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): Justine Bacchetta, MD, PhD

Project Title: Pathophysiology of bone disease in cystinosis: 2024 CYSTEABONE project

Objective/Rationale: Please write a lay-oriented statement of the scientific rationale for this project. Approximately 75-85 words.

Cystinosis metabolic bone disease (CMBD) has a significant impact on patients' quality of life because of an increased frequency of bone pains, deformations, and fractures. Local bone cell dysfunctions contributing to CMBD are still poorly understood, and the goal of the 2024 project is to keep dissecting the molecular mechanisms underlying the intrinsic defects not only in osteoblasts (Ob), the bone forming cells of mesenchymal origin but also in osteocytes, that represent 80% of the cell content of cortical bone.

Project Description: Please write a brief, lay-oriented description of how you will carry out the project. Approximately 125-135 words.

The first aim is to develop an accessible human model of bone forming cells carrying several *Ctns* mutations to study their impact on bone resident cells. We will differentiate induced pluripotent stem cells (iPSC) obtained from cystinotic patients into MSCs; this will allow us to have a closer model to mice model responding to 1,25VD3 and to produce the full range of mesenchymal cell types affected by cystinosis including Obs, myocytes and adipocytes.

The second aim is to study the osteocytes, by exploring lacunar and canalicular network in cortical bone of *Ctns* deficient mice. In order to support the hypothesis of a premature transition shift from osteoblast to osteocyte phenotype of *Ctns* -/- mice Obs, osteocyte and bone aging markers expression will be analyzed, bone formation dynamic parameters being quantified on 3D-reconstruction images.

Relevance to the Understanding and/or Treatment of Cystinosis: Please explain how the project will impact cystinosis treatment or increase our understanding of cystinosis. Approximately 75-80 words.

This model will allow us to better understand the relation between each *Ctns* mutation and specific bone resident cells phenotype. Understanding the premature transition shift from osteoblast to osteocyte phenotype may explain altered bone growth and quality leading to inadequate bone dimension and shape observed in cystinosis, as recently reported in patients.

These new models will keep gathering evidence to propose in the future to cystinosis patients with severe bone phenotype therapeutic perspectives based on antagonizing IL1.

Anticipated Outcome: Please write a lay-oriented description of what you expect to learn/discover. Approximately 75-80 words.

The study of several mature cells affected by *Ctns* mutations will give information on mediators secretion and intra-cellular communication in bone. If proved to be true, the deregulation of sclerostin and osteocalcin in the bone/endocrine axis may open new therapeutic perspectives, especially since osteocalcin has also a crucial role in regulating glucose and energy metabolism, fertility and muscular adaptation to exercise, all fields in which cystinosis induces specific impairment. This is one further step to personalized medicine in CMBD.