Call for Post-Doctoral position

Starts in 1st December 2011, 24 months
INSERM UMR 643 unit, Nantes, France

Title:
Pre-clinical application of patient-specific induced pluripotent cells for treatment of inherited metabolic liver diseases.

Human somatic cells such as fibroblasts can be reprogrammed into induced pluripotent stem cells (hiPSC) after transduction of exogenous factors such as Oct3/4, Sox2, Klf4 and c-Myc. Human iPSC have the ability to self-renew and differentiate into cell types derived from the three primordial germ line, ectoderm, mesoderm and endoderm. We have recently demonstrated that hiPSC can be generated from patients suffering metabolic inherited diseases, including familial hypercholesterolemia and Crigler-Najjar disease and subsequently be differentiated with high efficiency into hepatocytes modeling the human liver disease in vitro. Because patient-specific gene/cell therapy would avoids cell rejection and the need for immunosuppression, when long-term hepatocyte engraftment is necessary, hiPSC thus provide an excellent model to establish proof-of-concept that genetic defects can be corrected in vitro by vectors that express the missing or defective genes. Additionally, the therapeutic potential of the resulting cells can be tested in animal models of inherited human liver diseases, paving the way for "personalized medicine".

The project aims to:

(i) Correct in vitro the metabolic deficiency in hepatocytes generated from Crigler-Najjar patient-derived hiPSC

(ii) Assess the therapeutic potential of corrected hiPSC-derived hepatocytes in animal model modelling Crigler-Najjar disease.

Aim 1:
The objective is to provide the proof-of-principle that the genetic basis of certain inherited metabolic disorders can be corrected in vitro such that patient-specific hiPSC obtained from affected individuals can be differentiated to fully mature hepatocytes. The diseases to be addressed include Crigler-Najjar caused by mutations in the gene that encodes bilirubin uridinediphosphate-glucuronosyltransferase (UGT1A1) resulting in hyperbilirubinemia. Genetic modification of hiPSC will be performed by lentiviral vectors, or by gene editing using zing finger nuclease to correct deficiencies caused by the inherited mutations.

Aim 2:
The objectives are to demonstrate that corrected hiPSC-derived hepatocytes can (i) engraft and proliferate when transplanted in the liver of the immunosuppressed Gunn rat, the animal model of Crigler-Najjar type 1, and (ii) achieve correction of the metabolic defect of transplanted Gunn rats.

These studies will be conducted in a collaborative FP7 European network aimed at designing of personalized approaches to treatment of liver disease.

The Postdoc position will cover two years of research activity beginning on 1st December 2011 in a strong research environment. Participations to local seminars and national as well as international meetings will be covered. Further funding for additional years from other sources may be available.
The highly-motivated Postdoc candidate will conduct the project in the team of Dr Nguyen Tuan Huy and Anegon Ignacio (INSERM UMR 643 unit, Nantes, France) and in close collaboration of the laboratory of Dr Ludovic Vallier (University of Cambridge, UK) and of Anne Weber (INSERM U972 unit, Kremlin-Bicêtre, France).

The INSERM unit UMR 643 comprises laboratories and animal facilities (altogether ~3,000 m²). Clinical and research areas as well as meeting and teaching rooms are housed in the same Hospital building, which is located within the Nantes University Hospital. The institute is part of a local research institute (IFR 26) bringing together several other INSERM units and houses more than 750 faculty staff with several core facilities (e.g. confocal imaging, DNA microarrays, production of viral gene vectors). The INSERM unit UMR 643 is presently staffed by 130 people organized into 6 teams and houses several core facilities (Q-PCR, high-speed cell sorting, microsurgery, protein and antibody purification, rat transgenesis).

More detailed information can be found at http://www.ifr26.nantes.inserm.fr/ITERT/.

The city of Nantes offers an active cultural environment, and is conveniently located within 45 min drive (or train) from some strikingly beautiful sea resorts located on the West Coast and 2 hours train from Paris.

The post-doc candidate should have skills in cell culture, lentivectorology and animal experiments. Experiences in iPS or ES (human or other species) will be highly appreciated.

The application should be sent electronically to Tuan.Nguyen@univ-nantes.fr before 1st November 2011 and should include:

☐ a cover letter with
  ☐ a short description of achievements
  ☐ a short statement on career planning
☐ a CV with a complete list of publications and abstracts to international meetings
☐ two letters of reference/ or a list of 2 references with contact information (institution, email address, phone number)