Sciences de la Vie et de la Santé
Master BMC, Universités Paris Descartes – Paris Diderot

Parcours : **Biologie et Développement Cellulaires**
http://www.master2bdc.fr/
Fiche de Projet de Stage M2, Année 2020-2021

Insitut Cochin, INSERM U1016 **Receptor Signalling & Molecular Scaffolds** **ED d'appartenance : BioSPC** **Responsable de l'Equipe : S. Marullo**	**Responsable du Stage :** **Mark SCOTT** Institut Cochin, 27 rue du Fg St Jacques, 75014 Paris Email : mark.scott@inserm.fr Tel : 01 40 51 65 48

Titre du projet : A new molecular partner for Tumour Suppressor PTEN: implications for cell polarity and migration

Résumé du Projet de Stage (en 300 mots maximum, mots clés en gras)

Our group studies the regulation of important cellular communication pathways and how these may go awry in cancer settings. We have a particular interest in the **Tumour Suppressor PTEN.** PTEN is a non-redundant **phosphatase** that dephosphorylates the lipid phosphatidyl (3,4,5) trisphosphate (PIP3) and thus inhibits the pro-proliferative **PI3K/AKT signalling** pathway. By opposing the PI3K/AKT pathway, PTEN regulates many key **cell fate** decisions such as **proliferation**, **survival** and **motility**. These processes often go awry in **cancer** leading to inappropriate cell growth, migration and invasion.

Regulation of PTEN levels, localization and activity are subject to tight control: PTEN expression is controlled transcriptionally, post-transcriptionally via oncogenic miRNAs, and also at the **post-translational level** by phosphorylation, oxidation, acetylation, ubiquitination as well as **protein-protein interactions**. While the *PTEN* gene is mutated in a wide variety of human cancers, downregulation of PTEN activity can also occur via changes in posttranslational regulaion, in the absence of any *PTEN* gene alteration.

Following yeast 2-hybrid screening of a **breast cancer** cDNA library using PTEN as bait, we have identified a key **polarity protein** as a new molecular partner for PTEN. The project will involve investigating the effect of targeted gene disruption of *PTEN* and partner on signal transduction, cell polarity and migration, using breast cancer cell lines. The regions involved in PTEN-partner interaction will also be mapped using biochemical approaches. Techniques that will be used include yeast 2-hybrid, co-immunoprecipitations, BRET, gene targeting and cell migration assays.

Publications de l'équipe, relatives au stage proposé

-Kotelevets L, Trifault B, Chastre E and **Scott MGH.** Post-translational regulation and conformational plasticity of PTEN. **Cold Spring Harbor Perspect Med.** doi: 10.1101/cshperspect.a036095 (2020).

-Alexander R, Lot I, Saha K, Abadie G, Lambert M, Decosta E, Kobayashi H, Beautrait A, Borrull A, Asnacios A, Bouvier M, **Scott MGH**, Marullo S, and Enslen H. Beta-arrestins operate an on/off control switch for focal adhesion kinase activity. **Cell Mol Life Sci.** doi: 10.1007/s00018-020-03471-5 (2020).

-Javadi A, Deevi RK, Evergren E, Blondel-Tepaz E, Baillie GS, **Scott MGH** and Campbell FC. PTEN controls glandular morphogenesis through a juxtamembrane β-arrestin1/ARHGAP21 scaffolding complex. **eLife** 6. pii: e24578 (2017).

-Misticone S, Lima-Fernandes E and **Scott MGH**. Rapid detection of dynamic PTEN regulation in living cells using intramolecular BRET. **Methods Mol Biol.** 1388: 95-110 (2016).

-Paradis, JS, Ly S, Blondel-Tepaz E, Galan, JA, Beautrait A, **Scott MGH**, Enslen H, Marullo, S, Roux PP and Bouvier M. Receptor sequestration in response to ERK1/2-mediated phosphorylation of βarrestin-2 determines steady-state levels of GPCR cell surface expression. **Proc Natl Acad Sci U S A.** 112 E51160-8 (2015).

-Lima-Fernandes E, Misticone S, Boularan C, Paradis JS, Enslen H, Roux PP, Bouvier M, Baillie GS, Marullo S and **Scott MGH**. A biosensor to monitor dynamic regulation and function of tumour suppressor PTEN in living cells. **Nat Commun**. 5:4431 (2014).

-Lima-Fernandes E, Enslen H, Camand E, Kotelevets L, Boularan C, Achour L, Benmerah A, Pitcher JA, Chastre E, Etienne-Manneville S, Marullo S and **Scott MGH**. Distinct functional outputs of Tumor Suppressor PTEN signaling are controlled by dynamic association with β-arrestins. **EMBO J** 6; 30, 2557-2568 (2011).