

**ECOLE DOCTORALE BIOCHIMIE, BIOTHERAPIES, BIOLOGIE MOLECULAIRE,
INFECTIOLOGIE
B3MI**

Proposition de sujet de thèse
(Début de thèse : Septembre 2009)

Fiche thèse Documents administratifs

Renseignements relatifs à l'Equipe d'Accueil

Libellé de l'équipe d'accueil : **Biologie Physico-Chimique des Protéines Membranaires (LBPCPM)**

Nom et prénom du responsable (HDR) : **POPOT Jean-Luc**

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Nombre de doctorant(e)s encadré(e)s par le responsable : **1 (soutenance juillet 2009)**

Renseignements relatifs à l'Unité de recherche

Numéro, libellé et organisme : **UMR 7099 Laboratoire de Biologie Physico-Chimique des Protéines Membranaires (LBPCPM)**

Rattachement (Paris Diderot, Paris Descartes): **Université Paris-Diderot/CNRS**

Nom et prénom du directeur de l'Unité : **MIROUX Bruno**

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Spécialité principale (une seule):

Biomolécules, Biologie Structurale, Pathologies, Biothérapies

Spécialité secondaire (une seule) :

Microbiologie procaryote et eucaryote

Renseignements relatifs au sujet de thèse

Nom et prénom du directeur de thèse (HDR) : **MIROUX Bruno**

Téléphone : **0158415225** Email : **miroux@ibpc.fr**

Thèses en cours (étudiants rattachés à B2M/B3MI) : **0**

Thèses soutenues depuis 2006 (Titre, nom de l'étudiant) : **0**

Titre du sujet proposé en français et en anglais:

**The Mitochondrial Uncoupling Proteins: identification of regulating ligands and protein partners
Les protéines découplantes mitochondriales : identification de ligands et de partenaires protéiques**

Résumé du sujet de thèse (en anglais uniquement) : (1/2 page maximum)

The Uncoupling Proteins (UCPs) belong to the mitochondrial anion transporters family. UCP1 is highly expressed in brown adipose tissue and mediate non shivering thermogenesis by dissipating the electrochemical proton gradient across the inner mitochondrial membrane. UCP1 is a key gene for energy expenditure in rodent and may be a target gene in human to increase energy expenditure in obese patient. UCP2, present in many tissues of adult human including immune cells and neurones, is involved in reactive oxygen species regulation and in the metabolic regulation of glycolytic cells by promoting fatty acid oxidation¹. Mice lacking UCP2 are more resistant toward infection but more sensitive toward chronic inflammatory diseases such as atherosclerosis² or multiple sclerosis³. At the molecular level the situation is confusing because unlike all the mitochondrial anions transporters of the family, the UCPs may facilitate cations (H⁺) transport. In addition it has been shown that UCP1 is negatively regulated by CIDEA a scaffolding protein involved in apoptosis⁴. The aim of the project is to understand the structure function relationship of these proteins by:

1. a systematic search of protein partners using pull down assay coupled to mass spectrometry⁵ (collab. with Necker proteomic platform)
2. a systematic search of regulating ligands that might be of therapeutic uses.

To achieve these objectives, the native UCP1 from brown adipose tissue will be used and *E. coli* and yeast recombinant systems will be further developed in order to obtain sufficient amount of UCP2. For instance the use of amphipols, amphiphil molecules produced in house that maintain membrane proteins in solution, to refold recombinant UCPs inclusion bodies will be investigate as it is a well established method in the laboratory⁵. A functional test is also available⁶ and biophysical characterisation of the recombinant UCPs is accessible through external collaborations (CEA, Saclay, IBS, Grenoble). At the end of the PhD, the candidate can expect to have acquired a strong background in molecular biology and membrane protein chemistry

References:

1. Pecqueur, C.;Bui, T.;Gelly, C.;Hauchard, J.;Barbot, C.;Bouillaud, F.;Ricquier, D.;Miroux, B.;Thompson, C. B. Uncoupling protein-2 controls proliferation by promoting fatty acid oxidation and limiting glycolysis- derived pyruvate utilization. *Faseb J* 2008, 22, 9-18.
2. Blanc, J., Alves-Guerra, M.C., Esposito, B., Rousset, S., Gourdy, P., Ricquier, D., Tedgui, A., Miroux, B. and Mallat, Z. (2003) Protective role of uncoupling protein 2 in atherosclerosis. *Circulation*, **107**, 388- 390.
3. Vogler S, Pahnke J, Rousset S, Ricquier D, Moch H, Miroux B, Ibrahim SM. (2006) Uncoupling protein 2 has protective function during experimental autoimmune encephalomyelitis. *Am J Pathol.* 2006 **168**, 1570-5.
4. Bensalem, N., Masscheleyn, S., Mozo, J., Vallée, B., Brouillard, F., Trudel, S., Ricquier, D., Edelman, A., Guerrero, I. C., and Miroux, B. (2007) High Sensitivity Identification Of Membrane proteins by MALDI-TOF-Mass Spectrometry Using Polystyrene beads *Journal of Proteome Research* **6**, 1595-602.
5. Charvolin D, Perez JB, Rouvière F, Giusti F, Bazzacco P, Abdine A, Rappaport F, Martinez KL, Popot JL. (2009). The use of amphipols as universal molecular adapters to immobilize membrane proteins onto solid supports. *Proc Natl Acad Sci U S A.* 2009 Jan 13;106(2):405-10.
6. Mozo J, Ferry G, Masscheleyn S, Miroux B, Boutin JA, Bouillaud F. (2006) Assessment of a high-throughput screening methodology for the measurement of purified UCP1 uncoupling activity *Anal Biochem.* **351**, 201-6.