UMR_S 1033 Pathophysiology, diagnostic and treatments of musculoskeletal disorders.

Team 3-LYSBONE : Bone and Joint Pathophysiology: Bioactive lipids and mineral metabolism

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Job title: post-doc, INSERM 1033, Lyon, France

Degree required: PhD
Job duration: 2 years
Position to be filled immediately, in all cases before 31/12/2024 (post-doc salary scale Université Claude Bernard Lyon 1)
Research topic: inflammation and X-linked hypophosphatemia (XLH) in the mouse model of the disease and in patient samples (PBMCs).
Key words: rare diseases, nephrology, rheumatology, endocrinology, calcium, phosphorus, XLH, bone
Expected skills: bone biology, cell biology, molecular biology, bioinformatics

Brief description of the project

X-linked hypophosphatemia (XLH) is an orphan genetic disease (1/20 000 live births) most commonly associated with an inactivating mutation in the PHEX (Phosphate-regulating neutral endopeptidase X-linked) gene that induces chronic hypophosphatemia due to increased circulating levels of FGF23. XLH is usually diagnosed at walking age, and is clinically marked by rickets with progressive appearance of lower limb deformities associated with growth retardation, dental abnormalities (mainly abscesses), and often craniosynostosis. In adults, diffuse musculoskeletal disorders are described, associated with asthenia, enthesopathies, significant dental abnormalities and sometimes hearing abnormalities, all of these clinical symptoms having the potential to significantly affect patients' quality of life (QoL) in this genetic disease now considered as systemic.

Using the Reference Center for Rare Diseases of Calcium and Phosphate (CRMR-CAP) and the network from the French OSCAR network, we have initiated a translational program on XLH in Lyon. Notably, using our local and original model of peripheral blood mononuclear cells (PBMCs) directly extracted from total blood of patients, and allowing us to assess non-invasively osteoclasts differentiated in vitro from PBMCs, we have recently showed that XLH patients display a peculiar inflammatory profile as compared to healthy controls, shown both in PBMCs and osteoclasts.

Here we want 1/ to better understand the mechanisms behind obesity, enthesopathies and metabolic abnormalities beginning early in life in XLH, and 2/ to identify potential therapeutic targets for non-classical comorbidities. To do so, we want to evaluate anti-inflammatory approaches using pharmacological agents to prevent or even improve the onset of these complications in the Hyp Mice. We expect that our results will support future clinical trials in XLH.

Here in Lyon we have a structured and innovative research program around XLH. Our main strengths are the existence of the Reference Centre for Rare Diseases of Calcium and Phosphate (coordinated by J Bacchetta) with more than 50 pediatric and adult patients followed in Lyon, the involvement of many different specialists who are all XLH experts in their field working closely with the lab (e.g., renal physiology and functional imaging, odontology, neurosurgery, rheumatology), as well as a recognized lab internationally recognized in bone research (INSERM1033). This already existing network allows us to propose the applicant to create an independent research project on the long-term within our group.

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