1 YEAR POST-DOCTORAL POSITION  
(RENEWABLE 1 YEAR)  
CENTRE DE RECHERCHE DES CORDELIERS, PARIS, FRANCE

Title: Dent Disease – Evolution and treatments

Job offer: A one year post-doctoral position is available (renewable once), under the supervision of Stéphane Lourdel, in the Gilles Crambert team “Renal physiology and tubulopathies”, at the Centre de Recherche des Cordeliers, Paris, France.

The host group explores the cellular and the molecular mechanisms involved in Dent disease type 1, a rare inherited disorder of the proximal tubule characterized by low molecular weight proteinuria, hypercalciuria with nephrolithiasis, and progressive renal failure. The disease is caused by inactivating mutations in the CLCN5 gene encoding the 2Cl-/H+ exchanger ClC-5. Until now, there is no specific treatment. To understand more precisely the cellular and the molecular mechanisms involved in the physiopathology of Dent Disease type 1, we have generated a knock-in (KI) mouse model stably carrying a ClC-5 mutation that belongs to the most frequent class of mutants observed in patients with Dent disease type 1. Our previous investigations demonstrated that expression Lipocalin-2/NGAL in the kidneys of KI mice is increased as the animals become older as well as its circulating levels. In addition, we showed that its urinary excretion is increased in KI mice. Furthermore, a change in tubular expression of Lipocalin-2 was observed. Whereas Lipocalin-2 is expressed in proximal tubule cells of young KI mice, it is strongly expressed in the distal nephron of older KI mice. As well as the 24p3R, a Lipocalin 2 receptor, localized in the distal nephron. Activation of this receptor by Lipocalin 2 leads to internalization of the ligand and subsequent apoptosis of renal tubular cells. Furthermore, Lipocalin 2 is also involved in apparition of renal fibrosis during chronic kidney disease induced by subtotal nephrectomy. In this view, our data revealed that KI mice display progressive renal inflammation and fibrosis. As a whole, our project aims at to further investigate the cellular and molecular mechanisms involved in the evolution of Dent disease type 1, with a particular emphasis of the possible contribution of Lipocalin-2. We also aim at identifying whether Lipocalin-2 could be a relevant therapeutic target to slow down the progression of this disease. So far, no correlation between genotype and phenotype has been established for patients with Dent disease type 1 as several parameters were not taken into account. Therefore, the postdoc will also aim at studying clinical parameters in close collaboration with the hospital.

For the development of this project, the selected applicant will use in vivo and in vitro approaches, and will benefit from the strong expertise of the host laboratory in the analysis of the renal phenotype of transgenic mice, and their exploration at the cellular and the molecular levels. An access to state-of-the-art techniques will be provided in the Centre de Recherche des Cordeliers.

Qualifications and experience: Applicants will hold PhD in Physiology and Physiopathology with strong experience in molecular biology, biochemistry and immunohistochemistry. An official approved training for animal experimenting is required. Skills in renal pathophysiology would be an asset. The selected candidate should be highly motivated, enthusiastic, independent and team-oriented scientist.
**Scientific environment:** The laboratory belongs to the “Centre de Recherche des Cordeliers” (www.crcordeliers.fr) located in Paris. In addition to the scientific environment of this institute, the laboratory has access to extensive research core facilities including an animal facility.

**Contact:** Applicants are invited to send a CV with a list of publications, a summary of research experience, a letter motivation and contact information of referees to stephane.lourdel@sorbonne-universite.fr