MOLECULAR MECHANISMS INVOLVED IN FEMALE REPRODUCTION WITH IMPLICATIONS IN INFERTILITY, CONTRACEPTIVE DEVELOPMENT, CANCER & OTHER DISEASES.

Dr. Malini Laloraya

Rajiv Gandhi Centre for Biotechnology, *Thiruvananthapuram*

The most vital phenomenon for continued existence of man-kind is the ability to reproduce. Defects in reproduction, involving both the male & female partners, result in the inability to procreate which is classified as infertility. The study of embryo implantation is central to understanding female infertility as this is the most challenging event faced by clinicians in infertility clinics and is a major reason associated with low success rates of assisted reproduction. It's estimated that roughly "three-quarters of all embryos (70%) fail to dock successfully in the uterine lining". Also despite several efforts we are still way behind in the development of a contraceptive vaccine till date. This is largely due to our inability to understand embryo implantation. Although other countries might not have the need for development of contraceptive drugs, it should remain a high priority for countries facing a population explosion (eg. India & China). Thus, reproduction research holds a special place in the context of our country.

In mammals, successful implantation of the embryo is decided by the right stage of the invasive embryo, the accurate priming of the uterus by ovarian steroids, estrogen & progesterone, creating a transient and tightly regulated ***'window of receptivity'*** and an intimate 'crosstalk' between these two interacting partners. This intricate process is governed by multiple signaling mechanisms cascading the events related to the activation of several genes which are important for the success of the phenomenon. My lab's goal is to identify crucial steroid regulated pathways involved in creating an active maternal embryo dialogue during implantation leading to a successful pregnancy.

Our group was the pioneering lab to implicate a beneficial role of superoxide radical under an estrogen switch in female reproduction and establish abrogation of pregnancy by superoxide quenchers. This opens up a new vista to female fertility control without playing with the normal hormonal/immune system. Superoxide radical is a free radical which was widely publicized earlier for its detrimental role in various diseases but is now established to be critical in signal transmission.

Recent investigations on Estrogen receptor (ER) mechanisms highlight the complexities in gene regulation by estrogens, including many protein-protein interactions mediated via ER and its co-regulators. It is extremely crucial to understand the mechanism of estrogen action as devising drugs that target estrogen signaling pathway are key for contraception, menopausal symptoms & breast cancer therapy. We have identified new partners in the ER network and have shown that the association leads to increased tumorigenesis in vitro implying its role in pregnancy and cancer, two events which share parallels in growth, adhesion, invasion and immune tolerance.

Our lab has made recent progress in identification of protein networks of receptivity using proteomic technologies. We have also elucidating the function of these molecules in embryo implantation using computational and gene silencing technologies. Of interest is the modulation of sub-cellular protein distribution in order to regulate signaling. These studies would help us identify new biomarkers of uterine receptivity or contraceptive targets. We have also identified miRNA signatories in infertile women in order to test the sentinel principle whether changes in target tissue during a metabolic disorder are associated with changes in blood. This would greatly advance infertility diagnosis, assist in reproductive health management in future and aid in identifying contraceptive targets.