The TREAT-NMD Advisory Committee for Therapeutics (TACT): Facilitating Drug Development in Neuromuscular Rare Diseases

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The TREAT-NMD Advisory Committee for Therapeutics (TACT) was established in 2009 and is currently chaired by Dr Kathryn Wagner. Working closely with the chair is a core group and 70 additional international multidisciplinary experts, each with specific expertise in one or more of the areas of drug development: discovery, chemistry, preclinical pharmacology, toxicology, regulatory, biostatistics, clinical care and research, ethics and funding of development programs. TACT is supported by the TREAT-NMD secretariat and importantly includes patient organisation representation (Figure 1).

TREAT-NMD Advisory Committee for Therapeutics

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Lars Sandman

XLMTM
Jocelyn Laporte

Drug Development
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Chris Shillings

Regulatory
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Simon Day
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Figure 1. TACT Committee

TACT provides the neuromuscular community (clinicians, researchers, patient advocacy groups and industry) with independent and objective guidance on advancing new therapies (whether novel or repurposed) for neuromuscular diseases.

The goal of each review is to position the potential therapy along a realistic and well informed pathway to clinical trials, and eventual registration, by evaluating the supporting preclinical data and all other critical drug development considerations that are necessary for objective decision-making and for the design and conduct of studies that generate meaningful data and have the potential to be funded longer term.

Table 1. Previous TACT applications (February 2010 – December 2015)

Applicant	Proposal Title
Guiseppe Vita, MD & Sonia Messina, MD, PhD University of Messina, Italy	Randomized double-blind placebo-controlled trial of flavocoxid in Duchenne muscular dystrophy.
Emilio Clementi, MD, PhD & Grazia D'Angelo, MD, PhD Luigi Sacco University Hospital	A pharmacological treatment for muscular dystrophy combining NO-releasing and non steroidal anti-inflammatory drugs.
Christopher F. Spurney, MD Children's National Medical Center, USA	Treatment of early cardiac systolic dysfunction in Duchenne muscular dystrophy with lisinopril or Losartan: a prospective, randomized, blinded, crossover trial.
Bradley L. Hodges, PhD Prothelia Inc., USA	Recombinant human Laminin-111 for treatment of Duchenne Muscular Dystrophy.
James Symons, M.S., PhD Phrixus Pharmaceuticals Inc., USA	An open-label, fixed dose, exploratory study to assess the efficacy and safety of P-188 NF on left ventricular volume changes in patients with Duchenne muscular dystrophy (DMD)
Ana Ferreiro, MD Institute of Myology, France	Oxigen: AntiOXidants for a GEnetic Myopathy. The First Clinical Trial for a Congenital Muscle Disorder: N-Acetyl cysteine (NAC) Treatment for SEPN1 Related Myopathy.
Paul Higgins, PhD Paratek Pharmaceuticals	Tetracycline Derivatives as SMN2 Splicing Modifiers for the Treatment of SMA. Screen of a tetracycline library -identified a group of potential candidates. One of these will be selected as a final candidate.
Fredrick Sachs, PhD Rose Pharmaceuticals, USA	Therapy for Muscular Dystrophy by Inhibition of Mechanosensitive Ion Channels.
Marc Blaustein Halo Therapeutics, USA	A randomised, double-blind, placebo-controlled, multiple-dose, dose-escalation study to evaluate the safety, tolerability, pharmacokinetic, and pharmacodynamic effects of HT-100 in patients with Duchenne muscular dystrophy
Fabrizio Dolfi, MD, PhD NicOx SA, France	A 6-month multicenter, randomised, double-blind, placebo-controlled, Phase IIa proof of principle study of naproxcinod (HCT 3012) 750 mg bid in patients with Becker Muscular Dystrophy.
Chris N Airriess, PhD California Stem Cell, USA	Human Embryonic Stem Cell Derived Motor Neuron Progenitors for the Treatment of Motor Neuron Disease.
Fred Marin, PhD GMP-Orphan SAS, France	A new drug formulation development program of sodium phenylbutyrate in SMA patients.
Urs Ruegg, PhD University of Geneva	Proposal for clinical investigation of tamoxifen in DMD boys based on results in dystrophic mice.
Joel Braunstein, MD, FACC, MBA Tivorsan Pharmaceuticals, USA	Recombinant Biglycan for Treatment of Duchenne and Becker Muscular Dystrophy
Paolo Bettica, MD, PhD Italfarmaco SpA, Italy	A two part study to assess safety and tolerability, pharmacokinetics, effects on histology and on different clinical parameters of Givinostat in ambulant children with Duchenne Muscular Dystrophy
Dariusz C Gorecki , MD, PhD University of Portsmouth, UK	P2X7 purinoceptor as a target for pharmacotherapy of Duchenne Muscular Dystrophy
Joanne Donovan, MD, PhD Catabasis Pharmaceuticals, Inc., USA	CAT-1004, a novel anti-inflammatory agent for treatment of Duchenne Muscular Dystrophy
Erica Reeves, PhD ReveraGen BioPharma Inc., USA	VBP15 for the treatment of DMD
Patricio Sepulveda Myostin Therapeutics Pty Ltd, Australia	Novel myostatin antagonist peptides to enhance muscle function
Peter Flynn, PhD Fate Therapeutics Inc., USA	Wnt7a-Analog Protein Therapeutic for the Treatment of Muscular Dystrophy
Jon Tinsley, PhD Summit PLC, UK	Utrophin modulator for the treatment of Duchenne muscular dystrophy
Jens Schmidt, PhD University Medical Centre Göttingen, Germany	Blockade of nitric oxide-related cell stress as potential treatment for inclusion body myositis
Denis Guttridge, PhD Ohio State University, USA	NBD Therapy for Duchenne Muscular Dystrophy
Mimoun Azzouz, PhD University of Sheffield, UK	Viral vector containing DNA coding for the human SMN protein; for treatment of Sq spinal muscular atrophy
Richard Franklin, MD PhD Tarix Orphan LLC, USA	TXA127 for the treatment of muscular dystrophies
Gloria Vigliani	Clinical Trial of FG-3019 in patients with Duchenne muscular dystrophy (DMD)
Suyash Prasad, MD. Audentes Therapeutics, USA	A Phase 2 Single Arm, Open Label, Clinical Study to Evaluate the Safety and Efficacy of AAV8 Delivered Gene Therapy Delivered to Children with X-Linked Myotubular Myopathy (XLMTM)
Seth Porter, PhD. FibroGen, USA	Clinical Trial of FG-3019 in patients with Duchenne muscular dystrophy (DMD)
Ramon Marti, MD. Vall d'Hebron Research Institute (VHIR)	Gene Therapy for mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) using a new orphan drug consisting of an adeno-associated virus vector carrying the TYMP gene. Phase I/It clinical trial
Stefan Schäfer, MD. Peacock Pharma, Germany	The NHE-1 (sodium-hydrogen exchanger 1) blocker KR-33028 for the treatment of muscular dystrophies
Florence Porte-Thomé EspeRare Foundation	Rimeporide (EMD 87580)- a potential disease modifying drug for Duchenne muscular dystrophy (DMD)
Lynne Georgopolous PhaseBio Pharmaceuticals Inc., USA	Development of PB1046 (Vasomera), as an adjunctive therapy for the treatment and prevention of cardiomyopathy associated with dystrophinopathies; Duchenne Muscular Dystrophy (DMD), Becker Muscular Dystrophy (BMD), and X-linked dilated cardiomyopathy (XL-dCMP).
Dr Giiko-Kabir BioBlast Pharma Ltd.	BBRM2 (Intrathecal Azythromycin) for the treatment of Spinal Muscular Atrophy.

To date TACT have held 12 review meetings across Europe and the USA, and have reviewed a total of 34 program applications from both academic investigators and industry in the following areas: DMD, BMD, SMA, IBM, CMD, NMD, MNGIE, and XLMTM. Of the 34 compounds reviewed 23 (76%) were from industry and 11 (34%) were from academic applications; 15 (44%) were for novel compounds, 18 (53%) were for repurposed drugs and 1 had no lead compound (3%); 18 (53%) were small molecules and 16 (47%) were biologics; 18 (53%) were preclinical stage applications and 16 (47%) were clinical stage applications, as detailed in the pie charts below:

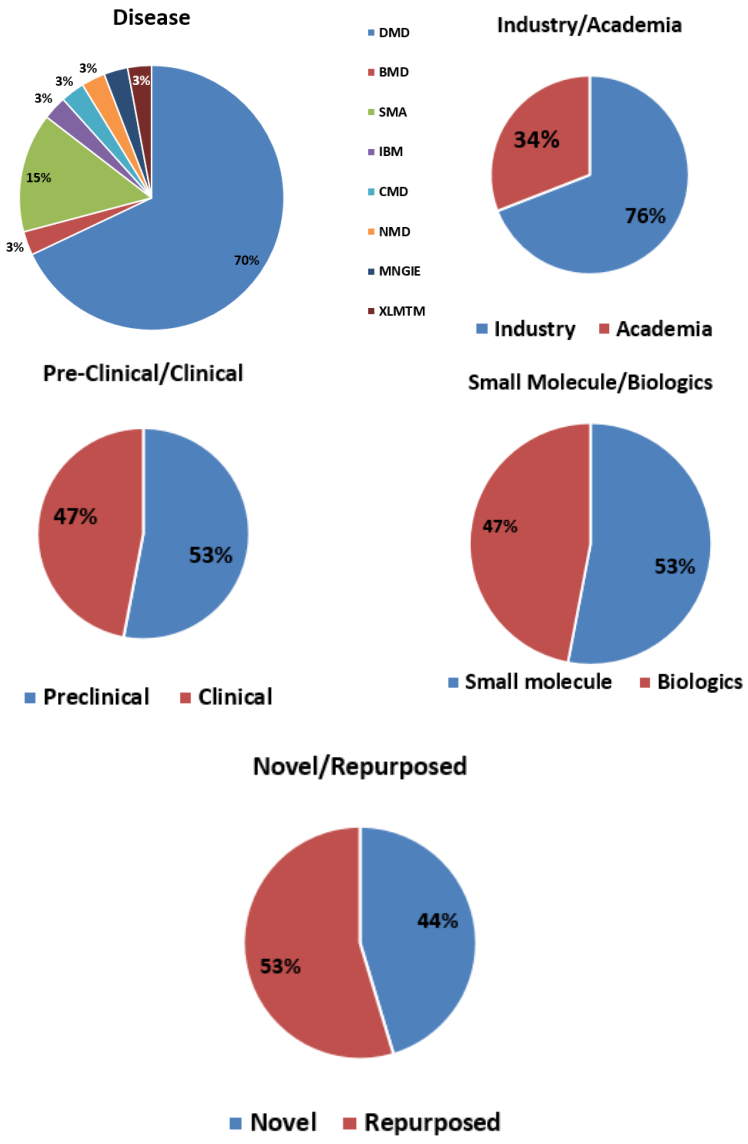

Figure 2. TACT Metrics

TACT has worked closely with existing infrastructures, and major patient organization funders in multiple regions to ensure the process is complementary and ideally synergistic to assists the neuromuscular community as a whole. Patient organisations (PPMD) are already working closely with the TACT as part of their evaluation for funding and there is significant interest in TACT by industry. The TACT review and detailed report, with recommendations, are confidential and provided directly to the investigator. Other parties interested, such as funders, can obtain the report from the investigator.

Feedback so far shows that TACT has generated recommendations that have greatly helped investigators, including industry, in evaluating their potential compounds and considering the development program in a methodical fashion with clear go /no-go decisions and with optimal use of funding and resources. TACT is a unique independent body of international experts in neuromuscular disease, that provides comprehensive advice that can greatly facilitate development and funding. TACT is not a funding body.

The next TACT review meeting will take place in October 2016 in Florida, USA. Anyone interested in submitting an application should therefore contact TACT secretariat (catherine.turner@ncl.ac.uk) as soon as possible.