Post-doctoral position

The project: Pulmonary arterial hypertension (PAH) is a devastating cause of PH due to a progressive narrowing of the distal pulmonary arteries (<500 μm in diameter) resulting in high pulmonary vascular resistance and right heart failure. PAH is characterized by pulmonary arterial (PA) smooth muscle (PASMC) and endothelial cells (PAEC) dysfunction, leading to their proliferation and resistance to apoptosis, vasoconstriction, inflammation and in situ thrombosis. To date, no cure exists for PAH and mortality after 3 years remains as high as 30-40% despite the available specific therapies that are mainly vasodilators and target PAEC dysfunction.
Recently, inactivating mutations in the KCNK3 gene have been identified in heritable PAH. KCNK3 encodes for an outward rectifier K^+ channel. We have recently demonstrated that KCNK3 dysfunction contributes to the development of heritable PAH (KCNK3 and BMPR2 mutated patients) and unexpectedly to idiopathic, demonstrating that KCNK3 dysfunction is a hallmark of PAH. Moreover, we also showed that KCNK3 dysfunction contributes to the development of experimental pulmonary hypertension (PH), thus providing an *in vivo* model for therapeutic modulation. However, the exact mechanisms linked to KCNK3 deficiency *in vitro* and *in vivo* is still needed in order to identify the right target for ion channel therapy directed to KCNK3 or downstream KCNK3 signaling pathway, which is the purpose of the proposal. It is important to emphasize that mouse is not a suitable model to study the role played by KCNK3 in PH. Indeed, KCNK3 does not form a functional channel in mouse PASMC and is replaced in mouse by KCNK6 channels. This is why we generated *Kcnk3*-deficient rats using CRISPR-Cas9 technology.

This project has three main objectives, which address fundamental, experimental and preclinical questions related to KCNK3 in the pathobiology of PAH.

Objective 1: Deciphering the role of KCNK3 channel in the regulation of proliferation/apoptosis imbalance and understanding the role of pro-inflammatory environment in the regulation of KCNK3 expression in PAH
Objective 2: Confirming the key role of KCNK3 in PAH using unique *Kcnk3*-deficient rats
Objective 3: Identifying an Ion Channel Therapy for PAH

Your profile: Candidates must have a PhD in electrophysiology, ion channels, solid background in cell and molecular biology and in physiology, interest in translational research, good publication record and excellent references.
Required skills: Autonomy, creativity, critical spirit, rigor, enthusiasm, organization, team spirit.

Temporary 2 years position, in Le Plessis-Robinson (92), INSERM U999 Hopital Marie Lannelongue 92350 le plessis robinson, France.
Starting date: beginning of January 2019
Financial support: ANR JCJC-2018 KAPAH ; KCNK3 channel A new therapeutic target in Pulmonary Arterial Hypertension
Principal investigator: Fabrice Antigny

Candidates must send the following documents as a single pdf file (multiple documents sent will not be taken into account) to antignyfabrice@gmail.com

- Cover letter including a motivation statement (1 page max)
- Detailed CV, including a summary of candidates research experience
- List of publications and communications
- Names of 2 referees qualified to provide a recommendation letter