

X-linked Hypophosphatemia pathobiology: Local effect of PHEX deficiency in the mineralization process of the extracellular matrix

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X-linked Hypophosphatemia (XLH) is caused by inactivating mutations of the *PHEX* (*phosphate-regulating gene with homology to endopeptidases on the X chromosome*) gene, resulting in severe skeletal deformities and dental manifestations.

In XLH, mineralized tissues disruption is due to a systemic effect associated to a local role of PHEX affecting proteins from the extracellular matrix. Indeed, Elevated FGF23 inhibits the expression of NaPi-IIa and -2c through Klotho/FGF-R complexes in the kidney leading to hypophosphatemia. Our preliminary data show that impaired phosphate homeostasis in XLH at the tissue level is independent of phosphatemia. Recently, PiT2 was shown to modulate FGF23 synthesis and secretion in bone *ex vivo*. The recent discovery of Klotho expression in bone support our hypothesis suggesting that FGF23 is involved in mineralization defect at the tissue level, through Klotho/FGF-R complexes pathway. We aim to decipher non-systemic consequences of PHEX deficiency on mineralization associated to FGF23 i) *in vitro* using a human biomineralization model, consisting in seeding dental pulp cells from patients with XLH and from control individuals into plastically compressed collagenous hydrogels and ii) *in vivo* using the Hyp model to further investigate the interplay between PHEX, FGF23/Klotho, phosphate and PiT2 and the effects of therapeutic strategies.

Application's information:

We are looking for a highly motivated PhD candidate with strong motivation to carry out experimental and basic research with the use of cell and mice models. A solid background in molecular and cell biology, and bone physiology will be the best suited for this project. The candidate will benefit from a highly dynamic and collaborative environment with the participation of Laurent Beck (INSERM U1229, Nantes) and Franck Oury (INSERM, Necker Hospital, Paris).

The candidate should be dynamic, interactive, and contribute to animating team's life, have good communication and English skills, willing to write scientific papers.

Applicants should submit their complete application file (CV, motivation letter and contact of at least two reference scientists) by email to claire.bardet@parisdescartes.fr