# French Polytech network form for PhD Research Grants from the China Scholarship Council

This document describes one of the PhD subjects proposed by the French Polytech network. The network is composed of engineering schools/universities. The document also provides information about the supervisor.

| Supervisor information | |
|---|---|
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| **Country** | France |

| PhD information | |
|---|---|
| **Title** | **Genetic and molecular dissection of signaling pathways driving endometriosis** |
| **Main topics regards to CSC list (3 topics at maximum)** | III-12 Health of reproduction; |

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| **Required skills in science and engineering** | Master degree in biology or biomedicine; skills in molecular and cellular biology; good level of English; knowledge in developmental biology and mouse genetics are not required, but are considered a plus |

# Subject description (two pages maximum including biblio)

*Context:* The endometrium is a unique tissue that under the influence of hormones undergoes successive phases of growth, differentiation and shedding during the menstrual cycles. Endometrial cells can undergo retrograde migration to end up in the peritoneal cavity where they may permanently attach to the mesothelial lining. As these ectopic cells maintain their endometrial identity they will also respond to hormone signals thus causing cyclic growth, secretion and bleeding at ectopic sites, a disease termed endometriosis. **Endometriosis is a chronic disease that affects up to 10% of women worldwide with patients suffering from severe, life-impacting pain during menstrual periods and a high risk of infertility** [1]**.** In addition to the devastating effects on the patient's life, endometriosis also has an enormous economic impact with an estimated cost as high as $78–119 billion annually in the US alone. Urgent action is therefore required.

In recognition of the endemic nature of endometriosis, the French government has launched a call to build a multidisciplinary consortium to gain a better understanding of the origins of this disease and to develop novel approaches for diagnosis and treatment. Our lab is interested in the molecular signalling pathways driving normal organ development and tissue homeostasis and over the past decade we have worked on a variety of organ systems including kidneys, adrenals and the reproductive system (see Refs. [2–7] ). Our team has been selected to be part of the endometrium consortium to study the molecular events involved in the normal and pathogenic state.

*Objectives and methodology:*

Endometrial growth and secretion during the menstrual cycle are regulated by sex hormones involving primarily estrogens and progesterone. During the proliferative phase, estrogens activate stem cells in a process that is believed to involve stromal-epithelial interaction and the induction of the WNT/beta-catenin signalling pathway. Estrogen and WNT signalling has also been identified as a major risk factor for endometriosis and genetic studies in large patient cohorts (GWAS studies) have revealed GREB1, a direct downstream target of estrogen signalling, and WNT4 as endometriosis associated genes [8]. Aim of the present PhD project is to further dissect some of the key players involved in these two signalling pathways in normal endometrial growth and secretion and study their involvement in endometriosis. To achieve these goals a wide range of technologies will be employed. Expression patterns of members of the estrogen and members of the WNT/beta-catenin pathways throughout the menstrual cycle will be determined using scRNA-Seq and RNA-Scope analysis in mouse and human tissue, and their potential deregulation in endometriosis evaluated using a unique set of tissue arrays from human patients. Direct

targets of estrogen signaling will be identified using ChIP-Seq analysis. Functional analysis of key genes involved in the menstrual growth phase will be performed using conditional gene targeting in mice and human organoids (CRISPR-Cas9 approaches).

*Expected impact:* Taken together the here proposed studies will provide important insights into the complex regulation of endometrial biology and endometriosis. Our molecular studies will identify key molecules and reveal regulatory cascades involved in endometriosis. In the long run this knowledge may help us to identify novel avenues towards therapeutic interventions.

**References:**


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3. Grabek, A., Dolfi, B., Klein, B., Jian-Motamedi, F., Chaboissier, M.-C.C., and Schedl, A. (2019). The Adult Adrenal Cortex Undergoes Rapid Tissue Renewal in a Sex-Specific Manner. ***Cell Stem Cell*** *25*, 290-296 e2. https://doi.org/10.1016/j.stem.2019.04.012.
4. Bandiera, R., Vidal, V.P.I., Motamedi, F.J., Clarkson, M., Sahut-Barnola, I., vonGise, A., Pu, W.T., Hohenstein, P., Martinez, A., and Schedl, A. (2013). WT1 Maintains Adrenal-Gonadal Primordium Identity and Marks a Population of AGP-like Progenitors within the Adrenal Gland. ***Dev Cell*** *27*, 5–18. https://doi.org/10.1016/j.devcel.2013.09.003.
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7. Motamedi, F.J.F.J., Badro, D.A.D.A., Clarkson, M., Lecca, M.R.R., Bradford, S.T.S.T.S.T., Buske, F.A.F.A., Saar, K., Hübner, N., Brändli, A.W.A.W., Schedl, A., et al. (2014). WT1 controls antagonistic FGF and BMP-pSMAD pathways in early renal progenitors. ***Nat Commun*** *5*. https://doi.org/10.1038/ncomms5444.
8. Rahmioglu, N., Mortlock, S., Ghiasi, M., Møller, P.L., Stefansdottir, L., Galarneau, G., Turman, C., Danning, R., Law, M.H., Sapkota, Y., et al. (2023). The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions. ***Nat Genet*** *55*, 423–436. https://doi.org/10.1038/S41588-023-01323-Z.