

1 | TACT Kick-Off meeting
3-4 Oct 2009, Newcastle UK



Action Duchenne Meeting, London, 23rd-24th October 2009

TREAT-NMD Advisory Committee for Therapeutics

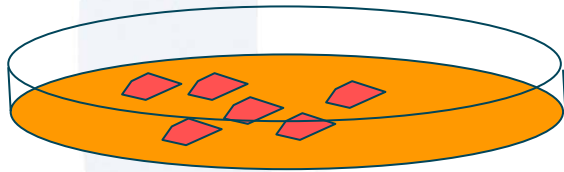
Dominic Wells, Imperial College London

Why set up a TREAT-NMD Advisory Committee for Therapeutics (TACT)?

- A range of therapeutic approaches show promise for DMD.
- Need to move to clinical trial ASAP.
- Limited number of patients eligible for trials – especially for some treatments.
- Limited funds for clinical trials
- Not all academics know about translational research.

Preclinical experiments 1

- Potential treatments developed in cell/tissue culture
- BUT need to evaluate effectiveness in a whole organism
- Test in context of range of cell types, 3D structure, immune system, nervous system, endocrine system.



Preclinical experiments 2



- Animal models
 - Mdx mice show no symptoms
 - GRMD dogs expensive and few in number
- Mice very resilient and respond to many treatments
- Doses for animal experiments mostly much higher than possible in man
- Dose for effect vs dose for safety

Types of treatment

- Novel approaches
 - not yet tested in other conditions
 - New compounds require full toxicology
- Retargeting of clinically approved drugs
 - Potentially more rapid approval
 - May not have been tested in paediatric population
 - Drug companies may not be keen to get involved
 - o Limited market
 - o Any adverse effects may be detrimental to 1^o application

Role of TACT

- People presenting a possible candidate for appraisal by TACT will be assured of getting impartial and excellent information allowing them to plan a route forward to registration.
- Academics often don't have easy access to information on pharmacology and toxicology requirements, and the regulatory issues are frequently underestimated.

TACT

- Suggestions for drugs to be appraised by the T-TAC will be solicited from amongst the TREAT-NMD network and collaborators. Applicants could include
 - principal investigators planning a study,
 - preclinical investigators who have promising results they wish to move to the clinical arena,
 - a potential trial sponsor or a
 - funding body seeking advice on the feasibility of a compound moving to trial.

List of current drug candidates

Drug currently on clinical trial (yellow)	Drugs currently on study in animal models (blue)	Drugs tested in cell cultures or where a role in disease pathogenesis was suggested but still need to be proved or used as potential treatment approach (green)
<ol style="list-style-type: none"> 1. ACE-031 2. Albuterol 3. Ataluren 4. Idebenone 5. Myo-029 6. nNOS/PDE5 inhibition 7. VPA 8. Debio 025/ CypD/ CsA 9. Coenzyme Q10 10. Creatine Monohydrate 11. Human Growth Hormone (HGH) 12. Green Tea Extract (Epigallocatechin-3-Gallate (EGCG)) 13. BMN-195 	<ol style="list-style-type: none"> 14. IGF-1/ Iplex, AAV delivery 15. Doxycycline, minocycline 16. Erythropoietin (Epo) 17. Flavocoxid 18. Halofuginone 19. Laminin 111 20. Losartan / TGFβ 21. Enalapril 22. Imatinib mesilate 23. Suramin 24. BKT-104 (oral TNF alpha inhibitor) 25. Omigapil 26. SEPN1/NAC 27. Sildenafil (Viagra) 28. Tamoxifen 29. Melatonin 	<ol style="list-style-type: none"> 30. SIRT1 agonists 31. α7 integrin 32. "2F12" c-erbB3 clone 33. Biglycan (Decorin?) 34. Bowman-Birk inhibitor (BBI) / Haelan 951 35. Carnitine 36. Dietary oils 37. HDAC (histone deacetylases) inhibitors 38. IPLEX (IGF-1) 39. MOR23 ligand 40. Myostatin/Act2BR 41. NFκB/NBD peptides (pyrrolidine dithiocarbamate, PDTC) 42. Osteopontin 43. P118 44. Pantothenate 45. PPARδ/GW1516 Peroxisome proliferator-activated receptors 46. recombinant αDG 47. RIP1 inhibition

Core Committee

Cristina Csimma	TACT Chair	Virdante Pharmaceuticals, USA
Raju Kannebojina	Preclinical	Children's National MC Washington, USA
Dominic Wells	Preclinical	Imperial College London, UK
John McCall	Drug Discovery/Medicinal Chemistry	PharmMac LLC, USA
Elizabeth McNeil	Regulatory	Food and Drug Administration, USA
Didier Caizergues	Regulatory	GENETHON, France
Rudolf Korinthenberg	Clinical	University of Freiburg, Germany
Petra Kauffman	Clinical	NIH, USA
Jerry Mendell	Clinical	Ohio State University, USA
Kate Bushby	TREAT-NMD secretariat	Newcastle University, UK
Emma Heslop	TREAT-NMD secretariat	Newcastle University, UK
Volker Straub	TREAT-NMD secretariat	Newcastle University, UK

Full TACT

- Panel of 40+ experts to provide advice on selected treatments
- Meetings 2-3 times per year
- Expert reviews from both within and outside of committee

Application Form

- The application form will be available on the TREAT-NMD website in November and interested groups should submit applications thereafter for appraisal at the first TACT drug review meeting scheduled for 6-8 February 2010.
- Range of points to consider including the following:

Questions to consider for clinical development 1

- Preclinical experiments
 - Appropriate model for disease?
 - How reliable is model in predicting for man?
 - Reliable assay for drug action? Biomarker?
 - Have results been replicated?

Questions to consider for clinical development 2

- Toxicology
 - No adverse effect level (NOAEL), maximum tolerated dose (MTD) – 2 species
 - Multiple dose safety
 - Genetic toxicity
 - Cardiovascular safety
 - Reproductive toxicology
 - CNS safety
 - Off-target pharmacology
 - Safety related target effects

Questions to consider for clinical development 3

- Pharmacokinetics (PK) in multiple species
- Absorption, Distribution, metabolism and excretion (ADME)
- Assays for clinical trials (e.g. immune responses etc)

Questions to consider for clinical development 4

- Manufacturing
 - Physical characteristics (solubility etc)
 - Can the candidate be produced routinely?
 - Is the cost of the drug(s) reasonable?
 - Is there a GMP process available?
 - Yield of current process?

Questions to consider for clinical development 5

- Clinical Plans

- Is there prior human experience with the study drug
- Has the study been discussed with a clinician
- Does it reflect clinical care based on most recent practice
- Can the study design be integrated in current clinical care
- Rationale for dose selection?
- Rationale for formulation? Route?
- Rationale for duration of treatment?
- Plans for blinding and for avoiding bias in evaluation?
- Number of sites, number of patients per site
- Can reliable measurements be obtained?

Questions to consider for clinical development 6

- Clinical Plans 2
 - What level of training is required for endpoint measurement?
 - Will phase II provide clear go/no go decision point?
 - Is the design efficient? Could question be answered with smaller sample size?
 - Ethical considerations: what does the study contribute to drug development, risk/benefit, patients available, invasiveness of procedures, etc?
 - Is the proposed drug delivery route realistic and appropriate?
 - Safety monitoring plan developed?
 - Estimated direct cost for clinical trial (per patient cost, plus infrastructure cost).

Questions to consider for clinical development 7

- What next after Clinical Trial?
 - Ensured supply of drug?
 - Who would fund next step?
 - Who would fund drug to registration and general availability
 - IP status?

Summary - Who will use TACT?

- TACT is an ambitious group with an aim to be useful and helpful to many different groups.
- For the researcher with interesting preclinical results on a compound –specific advice
- For a clinician, access to toxicology and pharmacology know-how.
- TREAT-NMD hopes that industry will also use TACT as a way to understand the target community more
- TACT will also work with funders to show how a TACT review can add value to a proposal.

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Questions?