My research interests center around deciphering Molecular Mechanisms involved in Embryo Implantation and Metabolic syndromes particularly Polycystic ovary syndrome (PCOS).

Implantation Research: One of the most vexing causes of infertility is the failure of the embryo to implant in the uterus. It's estimated that roughly three-quarters of all embryos fail to implant properly. Our group focuses on deciphering the basic molecular mechanisms underlying the process of embryo implantation. I pioneered the work on beneficial role of free radicals as early as 1990's by trapping superoxide in uterus using Electron Spin Resonance Spectroscopy. We found an estrogen-sensitive spurt in NAD(P)H oxidase-generated superoxide at the window of embryo implantation which is important in 'tissue remodeling, specifically the 'endometrial membrane fluidity' and triggering 'zona hatching' during implantation. The abrogation of pregnancy by superoxide quenchers represents their novel therapeutic potential. We now focus on the mechanistic aspects of superoxide action on uterus and embryo during implantation. In addition, we also reported the formation of a free radical iodine intermediate in the course of tyrosine iodination during Thyroid hormone synthesis. During 1994-96, I identified a 32.6kDa progesterone-induced protein in Koide Lab at Population Council, Rockefeller University, NY, USA. Later, she was involved in proving the contraceptive efficacy of anti-progestin RU486 (Mifepristone) (The abortion Pill) at DAVV (Indore, India) via the Rockefeller Foundation and CONRAD grants.

For implantation studies, my group utilizes various *in vivo* mouse models, *in utero* gene silencing approaches, and spheroid models. We showed that estrogen-arbitrated endometrial epithelial E-cadherin expression was a key driver of embryo adhesion. Our findings about the indispensable role of DOCK180-AIRE nexus in decidualization represent an advance in our knowledge of decidual complications in *pregnancy (pre-eclampsia/pre-term loss). This work has been translated by clinicians in improving the treatment regime by including low dose aspirin for APECED patients to prevent hypertension related disorder which led to the first ever successful pregnancy in an APECED patient. This has led us to study Pre-eclampsia using OMICS tool. Our group is currently studying Recurrent Implantation* Failure (RIF) using OMICS tools and endometrial organoids. Our eventual target is to improve the diagnostic tools of uterine receptivity.

Nuclear-Initiated Steroid-Signalling (NISS) - Embryo implantation events are dictated by a 'nidatory' estrogen surge on a progesterone background which determines the *'window of uterine receptivity'*. Estrogen mediates steroid hormone-initiated cellular signaling via nuclear receptor ERα in the uterus. We identified the nuclear estrogen receptor interactome in the uterus at the WOI. My group identified new nuclear ERα interacting partners viz., CrkL as its co-activator modulating tumorigenesis; SOS1 as a Moonlighting protein with novel HAT activity orchestrating EMT, estrogen-facilitated STAT3-MCl1 interaction resulting in improving our understanding of epithelial-mesenchymal transitions suggesting that during embryo implantation transitions between EMT-pEMT-MET lead to cellular plasticity.

Polycystic ovarian syndrome (PCOS) Research: The second program in my laboratory focusses on understanding metabolic syndromes involving aberrant insulin signalling viz., polycystic ovarian syndrome and diabetes. My work in collaboration with Jin-Xiong She on T1D identified a mutant *Stat5b* and its rescue by CrkL. We have advanced this work using a systems biology approach to elucidate the role of Stat*5b* in diabetic pathology. My groups work on PCOS established an immune etiology for PCOS showing low Tregs due to reduced FOXP3 orchestrated by inappropriate STAT5B/NOS and AIRE/HIF1 axis opening up newer vistas in PCOS management. Using a systems biology approach by integrating miRNA-

mRNA networks, we have identified key dysregulated pathways in PCOS pathogenesis. We have recently shown that impaired peripheral circadian gene expression alters peripheral conversion of androgen synthesis highlighting the importance of chronobiology-based interventions in PCOS. The increasing prevalence of PCOS could be attributed to the rising frequency of insufficient sleep among women due to night-shift work, emphasizing the desideratum of sleep management as an important strategy in PCOS therapy. Our work warrants the need for a public policy framework for regulating night-shift work. **My current research aims to decipher metabolic signatures of PCOS.**