

# Therapeutic Targets in the CMDs

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“Therapeutic Targets in the CMDs” was a conference uniquely devoted to the identification and development of opportunities for translational research specifically in the field of congenital muscular dystrophies (CMDs). The primary goal of the workshop was to address, evaluate and achieve consensus on therapeutic targets in the CMDs by bringing together experts with expertise ranging from basic science to clinical trial design in rare disorders.

The conference led to the outline of a CMD roadmap and preliminary prioritization of efforts based on the identification of short term, mid term and long term scientific targets and their development into treatment strategies with strong translational potential

Amongst drugs with potential to enter into clinical trials relatively soon, the anti-apoptotic agents Debio 0025 (debiopharm) and omigapil (santhera) were discussed with potential applicability in the collagen VI and MDC1A CMD forms, recognizing that they treat secondary effects not target primary pathways and therefore at best will decrease rate of disease progression. The antioxidant N-acetyl-L-cysteine (NAC) has shown potential in SEPN1 patient cells and is slated to proceed to clinical trials in SEPN1 patients within the next 2 years. Anecdotal evidence suggests that prednisone may have a beneficial effect in the alpha-dystroglycanopathies similar to its effect in dystrophinopathies, suggesting another immediate clinical trial possibility. The antihypertensive and antifibrotic agent losartan could be of potential use in MDC1A as there is evidence for upregulated TGF beta signaling in human biopsies and the mouse model.

Midrange targets on the translational map included protein therapy with laminin 111 for use in MDC1A patients, either alone or in combination with strategies directed at upregulation of alpha 7 integrin expression. Several screens are directed at upregulation of glycosylation of alpha-dystroglycan are currently actively pursued. Long range targets include stem cell therapy the pharmacological manipulation of regenerative capability of muscle, gene delivery to muscle and gene corrective strategies such as the knock-down of dominant negative mutations in collagen VI .

The conference also explored a number of additional potential targets related to muscle atrophy, necrosis, mitochondrial function, growth factor signaling including myostatin inhibition and the regulation of fibrosis formation.

To help establish an inventory of currently available tools and models, a working group within the conference delineated current parameters used in physiologic assessment of dyw, dy3k and col6a1 knockout mouse ([www.curecmd.org/scientists](http://www.curecmd.org/scientists) ). In addition, a list of dystroglycanopathy mouse models, CMD zebrafish and CMD drosophila models was established ([www.curecmd.org/scientists](http://www.curecmd.org/scientists))

Discussions concerning the readiness for clinical trials readiness in the CMDs centered around innovative clinical trial design and support for the CMD International Registry, to be launched August 2009 and modeled after the DMD patient initiated database curated by Emory Genetics. Discussions included experiences and lessons from previous trials in rare neuromuscular disorders, consideration of innovative trial designs, as well as perspectives provided by the FDA and representatives of pharmaceutical companies with an active investment in neuromuscular disease.

A CMD Toolkit panel led by Dr. John Porter and Dr. Glen Nuckolls from the NIH summarized currently available scientific and clinical resources, including at the NIH and the CDC. Dr. Volker Straub presented TREAT-NMD neuromuscular global resources and discussed the TACT committee focused on preclinical therapeutic candidate review. Currently available genetic resources were highlighted, including high throughput genetic testing for the

CMDs currently being validated at Emory Genetics. Amongst the high priority items necessary for the CMD Toolkit was the development of immortalized cell lines and assays suitable for high throughput screening assays and a continued effort to make standard CMD mouse models available at Jackson laboratories.

Postdoctoral candidates applied for travel grants supported by the conference grant awarded by the NIH. The list of the 5 successful young scientist can be viewed at <http://curecmd.org/scientists/winners>

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Atlanta, Georgia

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