Medicines Initiative, is to facilitate the development and availability of new medicines for neonates, paediatric patients and adolescents, through the creation of a large collaborative paediatric network. Through the European Joint Programme for Rare Diseases, an Advisory Committee for Therapeutics (ACT) toolkit will be created based on the TACT model to enable other rare disease networks to develop their own ACT.

Using TACT as a model of multidisciplinary, unbiased expert opinion provided in a supportive environment de-coupled from funding considerations, other fields can help de-risk drug development and facilitate the approval of novel therapeutics for rare diseases.

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Competing interests
The authors declare no competing interests.

Supplementary information
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