The principal goal of this project is to check the functionl implications of all the nuclear and membrane progesterone receptors in order to understand the biology of uterine leiomyomas and to determine the molecular mechanisms underlying the progesterone (P4) and selective progesterone receptor modulators (SPRMs) action in leiomyomas and uterine leiomyoma cell lines.

Uterine leiomyomas are common benign uterine smooth muscle tumors affecting 60 to 80% of women at their reproductive age and are the leading indication for hysterectomy occurring in reproductive age females. Leiomyomas in symptomatic women may cause excessive menstrual bleeding, anemia and pelvic pain. Biology, as well as the causes of leiomyomas development is not yet fully understood. The key factors for leiomyomas growth are gonadal steroid hormones, estrogen (E2) and P4. It is already established that in leiomyomas compared with normal myometrium expression of nuclear progesterone receptors is increased. P4 may induce proliferation, increase extracellular matrix (ECM) production and inhibit apoptosis in leiomyomas cells.

Current medical treatments of leiomyomas include progestins and selective progesterone receptors modulators (SPRMs), oral contraceptives, nonsteroidal anti-inflammatory drugs, tranexamic acid and gonadotropin-releasing hormone agonists. Medical therapies mainly work through inhibiting estrogen or progesterone production/action. Unfortunately, leiomyomas often regrow after the treatments end. It has been shown that a SPRM, mifepristone, reduces proliferation of leiomyoma cells. Additionally, another SPRM ulipristal acetate (UPA), recently received approval of the European Medicine Agency for treatment of leiomyoma. The UPA has been shown to effectively reduce leiomyomas size due to its anti-proliferative, anti-fibrotic and pro-apoptotic activity. In some cases even could temporarily reduce the leiomyomas symptoms. However, the precise functional roles of SPRMs in leiomyomas biology are still incompletely examined.

In this project, we will use cells and tissues cultures of uterine leiomyomas and normal myometrium and advanced molecular biology techniques. The following research tasks will be carried out: 1) characterization the expression profile of all progesterone receptors (PGRs/mPGRs) and SPRMs antagonist/agonist effects on their expression in leiomyomas before and after PGRs/mPGRs gene silencing; 2) study of the potential interaction between PRs, P4, SPRMs and their coactivators/corepressors; 3) study of P4 and SPRMs effects on the RhoA activity; 4) study of P4 and SPRMs effects on lysophosphatidic acid receptors (LPARs) gene expression; 5) study the P4 and SPRMs effect on ECM-related genes expression; 6) selection and further study of the potential interaction between P4, SPRMs, PRs and specific miRNAs; 7) study of the putative activation of cell death pathways by SPRMs through PRs. Proposed study of P4 and SPRMs mechanism of action in leiomyomas may be very important for understanding the mechanistic interplay between all the PRs, P4, SPRMs and downstream regulators. These finding will tell us about the leiomyoma cells biology. These results might have a significant human clinical relevance and could be very promising in better future treatment strategies for leiomyomas. We will disseminate our results from this project through publication in high quality medical journals and during scientific medical international conferences. We expect that for scientific and medical environments our findings will be very promising and could contribute in better treatment strategies of human leiomyomas using SPRMs by highlighting the biological aspects.