We are seeking for a highly motivated **PhD thesis candidate** with background and interest in GPCR pharmacology, therapeutic antibodies and/or reproduction. The student, holding a master degree in biology or equivalent, will benefit from a stimulating interdisciplinary environment. A 3 year funding is available from October 2016.

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Title: Exploration and modulation of FSH receptor transduction efficacy using antibody fragment conjugates

Summary:

Follicle stimulating hormone (FSH) plays a major role in the reproductive fonction both in male and female. Hormonal treatments aiming at controlling reproduction which are widely used in human medicine as well as in farm animals, lead to FSH receptor (FSHR) activation. Current treatments are hampered by significant issues (ovarian hyperstimulation syndrome in patients; sanitary hazard/immunogenicity in farm animals). From a mechanistic stand point, FSHR activation triggers the Gαs, cAMP, PKA, CREB pathway but also promote the assembly of signaling platforms on β-arrestins recruited to the active FSHR. The physiological relevance of β-arrestin-dependent pathway in reproduction remains poorly understood. In this thesis, we propose to develop original tools combining the exquisite specificity and affinity for FSHR carried by antibody fragments on the one hand to selective pharmacological modulations allowed by small molecule ligands on the other hand. For several decades, the development of pharmacological ligands at G protein-coupled receptors (GPCR) has been mainly based on medicinal chemistry. Over the last few years, alternative strategies for GPCR targeting have come to the fore and have notably led to the development of antagonist antibodies. In parallel, pharmacological agents combining antibodies and small chemical ligands are regaining considerable attention and are known as ADC (antibody-drug conjugates). So far, this strategy has been applied to therapeutic targeting of tumors. In this thesis, we propose to adapt the ADC concept to the pharmacological modulation of FSHR. By doing so, we should generate original pharmacological tools which will allow us to explore the relative contributions of cAMP and β-arrestin-dependent pathways in animal models.

The BIOS group already has in-house expertise in structural bioinformatics which will allow the determination of epitopes corresponding to the antibody fragments available as well as the rational design of optimal linkers. The chemical synthesis steps which will be necessary to grafting small molecule ligands to the antibody fragments, will be carried out in collaboration with Marie-Claude Viaud-Massuard's group (UMR GICC, Tours) which has expertise in ADCs' chemistry. All the expertise, equipment and models necessary to biochemical and pharmacological characterization *in vitro* as well as *in vivo* are already available in the BIOS group.