Cystinosis Research Foundation

Lay Abstract Template for Awardees

Please complete this lay-oriented grant abstract form which will be published on the CRF web site, in CRF Star Facts and in the CRF magazine when we announce your grant award. *Please do not exceed 400 words (no more than 1-1/4 page total).* Please submit this form electronically to nstack@cystinosisresearch.org as a Word document.

Principal Investigator (s): PD Dr. rer. nat. Maren Leifheit-Nestler, Dr. rer. nat. Malgorzata Szaroszyk, Prof. Dr. med. Dieter Haffner

Project Title: Cystinosis-associated myopathy: Impact of musclin gene therapy and exercise

Objective/Rationale:
Cystinosis-associated myopathy is a frequent complication in children and adults suffering from nephropathic cystinosis. The direct association between cystinosis and muscle wasting has not yet been adequately investigated and innovative, effective and preventive therapies are of utmost importance. We recently identified that the skeletal muscle-derived myokine musclin (encoded by osteocrin, *OSTN*) is reduced in wasting muscles from *Ctns*$^{-/-}$ mice, which was associated with the induction of cachectic genes suggesting a causative role of musclin deficiency in the pathogenesis of cystinosis-associated myopathy. Interestingly, preclinical studies have shown that musclin can be stimulated by exercise, thereby improving muscle strength in mice. Therefore, we propose that re-induction of musclin in cystinosis restores muscle strength thereby improving cystinosis-associated myopathy.

Project Description:
In this study, we propose to investigate whether a therapeutic re-induction of musclin synthesis in *Ctns*$^{-/-}$ mice via AAV (adeno-associated virus) based gene therapy can mitigate pathological muscle loss in progressive cystinosis-associated myopathy and improve muscle strength, structure and function. By targeting gene therapy with AAV-*Ostn*, we expect to improve muscle health and thereby an important cystinosis-associated comorbidity. In addition, we will evaluate if exercise in *Ctns*$^{-/-}$ mice stimulates musclin synthesis in skeletal muscles thereby reducing myopathy and enhancing physical endurance. As an extension to transcriptional, biochemical and histological analyses of skeletal muscles und kidney function, we also want to assess muscle strength and function by measuring grip strength, tetanic muscle strength, fatigue and endurance capacity *in vivo*. Finally, we will investigate underlying molecular pathways of musclin-mediated improvement of muscle strength, structure and function in *Ctns*$^{-/-}$ mice, with the focus on mitochondrial biogenesis, to generate preliminary data and thus a working hypothesis for future specific studies.

Relevance to the Understanding and/or Treatment of Cystinosis:
The proposed studies address directly the goal of the CRF to find treatments to improve life for cystinosis patients. Data obtained in this project will investigate for the first time the role of musclin in cystinosis-associated myopathy and draw attention to a promising new biomarker that will assess muscle health. At best, musclin could be used as a therapy to counteract muscle wasting and improve muscle strength and overall quality of life with cystinosis.

Anticipated Outcome:
Cystinosis patients present with progressive muscle weakness, impaired grip strength and muscle atrophy despite adequate nutrition, which markedly impairs the quality of life. Our central hypothesis is that re-induction of musclin restores muscle strength and overall muscle health and thereby improves myopathy in cystinosis. We propose to investigate if a re-expression of musclin by AAV-based gene therapy or exercise regenerate muscle strength and ameliorates cystinosis associated myopathy. Of note, should our hypothesis be confirmed, musclin therapy would be a promising intervention to improve muscle health and thereby overall quality of life and psychosocial rehabilitation in cystinosis patients.