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IN REPRODUCTIVE AND CHILD HEALTH

वार्षिक प्रतिवेदन Annual Report 2023-2024



आई सी एम आर - राष्ट्रीय प्रजनन एवं
बाल स्वास्थ्य अनुसंधान संस्थान

ICMR - National Institute for Research
in Reproductive and Child Health

राष्ट्रीय प्रजनन एवं बाल स्वास्थ्य
अनुसंधान संस्थान

National Institute for Research
in Reproductive and Child Health



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ANNUAL REPORT

2023-2024

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Director

ICMR-National Institute for Research in Reproductive and Child Health, Parel, Mumbai 400012, India

Tel.: (022) 24192002, 24192100

Fax: (022) 24139412

E-mail: dir@nirrch.res.in

Website: www.nirrch.res.in

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From the Desk of the Director...

“No one can whistle a symphony. It takes an orchestra to play it.”

- H. E. Luccock

The symphony of ‘Science’ at the ICMR - National Institute for Research in Reproductive and Child Health has always been in sync with the vision of the Council and in tune with the national health priorities. Our scientists, students and support staff played their roles in this orchestra with elan this year too. Annual report for 2023-24 is a brief account of the research endeavors of our scientists and students in the areas of women’s health, maternal health, child health, paternal contribution to pregnancy losses, infections, drug discovery and also sums up our efforts in the areas that have been of pertinence to the under-served populations.

Our research on Polycystic Ovary Syndrome (PCOS) demonstrated that women with PCOS are more prone to a procoagulant state as compared to women without the disease. We identified 305 rare variants in 253 genes associated with PCOS. These variants are linked to ovarian steroidogenesis, insulin resistance, and insulin secretion. This has expanded the genetic susceptibility landscape of Indian women with PCOS. A comprehensive database on Premature Ovarian Insufficiency (POI) was also developed. This database compiles information on 166 genes associated with POI. Our ECGRI study, the largest in India with standardized recruitment (WERF-EPHect), identified geographic differences in endometriosis lesion types among Indian women. The findings underscore the need for multidisciplinary endometriosis care centers across India. Genome-wide epigenetic studies on the male partners of idiopathic recurrent pregnancy loss (iRPL) cases revealed differentially methylated landscapes in the sperm genome, thereby highlighting the role of paternal factors in pregnancy losses. An animal model of male hypertension was developed and their fertility assessments revealed a significant reduction in sperm count and an increase in abnormal sperm morphology. This indicates an impact of systemic detangements on reproductive parameters.

A study on *Mycoplasma genitalium* infection among women attending STI clinics revealed a significant prevalence of this emerging STI. A gene regulating arginine metabolism was identified for its role in the growth of candida. Further, a mutant of candida knocked down for this gene demonstrated attenuated virulence. An online database, EpiCandIn, was created to compile epidemiology data of Candida infections in India. Another study highlighted unique gut microbiome compositions in HIV-infected individuals with latent and active TB. HIV treatment led to the restoration of alpha diversity, suggesting potential microbiome modulation strategies. Robust humoral immune responses against SARS-CoV-2 were detected in cord blood, peripheral blood, and breast milk following childbirth in women vaccinated at least two years ago. This suggests a possibility of vaccinated mothers passing protective immunity to newborns.

Our studies highlighted the importance of maternal human cytomegalovirus (HCMV) screening in high-risk pregnancies and identified correlates for poor pregnancy outcomes. Investigations into the role of gut microbiota revealed a novel microbiome-immune axis influencing disease severity in cholestatic infants with active HCMV infection, identifying candidate microbes for potential probiotic therapy. Our programs on genetic contribution to fetal malformation identified trisomy, copy number variations and monogenic causes in malformed fetuses with whole exome sequencing, revealing seven novel candidate genes.

Health technology assessment on a point of care test – “Gazelle” for Sickle Cell diagnosis indicated its cost effectiveness for facility-based screening. Through a multicentric costing study, package costs of IVF were

derived for inclusion in PMJAY. Another HTA study revealed clinical effectiveness and cost effectiveness of IV Ferric Carboxymaltose (IV FCM) for treating anemia in pregnant women.

Like last year, this year too we organized two training courses that were sponsored by DHR, each of 4-week duration. One of these was on 'Medical Genetics' and the other one on 'Harnessing the Power of Immunology in Medicine: Tools, Translation and Therapy'. These courses were specially designed for clinicians and researchers from various medical colleges across India.

This year the inauguration of the new Model Rural Health Research Unit (MRHRU) in Vani, Nashik, marked a significant milestone in our ongoing efforts to improve healthcare accessibility through research in rural and tribal areas. This facility will address unique health challenges of rural and tribal populations. During the year, we also expanded our technical cadre by recruiting 57 new employees. It is anticipated that this expansion will further strengthen our research activities. During the year, our administrative section moved to a bigger and better place in the Annex building. Also, we successfully implemented operationalization of the e-office procedure for administrative matters during the year.

I sincerely thank Secretary, Department of Health Research, Government of India and Director General, ICMR, for his leadership. I also extend my gratitude to Additional Director General; Sr Deputy Director General (Administration); Senior Financial Advisor; Head and Staff of the Reproductive, Child Health & Nutrition Division; Assistant Director General (Administration); and Deputy Director General (Administration), ICMR for their valuable support. I am grateful to the members of the Scientific Advisory Committee, Ethics Committee for Human Studies and Institutional Animal Ethics Committee for their expert comments, suggestions and criticisms for ongoing and new research projects.

On a personal note, I express my appreciation towards our scientific, technical, administrative, accounts, security, housekeeping staff and students for their dedication, energy and enthusiasm that keep the institute running at full steam. I greatly acknowledge the time and effort our researchers put in their work and bring glory to our institute in form of awards, fellowships and grants. We shall continue our journey with unbridled enthusiasm and immense energy towards, one major and constant goalpost "health for all".

Dr Geetanjali Sachdeva
Director

1. FEMALE INFERTILITY AND ASSOCIATED REPRODUCTIVE DISORDERS

1.1 PON1 Expression, Activity and its Relationship with Oocyte and Embryo Quality in Women with PCOS undergoing Assisted Reproductive Techniques (Partly Funded by Board of Research in Nuclear Sciences)

Principal Investigator : **Srabani Mukherjee**
 Co-Principal Investigator : D Modi
 Project Associates : A Naigaonkar, Sushma Khavale, Gayatri Shinde
 Collaborator : Indira Hinduja, PD Hinduja Hospital, Mumbai
 Duration : 2014-2023

Congruous cross-talk between oocyte and granulosa cells (GCs) is quintessential for oocyte competence. It is known that oocyte/embryo quality is poor in women with Polycystic ovarian syndrome (PCOS) the most common endocrinopathy in women of reproductive age. It is characterized by several endocrinological, reproductive and metabolic abnormalities, inducing infertility in many of the affected women. Infertile women with PCOS elect IVF to achieve pregnancy. IVF outcome largely depends upon the specialized niche around the oocyte. Earlier we had shown that glucose uptake is reduced and GLUT4 transcript expression is lower in the GCs from PCOS women (Annual report, 2017-18 p. 3, 2018-19 p. 7).

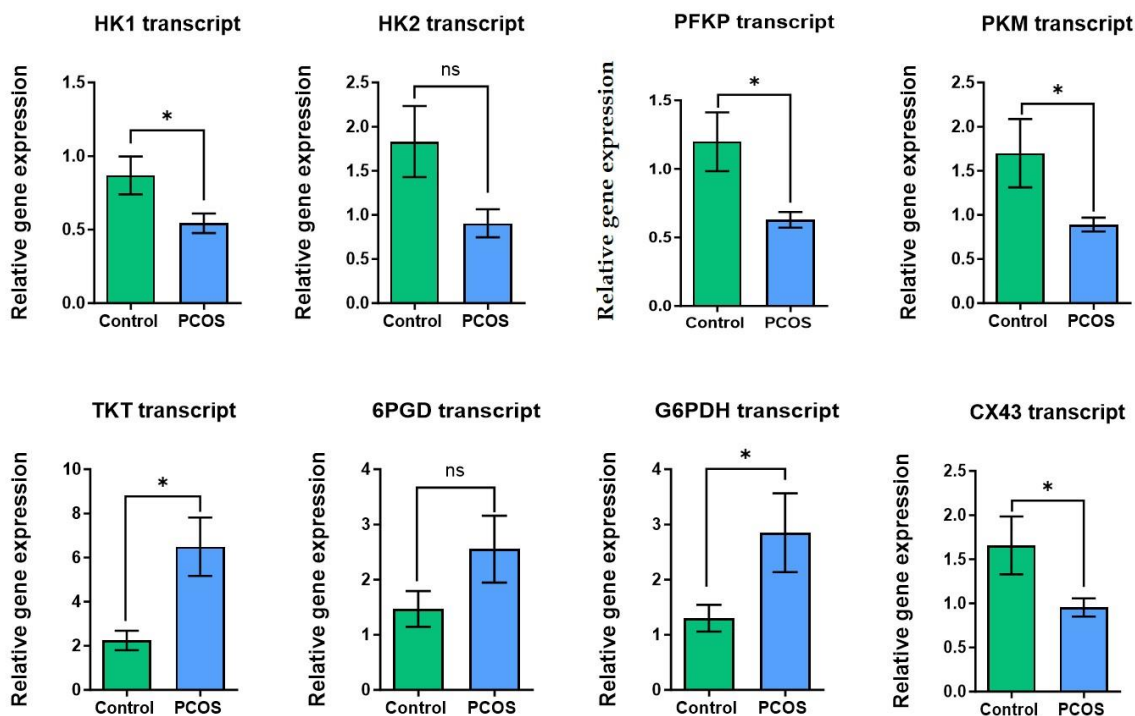


Figure 1: Expression of genes encoding enzymes involved in glycolysis, pentose phosphate pathway and gap junction protein in the granulosa cells of controls (n = 12) and women with PCOS (n = 12). Relative quantity and transcripts is expressed as mean $\pm$ SEM, *P<0.05, HK1 and 2: Hexokinase 1 and 2; PFK: Phosphofructokinase; PKM: Pyruvate Kinase; TKT: Transketolase; 6PGD: 6-Phosphogluconate dehydrogenase; G6PDH: Glucose-6-phosphate Dehydrogenase; CX43: Connexin 43.

In the reporting year assessed the expression of transcripts encoding the rate limiting enzymes of glycolysis (HK1, HK2, PFKP, PKM) and Pentose Phosphate Pathway (PPP), (G6PDH and 6PGD) along with TKT enzyme that regulates balance between glycolysis and PPP in GCs. Our results indicate that glycolysis is decreased while PPP is elevated in women with PCOS (Fig. 1). This is of crucial relevance as GCs act as metabolic drivers of the oocyte and supply oocytes with smaller energy substrates. Oocyte cannot generate energy from glucose. Additionally, transcript levels of the gene encoding gap junction protein, connexin 43, which is involved in the transport of smaller metabolites (pyruvate, amino acids etc.), was also downregulated in the GCs of PCOS women. This can further hamper the transport of energy rich molecules to oocyte and negatively influence its competence. We have previously reported several markers of oxidative stress are altered in the oocyte microenvironment (Annual report 2018-2022). Also higher oxidative DNA damage levels (8-oxoguanine) and intracellular lipid peroxidation levels were observed, in the GCs from PCOS women (Fig. 2). Upregulation of PPP may be a compensatory response to higher oxidative stress (to generate NADPH) and may give rise to metabolic reprogramming in GCs from PCOS women. Our data indicate that glucose metabolism and redox regulation can be considered as potential targets for improving oocyte/embryo quality and prognosis/outcome of IVF.

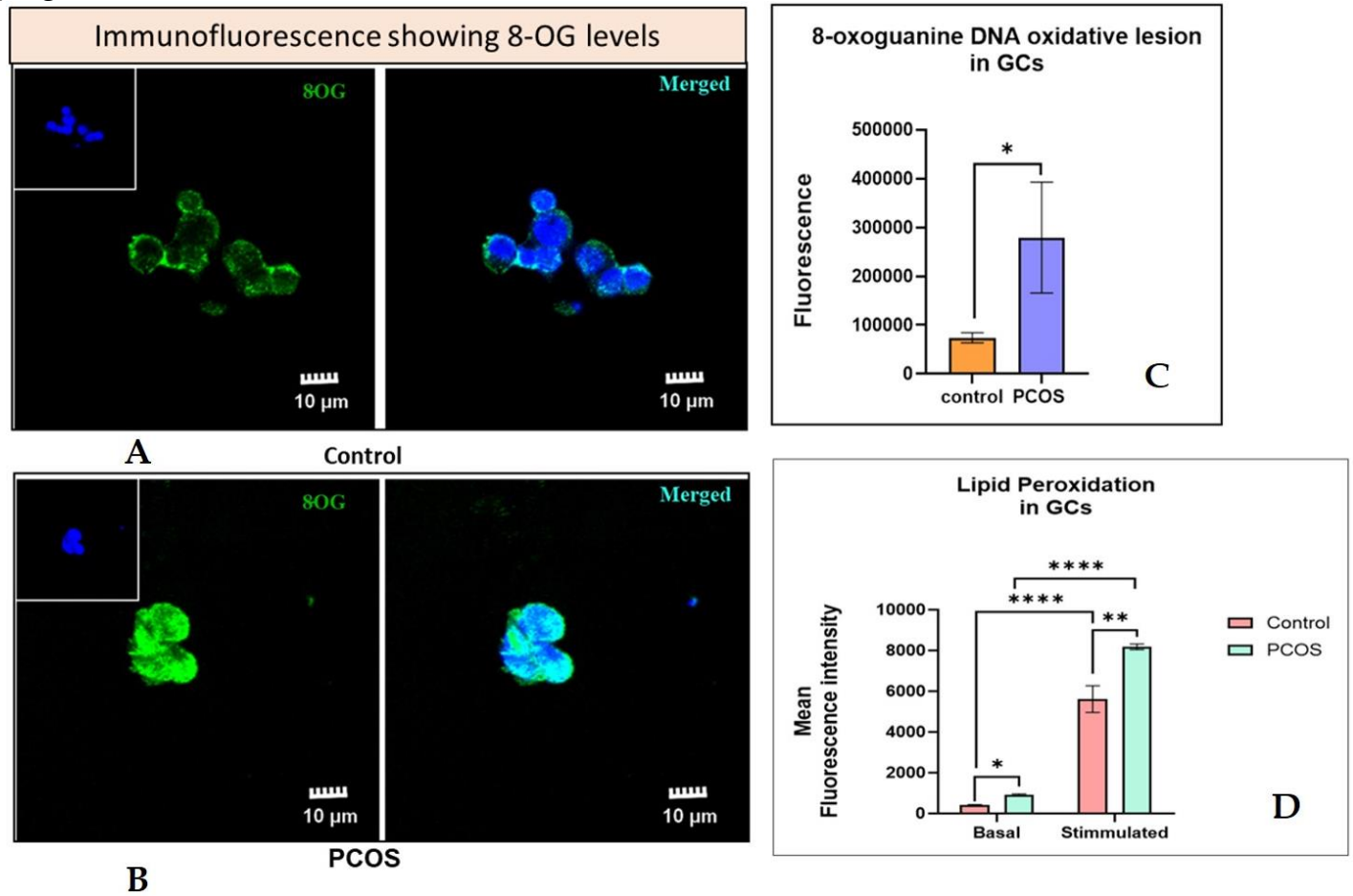


Figure 2: Immunolocalisation of 8 - Oxoguanine (green) for oxidative DNA lesion in the GCs from (A) controls (n = 6) and (B) women with PCOS (n = 7), Panel C denotes bar graph showing the fluorescence intensity of 8 - Oxoguanine in controls and PCOS. Panel D represents intracellular lipid peroxidation by flow cytometry in the GCs of controls (n = 6) and women with PCOS (n = 7) represented as mean $\pm$ SEM, *p<0.05.

1.2 Integrated Analysis of Gut Microbiome and Metabolome in Women with Polycystic Ovary Syndrome (Partly Funded by Department of Biotechnology)

Principal Investigator : **Srabani Mukherjee**
 Co-Principal Investigator : V Bhor
 Project Associates : Komal Khade, R Patel
 Collaborator : Anushree Patil
 Duration : 2023-2026

PCOS is the most common gynaecological and endocrine disorder in women of reproductive age. Women with PCOS often present co-morbidities like obesity, insulin resistance, and chronic state of low-grade inflammation. Emerging studies have reported a link between gut dysbiosis and PCOS and its related traits. The present study aims to investigate gut microbiota and gut metabolome in women with PCOS. We have recruited 64 women with PCOS, and 36 healthy control women. Increased LH: FSH ratio, higher levels of testosterone and reduced levels of SHBG were observed in PCOS group as compared to healthy controls. Our preliminary data showed that alpha diversity, which is a measure of diversity of species within an individual ecosystem, was not significantly different between PCOS and healthy controls (Fig. 1A). However, beta diversity, which illustrates relative differences in species composition between two ecosystems, was found to be significantly altered between the two groups ($p = 0.013$), as evident by Principal Coordinates Analysis (PCoA) based on Bray–Curtis distance matrix (Fig. 1B).

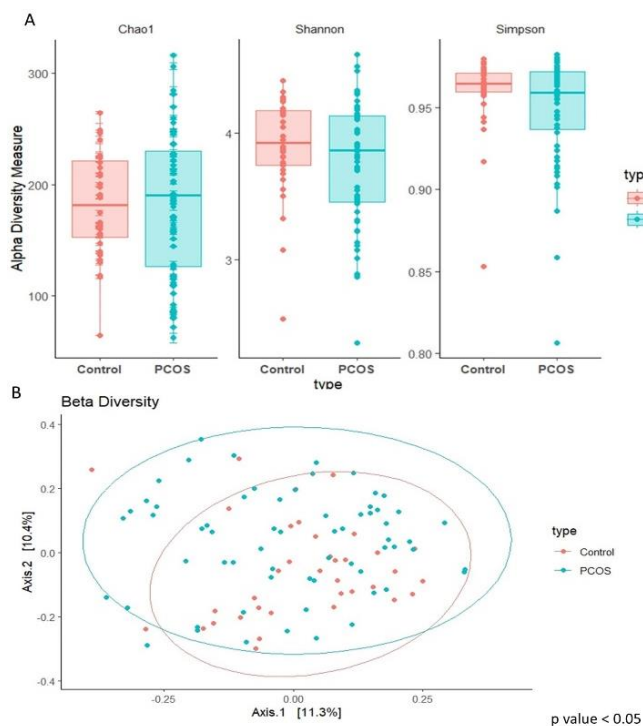


Figure 1: A) Alpha diversity indices comparison between healthy controls and women with PCOS. B) PCoA analysis through Bray Curtis dissimilarity matrix for Beta diversity visualisation.

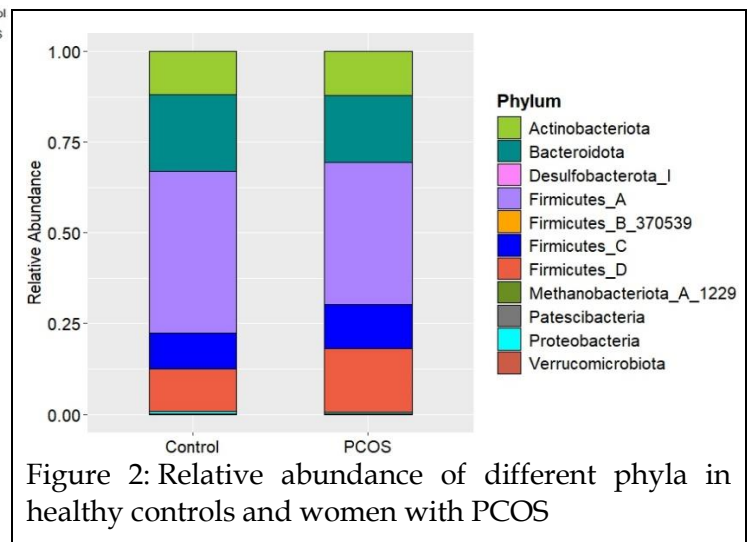


Figure 2: Relative abundance of different phyla in healthy controls and women with PCOS

This indicates differences in gut microbiota composition of women with PCOS and healthy control women. Further the relative abundance of phyla differs between the two groups (Fig. 2). The phylum Firmicutes and Bacteroidetes represent 90% of the community and alterations in the ratio of Firmicutes and Bacteroidetes (F/B) has been reported to be marker of gut microbiota dysbiosis. However, we did not find any significant difference in F/B ratio between the two groups. The preliminary analysis indicates a gut microbiota dysbiosis in women with PCOS. Further study of gut metabolites along with gut microbiota dysbiosis may add new insights into PCOS pathophysiology.

1.3 Assessing the Coagulation and Fibrinolytic System as Contributors of Thrombotic State in Polycystic Ovary Syndrome

Principal Investigator : **Srabani Mukherjee**

Project Associates : Roshan Dadachanji, Gayatri Shinde, Sushma Khavale, Nanda Joshi

Collaborators : Anushree Patil, B Kulkarni

Duration : 2021-2026

PCOS is the primary cause of anovulatory infertility in women of reproductive age with a strong predisposition to cardiometabolic disorders such as obesity, glucose intolerance, dyslipidemia, type 2 diabetes, metabolic syndrome, and cardiovascular disease. Prothrombotic conditions have also been reported in PCOS. This may be due to an imbalance in the levels of coagulation and fibrinolytic markers. Coagulation and fibrinolysis cascades may not only contribute to cardiometabolic perturbations but also reproductive anomalies such as anovulation, and recurrent miscarriages. We previously reported that women with PCOS present with significantly lower Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT), and Thrombin Time (TT) than controls. Also, higher circulating levels of Tissue Factor, Plasminogen Activator Inhibitor-1 (PAI-1), Tissue Plasminogen Activator Enzyme and Plasminogen levels were observed in women with PCOS, as compared to controls (Annual report 2022-2023, pp. 4-5). In the reporting year, we demonstrated that the level of antithrombin, an anticoagulant that inactivates important common pathway factors, thrombin and factor Xa, was significantly reduced in the serum of women with PCOS compared to controls, while levels of other anticoagulant factors, protein C and protein S, and coagulation factors 12 and 13 were comparable between both groups (Fig. 1). Overall, our results demonstrate that PCOS women show procoagulant and hypofibrinolytic states. We further investigated candidate genes [(plasminogen receptor with a C-terminal lysine (PLGRKT), methylenetetrahydrofolate reductase (MTHFR), PAI-1] reported to be associated

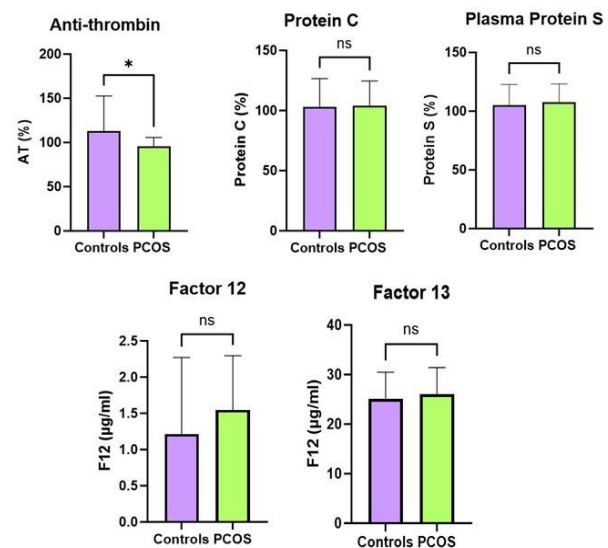


Figure 1: Levels of serum coagulation and anti-coagulation factors in controls and women with PCOS.

with a risk of PCOS development and thrombotic disorders. Our analysis has shown that there is no significant difference in the genotype frequency distributions for rs10739076 of PLGRKT, C677T polymorphism of MTHFR, and -675 4G/5G polymorphism of PAI-1 (Fig. 2). Thus, these polymorphisms do not influence PCOS risk in Indian women. We further investigated the relationship between rs10739076 of PLGRKT variants with PCOS and its hormonal and metabolic traits. To the best of our knowledge, we have shown for the first time, significant association of this variant of PLGRKT with decreased fasting glucose levels in both lean ($\beta = -0.176$, $p = 0.036$) and obese ($\beta = -0.119$, $p = 0.023$) women with PCOS, increased total testosterone levels in lean women with PCOS ($\beta = 0.243$, $p = 0.004$) and decreased 2-hour glucose levels ($\beta = -0.153$, $p = 0.004$) and ApoB: ApoA1 ratios ($\beta = -0.159$, $p = 0.044$) in obese women with PCOS. The recruitment of participants and data collection are ongoing.

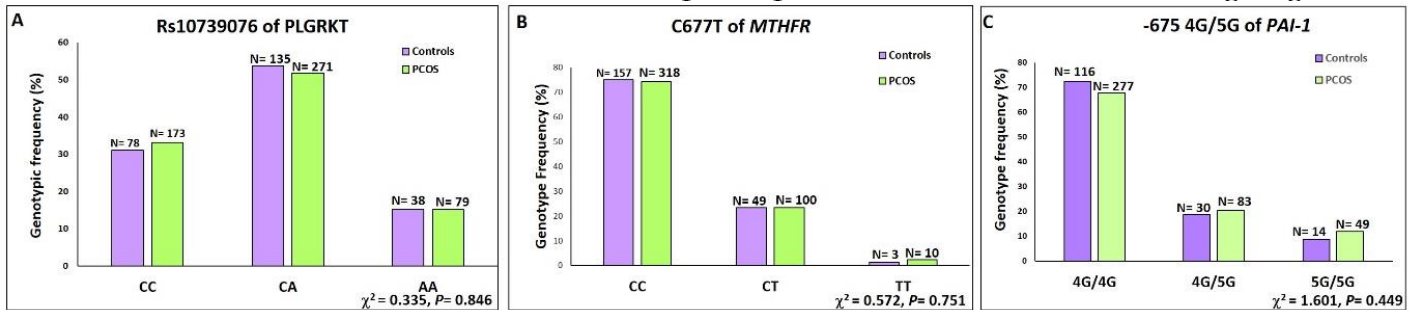


Figure 2: Genotype frequency distribution of polymorphisms (A) rs10739076 of PLGRKT (B) C677T of MTHFR and (C) -6754G/5G of PAI-1 in women with and without PCOS.

1.4 Exploring the Epigenetic Alterations Regulating miRNA Expression in Women with Polycystic Ovary Syndrome

Principal Investigator : **Srabani Mukherjee**
 Co-Principal Investigator : Pallavi Shukla
 Project Associate : Snehal Bhingardeve
 Collaborators : Sadhana Desai, V Mangoli, Richa Jagtap
 Duration : 2020-2026

Polycystic Ovary Syndrome (PCOS) is a prevailing cause of anovulatory infertility, affecting 8-13% of reproductive-age women worldwide. Emerging reports attribute important roles to epigenetic modulators like DNA methylation, and non-coding regulatory RNAs, mainly microRNAs (miRNAs), in governing the gene expression profiles of tissues in PCOS. This study aims to investigate the DNA methylation level and expression of DM-miRNA encoding genes (DM-miRNA) and also expression of the target genes in PCOS. We previously reported that aberrant DNA methylation of miRNA genes (DM-miRNA) regulate their transcript level in the granulosa cells (GCs) of women with PCOS (Annual report 2022-23, pp. 5-6). This year we identified that DM-miRNAs negatively regulate the expression of target mRNAs and contribute to a dysregulation of key processes which underline the PCOS pathophysiology. In the GCs of women with PCOS, both miR-10b-5p and miR-127-3p were found to be hyper-methylated with their transcript levels downregulated. Expressions of their target genes PTEN (miR-10b-5p) and MMP13 (miR-127-3p) were decreased in the GCs of women with PCOS, which

may in turn contribute to dysregulated insulin signaling and ECM remodeling during follicular development in PCOS (Fig. 1A&B).

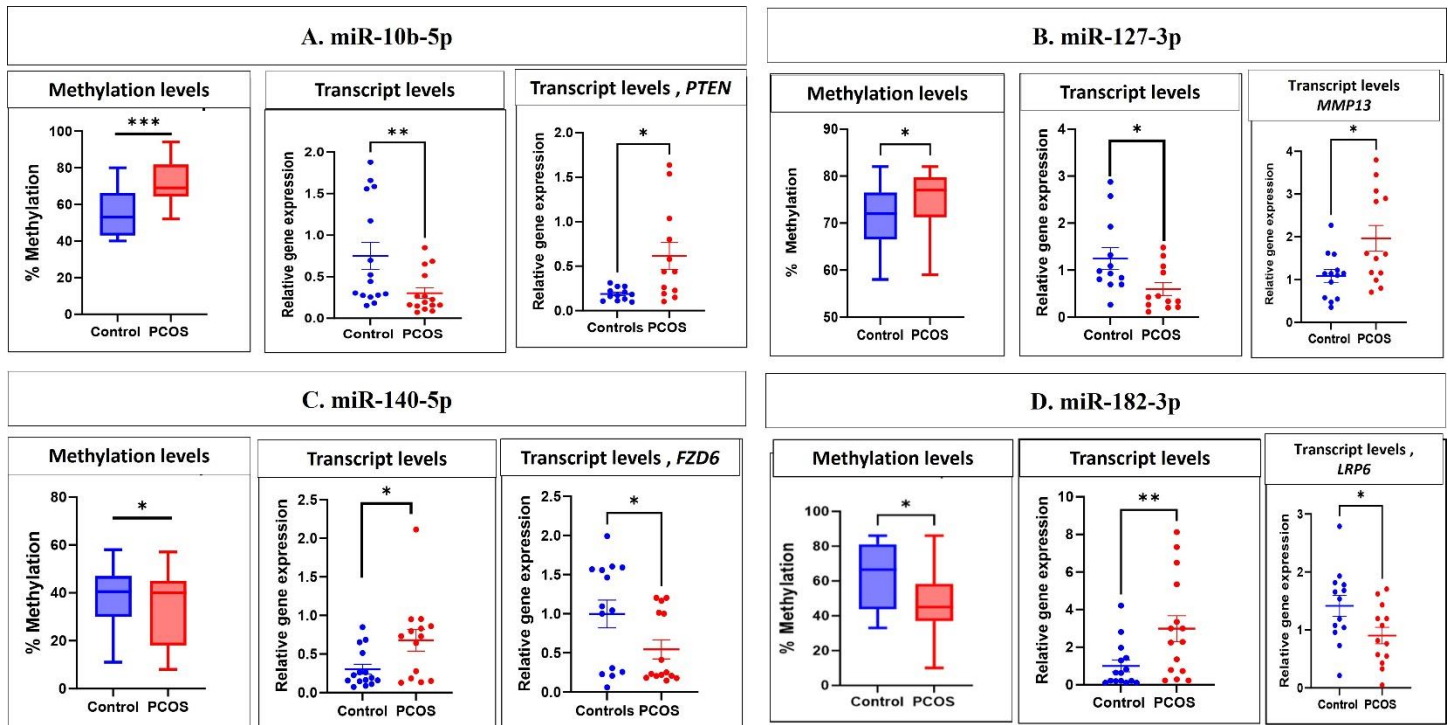


Figure 1: Methylation status and transcript levels of MiRNA's and expression of their target genes of miR-10b-5p (A), miR-127-3p (B), miR-140-5p (C), miR-182-3p (D) in the GCs of women with PCOS (n=15) and controls (n=15) represented as mean $\pm$ SEM, *p<0.05

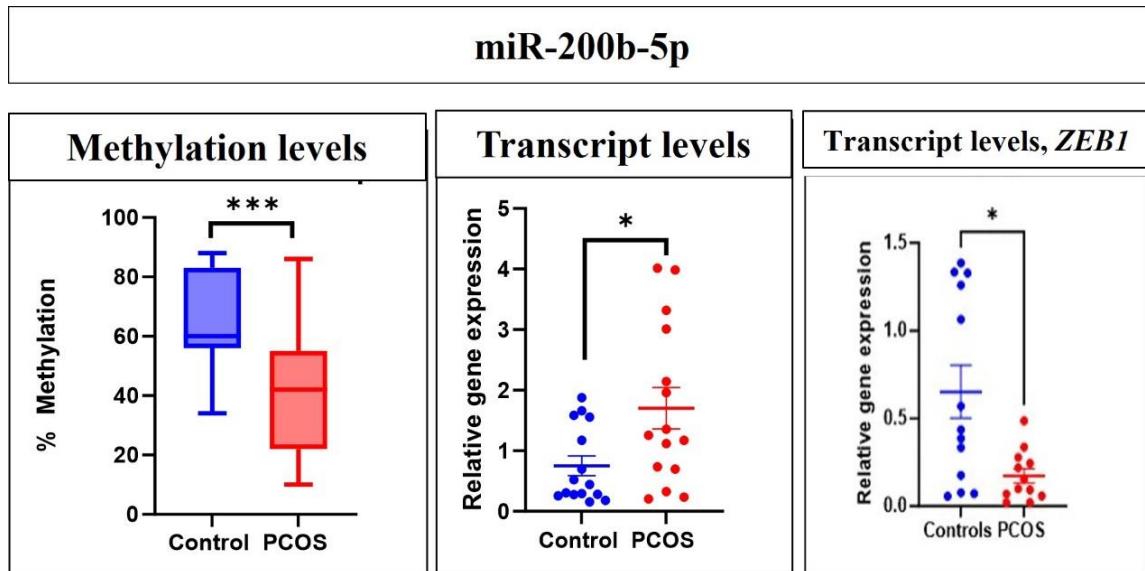


Figure 2: Methylation status and transcript levels of miR-200b-5p and transcript levels of miR-200b-5p target gene i.e. ZEB1 in GCs of women with PCOS (n=15) and Controls (n=15) represented as mean $\pm$ SEM, *p<0.05, **p<0.005, ***p<0.0005

We previously reported hypomethylation and increased transcript levels of miR-140-5p and miR-182-3p. The expression of two receptors, FZD6 and LRP6 of Wnt-signaling pathway which play an important role in follicle maturation, steroidogenesis, granulosa cell apoptosis in ovary, were found to be negatively regulated by miR-140-5p and miR-182-3p respectively in the GCs of women with PCOS compared to controls (Fig. 1C&D). We also identified a class of epi-miRNAs- which target genes of the methylation machinery. We found miR-200b-5p to be hypomethylated with upregulated transcript levels. The target of miR-200b-5p ZEB1 which is the recruiter of maintenance methyltransferase DNMT1, showed decreased expression in the GCs of PCOS compared to control (Fig. 2). In addition, TET enzymes (TET1 and TET2) which are instrumental in DNA demethylation, and previously reported to be altered by our group are the target miR-410-3p and miR-23a-5p. Our study reports that an intricate interplay between two epigenetic regulators, DNA methylation and miRNA, may alter gene expression in the GCs and thus may play a key role in PCOS pathophysiology.

1.5 Unravelling Pathogenetic Mechanisms of Polycystic Ovary Syndrome by Whole Exome Sequencing *(Partly Funded by Department of Science and Technology)*

Principal Investigator	: Srabani Mukherjee
Co-Principal Investigators	: Pallavi Shukla
Project Associates	: Medini Samant, Roshan Dadachanji, Sushma Khavale, Gayatri Shinde, Nanda Joshi
Collaborator	: Anushree Patil, Beena Joshi
Duration	: 2017-2024

PCOS is a highly heritable complex genetic disorder affecting women of reproductive age. Candidate gene studies, familial studies and genome-wide association studies (GWAS) carried out across various ethnicities have identified multiple loci associated with PCOS. GWAS have primarily identified polymorphisms in non-coding regions across different populations, while the role of genetic variants in the exome has not been well studied in PCOS. Therefore, we employed whole exome sequencing (WES) to unravel the role of functional variants in predisposition to PCOS and its symptoms in well-characterized individuals with PCOS. Exome sequencing was done for 85 women with PCOS using the Agilent SureSelect CREV2 platform. ANNOVAR was used to annotate the sequenced variants, and these annotated variants were used for further analysis. The variants were categorized based on their gnomAD minor allele frequency (MAF) as rare variants (MAF range: 0 - <0.01), and low-frequency variants (MAF range: ≥ 0.01 - ≤ 0.05). These variants were subjected to quality check filtration and all the variants with PASS score as quality filter and allele depth >30 and percentage of reads of alternate allele >20 were selected. The variants with SIFT and PolyPhen-2 prediction as pathogenic or likely pathogenic were retained. Gene enrichment done by VarElect identified 275 genes with rare variants and 13 genes with low-frequency variants associated with PCOS. The MAF of these variants was compared with their gnomAD MAF by MedCalc online calculator which revealed association of 305 rare significant variants with PCOS while no association with low-frequency variants was found. Pathway analysis of the genes harbouring significantly associated rare variants showed their involvement in ovarian steroidogenesis, steroid hormone biosynthesis, cell signaling pathways, insulin resistance pathway, and complement and coagulation cascades, which in turn have been reported to

be influential in PCOS pathophysiology. The top 10 enriched pathways are mentioned in Table 1. Dysregulation of ovarian steroidogenesis leads to hormonal imbalances including hyperandrogenism, irregular menstrual cycles, and ovarian cyst formation, which are characteristic features of PCOS. In our study, we have observed that women carrying these variants presented with altered hormonal profiles and clinical signs of hyperandrogenism and hyperinsulinemia, thus suggesting a possible role of these rare variants in contributing to PCOS pathophysiology. Further, analysis of genes carrying polymorphic variants will be conducted. The significant pathogenic variants will be validated in a sufficiently sized replication cohort of PCOS and control individuals.

Table 1: List of top 10 pathways enriched by Enrichr and their genes

Term	Genes
Ovarian steroidogenesis	<i>CYP11A1, HSD17B1, LHB, CYP1A1, CYP1B1, CYP19A1, BMP6, BMP15, IGF1R, CYP17A1</i>
Steroid hormone biosynthesis	<i>CYP21A2, CYP11A1, HSD17B1, CYP1A2, CYP1A1, CYP1B1, CYP3A4, CYP19A1, CYP3A5, CYP17A1</i>
Focal adhesion	<i>PDGFRB, TNXB, VWF, EGF, HGF, FN1, ACTN4, THBS2, MYLK, IGF1R, COL2A1, KDR, FLNA, COL4A5, COL6A3</i>
Chemical carcinogenesis	<i>RB1, VDR, EGF, CACNA1D, CACNA1C, CYP2C19, CYP3A4, CYP3A5, ESR2, MTOR, AR, FGF8, CYP1A2, CYP1A1, CYP1B1, CACNA1S</i>
Insulin resistance	<i>SLC27A1, TBC1D4, NOS3, IRS2, TRIB3, PYGM, CPT1B, ACACB, AGT, MTOR, PCK2</i>
PI3K-Akt signaling pathway	<i>PDGFRB, TNXB, ANGPT2, VWF, NOS3, EGF, HGF, FN1, THBS2, MTOR, IGF1R, COL2A1, FGF8, KDR, COL4A5, COL6A3, TLR4, PCK2</i>
Vascular smooth muscle contraction	<i>NPPC, KCNMA1, MYH9, CACNA1D, MYH11, CACNA1C, CACNA1S, AVP, PLA2G6, AGT, MYLK</i>
Insulin secretion	<i>RYR2, KCNMA1, ATP1A4, PDX1, CACNA1D, FFAR1, CACNA1C, CACNA1S, STX1A</i>
cGMP-PKG signaling pathway	<i>NPPC, NOS3, KCNMA1, ATP1A4, IRS2, CACNA1D, GTF2IRD1, CACNA1C, CACNA1S, MYH6, MYLK</i>
Complement and coagulation cascades	<i>C3, ITGAM, SERPINA1, VWF, F12, PLAT, F2, F5</i>

1.6 Analysis of Mitochondrial DNA Sequence Variants in Polycystic Ovarian Syndrome Women with Insulin Resistance

Principal Investigator : **Pallavi Shukla**
Project Associate : Srabani Mukherjee
Collaborators : Anushree Patil, Beena Joshi
Duration : 2018-2023

Mounting evidences suggest mitochondrial dysfunction as a novel contributor in the pathogenesis of PCOS. Herein, mtDNA copy number, a biomarker of mitochondrial function, was analysed for its correlation with clinical characteristics of PCOS. Further we studied association of 383 mtDNA variants (detected by NGS) with characteristic traits of PCOS. The study revealed that peripheral blood mtDNA copy number to be significantly reduced in women with PCOS compared to non-PCOS group. Further

peripheral mitochondrial copy number was significantly inversely related to waist to hip ratio (WHR), triglycerides levels and positively related to High Density Lipoprotein-Cholesterol (HDL-C). An unsupervised hierarchical clustering analysis revealed rare, low heteroplasmic mtDNA variants such as 12556G, 1488T, 9200G, 9670G, 3308G, 14480G, 15914T and 5426G to be strongly associated with PCOS related traits; hirsutism, acne, hyperpigmentation, WHR, body mass index (BMI), fasting blood sugar (FBS), triglycerides (TG), HDL-C and metabolic syndrome (Fig. 1). Out of these variants, 12256G variant was found to affect the stability of NADH dehydrogenase protein structure (Fig. 2a&b).

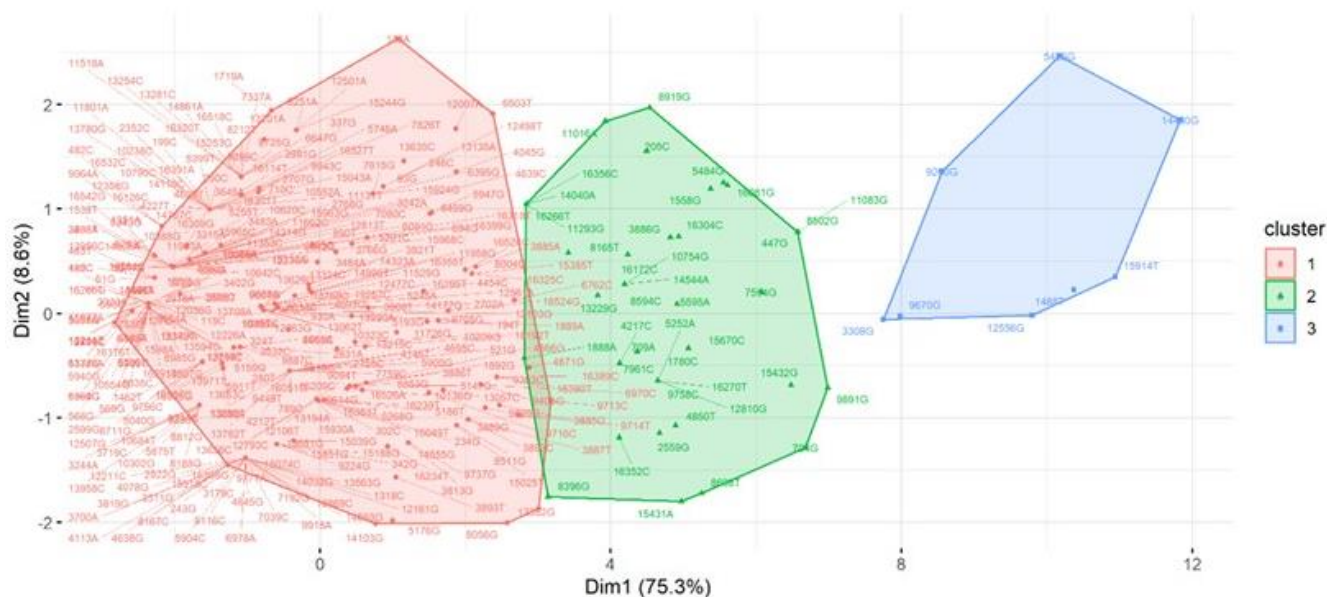


Figure 1: Cluster analysis of mtDNA variants. Each cluster has a different color and contains mtDNA variant. The cluster plot was generated using factoextra R package

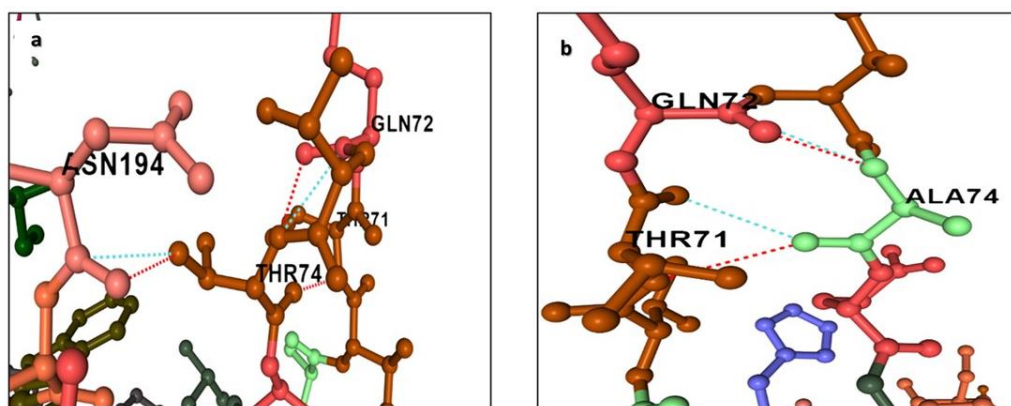


Figure 2: Interatomic Interactions of (a) Wild Type (Threonine) and (b) Mutant (Alanine) at the 74th amino acid in the ND5 Subunit of NADH Dehydrogenase

This variant caused a substitution of Threonine with Alanine at the 74th position, leading to the loss of interaction with Asn194 and therefore could potentially affect both the flexibility and overall stability of the protein. This study is first to reveal significant correlation of mtDNA copy number with WHR in women with PCOS indicating a link between mitochondrial dysfunction with central

obesity in PCOS. In addition, we also for the first time showed association of rare mtDNA variants with characteristic traits of PCOS. These mitochondrial DNA variants may cumulatively act as early predictors of risk of PCOS and its related comorbidities and hence identifying them may help in the management of PCOS.

1.7 Study of Maternally Inherited Mitochondrial DNA Variants in Women with Polycystic Ovarian Syndrome *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : **Pallavi Shukla**
Co-Principal Investigators : Srabani Mukherjee, Anushree Patil
Project Associate : Samia Palat Thariyal
Collaborator : V Patil
Duration : 2021-2024

As mitochondrial DNA (mtDNA) is exclusively maternally inherited, mtDNA variants may contribute to missing heredity of PCOS. The study groups include PCOS mother-daughter pairs as following; Group I: PCOS Daughters-PCOS Mothers (n=8 pairs), Group II: PCOS Daughters- Non-PCOS Mothers (n=42 pairs), Group III (n=18 pairs): Non-PCOS daughters- Non-PCOS mothers (n=18 pairs). Peripheral blood mtDNA of mother-daughter pair of group I, mother-daughter pairs of group II, mother-daughter pairs of group III have been sequenced using next generation sequencing to identify maternally inherited mtDNA variants. Study revealed numerous variants that were found to be shared between the groups, 29 unique variants were found in group II vs. group III such as 11947G, 11674T, 3505G, 12414C, 1243C, 8994A, 5046A, 515C, 515G etc. Majority of these variants were present in mitochondrial OXPHOS complex 1 and D-loop region. Defects in Complex I contribute to ROS production. Identification of mtDNA variants may help in understanding pathogenesis and better managing PCOS.

1.8 Study of Epigenetic Factors involved in Mitochondrial Dysfunction in Obese Polycystic Ovarian Syndrome Women

Principal Investigator : **Pallavi Shukla**
Co-Principal Investigators : Srabani Mukherjee
Collaborator : Anushree Patil
Duration : 2019-2027

Polycystic Ovary Syndrome (PCOS) a leading cause of infertility among women of reproductive age and is characterized by irregular menses, hyperandrogenism, and polycystic ovaries. Two types of PCOS phenotypes are widely known, i.e. overweight/obese (35%–60%) and lean with different biochemical, hormonal, and metabolic profiles among two phenotypes. Menstrual disturbances and infertility are more common in obese PCOS women than in lean PCOS women. Obese PCOS women have greater prevalence of Type 2 Diabetes, impaired glucose tolerance and endometrial hyperplasia than in lean PCOS women suggesting that they are at a greater risk of morbidity at a younger age than lean PCOS women and need to be treated more rigorously. Moreover, obese PCOS women have a

lower chance of conception following Assisted Reproductive Technology (ART) as they respond poorly to ovarian stimulation and have a higher risk of miscarriage. Hence there is a need to understand how obesity leads to PCOS or vice-versa. Obesity may trigger mitochondrial epigenetic changes leading to mitochondrial dysfunction (MD). In the reporting period, we evaluated mitochondrial functions in obese and lean PCOS and non-PCOS groups. The study recruited 132 PCOS women and 88 control (non-PCOS) women. Among these, 70 out of 132 PCOS women were obese (53%, BMI ≥ 25 kg/m²) and 20 out of 132 (15%, BMI 18.5-22.9 kg/m²) were lean. Among non-PCOS women, 43 out of 88 were obese (48.8%, BMI ≥ 25 kg/m²) and 24 out of 88 (27%, BMI 18.5-22.9 kg/m²) were lean. mtDNA copy number was reduced albeit no significantly in obese PCOS women (n= 39) compared to lean PCOS women (n=21) and also copy number did not change significantly between non-PCOS obese women and non-PCOS lean women (Fig. 1). However mtDNA copy number was significantly reduced between obese PCOS and obese non-PCOS group (p<0.0001) and lean PCOS and lean non-PCOS group (p<0.0008). The data suggested aggravation of mitochondrial dysfunction in obese participants, particularly obese PCOS ones. However, large number of samples are needed to attain any definite conclusion.

1.9 Deciphering the Functional Significance of Candidate Genes Associated with PolyCystic Ovary Syndrome (PCOS) Identified from Network Analysis

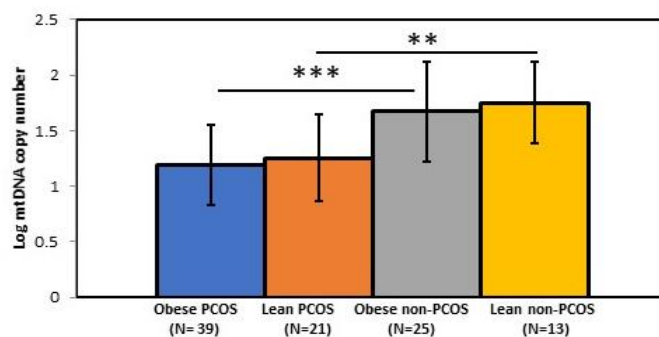


Figure 1: mtDNA copy number in obese and lean PCOS and non-PCOS women

Principal Investigator : **Shaini Joseph**

Co- Principal Investigator : S Pande

Collaborators : Smita Mahale, Srabani Mukherjee, Vandana Bansal, Grishma Desai

Duration : 2021-2025

The potential candidate genes identified by network analysis were validated using in-silico approaches. In the first approach, six gene expression datasets on PCOS in an ovarian environment were shortlisted and analysed. The association of the potential candidate genes with PCOS was confirmed if the gene was found to be differentially expressed in one or more of the analysed datasets. Five hundred and forty-seven genes were found to be differentially expressed in women with PCOS in at least one of the gene expression datasets used for validation. In the second approach, a search query for each of these potential candidate genes was built together with PCOS keywords and queried in the PubMed database. Genes were considered to be validated if there was literature evidence supporting their association with PCOS. The genes with literature evidence were further segregated based on type and strength of evidence i.e human studies were given a higher weightage as compared to in-silico, in vitro or animal studies. Five hundred and fourteen genes were validated based on

different sources of evidence. One hundred and twenty-three genes were validated by both the in-silico approaches.

1.10 Understanding the Role of Antioxidants in Endocrine Disrupter-Induced Polycystic Ovary Syndrome (PCOS) like Condition

Principal Investigator : **V Dighe**
Project Associates : B Saha, S Jadhav, P Salunke
Duration : 2024-2027

Polycystic Ovary Syndrome (PCOS) is an endocrine and metabolic disorder in women of reproductive age group. This disorder also predisposes women to other conditions like infertility, endometrioma, hyperinsulinemia, and hyperandrogenism. A high-fat diet (HFD) is one of the key factors responsible for causing PCOS in women. HFD causes increased androgen levels, insulin resistance, anovulation, and glucose intolerance. BPA is an aromatic phenolic chemical compound mainly used as a synthetic plastic polymer. Data from animal studies have proven an association of the urinary as well as serum BPA concentration, with obesity and insulin secretion. BPA tends to accumulate in lipocytes in the body. In high-fat diet-induced PCOS-like conditions or obese women, BPA exposure results in the severity of PCOS pathophysiology. In addition, BPA causes hormonal imbalance, oxidative stress, and pro-inflammatory factors, which are leading causes of PCOS. Oxidative stress perturbs several steroidogenic enzymes like CYP17 and CYP19 and leads to hyper-androgenemia. Antioxidants like Eugenol (anti-inflammatory), Curcumin, Vitamin C, E, Q10, etc. have the potential to down-regulate oxidative stress and inflammation and improve hormonal balance. We hypothesize that exposure to BPA alone or combined with a high-fat diet leads to PCOS-like conditions in rats.

The present study aims to understand the role of antioxidants in the endocrine disruptor/and high-fat diet-induced PCOS model. In the reporting year, attempts were made to develop and characterize high-fat diet-induced PCOS-like conditions in rats exposed to BPA. Total 4 groups of female Wistar rats (n=7) were induced: Group-I: control (standard diet), Group-II: only HFD, (38% fat); Group-III: standard diet with 100µg/kg BW/day BPA; Group-IV: HFD with 100µg/kg BW/day BPA). The dose was given from postnatal day 21 to 75. During this period, body weight, vaginal opening, onset of estrous cyclicity, oral glucose tolerance test, biochemical parameters (triglycerides, total cholesterol, Low-density lipoprotein, high-density lipoprotein) and reproductive hormones such as testosterone, estrogen, and prolactin were assessed. A significant increase in body weight was observed in the HFD and HFD+BPA groups compared to the control and only BPA treated group (Fig.1(B)). A considerable decrease in the number of estrus cycle was observed in the HFD, HFD+BPA treatment, and BPA group compared to the control (Fig.1(A)). A significant increase in serum glucose at 120 minutes was observed in the BPA, HFD, and HFD+BPA groups (Fig.1 (C)). Compared to the control, an increasing trend in Serum LDL and total cholesterol was observed in the BPA, HFD, and HFD+BPA groups (Fig.2 A and B). Serum estradiol was reduced in only BPA and increased in HFD and HFD+ BPA compared to the control (Fig 2 D) and the testosterone level was significantly increased in BPA alone group with a minor increase in HFD and HFD+ BPA. (Figure 2 C). Compared to the control, a significant decrease in serum prolactin was observed in the BPA, HFD, and HFD+BPA groups (Fig 2 E). After 75 days, animals were

sacrificed, and organ weights were taken. Ovarian histological analysis and estimation of other critical hormones such as LH, FSH, and progesterone have yet to be done.

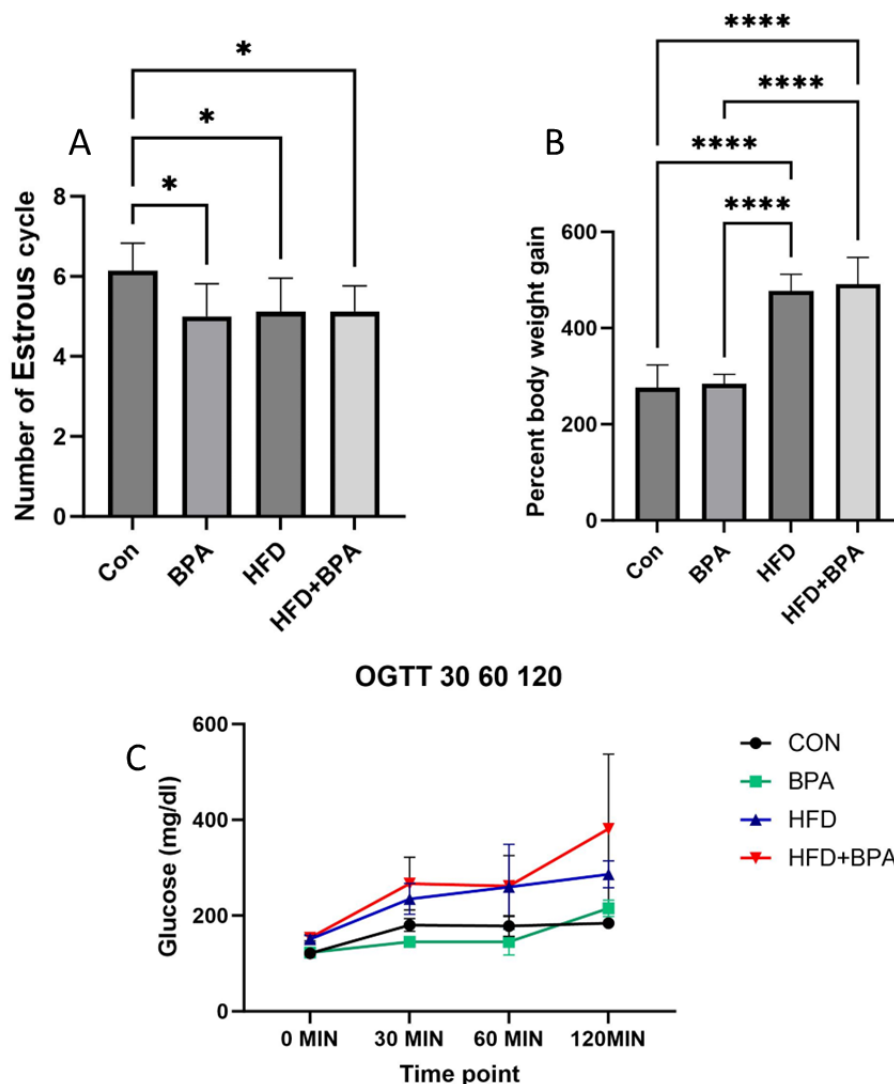


Figure 1: Effect of exposure to BPA and high-fat diet during PND 21-75 (A) The estrus cycle was determined by the vaginal smears of all animals (n=5 in each group). Bars represent the mean $\pm$ SE. * $p \leq 0.05$ (B) Percent Body weight gain. % body weight gain was calculated using $\{100 \times (\text{final body weight} - \text{initial body weight}) / \text{final body weight}\}$. Bars represent the mean $\pm$ SE. The experiment was performed in triplicates. **** $p \leq 0.0001$ (n = 7) (C). Oral glucose tolerance test: Blood was collected at 30, 60, 120 minutes timepoint, and serum glucose levels were estimated. Bars represent the mean $\pm$ SE. * $p \leq 0.01$ (n = 7)

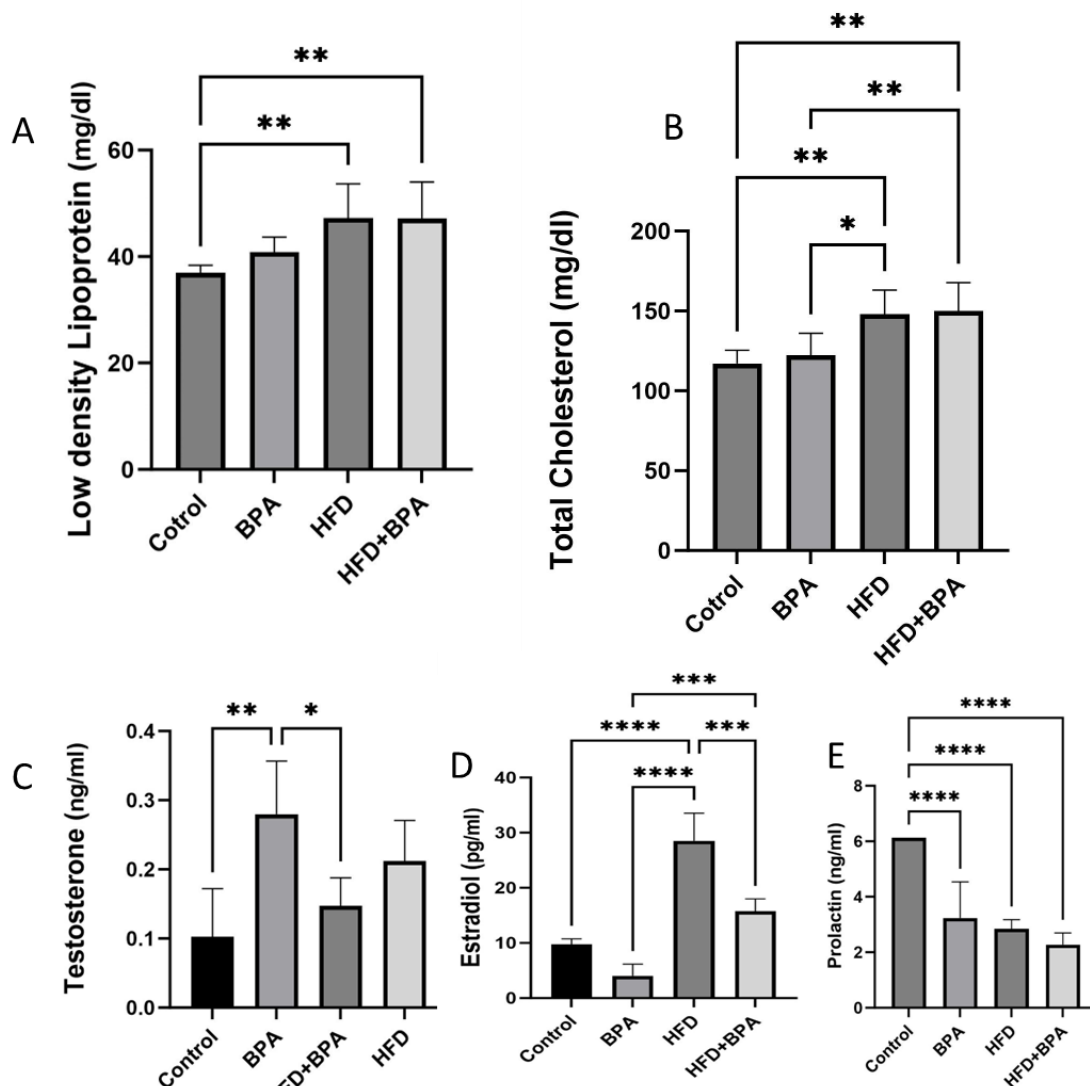


Figure 2: Effect of exposure to BPA and high-fat diet during PND 21 -75 on serum low density lipoprotein(A), total cholesterol(B), testosterone (C), estradiol (D) and prolactin (E) levels. Bars represent the mean $\pm$ SE. * $p \leq 0.01$, ** $p \leq 0.005$, *** $p \leq 0.005$,**** $p \leq 0.0005$ (n = 5)

1.11 ICMR Advanced Centre for Product Development: Development of Recommendations and Algorithms for Multidisciplinary Management of Polycystic Ovary Syndrome (PCOS) in the Indian Health Care System (Partly Funded by ICMR - Indian Council of Medical Research)

Principal Investigator : **Anushree Patil**
 Co-Principal Investigators : Rama Vaidya
 Project Associate : Nupoor Limaye
 Collaborator : Jayashree Joshi, Ashwini Kumar Raut, KHS-MRC, Shobha Udipi, KHS-MRC
 Duration : 2019-2024

Objectives of the study are to review the existing guidelines and management practices for PCOS and develop multidisciplinary clinical and operational recommendations and easy-to-use algorithms for the management of PCOS for the Indian health care system (three tier- primary, secondary, and tertiary level). 2. To pilot test guidelines at different levels of the healthcare system for user-friendliness. The revision of the draft guidance in light of the 2023 International guidelines has been completed. This involved a thorough review of the guidance material and international recommendations. To achieve this, a series of meetings was held with the KHS-MRC. These efforts ensured that the updated guidance aligns with the latest international recommendations as well as enhancing its relevance and applicability. Furthermore, the recommendations were not confined to specific sections but were systematically incorporated across all relevant chapters, ensuring a comprehensive and cohesive update. In parallel, ongoing tasks include the pilot testing of the revised guidelines with the healthcare providers to gather feedback and to understand the feasibility, acceptability, and training needs in PCOS management. A specialized tool for this pilot testing has been developed, aimed at validating the effectiveness, utility, and user-friendliness of the guidelines. The operational guidelines, once finalized, will benefit from this process, ensuring they are robust, user-friendly, and aligned with both international standards and the practical needs of our healthcare system as identified during the validation process. A meeting was held on 4th May 2024 with the district health officer and medical officers of Palghar to facilitate the validation of this tool through a Continuing Medical Education session. During this CME, we distributed the tool, which was designed as a questionnaire, to collect valuable responses from health care providers. These responses will be critical in assessing the practical applicability of the guidelines and identifying any areas that may require further improvement for finalizing the recommendations.

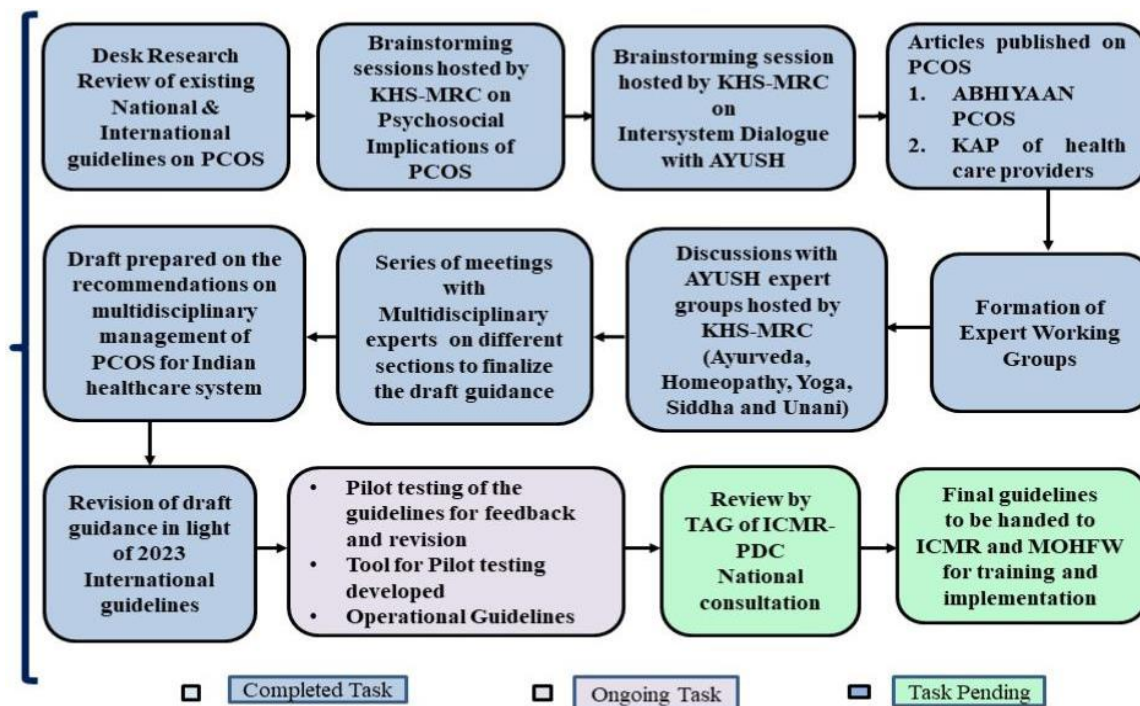


Figure 1: Process of development of guidance for multidisciplinary management of PCOS for the Indian healthcare system

1.12 Investigating DNA Methylation and Histone Modifications in Cystic Ovarian Murine Model

Principal Investigator : **Srabani Mukherjee**
Project Associates : Gayatri Shinde, Sushma Khavale, P More
Duration : 2021-2024

Polycystic Ovary Syndrome (PCOS) is a complex heterogeneous disorder in which both genetic and environmental factors contribute to pathophysiology. However, the exact etiology of this disorder remains elusive. Environment and lifestyle factors may exert their effects via the epigenetic mechanisms such as DNA methylation and histone modifications. Recent evidence has indicated that epigenetic modification plays a role in development of PCOS. As it is difficult to obtain different tissues such as ovaries from humans in order to assess epigenetic marks, animal models have been considered to be valuable tools for investigating putative global as well as tissue-specific epigenetic alterations in a multi-organ disorder like PCOS. We investigated the global and tissue-specific epigenetic modifications in estrogenized cystic murine model (E2-T) previously developed by our lab. We reported altered methylation not only in ovarian tissue but also in hypothalamus-pituitary (Annual report 2022-2023 pp. 10-11) of estrogenized animals compared to control animals. Last year, we reported global 5mC (methylation) levels to be significantly decreased in the liver tissue of E2-T animals compared to Vehicle Control (VC) animals. 5hmC (demethylation) levels were comparable in both groups (Annual Report 2022-2023, pp. 10).

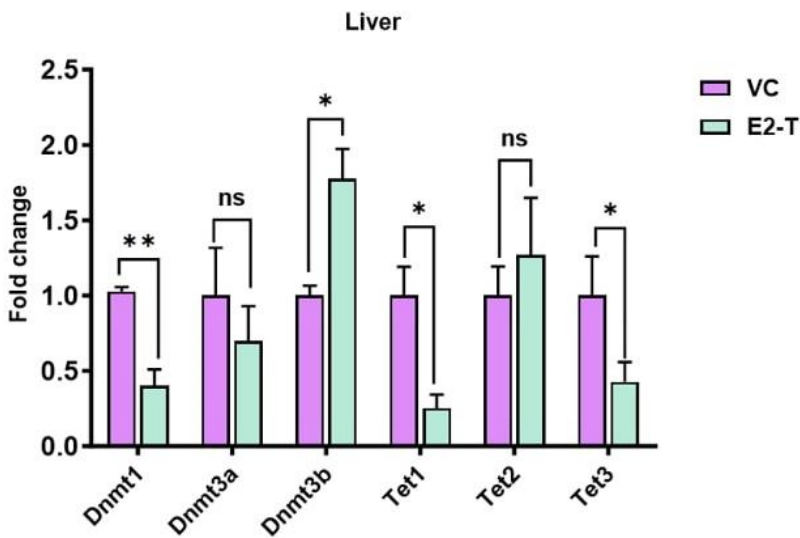


Figure 1: Transcript levels of DNA Methyl Transferases (Dnmt1, Dnmt3a, Dnmt3b) and Ten Eleven Translocases (TET1, TET2 and TET3) as measured in the Liver of vehicle- controls (VC, n=4) and E2-treated adult mice (E2T, n=4) at 12-week post-treatment. Fold change evaluated over Gapdh as an internal housekeeping gene. Data is presented as "mean + SEM" and was analysed using the Student's T test. *p < 0.05; **p < 0.01.

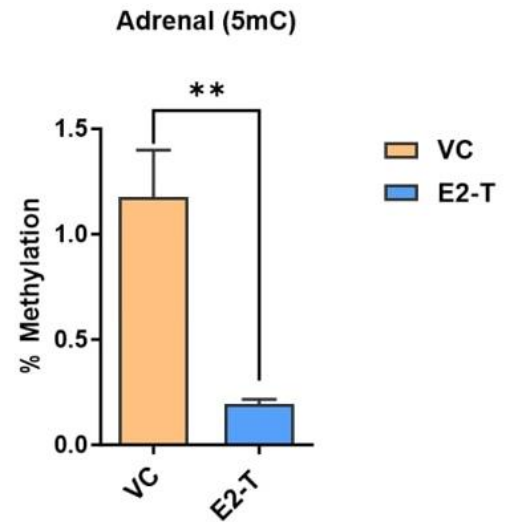


Figure 2: Global DNA 5-methyl cytosine (% 5mC) levels assessed in the adrenal gland of VC (n=4) and E2-T adult mice (n=4) at 12 weeks post-treatment.

In the current year, we compared transcript levels of DNMTs (Dnmt1, Dnmt3A, Dnmt3B) and TET (Tet1, Tet2, Tet3) enzymes in liver tissue. The transcript levels of DNMT3B were found to be significantly higher, while of DNMT3A were lower in E2-T animals as compared to control animals. On the other hand, DNMT1, which is involved in maintenance methylation, was found to be significantly decreased in E2-T animals as compared to VC. The relative expression of DNA hydroxymethylation machinery mediated by demethylases such as TET1 and TET3 was found to be significantly decreased whereas TET2 showed increased expression in E2-T animals as compared to VC. Our findings have shown that DNA methylation as well as DNA hydroxymethylation machinery is altered in the liver of estrogenized animals (Fig 1). Further, to investigate the effect of estrogen treatment on epigenetic status of adrenal gland, we initially assessed global 5mC levels by ELISA and flowcytometry and our preliminary findings found global 5mC levels to be significantly decreased in E2-T animals compared to VC (Fig 2).

1.13 Clinical Phenotypes and Genetic Regulation of Endometriosis in Indian Women (ECGRI study) *(Partly funded by Department of Biotechnology Wellcome India Alliance)*

Principal Investigator : **R Gajbhiye**

Duration : 2019-2024

Zone	City, State	Study site	Collaborator
North-East/ East	Dibrugarh, Assam	Assam Medical College	P Phukan
East	Kolkata, Bengal	Spectrum Clinic & Endoscopy Research Institute, Kolkata	P Das Mahapatra
North	Lucknow, UP	King George's Medical University, Lucknow	SP Jaiswar
	Jodhpur, Rajasthan	All India Institute of Medical Sciences, Jodhpur	Pushp Lata Sankhwar S Shekhar
Central	Nagpur, Maharashtra	Government Medical College, Nagpur	A Humane
	Raipur, Chhattisgarh	Omega Hospital, Nagpur	C Shembekar
		All India Institute of Medical Sciences, Raipur	Nilaj Bagde
		Sai Baba Nursing Home, Raipur	Swati Mahobia
West	Panaji, Goa	Dr Kedar's Maternity, Infertility and Surgical Hospital, Endoscopy and IVF Center, Panaji	K Padate
	Mumbai, Maharashtra	Progeny IVF Center & Clinic for Women, Mumbai	A Ganatra
		Nowrosjee Wadia Maternity Hospital, Parel, Mumbai	Deepali Kale
		Worli Hospital for Women, Mumbai	N Sardeshpande
		Fortis Hospital, Mumbai	A Ganatra, Sonal Kumta
		Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital, Mumbai	N Mahajan
	Solapur, Maharashtra	Naval Maternity Endoscopy & Infertility Center, Solapur	M Shah
South	Manipal, Karnataka	Kasturba Medical College, Manipal	M Pai, Rekha Upadhyay
	Trivandrum, Kerala	Credence Hospital, Trivandrum	Bimal John
		Sree Avittam Thirunal Hospital (SAT) Hospital, Trivandrum	Sheila Balakrishnan, R Mohan

List of Project Associates

Mentor	G Montgomery, Institute for Molecular Biosciences, The University of Queensland, Australia
Supervisor	Smita Mahale
Collaborator	Gita Mishra, School of Public Health, University of Queensland, Australia
(Epidemiology)	R Dikshit, Tata Memorial Center, Mumbai
Project Associates	Geetanjali Sachdeva, H Munshi, Sandhya Anand, Shahina Begum, Shagufta Khan, Akshata Shetty, Ashwini Patel, Arti Kushwaha, Kiran Kharsodiya, Komal Khade, Tabassum Khan, Naffifa Rehman, Sheetal Dubey, Sindhya Raju, Teesta Banerjee, Sakshi Gangurde, Nayana Barada, Narayani Bhat, Namita Naik, Priya Ingle

Endometriosis is a chronic, estrogen-dependent, inflammatory condition associated with pelvic pain, subfertility, dysmenorrhea, and dyspareunia, affecting 6-10% of women of reproductive age. We have undertaken a large-scale case-control study to investigate the clinical phenotypes and genetic risks associated with endometriosis in the Indian population. Replication analyses for genetic risk factors proposed for our Endometriosis Clinical and Genetic Research in India (ECGRI) study will consider new results from the latest IEGC meta-analysis. ECGRI is a large-scale, multi-site, case-control study covering representative Indian populations of eastern/north-eastern, northern, central, western, and southern geographical zones of India. During the reporting year, a total of 525 endometriosis cases and 587 hospital controls were recruited making a total of 1658 cases and 1651 Controls till March 31, 2023. A total of 3309 study participants were recruited against the total sample size of 4000. The clinical and surgical data of the 1147 cases and 1147 controls was analysed during the reporting year. All three sub-phenotypes of endometriosis: superficial peritoneal (SUP), ovarian endometrioma (OMA), and deep infiltrating endometriosis (DIE) were observed in Indian women. Isolated and/or overlap of the subtypes of endometriosis was seen in Indian women. The distribution of isolated lesion types reported in our study cohort was as follows: 40.1 % OMA, 17.9 % SUP and 7 % DIE. OMA (55.4%) is the most common lesion type reported in Indian women followed by DIE (26.8%) and SUP (17.9%). This observation of OMA as most common lesion type in Indian population is in contrast to European populations wherein superficial peritoneal (SUP) accounts for ~80% of endometriosis. There was an average delay of 7.3 years from onset of symptoms to diagnosis of endometriosis in Indian women. There is a small significant difference between mean age of endometriosis cases and controls. Nearly 70% of the women suffering from endometriosis were unemployed suggesting the impact of endometriosis on their career. There is evidence of association between age, education, marital status, and occupation with endometriosis in Indian women. There is evidence of association of comorbidities with endometriosis in Indian women.

Following comorbidities were significantly associated with endometriosis: cancer, asthma, diabetes mellitus, epilepsy, hypertension, spine disorders, anaemia, thyroid disorders, pelvic inflammatory disease, PCOS, Tuberculosis, liver and gastric disorders. Two batches of 192 samples (randomized cases and controls) were sent to National Institute of Biomedical Genomics (NIBMG), Kalyani, West Bengal for genotyping using Illumina Infinium beadchip (GSA v3+ MD). Detailed clinical and genotype data analysis is under progress.

1.14 Omics of Serum Exosomes in Endometriosis: An Attempt to Identify a Possible Biomarker *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator	:	D K Das
Co-Principal Investigator	:	Geetanjali Sachdeva
Project Associate	:	Kanchan Sharma
Collaborators	:	V Salunke, Shinjini Pande, Nalini Speciality Hospital, Mumbai
Duration	:	2022-2027

Endometriosis is a chronic estrogen dependent disorder inflammatory disorder that affects approximately 10% of women of reproductive age. The quality of life is affected in women with endometriosis. Clinical signs and symptoms are non-specific, hence, definite diagnosis of endometriosis is only by laparoscopic examination, which is an invasive procedure. Therefore, there is a need to develop a simple non-invasive technique that can identify/diagnose the disorder.

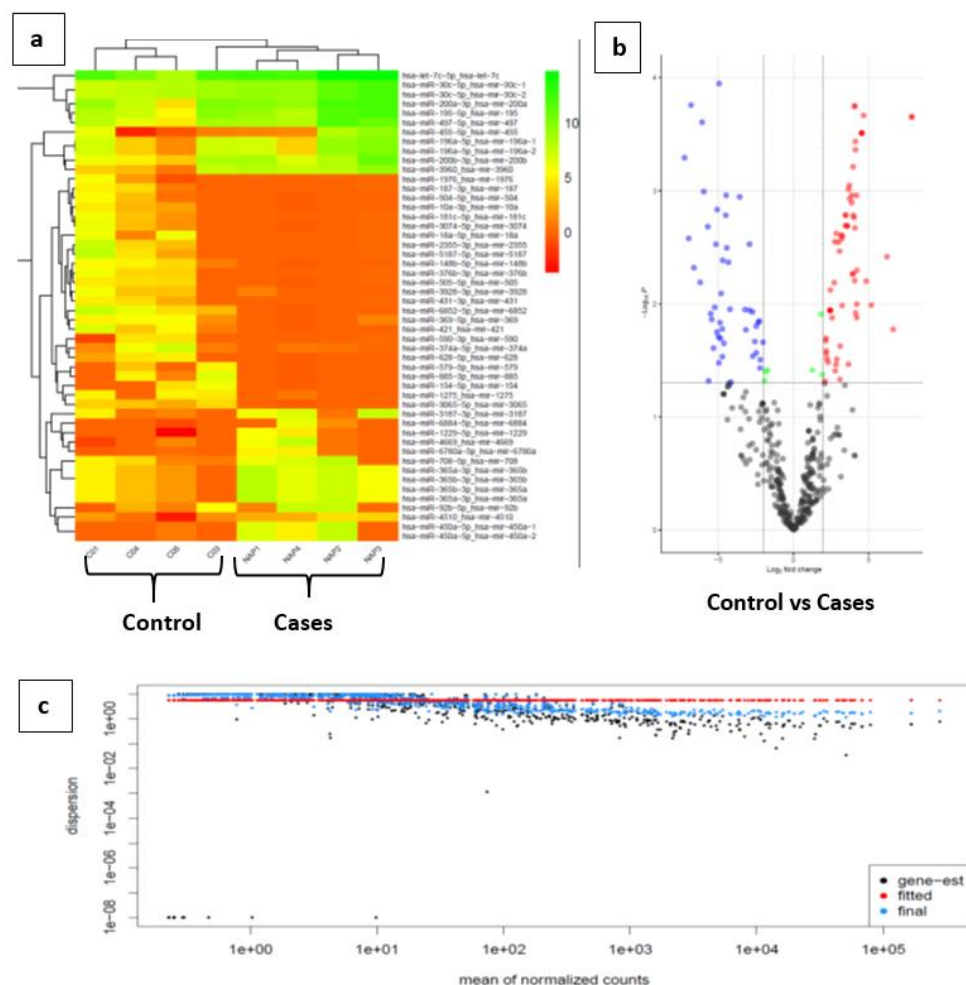


Figure 1: Differential expression of miRNAs between the endometriosis and control groups. a. Heat map analysis of differentially expressed miRNAs; b. Volcano plot of differentially expressed miRNAs; c. Dispersion analysis of the differential expression of miRNAs.

In this project, a total of 9 patients and 19 controls have been enrolled in the reporting year. The size of isolated exosomes was found to be within the range of exosomes (114.9±82.7nm and 141.8±48.8 nm).

Further, they were also characterized for the presence of exosomal protein marker. Upon analysis of 4 samples in each cases and controls, a total of 56 miRNAs were found to be differentially expressed, of which 32 were downregulated and 24 upregulated. Among the differentially expressed miRNAs, 27 miRNAs were selected (Table 1) for further validation. A customized miRNA arrays has been designed using Qiagen LNA miRNA PCR chemistry. The validation of the customized panel is ongoing in a larger cohort of patients.

Table 1: List of significant by upregulated and downregulated miRNAs identified in the serum exosomes of endometriosis patients

Upregulated miRNAs			Whether previously reported in endometriosis
miRNA ID	log2 Fold Change	p value	
hsa-miR-199b-3p	2.4364688	0.0114246	YES
hsa-miR-30c-5p	4.0631689	0.0001784	YES
hsa-miR-145-5p	3.8742029	0.0012736	YES
hsa-miR-200a-3p	3.9743843	0.0016501	YES
hsa-miR-30a-5p	3.0690754	0.0034234	YES
hsa-miR-708-5p	4.1279019	0.012048	YES
hsa-miR-125b-5p	3.9664103	0.0006116	YES
hsa-miR-196b-5p	3.7370166	0.0011721	YES
hsa-miR-30b-5p	3.4521235	0.0020277	YES
hsa-miR-3960	4.0888948	0.0021318	YES
hsa-miR-450a-5p	7.861592	0.0002223	YES

Downregulated miRNAs			Whether previously reported in endometriosis
miRNA ID	log2 Fold Change	p value	
hsa-miR-223-3p	-2.26936	0.0141885	YES
hsa-miR-148b-5p	-6.07443	0.0002476	YES
hsa-miR-628-3p	-4.37747	4.34E-07	YES
hsa-miR-6852-5p	-7.56369	6.83E-06	YES
hsa-miR-150-5p	-1.8591111	0.0397695	YES
hsa-miR-181c-5p	-5.50107	0.012204	YES
hsa-miR-365a-3p	4.53971	0.0003086	YES
hsa-miR-485-3p	-4.67486	3.16E-07	YES
hsa-miR-143-3p	3.9664103	0.0006116	YES
hsa-miR-1275	-5.43676	0.0137143	YES
hsa-miR-191-3p	-3.16253	0.0169471	YES
hsa-miR-369-5p	-5.0727	0.0014667	YES
hsa-miR-409-3p	-2.22639	0.0369012	YES
hsa-miR-1277-5p	-5.43676	0.0137143	YES
hsa-miR-93-3p	-4.47837	0.0010963	YES
hsa-miR-144-3p	-2.2063634	0.0311815	YES

1.15 Human Endometrial Stem Cells and their Possible Role in the Etiology of Endometriosis *(Partly Funded by Department of Biotechnology)*

Principal Investigator : **D K Das**
 Co-Principal Investigator : Geetanjali Sachdeva
 Project Associate : Mousumi Bal
 Collaborators : V Salunke, Shinjini Pande, Nalini Speciality Hospital, Mumbai
 Duration : 2023-2028

Endometriosis (EM) is a chronic estrogen-dependent disorder defined by endometrium-like tissues outside the uterus. Human endometrium is a dynamic tissue with a high capacity of regenerative ability. The "stem cell" theory for endometriosis revealed that the retrograde flow of menstrual efflux with endometrial stem cells gives rise to endometriotic lesions such as Deep Infiltrating Endometriosis (DIE), Ovarian Endometriosis (OMA), Superficial Peritoneal Lesion (SUP). The aim of the study is to elucidate the putative role of tissue-resident endometrial stem cells in disease pathophysiology. Endometriotic samples and paired eutopic endometrial samples from women with endometriosis (Group 1; n=15), women with endometriosis with comorbidities such as adenomyosis and fibroid (Group 2; n=39), and eutopic endometrial samples from women with adenomyosis/fibroid (control EU; n=14) were collected during the reporting period. In-vitro experiments were conducted to characterize eMSCs isolated from ectopic and eutopic endometrium. eMSCs isolated using MACS with SUSD2 antibody were cultured. Spindle-shaped, fibroblast-like morphology with a radial or helical growth pattern was observed in the cultured control EU eMSC. However, MSCs from ectopic lesions exhibited an irregular morphology (Fig. 1A). MSCs were also characterized at passage 3 using immunofluorescence for MSC markers [co-staining of SUSD2 with CD90/ CD105] (Fig. 1B). Mesodermal lineage differentiation into osteogenic and adipogenic were carried out to confirm MSC characteristics. The presence of oil droplets confirmed the adipogenic differentiation using Oil Red O staining. Bone nodule formation and extracellular calcium deposition confirmed osteogenic differentiation, visualized by alizarin red staining (Fig. 1C & 1D).

To elucidate the functional properties of eMSC, two functional assays were performed. Wound healing assay demonstrated that ectopic eMSCs had higher migration property across different time points (Fig. 2A). The migratory capacity of Group2 DIE eMSCs was found to be significantly higher at 24 hours and 30 hours compared to control EU eMSCs and Group 2 EU eMSCs. Group 1 DIE eMSCs showed significantly higher migratory capacity compared to Group 2 EU eMSCs only at 30 hours (Fig. 2B). Transwell assay revealed that Group2 DIE eMSCs has enhanced migratory capacity compared to control EU eMSCs, as evidenced by the higher number of cells migrating through the insert to the lower surface (Fig. 2C). This preliminary evidence indicated altered phenotype of ectopic eMSC with an enhanced migratory capacity.

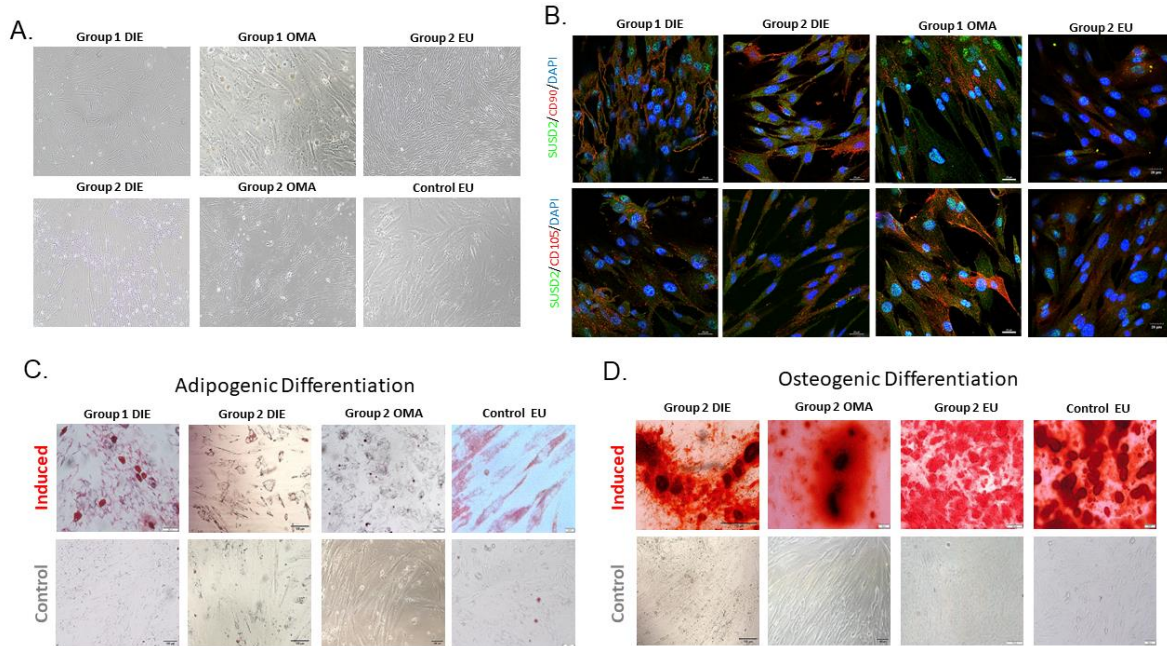


Figure 1: Characterization of endometrial Mesenchymal stem cells isolated from ectopic and eutopic tissues. (A) Cell morphology of cultured endometrial mesenchymal stem cells (B) Immunolocalization of SUSD2, CD90, and CD105 eMSCs markers (C) Adipogenic differentiation of eMSCs observed with Oil Red O staining (D) Osteogenic differentiation observed with alizarin red staining.

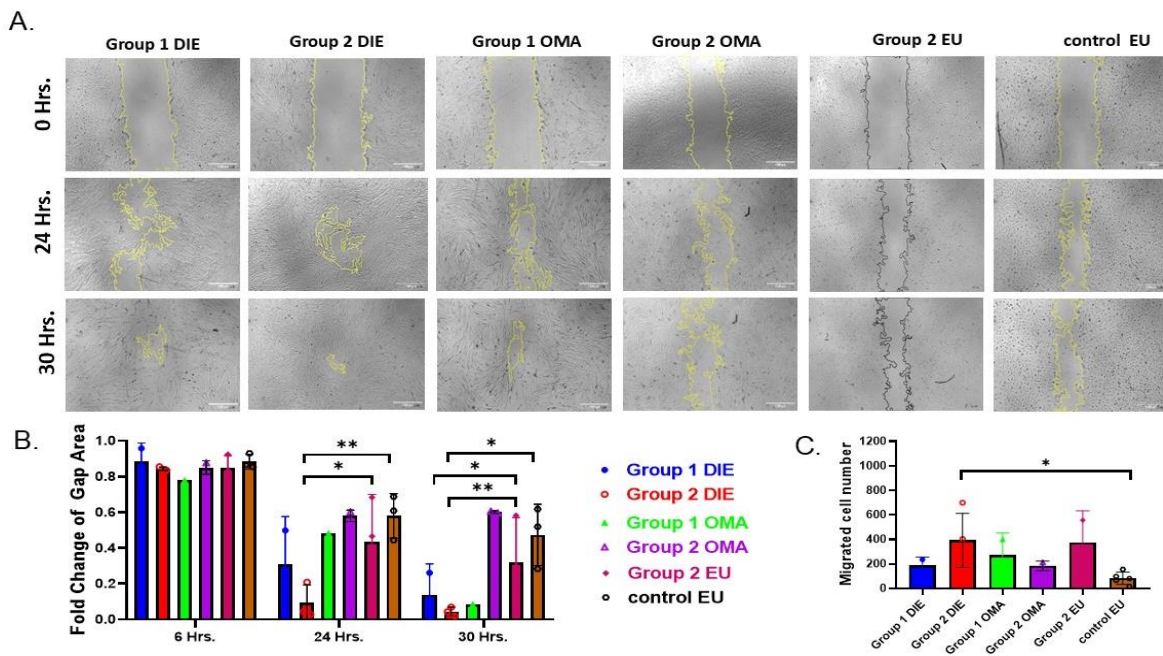


Figure 2: Functional assays of eMSCs isolated from ectopic and eutopic tissues. (A) Representative images of wound healing assay performed on 95% confluent eMSC cells (passage 3) on 6-well plates to examine the migration capacity of eMSC into the wounded area at the indicated time points are shown (B) Fold change of Gap area was calculated compared to 0 hours for each time points. Data represented as mean $\pm$ SD (C) Quantification of migrated cell number in the Transwell assay. Data represented as mean $\pm$ SD. * $p < 0.05$, ** $p < 0.01$.

1.16 Investigating the Contribution of DNA Damage, Repair and Demethylation in Pathogenesis of Endometriosis (Partly Funded by Department of Biotechnology)

Principal Investigator : Geetanjali Sachdeva
Co-Principal Investigator : R Gajbhiye
Project Associates : Itti Munshi, U Chaudhari
Collaborators : A Mangeshikar, Jaslok Hospital, Mumbai
Pratima Thamke, MGM Hospital, Navi Mumbai
Duration : 2019-2024

Endometriosis is defined by the presence of endometrium like tissue outside the uterus. These eutopic endometrium like tissue can form lesions at ectopic sites such as the peritoneal wall, ovary, intestine or rectum. Higher oxidative stress, inflammation and higher proliferation are well established traits of eutopic and ectopic endometrium from women with endometriosis. These attributes together with higher levels of estrogen can contribute to DNA damage in the eutopic (EUE) and ectopic endometrium (ECE) in endometriosis. In addition, numerous studies have reported an altered methylome in the eutopic and ectopic endometrium from women with endometriosis compared to women without endometriosis. These methylation changes aid in survival and proliferation of endometriotic cells.

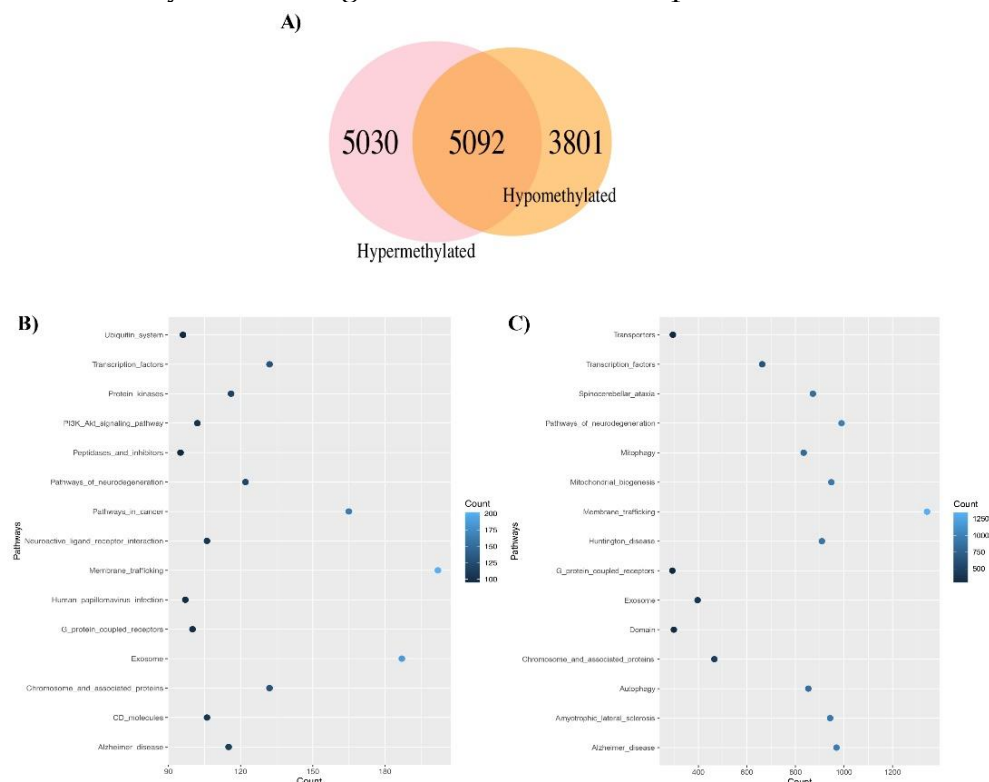


Figure 1: Genes undergoing differential methylation (5mC) in response to oxidative stress (10µM, 8 hours) in t-HESC cell line. (A) Venn diagram showing number of hypomethylated and hypermethylated genes in oxidative stress induced t-HESC cell line. Top 15 pathways found (B) hypomethylated and (C) hypermethylated in response to oxidative stress.

To elucidate the methylation changes induced by DNA damaging stimulus in the endometrium. Oxidative stress was induced in the endometrial stromal cell line (t-HESC). Oxo-bisulfite sequencing revealed alterations in the 5-methylcytosine (5mC) levels in the t-HESC cells exposed to oxidative stress compared with untreated cells (Fig. 1A). Genes involved in PI3K-Akt signalling, ubiquitin system, pathways in cancer and membrane trafficking were amongst the hypomethylated pathways (Fig. 1B). Whereas genes involved in autophagy, mitophagy and mitochondrial biogenesis were found to be hypermethylated (Figure 1C). 5mC hypomethylation was observed in 67 genes involved in the pathways of cancer at the promoter region. These included genes like FGFR3, CTBP2, CTTN, DVL2, PFKP, F2RL3 and NFATC1. The expression of these genes showing hypomethylation at the promoter region was checked in the largest endometriosis expression dataset (GSE11691). These investigations revealed alterations in the expression levels of DVL2, FGFR3, CTBP2 and NFATC1.

1.17 Damage Associated Molecular Patterns (DAMPs) and their Receptors in Endometrial Repair *(Partly Funded by Science and Engineering Research Board)*

Principal Investigator : **U Chaudhari**
 Co-Principal Investigator : Geetanjali Sachdeva
 Project Associates : A Khandvilkar, SM Metkari
 Collaborators : Vandana Bansal, Deepti Tandon
 Duration : 2019-2024

Endometrium is a highly dynamic tissue which proliferates, differentiates, degenerates and undergoes repair in each human menstrual cycle. Initial events of endometrial repair occur simultaneously during the menstrual phase, independent of steroid hormones. Damage Associated Molecular Patterns (DAMPs) are molecules released extracellularly during physiological or pathological damage of cells. Extracellular DAMPs act as cytokines and induce inflammatory responses that promote tissue repair. The aim of the present study is to understand the role of DAMPs (HMGB1) and their receptor (RAGE) in endometrial breakdown and repair. In the previous year (Annual report 2022-23), we reported involvement of HMGB1-RAGE axis in endometrial break-down and repair using Rat model of induced menstruation. The ovariectomised rats were sequentially administered with estrogen and progesterone to induce decidualization of the endometrium. On systemic withdrawal of the progesterone the endometrium undergoes breakdown by 24 hrs and repair by 48 hrs on progesterone withdrawal. In the reporting year, we made attempts to delineate the role of HMGB1-RAGE axis in endometrial repair. To achieve this rat model of induced menstruation were treated with glycyrrhizin (HMGB1 antagonist) and FPS-ZM1 (RAGE antagonist) 24h after progesterone withdrawal. All the rats were sacrificed at 48h post-progesterone withdrawal. Glycyrrhizin binds directly to the HMGB1 and also prevents its release as DAMP, from the cells while FPS-ZM1 prevents interaction of RAGE with its ligands thereby attenuating its signalling. After sacrifice, the endometrium was histologically categorized on the basis of morphological stages ranging from stage 1 (intact endometrium without shedding) to stage 5 (complete re-epithelialization of the endometrium). In control group, the endometrium of all the rats (100%) were completely re-epithelialized i.e. stage 5 (Fig. 1 A, B & C; Fig. 2) while endometrium of all the glycyrrhizin treated rats (100%) showed in-complete re-epithelialization i.e. stage 4 (Fig. 1 D, E & F; Fig. 2). In FPS-ZM1 treated group, the endometrium of 87% rats was at stage 5 (Fig. 1 G, H & I; Fig.

2) while on combined treatment with both the antagonist, endometrium of 75% of rats showed complete breakdown but no signs of re-epithelialization hence categorised into stage3 (Fig. 1 J, K & L ;Fig. 2). These findings suggest that the HMGB1-RAGE axis is essential for activating the mechanisms involved in re-epithelialization, a prerequisite for the regeneration of the endometrium. Further studies are underway to delineate the mechanisms of HMGB1-RAGE axis in endometrial re-epithelialization.

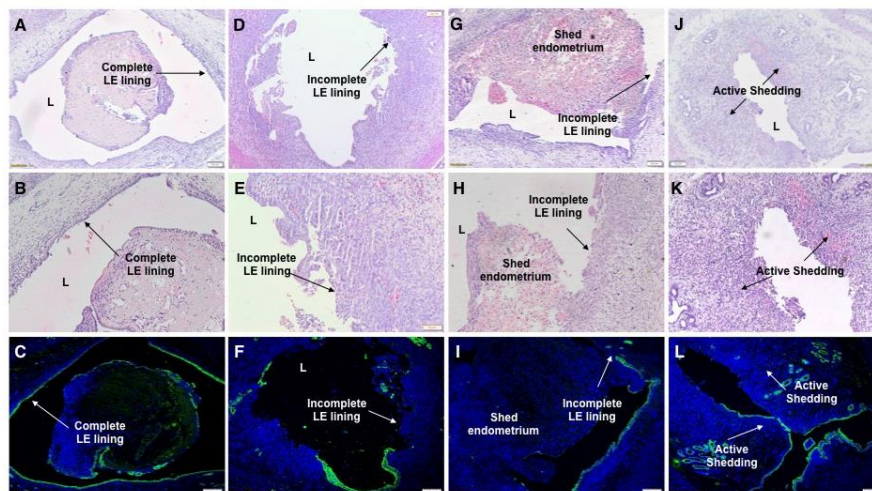


Figure 1: Representative image of Hematoxylin & Eosin staining of the rat uterine horn section of vehicle control (A & B), glycyrrhizin treated (C & D), FPS-ZM1 treated (E & F) and treated in combination of both glycyrrhizin and FPS-ZM1 (G & H), sacrificed 48 hrs after P4 implant removal. Panel C, F, I & L depicts pan-cytokeratin staining of uterine horn sections of rats treated with vehicle, glycyrrhizin, FPS-ZM1 and combined treatment of glycyrrhizin and FPS-ZM1. Magnification 4X (A, C, E & G) and 20X (B, D, F & H).

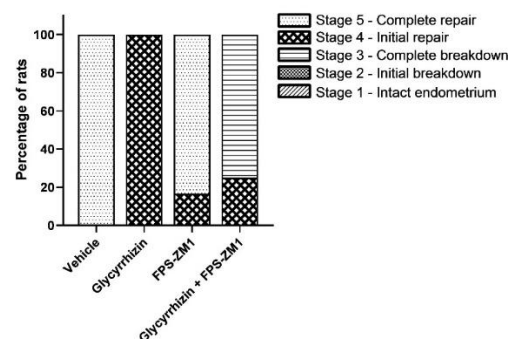


Figure 2: Graph showing percentage of rats displaying different morphological stages ranging from 1-5, treated either with glycyrrhizin (HMGB1 antagonist), FPS-ZM1 (RAGE antagonist) or both, along with a vehicle control.

1.18 Effects of Metformin on Reproductive Aging in Rats

Principal Investigator : **U Chaudhari**
 Co-Principal Investigator : Geetanjali Sachdeva
 Project Associates : G Paswan, S M Metkari
 Duration : 2022-2025

The reproductive aging is a gradual decrease in both the quantity and quality of the oocytes residing within the follicles. Metformin, an anti-diabetic drug, has been found to extend the lifespan by eliciting anti-aging effects in mice. Ovary is one of earliest-aging organs. Metformin has been shown to have beneficial effects on PCOS ovary as it improves ovulation and pregnancy rates. However, anti-aging effects of metformin have not been investigated in normal ovary. The aim of present study is to delineate the effects of metformin on ovarian aging in a rat model. Six month old rats were administered metformin 0.1% and 0.5% in drinking water for 6 months. Ovaries were sectioned serially (5-micron thickness) and follicles were counted in every fifth section, in total of the five

sections. The follicles in the ovary were counted such as primordial follicle (having a single layer of squamous granulosa cells), primary follicles (with single layer of cuboidal granulosa cells), secondary follicles (with two or more layers of granulosa cells), antral follicles (having the presence of fluid filled antrum). There was no significance difference in the number of follicles at different stages of development in the rats treated with metformin compared to control. We reported previously that there occurs no change in the serum levels of markers of ovarian aging, AMH in both 0.1% and 0.5% metformin treated rats compared to control. Our finding suggests that that treatment with 0.1% and 0.5% metformin in drinking water does not have effects on the marker of ovarian aging in spontaneously aged rats. Further studies have been planned to administer metformin through oral gavage to investigate the effects of metformin on reproductive aging.

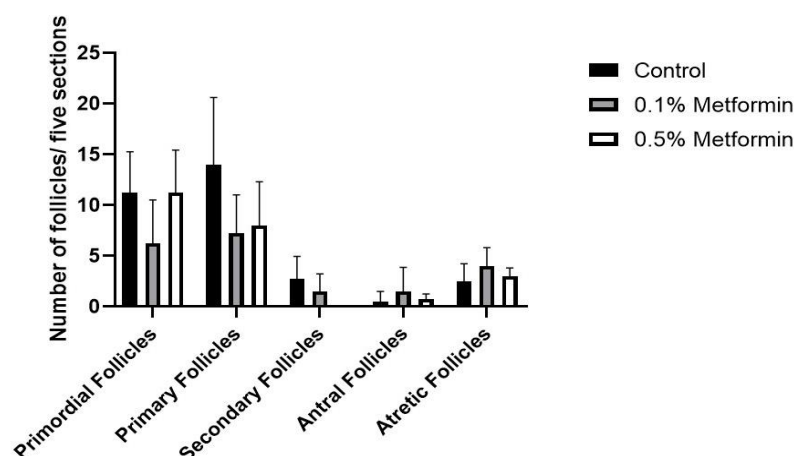


Figure 1: A grouped bar graph showing the number of follicles at different stages in metformin treated rats.

1.19 Uterine Alarmins and their Relevance in Implantation *(Partly Funded by Science and Engineering Research Board, Department of Science and Technology)*

Principal Investigator : **Geetanjali Sachdeva**
 Co-Principal Investigator : SK Adiga, KMC, Manipal
 Project Associates : U Chaudhari, V Patel, SM Metkari, RR Katkam, Rithika Rajendran, Sheetal Singhania
 Collaborators : P Narayan, Anjali M, Kasturba Medical College (KMC), Manipal
 Duration : 2019-2024

Alarmins or damage associated molecular patterns are endogenous molecules that are secreted in response to stress or other stimuli. Alarmins elicit an inflammatory response in the absence of any pathogen, a phenomenon known as sterile inflammation. Regulated inflammatory responses are crucial in several reproductive events such as menstruation, implantation and parturition. Regulated inflammation is essential for breaching of an embryo to endometrial lining and tolerogenic immune responses for semi allogene embryo. Unopposed inflammation during implantation can lead to early pregnancy loss or recurrent implantation failure. Previously, our laboratory had identified the presence of the alarmin HMGB1 in the uterine fluid of healthy women, with lower levels in the receptive phase as compared to the pre-receptive phase (Annual report 2010-11, pp. 25-26). Similarly, HMGB1 levels

across the estrus cycle in rats were measured and was found to be the highest in diestrus phase and lowest in the receptive, i.e. the metestrus phase. Furthermore, it was demonstrated that excess of HMGB1 in the uterine milieu at the time of implantation led to implantation failure in rats (Annual report 2013-14, pp. 23-24).

In this reporting year our focus was on the effect of excess of HMGB1 on the uterine immune profile during implantation. Recombinant HMGB1 (rHMGB1) was exogenously administered in the rat uterine horns on day 3 post coitum (p.c.) and the animals were sacrificed on day 5 p.c. Flow cytometry analysis showed reduced frequency of DBA-lectin⁺ uterine natural killer (NK) cells in the uterus of rHMGB1-treated rats during implantation. Similarly, a lower frequency of uNK cells was observed in the diestrus phase as compared to the metestrus phase in the uterus of non-conception cycle in rats. Thus, the abundance of the uNK cell population in the rHMGB1-treated uterine horns during implantation was comparable to their frequency in the non-receptive diestrus phase. Additionally, immunofluorescence of stromal cell decidualization marker prolactin revealed lower expression of the protein at the implantation sites in rHMGB1-treated uterus as compared to sham control. A trend towards lower level was also observed in the immunolocalisation of IGFBP1, also a marker for decidualization, in the treated horns (panel 2B & 2D). These results suggested that altered uNK cell profile in rHMGB1-treated uterine horns was associated with impaired stromal cell decidualization. Further studies are underway to characterize other inflammatory markers in gestational and non-gestational uterus in response to rHMGB1.

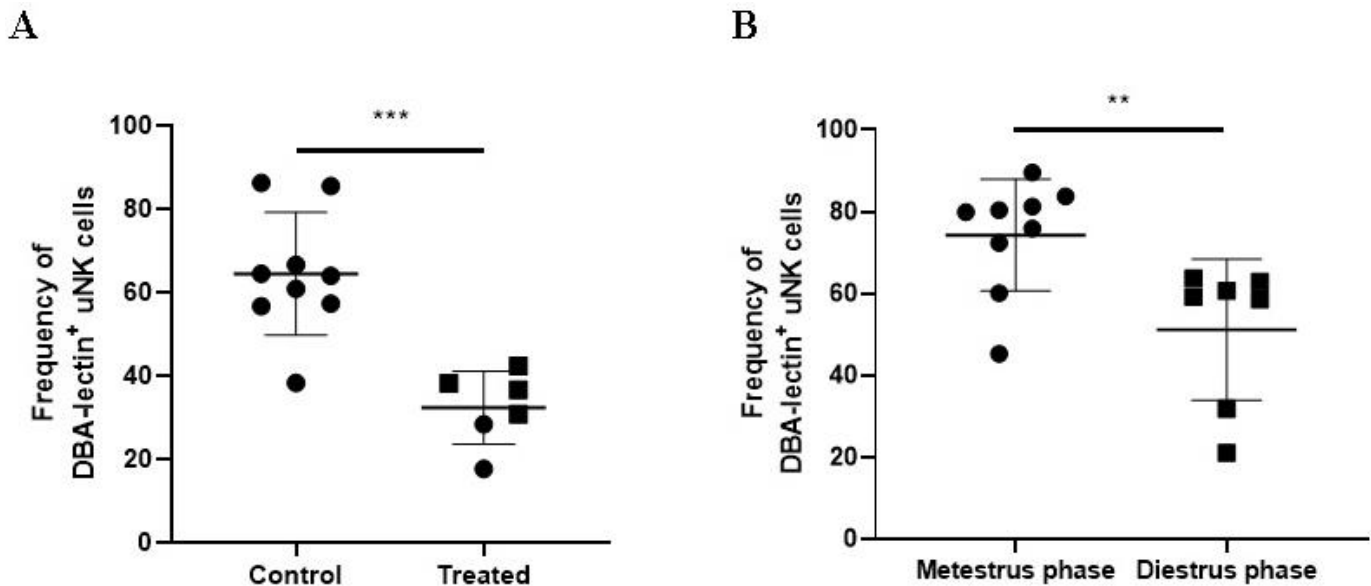


Figure 1: Excess of HMGB1 alters the frequency of DBA-lectin⁺ uNK cells on day 5 p.c. (panel A) as determined by flow cytometry of endometrial cells isolated from sham and rHMGB1-treated animals. DBA-lectin⁺ uNK cells were found to be fewer in the diestrus (non-receptive) phase, as compared to metestrus (receptive) phase (panel B). * in panels A (p=0.0004) and B (p=0.0095) indicate statistical significance of the difference between the two groups.

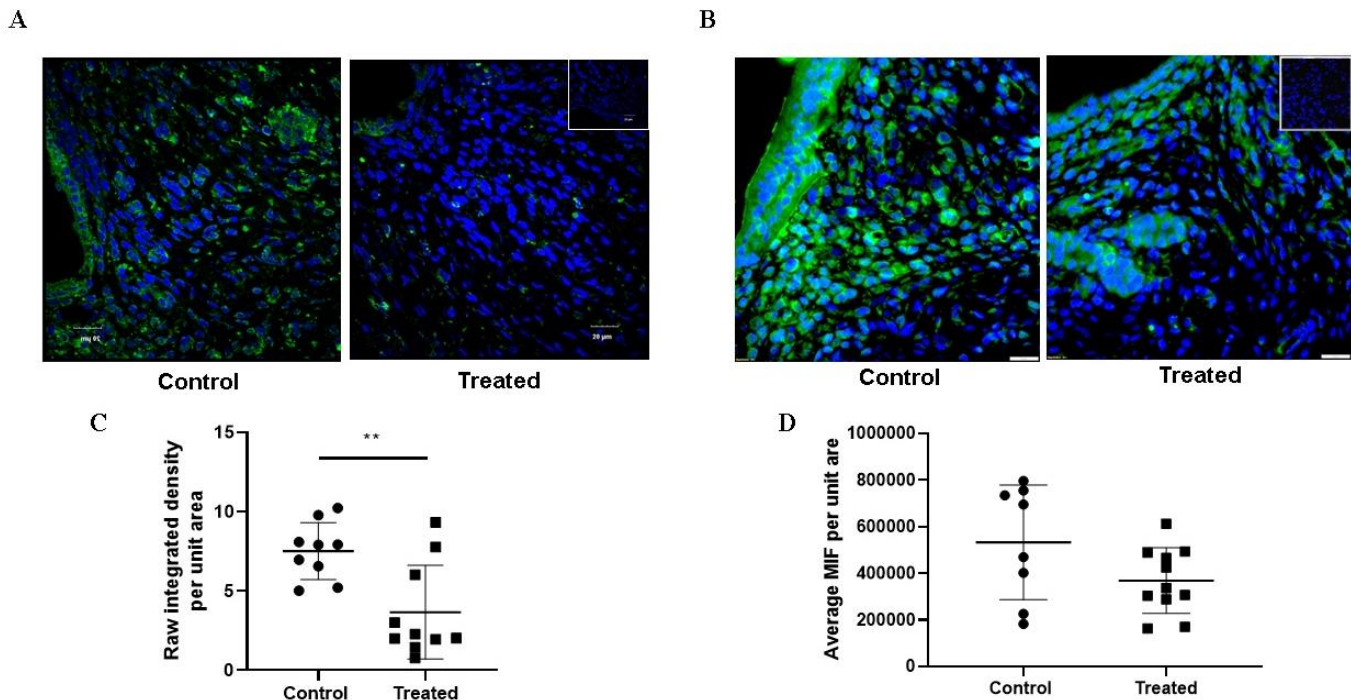


Figure 2: Immunofluorescence localisation of stromal cell decidualization markers i.e. prolactin (panels A and C) and IGFBP1 (panels B and D). Images in panels A & B are at 60X magnification. * in panel C ($p=0.0035$) indicates statistical significance of the difference between the two groups.

1.20 Deciphering the Immunomodulatory Roles of Homeobox A10 in the Endometrium during Embryo Implantation (Partly Funded by Department of Biotechnology)

Principal Investigator : **DN Modi**
 Co-Principal Investigator : Nupur Mukherjee
 Project Associates : Richa Sharma, Babita Negi
 Collaborator : S Chauhan
 Duration : 2021-2025

The success of embryo implantation depends on genetic and cellular interactions which must be executed during the window of implantation. Immunomodulation in the endometrium is a central event as the system has to prepare itself for accommodating the semi-allogenic blastocyst along with continuous maternal surveillance against the pathogens. Studies have shown that embryo implantation requires a pro-inflammatory condition which is characterized by an increase in inflammatory cytokines and recruitment of immune cells in the endometrium during embryo implantation. Despite this, the classical inflammation reaction does not take place and the fetus is retained suggesting the controlled inflammation during embryo implantation. The mechanism underlying controlled inflammation during implantation is still not clear. IL-1 β processing is driven by inflammasomes (oligomeric multi-protein complexes) and is impeded via autophagy. Therefore, an equilibrium between autophagy and inflammasome is important for controlling inflammation. Immunity-related GTPase M1 (Irgm1) negatively regulates inflammasomes by blocking the oligomerisation of inflammasome components and activating autophagy. Thus we aim to investigate the role of Irgm1 in the process of embryo

implantation. The litter size of Irgm1 knockout was compared with wild-type mice. The knockouts showed significantly reduced litter size (Fig. 1a) and took minimum three times longer to conceive than the wild-type indicating they are sub-fertile (Fig. 1b). Moreover, 10% of knockouts were found to be infertile. Thus, Irgm1 does seem to play a role in embryo implantation. Further studies related to the expression of Irgm1 with respect to inflammasomes are ongoing.

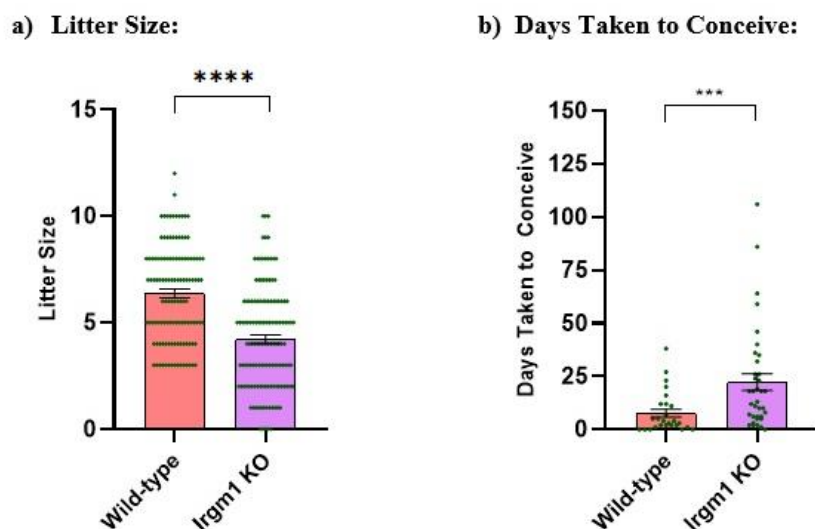


Figure 1: a) Litter size of wild-type vs Irgm1 knockout (Litter Size: $p = <0.0001$) b) Number of days taken by wild-type and Irgm1 knockout to conceive after mating (Days taken to conceive: $p = 0.008$)

1.21 Investigating the Role of Epithelial to Mesenchymal Transition in the Process of Embryo Implantation *(Partly Funded by Department of Science and Technology, Science and Engineering Research Board)*

Principal Investigator : **DN Modi**
 Project Associates : Nancy Ashary, Pranya N
 Duration : 2019-2023

Embryo implantation involves three stages adhesion, attachment, and invasion. This process eventually allows the trophoctoderm to demolish the LE barrier and make direct contact with the underlying stroma. Genetic studies show that blocking trophoctoderm passage through the LE barrier is a contributing factor to implantation failure. Even while trophoctoderm-LE interactions have been researched for decades; it is still unknown how LE cells get cleared up. Based on our preliminary research, we hypothesized that the epithelial to mesenchymal transition (EMT) causes luminal epithelium to dislocate, leading to embryo invasion. In the reporting year, we knock downed HOXA10 expression in endometrial epithelial cells using shRNA against HOXA10. Next, we studied E cadherin and N cadherin EMT marker and the results showed that HOXA10 loss led to a decrease in E cadherin and an increase in N cadherin, which is quantified and depicted in graph (Fig. 1).

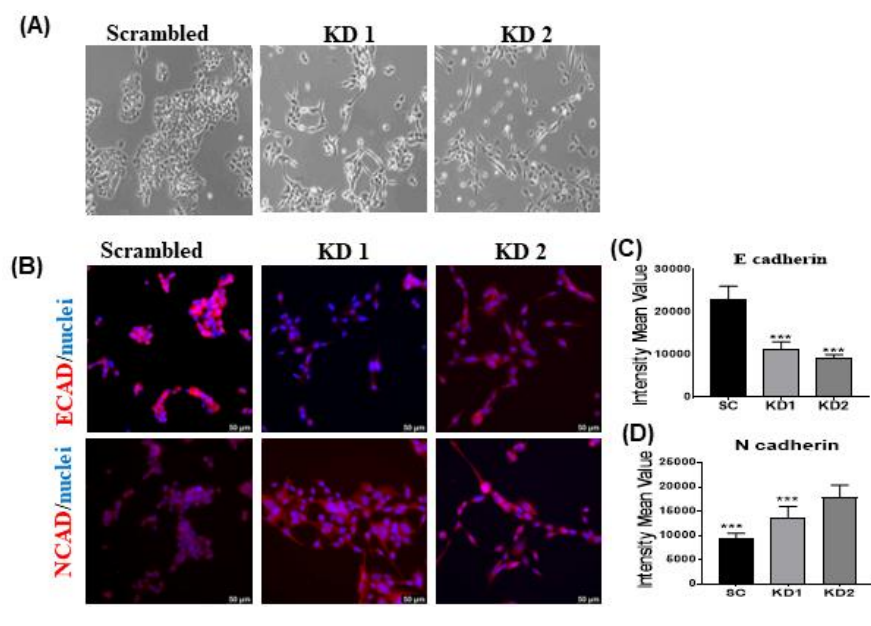


Figure 1: Effect of loss of HOXA10 on expression of EMT markers in the endometrial epithelial (RL 95) cells. (A) Morphological changes in scrambled and HOXA10 knockdown (KD1 and KD2), (B) Immunofluorescence for E CAD and N CAD (red) and nuclear (blue) in scrambled and HOXA10 knockdown (KD1 and KD2) cells, (C) Fluorescent intensity of E cadherin in scrambled and HOXA10 knockdown (KD1 and KD2) cells, (D) Fluorescent intensity of N cadherin in scrambled and HOXA10 knockdown (KD1 and KD2). KD= Knockdown. ***p<0.001

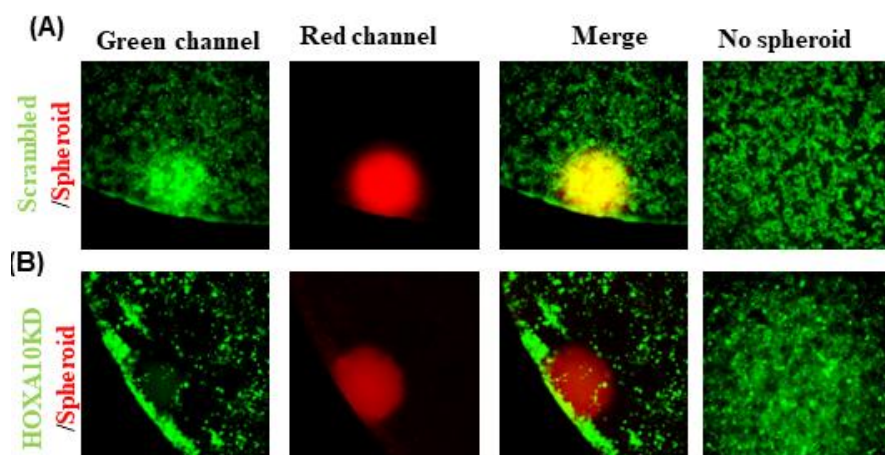


Figure 2: Effect of trophoblast spheroid on human endometrial epithelial cells. (A) Endometrial epithelial cells (green channel), trophoblast spherical (red channel) of scrambled cells. (B) Endometrial epithelial cells (green channel), trophoblast spherical (red channel) of HOXA10 knockdown cells.

Furthermore, we demonstrate that endometrial epithelial cells undergo morphological alterations in response to loss of HOXA10. Cuboidal cells with appropriate cell-cell interaction are visible in transfected cells with scrambled siRNA. On the other hand, HOXA10 knockdown resulted in a lack of cell-cell contact, flattening and elongation of cells which exhibit EMT features. We have validated the result using two different shRNA target against HOXA10 (KD1 and KD2) and we have obtained similar result showing loss of HOXA10 induces EMT in endometrial epithelial cells. We then performed a displacement assay in which endometrial epithelial cells were seeded with trophoblast spheroid and allowed to adhere. We examined the clearing region surrounding the spheroid following a 24-hour incubation period. In contrast to the cells transfected with scrambled shRNA, where no alterations were detected, the HOXA10 knockdown endometrial epithelial cells migrated away from the spheroid. This suggests that the loss of HOXA10 causes endometrial cells to acquire an EMT phenotype and migrate away from the trophoblast spheroid (Fig. 2). This work mimics in vivo embryo implantation. To summarise, HOXA10 appears to be a regulatory molecule to preserve the epithelial phenotype in the endometrium, its reduction induces EMT state at the time when the embryo has to breach the LE.

1.22 Elucidate the Endometrial Mesenchymal Stem Cells' Role in Mediating Early Pregnancy: Function of Reversible Mesenchymal-Epithelial Transition (Partly Funded by India Alliance DBT/Wellcome Trust)

Principal Investigator : **Jayeeta Giri**
 Co-Principal Investigator : D Modi
 Project Associates : Deepti Tandon, R Sreedharan
 Duration : 2023-2028

Major objectives of the study are to delineate the role of endometrial Mesenchymal Stem Cells (eMSCs) in embryo implantation and study if eMSCs function is altered in women with Recurrent implantation failure (RIF). Specific aims were in vitro/ in vivo characterization of the eMSCs, investigating the occurrence of mesenchymal-epithelial transition events during the course of mouse embryo implantation, to compare the transcriptome profiles of MSCs isolated from the mouse endometrium during the course of embryo implantation, to probe the pregnant mice-derived eMSCs' ability in regulation of decidualization, immunomodulation and angiogenesis in vitro, to characterize the eMSCs derived from women with and without RIF, to compare the ability of eMSCs derived from women with and without RIF in regulation of decidualization, immunomodulation and angiogenesis in vitro.

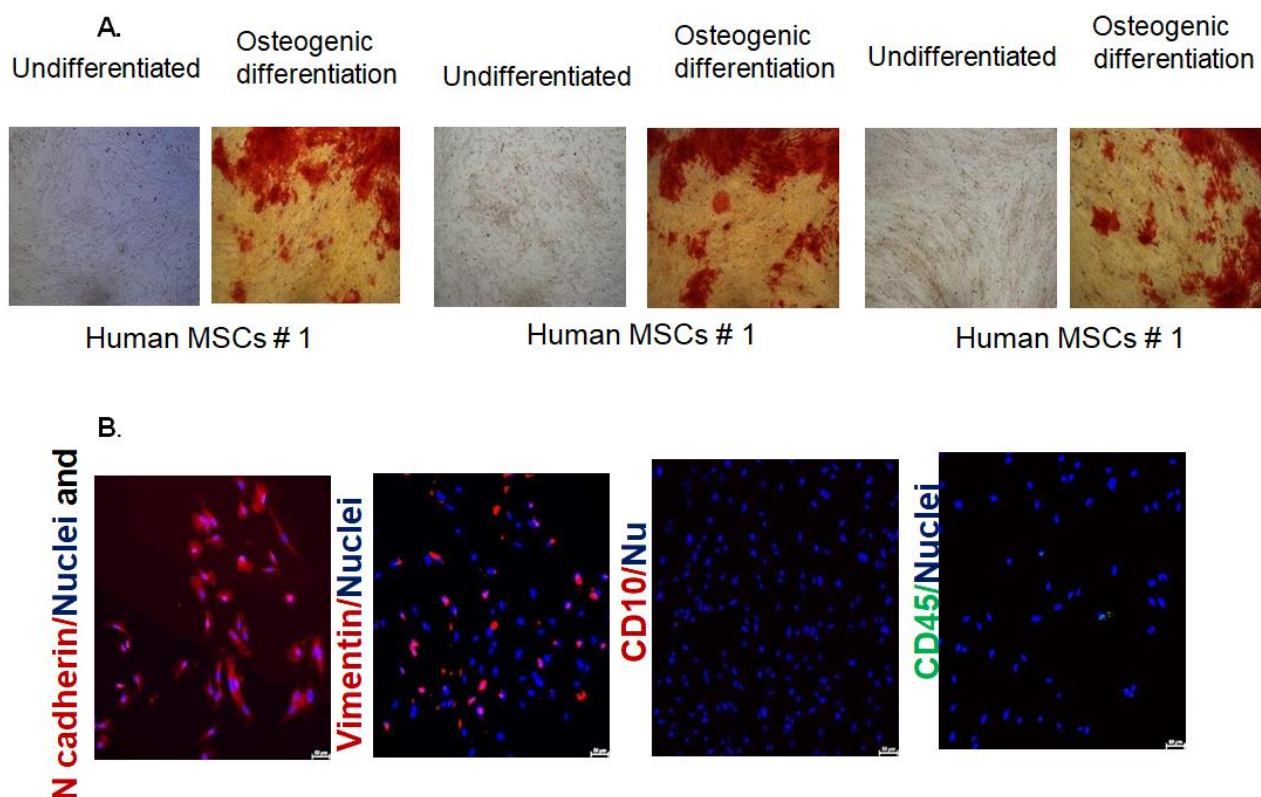


Figure 1: (a) Human MSCs derived from menstrual blood from three healthy women were characterized on the basis of osteogenic differentiation potential. (b) The cells were immunostained for N cadherin, Vimentin, CD10, CD45. The cells express mesenchymal markers N cadherin, Vimentin. However, the cells do not express hematopoietic markers CD10 or Cd45.

In order to characterize eMSCs during the course of embryo implantation, C57BL/6 male and female mice (10 weeks age) were mated. At different days after vaginal plug formation (Day 5, Day 6 and Day 7), pregnant mouse endometrial tissue was collected and flash frozen. Now we are standardizing the protocol for single cell nucleus isolation from endometrium tissue for single cell RNA sequencing. eMSCs have been collected from menstrual blood from healthy women and characterized on the basis of multilineage differentiation capacity and receptor expression. To study whether MSCs alone or MSC macrophage interaction is required for successful embryo implantation, MSCs with human monocyte cell line THP1 were cocultured. Condition media was collected from the cocultured cells after 24hrs. We studied MSCs' condition media alone or (MSCs + macrophages)-condition media induce wound repair by wound healing assay. We will also study induction of decidualization in stromal cells by assessing the Prolactin and IGFBP1 expression, and induction of stromal cell proliferation by MTT assay.

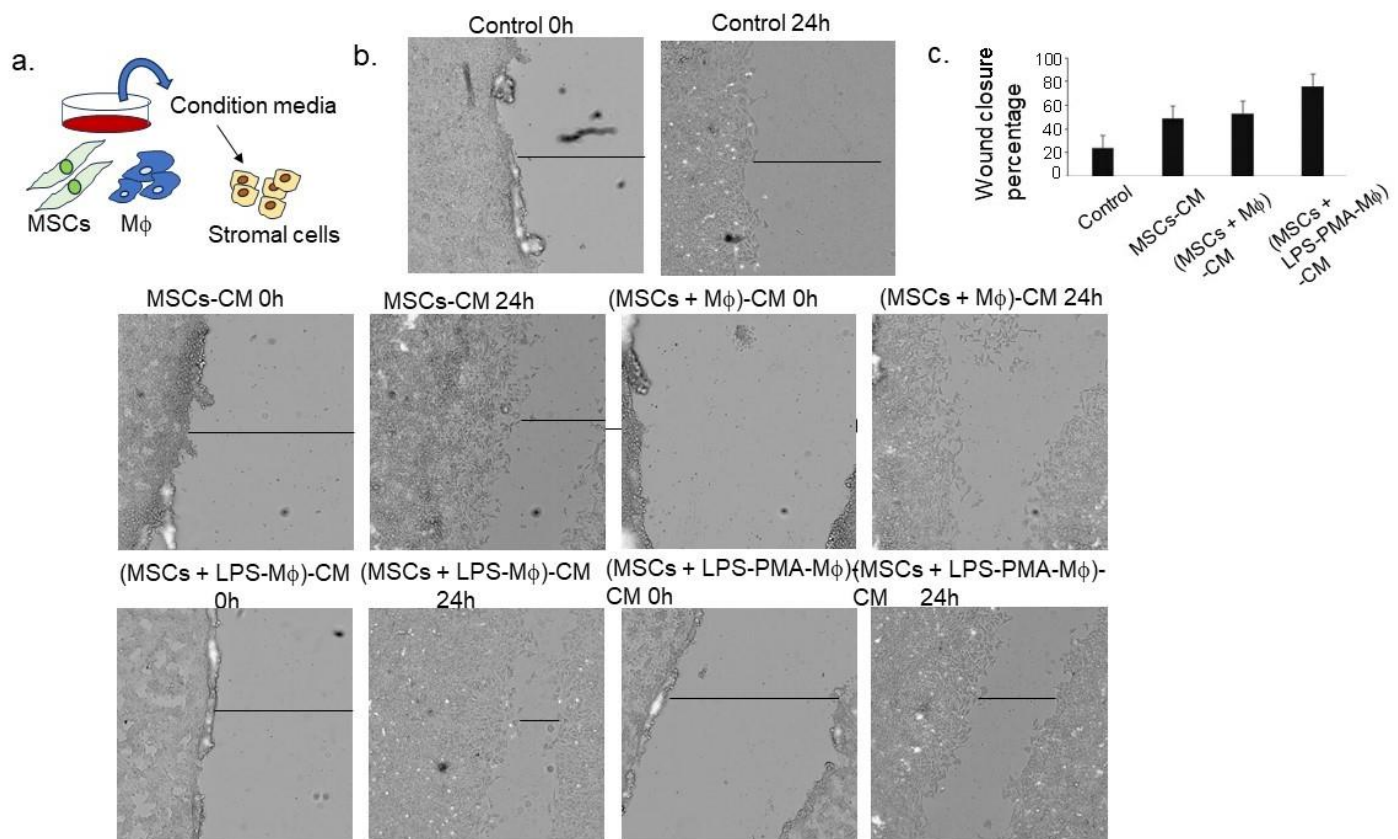


Figure 2: a. Schematic of experimental design to explore THP1 (monocyte cell line), cells were treated with PMA to differentiate cells to macrophage. Macrophages (MSC-macrophage interaction) were treated with LPS and this was followed by coculture with MSCs. After 24h conditioned media was collected. We treated stromal cells with condition media and studied the wound healing assay. b. As evident from the graph, the MSC-conditioned media significantly induced wound healing in scratched stromal cells compared to control and MSCs cocultured with macrophage augment the effect shown by MSCs alone.

1.23 Development of a Microfluidic-Based Tool for Assessing Placental Functions and Evaluating its Potential Application in Pregnancy-Related Disorders *(Partly Funded by Department of Science and Technology - Imprint II C)*

Principal Investigator : **DN Modi**
Project Associate : A Bhide
Collaborator : A Majumder, IITB, Mumbai
Duration : 2020-2025

This project aims to develop a placenta-on-a-chip device to help biologists and pharmaceutical industry study various aspects of placental biology, including high-throughput screening. We have developed and validated a device mimicking the barrier function of the placenta. These devices will help in understanding transplacental drug transport under static and flow conditions. In these devices, BeWo and HUVEC cells mimicking placental barrier were co-cultured. Further, active transport of glucose across the barrier has been studied in normo-glucose condition and gestational diabetic condition (high glucose). Compared to normo-glucose condition, more glucose was transferred from the maternal chamber to the fetal chamber in high glucose condition. The rate of glucose transfer across the fetal maternal interface in high glucose condition was also observed to be higher. Further metabolomics analysis to understand differences in the metabolomics profiles of the cells under high glucose and normo-glucose condition is ongoing.

1.24 Comprehensive Assessment of Women Diagnosed with Spontaneous Premature Ovarian Insufficiency- A multicentric study *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : **Deepti Tandon**
Co-Principal Investigator : S Pandey, Shaini Joseph
Project Associates : Anushree Patil, Shahina Begum, Anamika Akula
Collaborators : R Ravindrum, Consultant clinical immunologist, Mumbai
D Bhenki, Obstetrician Gynaecologist Infertility specialist, Mumbai
Duration : 2023-2026

A specialized Premature Ovarian Insufficiency (POI) Clinic, recently initiated at the infertility clinic of ICMR - National Institute for Research in Reproductive and Child Health, operates once every three months and offers a multidisciplinary approach to address the unique challenges faced by women with POI. Led by a team of specialized experts including gynecologists, immunologists, genetic experts, IVF specialists, and basic scientists, the clinic aims to comprehensively assess and manage women diagnosed with POI. Fig. 1 elaborates the model of POI Clinic initiated at ICMR NIRRCH. This model focuses on three pillars for addressing POI. The first pillar entails meticulous assessment of clinical symptoms, specialized investigations for genetic predispositions, evaluation of metabolic parameters, autoimmune component and quality of life. The second pillar involves establishing a longitudinal cohort for continual monitoring and evaluation of clinical features and metabolic parameters. The third pillar emphasizes collaborative research with specialized POI clinics, aiming for a paradigm shift in

POI management. This multidisciplinary care model in India could serve as a blueprint for improving outcomes and quality of life for women with POI. A cohort of 12 women diagnosed with spontaneous POI have been recruited for this study. Their mean age was 30.4 ± 4.01 years. Among them, 91.6% (11) are married, while 8.3% (1) remained unmarried. Socioeconomic distribution showed that 41.6% (5) belonged to the lower middle class, 33.3% (4) to the upper lower class, and the remaining 25% (3) to the upper and upper middle classes. Only one participant (8.3%) reported both smoking and alcohol intake. The mean age of menarche among these women was 13.6 ± 1.6 years. All participants 100% (n=12) reported amenorrhea with only withdrawal bleeding. Associated symptoms included hot flushes in 41.6% (5), vaginal dryness in 25% (3), hair loss in 75% (9), changes in skin pigmentation in 50% (6), joint pain in 16.6% (2), sleep disturbances in 33.3% (4), and decreased sexual desire in 33.3% (3). Clinically, 16.6% (2) exhibited goitre, while 8.3% (1) presented with webbing of the neck. The mean BMI of the participants was 26.9 ± 3.2 kg/m. Hypothyroidism was diagnosed in 16.6% (2) of the participants, and hypertension in 8.3% (1). 75% (9) of the participants are nulligravida. Genetic evaluation was conducted for eight patients, revealing that 50% (n=4) had a normal karyotype, while 12.5% (n=1) exhibited Turner syndrome (45XO). Additionally, three patients displayed polymorphic variations such as 46XX,14ps; 46XX,9qh+; and 46XX,1qh+1. Microarray analysis identified pathogenic abnormalities in 16.6% (n=2) of the women and for rest results are awaited. Testing for Fragile X mutation was negative in 41.6% (5) women and for rest results are awaited. Autoimmune profile evaluation indicated that 33.3% (n=4) tested positive for antinuclear antibodies, all at a titre of 1:100. Notably, all 12 participants tested negative for antiovarian antibodies. The cohort is currently being followed up.

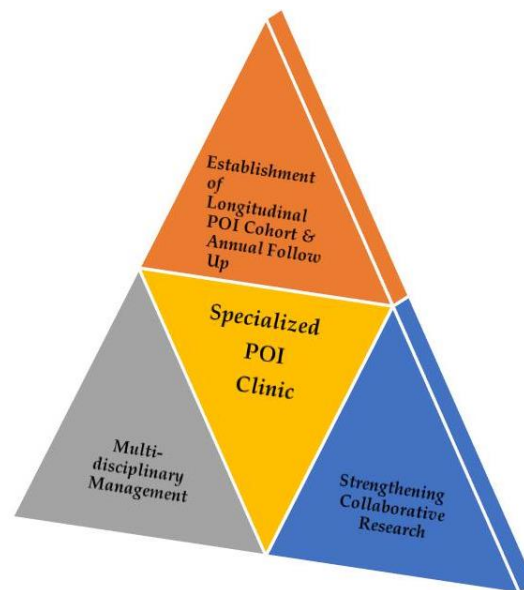


Figure 1: The model of POI Clinic initiated at ICMR-NIRRH

2. MALE INFERTILITY AND ASSOCIATED REPRODUCTIVE DISORDERS

2.1 Molecular Mechanisms Involved in Prolactin and Dopamine Signalling in Male Reproduction (Partly Funded by Science and Engineering Research Board, Department of Science and Technology)

Principal Investigator : **Nafisa H Balasinor**
Co-Principal Investigators : Priyanka Parte, Dipty Singh
Project Associates : Sanketa Raut, Kushaan Khambata
Duration : 2020-2023

Prolactin and dopamine receptors (PRLR & D2R) are present on various testicular cells; however, physiological role of these receptors in spermatogenesis or male reproduction remains unexplored. Hyperprolactinemia, characterized by increased level of serum prolactin, is prevalent in up to 16% of the infertile males, implying an important role of these hormones in male fertility. The aim of this study is to delineate the mechanisms by which prolactin and dopamine affect male reproduction. In the previous year, we reported gene alterations associated with D2R stimulation with bromocriptine in *in vitro* seminiferous tubule culture (STC). Microarray identified a total of 1077 differentially expressed genes (DEGs) regulated by bromocriptine (D2R agonist). Among these top-regulated genes along with genes involved in sperm motility were validated by qPCR. Furthermore, *in vivo* male rat models for hypo- and hyper-prolactinemia (Prl) were established by injecting D2R agonist, Bromocriptine (Brm) and antagonist, Fluphenazine (Flu), respectively, for 60 days. An increase in pre- and post-implantation loss (PIL and POL) along with a decrease in the litter size was observed in both groups (Annual Report 2022-23, pp. 29-30).

In the reporting year, hormonal profiles including FSH, LH, testosterone, and estrogen were investigated in animals treated with Brm or Flu. Serum FSH levels were not affected by Brm or Flu treatment. Serum LH levels were unaffected in Brm treated but decreased in Flu treated animals. Serum testosterone levels were decreased after both Brm and Flu treatments. Serum estrogen was unaffected in Brm treated but decreased in Flu treated animals (Fig. 1A-1D). There was a significant increase in apoptotic cells in seminiferous tubules upon Brm and Flu treatment in post-spermiation stages, i.e. Stage IX-XIV. TUNEL positive or apoptotic cells were observed in the region of primary spermatocytes (Fig. 1E-1F). Further, testicular expression of Bax gene is a pro-apoptotic marker, was found unaffected, and of Bcl2, an anti-apoptotic marker, was significantly decreased after Brm and Flu treatment. RNA-Seq identified a total of 1539 differentially regulated genes by Brm (869 up-related and 670 down-regulated) and 824 genes differentially regulated by Flu (453 up-regulated and 371 down-regulated). Enrichment map analysis showed hormone biosynthesis and response to steroid hormone to be significantly affected by both Brm and Flu treatment. Hub genes analysis of the DEGs network of proteins obtained by Cytohubba plugin in Cytoscape software identified genes involved in ribosomal biogenesis to be enriched. A total of 10 genes were validated by qPCR, 5 genes altered by Brm and Flu each. Uba52, Rps27a, Rpl23, Rpl5, Rps16 were significantly down-regulated by Brm treatment, and Rps27a, Rps29, Rps15, Rps27, Fau11 were significantly down-regulated by Flu treatment as compared to the control (Fig. 2). The present study delineated plausible molecular mechanisms underlying hypo-

and hyper-prolactinemia and demonstrated that prolactin and dopamine are crucial for different aspects of male fertility.

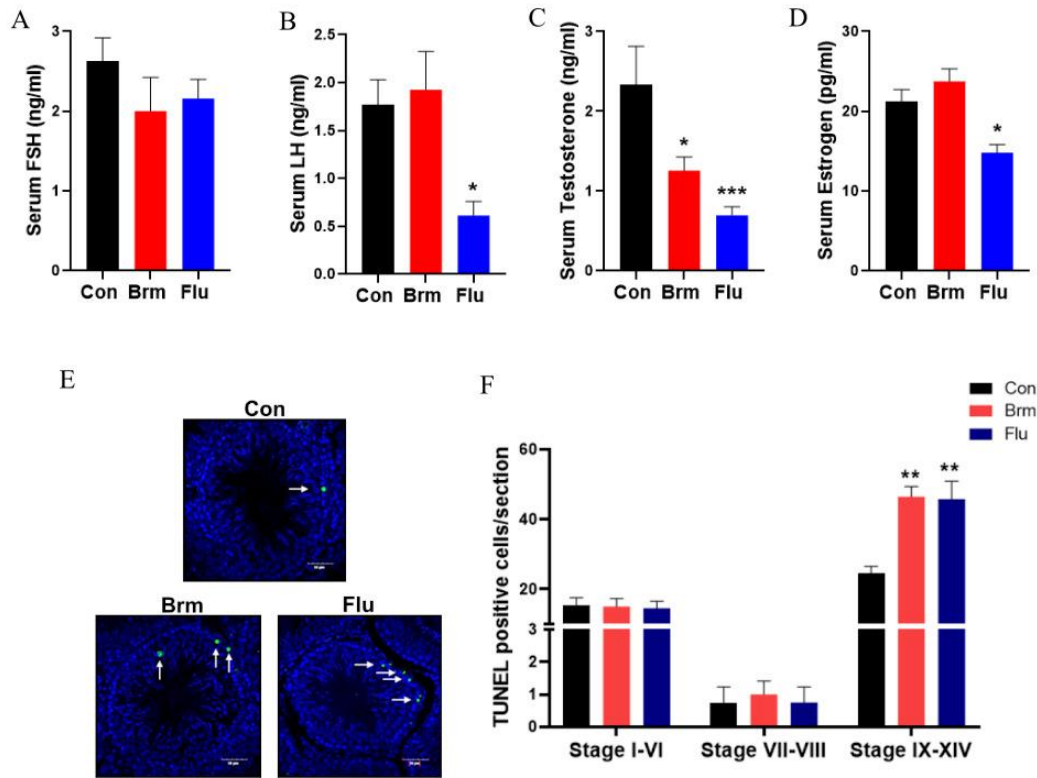


Figure 1: Serum levels of FSH (A), LH (B), testosterone (C), and estrogen (D) after 60 days of Brm and Flu treatment. Representative TUNEL positive cells on testicular sections (E) Stage-wise quantification of TUNEL positive cells (F). Con: Control, Brm: Bromocriptine, Flu: Fluphenazine. Arrow indicates TUNEL positive cells (green). Values are represented as mean $\pm$ SEM; N = 6; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

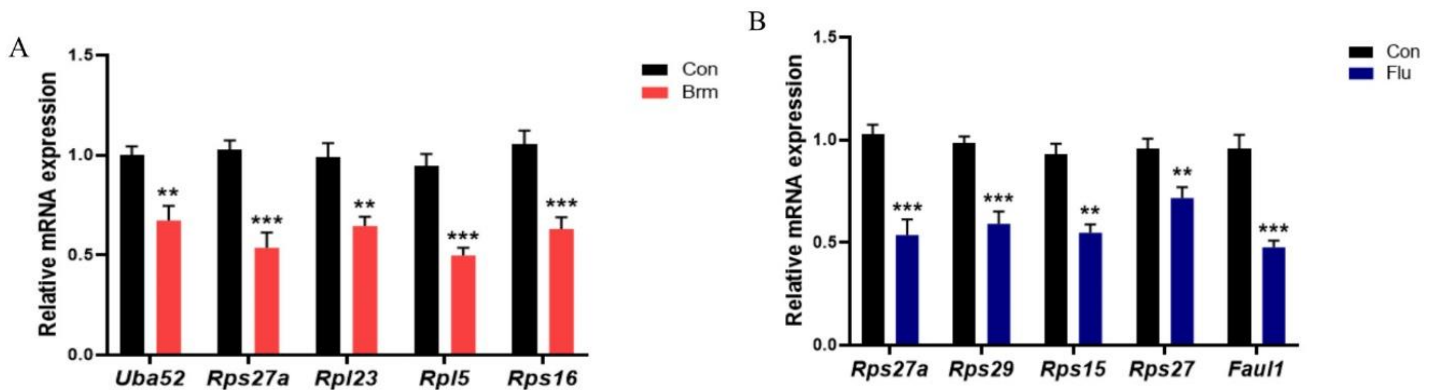


Figure 2: qPCR expression validation of hub genes identified by Cytoscape software in the testis after treatment with Brm (A) and Flu (B) as compared to control group. Con: Control, Brm: Bromocriptine, Flu: Fluphenazine. Values are represented as mean $\pm$ SEM; N = 6; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

2.2 Unravelling Sperm Epigenetic Landscape Regulated by Estrogen Receptors in Adult Male Rats (*Funded by SERB-Start-up Research Grant*)

Principal Investigator : **Kushaan Khambata**
Project Associate : Priyanka Bera
Duration : 2020-2025

Estrogen through its receptors (ER α and ER β) plays an important role in regulation of various aspects of spermatogenesis and male fertility. To study the roles of ERs in male fertility, rat models have been established. Rats treated with propyl pyrazole triol (PPT), selective ER α agonist and diarylpropionitrile (DPN), an ER β agonist for 60 days leads to decreased fertility in adult male rats. Since epigenetic marks such as DNA methylation in the sperm play a crucial role in embryogenesis, the present study aims to investigate the effects of estrogen signalling via ER α and ER β on sperm DNA methylome in rat models. Whole genome bisulfite sequencing (WGBS) revealed 4653 differentially methylated genes (DMG) in PPT and 314 DMG in DPN treated rats (Annual report 2022-2023, pp. 31-33). In the reporting year, genes involved in spermatogenesis were investigated. Of the PPT DMGs Cdy1, Zymnd15, H1f7, H3f3b, Rnf8, Rnf17, Catsperd, Txndc8, Zbp2 and Zbp2 were selected for validation by pyrosequencing. Cdy1 and Zymnd15 function as transcriptional repressors, while H1f7, H3f3b, Rnf8, Rnf17, are structural proteins involved in spermiogenesis, which was affected after PPT treatment. Since the processes of spermatocyte survival and sperm motility were affected after DPN treatment, genes such as Aurkc and Ndc1 involved in meiotic recombination and Parc, Dnah1, and Hsbn11 involved in sperm motility were selected for validation.

Selected genes showed the same trend of hypo or hypermethylation in sperm thereby validating the WGBS results (Fig. 1). Genes such as Cdy1, Zymnd15, H1f7, Rnf17, Catsperd, Zbp2 and Zbp2 (Fig. 1A, B, C, F, G, I, J) were hypermethylated; H3f3b, Rnf8, Txndc8 were hypomethylated after PPT treatment (Fig. 1D, E, H). For DPN, Aurkc, Dnah1 and Parc (Fig. 2A, C, D) were found to be hypermethylated, while Ndc1 and Hsbn11 (Fig. 2B, E) were hypomethylated by WGBS and pyrosequencing.

Testicular expression of the validated DMGs was assessed after PPT and DPN treatments. All the genes were found to be dysregulated, with the exception of Rnf17 (Fig. 1K and 2F). Expression of Cdy1, Zymnd15, H1f7, H3f3b, Rnf8, Txndc8 genes was found to be increased while that of Catsperd, Zbp2 and Zbp2 was decreased (Fig. 1K). In DPN treated rats, genes Aurkc, Ndc1, Dnah1, and Hsbn11 were found to be up-regulated, while Parc was down-regulated (Fig. 2F). Genes differentially methylated in the promoter region (Catsperd, Zbp2, Zbp2) showed a down regulation in their expression; whereas, some genes hypermethylated in the intronic regions (Cdy1, Zymnd, Aurkc, Dnah1) showed increased expression.

Taken together, aberrant methylation and expression of critical transcriptional repressors such as Cdy1 and Zymnd15; and of various chromatin remodelling factors such as H1.7, H3f3b, Rnf8, may lead to defects in spermiogenesis. Moreover, decreased expression of genes involved in sperm function such as Catsperd, Zbp2 and Zbp2, and increased expression of Txndc8 could contribute to sub-fertility upon PPT treatment.

It is probable that aberrant methylation and altered expression of key meiosis gene such as Aurkc and Ndc1 could affect the spermatocyte survival upon DPN treatment. Similarly, deregulation of critical

genes such as *Parcg*, *Dnah1* and *Hsbp11* could contribute to reduced sperm motility observed after DPN treatment.

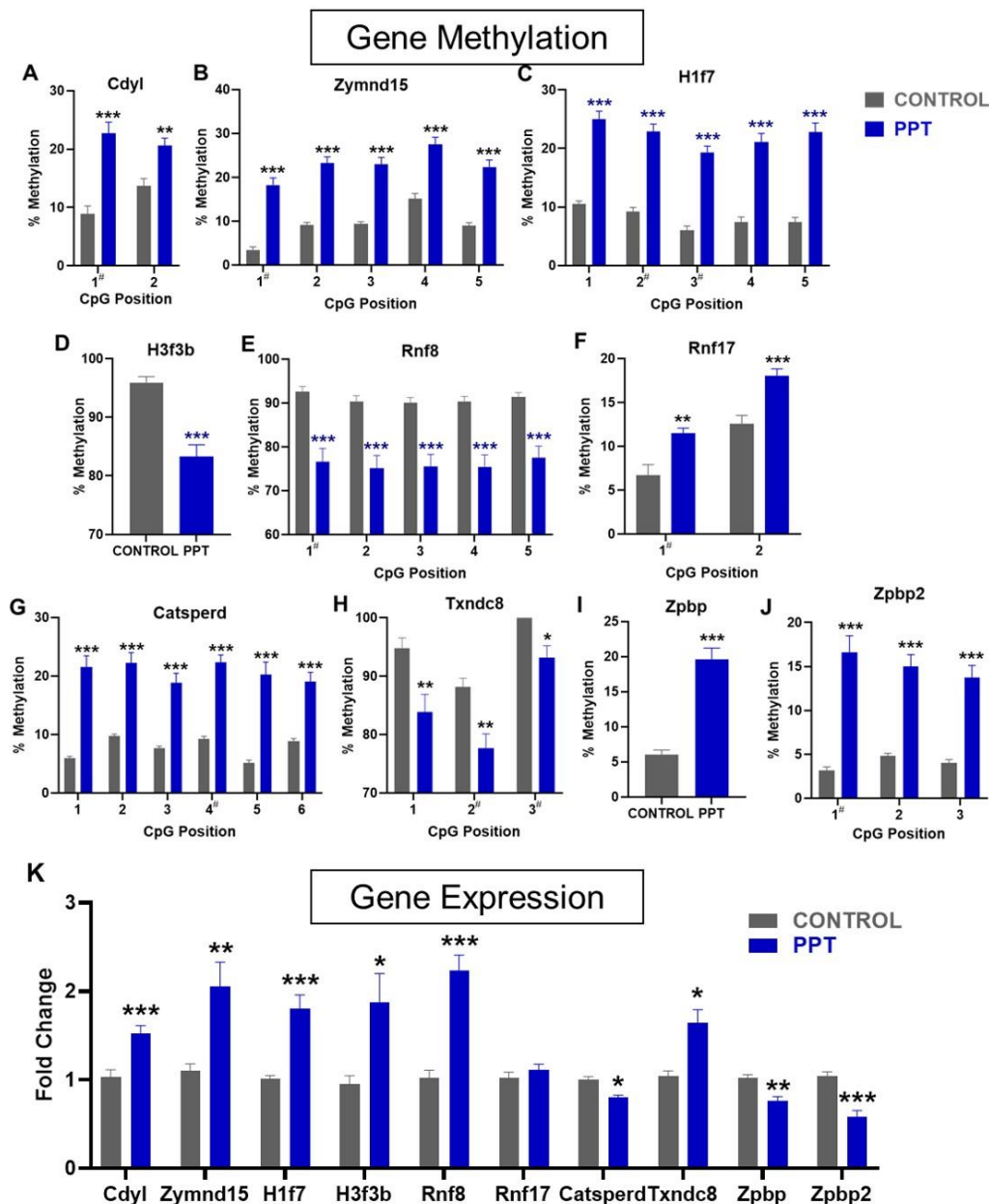


Figure 1: Pyrosequencing based validation of genes displaying differential methylation (DMGs) on PPT treatment, as identified by WGBS. *Cdyl* (A), *Zymnd15* (B), *H1f7* (C), *H3f3b* (D), *Rnf8* (E), *Rnf17* (F), *Catsperd* (G), *Txndc8* (H), *Zpbp* (I), *Zpbp2* (J) were validated. # indicates the CpG position found differentially methylated in WGBS. Gene expression in testis (K) was analysed by q-RT-PCR. * p-value <0.05. The results are represented as mean $\pm$ SEM of at least 8 animals in control and PPT groups.

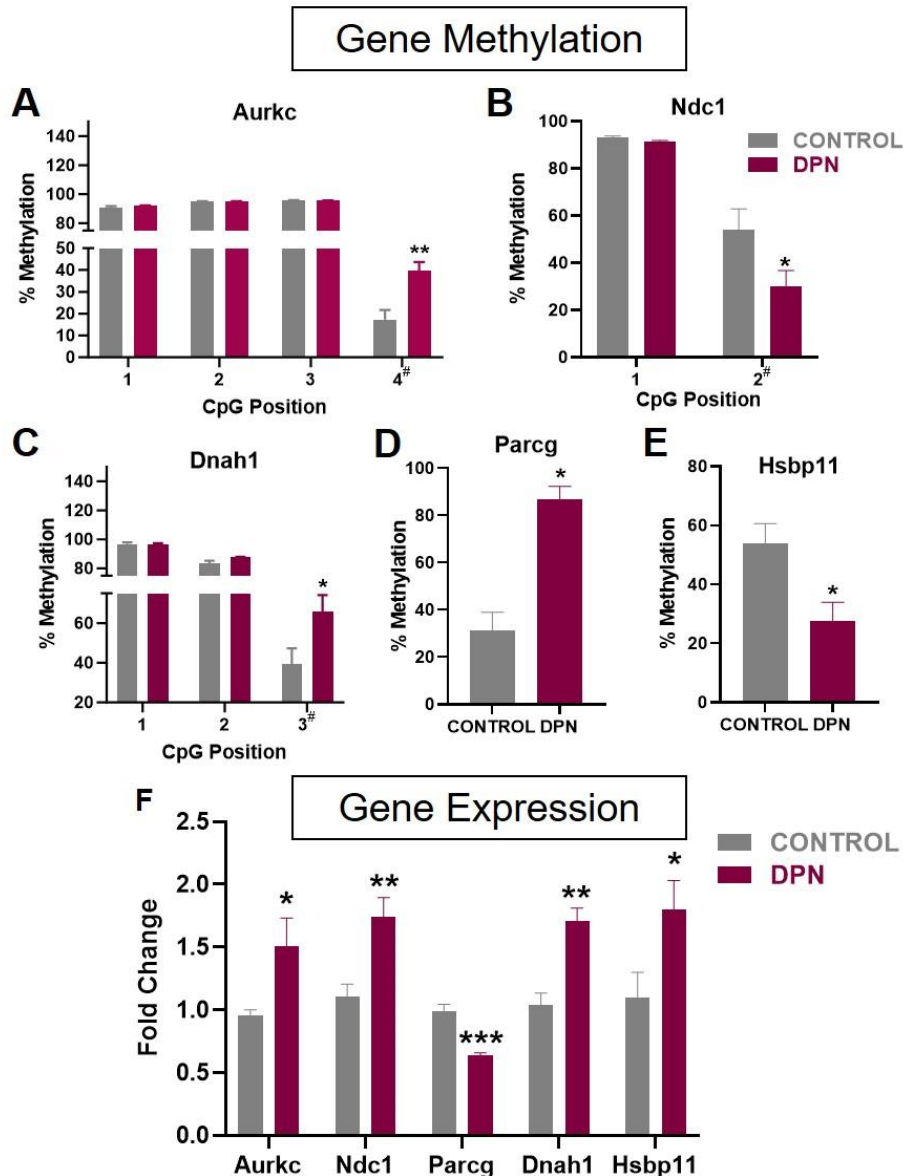


Figure 2: Pyrosequencing based validation of genes displaying differential methylation (DMGs) on DPN treatment, as identified by WGBS. Aurkc (A), Ndc1 (B), Dnah1 (C), Parcg (D), Hsbp11 (E) were validated. # indicates the CpG position found differentially methylated in WGBS. Gene expression in testis (F) was analysed by q-RT-PCR. * p-value <0.05. The results are represented as mean $\pm$ SEM of at least 8 animals in control and PPT groups.

2.3 Deciphering the Molecular Mechanism of Triclosan on the Hypothalamus Pituitary Gonadal Axis

Principal Investigator : **V Dighe**
 Project Associates : Shruti Desai, Amruta Gadade, S Jadhav, P Salunke
 Duration : 2021-2025

Triclosan (TCS), or 5-chloro-2-(2, 4-dichlorophenoxy) phenol, is a broad-spectrum antimicrobial that is classified as a Class III drug by FDA. It is widely used in consumer products- toothpaste, deodorants, hand-washes, furniture, and surgical scrubs. It has strong lipophilicity and accumulation ability. It is also reported to cause immune suppression and is responsible for impaired embryonic development. According to literature, Triclosan adversely affect reproductive functions. Taking this into consideration, trans-generational effects of TCS on developmental and reproductive toxicity were studied. Pregnant dams were administered with 0.1mg/kg bw, 4 mg/kg bw, and 150 mg/kg bw of Triclosan through subcutaneous injection during the perinatal period, i.e., Gestational Day (GD) 6 to Post-Natal Day (PND) 21. Dams were allowed to deliver and followed for PND 22, PND 45, and PND 75. Sexual maturation, hormonal assays, biochemistry parameters, and sperm parameters of F1 progeny were observed. The remaining half of the F1 generation offspring was allowed to mature and mated with naïve males and naïve females respectively. F2 generation pups were followed for PND30, PND45, and PND75 for their sexual maturation; hormonal assays, biochemistry parameters, and sperm parameters. Serum testosterone levels were decreased across the TCS treatment group in F1 males. % sperm motility, % progressive sperm, and sperm count were significantly lower in the high treatment group. At day 75, F2 males also showed a decrease in % sperm motility, % progressive motile sperm, and daily sperm production in the treated group compared to the control group. There was a decrease in testosterone serum levels while estradiol serum levels showed no significant change in the F2 male rats (Fig. 1). F1 and F2 males (at day 75) had a decrease in the serum testosterone levels and an increase in serum estradiol level in the treatment group as compared to the control group (Fig. 2A). Exposure to TCS led to downregulation in the mRNA expression levels of steroid hormone receptors - Androgen Receptor (AR) and Estrogen Receptor β in the group exposed to 0.1mg/kg-bw of TCS as compared to control while no significant alteration was observed in estrogen receptor α expression in F2 generation female rats (Fig. 2B). The present study demonstrated perinatal exposure to TCS leads to a perturbation in sexual maturation, hormonal profile, and expression of steroid receptors in the F1 generation, and these effects were also observed in F2 progeny.

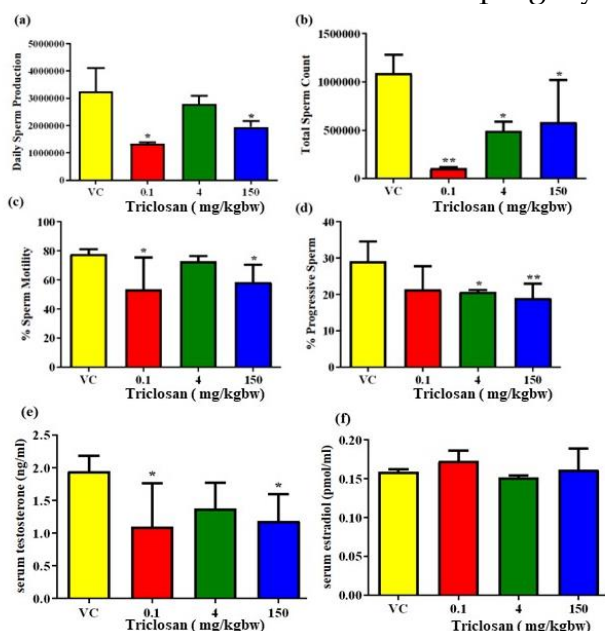


Figure 1: Effect of TCS on (a) daily sperm Production, (b) total sperm count, (c) % sperm motility, (d) % progressive sperm, (e) serum testosterone levels and (f) serum estradiol levels in F2 generation male rats at PND 75. * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$ (VC: Vehicle Control, 0.1 mg TCS/kg bw, 4 mg TCS/kg bw, and 150 mgTCS/kgbw).

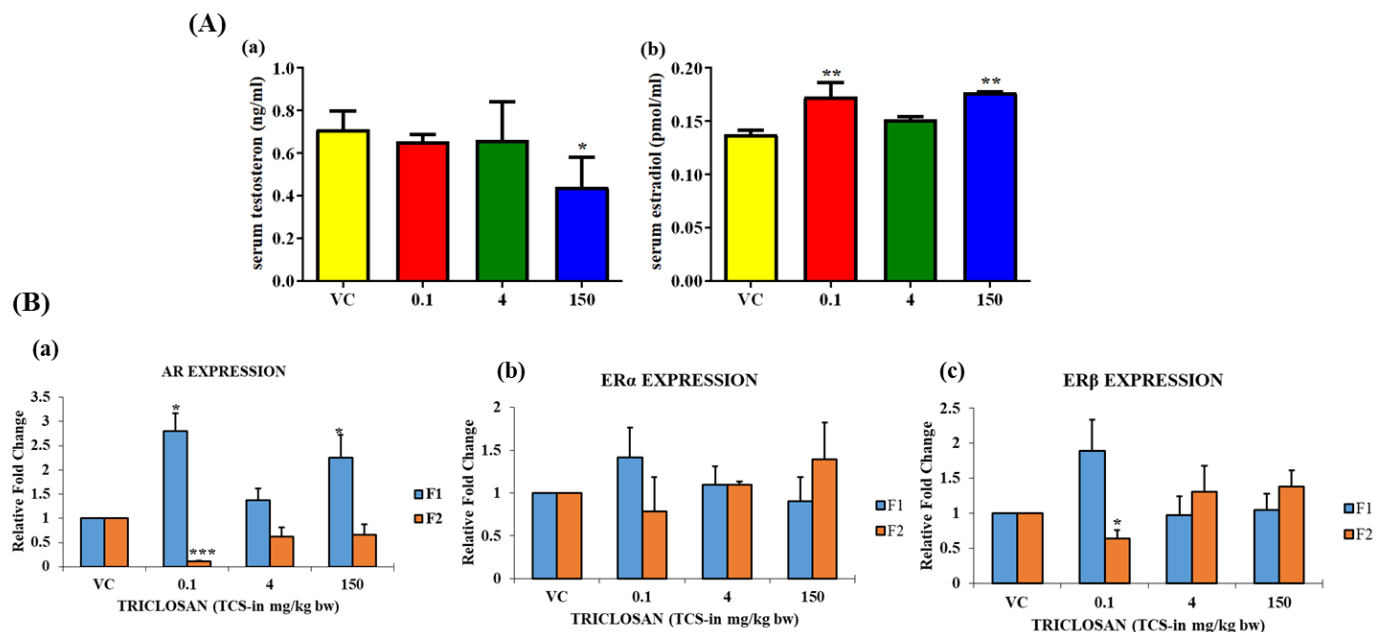


Figure 2: (A) Hormone levels in F2 generation females (a) serum testosterone and (b) serum estradiol levels in F2 generation female rats at PND 75. (B) Effect of TCS on the expression of steroid receptors in F2 generation females a) Androgen Receptor (b) Estrogen Receptor - α and (c) Estrogen receptor β . (VC: Vehicle Control, 0.1 mg/kg bw, 4 mg/kg bw, and 150 mg/kg TCS) * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$.

2.4 Implications of Gonadotropin and their Receptor Gene Variants in Male Infertility

Principal Investigator : **P Kuppusamy**

Project Associates : R Gajbhiye, S Pande, DVS Sudhakar, Shagufta A Khan

Collaborators : P Kothari, V Kulkarni, Consultant Andrologists

D Kale, G Desai, Nowrosjee Wadia Maternity Hospital, Mumbai

J Shah, Kamala Polyclinic and Nursing Home, Mumbai

Duration : 2022-2026

Worldwide, 15% of couples within the reproductive age are unable to conceive. Male factor infertility affects 40-50% of infertile couples. Infertility problems can be diagnosed in approximately 60% of infertile men, and in the other 40%, the cause remains unidentified. Since reproductive hormones are key regulators for germ cell development and its regulation, hormones can be surrogate markers of sperm quality and quantity. Studies have shown different levels of reproductive hormones in different sub-categories of infertility. Here, we present a sub-analysis of longitudinal prospective cohort of idiopathic infertile men for hormonal level. During the reporting period, a total of 204 study participants were recruited of these 123 cases were from three infertility clinic and IVF centers, and 81 were fertile healthy controls from out-patient department at a maternity tertiary care hospital in Mumbai. Serum FSH, LH, testosterone and inhibin-B levels were measured using commercially available ELISA kits. A majority of infertile cases had primary infertility (80%). Significantly elevated levels (median) of FSH (4.0 vs 2.5 mIU/ml) and LH (7.6 vs 5.9 mIU/ml) were observed in infertile cases as compared to fertile controls ($p < 0.05$). However, no differences in total testosterone (418.8 vs 404.3

ng/dl) and inhibin-B (213.3 vs 212.5 pg/ml) levels were found between cases and controls. The median sperm concentration of 10 million per milliliter was determined ranging from 2.0 to 20.0 million per milliliter of semen samples in idiopathic infertile group. Hormonal level variations particularly in FSH, and LH levels, but not in testosterone and inhibin-B levels in idiopathic cases indicate dysfunctions of germ cells in the testes. Further studies exploring genetic variability that control the HPG and gonadal functions are in progress.

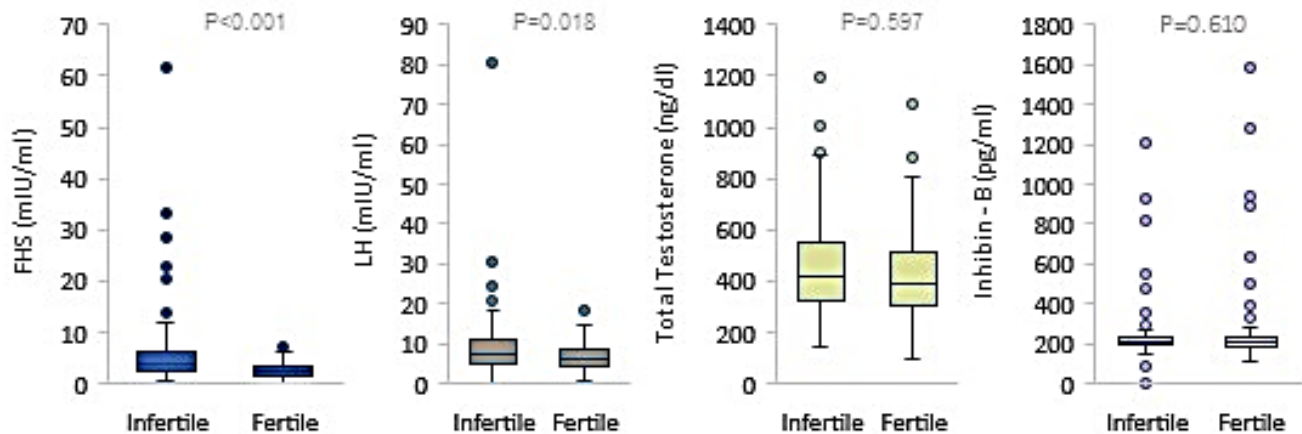


Figure 1: Peripheral Levels of FSH, LH, total testosterone and Inhibin-B in idiopathic infertile and fertile men

2.5 Deciphering the Role of PSP94 and CRISP Family Proteins in Ion Channel Modulation (Partly Funded by Science and Engineering Research Board)

Principal Investigator : **Bhakti R Pathak**
 Project Associates : Vaidehi Miya, Antara Banerjee, Ananya Breed
 Duration : 2018-2024

Cysteine Rich Secretory Proteins (CRISP) are 25-30 kDa proteins characterised by the presence of an ion channel regulatory motif in C-terminus which is linked to a conserved Sperm Coating Protein (SCP) domain in the N-terminus by the hinge region. Mammalian CRISPs are predominantly expressed in the reproductive tract tissues with an exception of CRISP3 which has a more widespread tissue distribution. CRISP3 is expressed in the prostate gland and its expression is regulated by androgen. In addition to prostate, CRISP3 expression is reported in uterus, ovaries, salivary glands, sweat glands and peroxidase negative granules of neutrophils. Due to its presence in neutrophils and in various secretions, CRISP3 is thought to have a role in innate immunity. In the seminal plasma, CRISP3 interacts with PSP94 (Prostate Secretory Protein of 94 amino acids). Interestingly, in prostate tumorigenesis, the levels of CRISP3 are reported to be upregulated which has further been linked to poor prognosis in patients with prostate cancer. Previously, by generating CRISP3 knockdown clones in LNCaP (a prostate cancer cell line which endogenously expresses CRISP3) our lab unveiled its potential in regulating inflammation. P2RX7, a purinergic receptor X7 was found to be upregulated in the microarray analysis of CRISP3 knocked down LNCaP cells. P2RX7 is an ATP-gated ion channel

which is predominantly expressed in immune cells. P2RX7, an important player in the NLRP3 inflammasome pathway is also reported to be dysregulated in cancer. Validation experiments were carried out. In the reporting year, CRISP3 silencing in LNCaP cells was shown to result in a significant upregulation of P2RX7 by qRT PCR and immunoblotting as compared to the parental cells (Fig. 1A). On the other hand, exogenous addition of CRISP3 in PC3 cells (which lack endogenous CRISP3) resulted in downregulated P2RX7 expression (Fig. 1B). Interestingly, addition of PSP94 reversed this effect. CRISP3 induced downregulation in the expression of P2RX7 was disappeared when PSP94 was added with CRISP3. Activation of P2RX7 by high levels of ATP (mM range) is known to induce formation of pores in the cell membrane inducing cytotoxicity and release of pro-inflammatory mediators such as IL-1 β . Therefore, to understand the role of CRISP3 in ATP induced cytotoxicity via P2RX7, LNCaP cells and CRISP3 knockdown clones were stimulated with 2mM ATP. Cell cytotoxicity was assessed in the supernatants via LDH (lactate dehydrogenase) assay. CRISP3 knockdown clones demonstrated significantly higher ATP induced cytotoxicity as compared to parental cells (Fig. 2A). Further, ATP mediated cytotoxicity was significantly reduced in PC3 cells treated with 1 μ g/ml CRISP3 alone but not in those treated with PSP94 (Fig. 2B). Further experiments are being conducted to elucidate the effect of CRISP3 on downstream mediators of P2RX7 and inflammation triggered by ATP-induced activation of P2RX7.

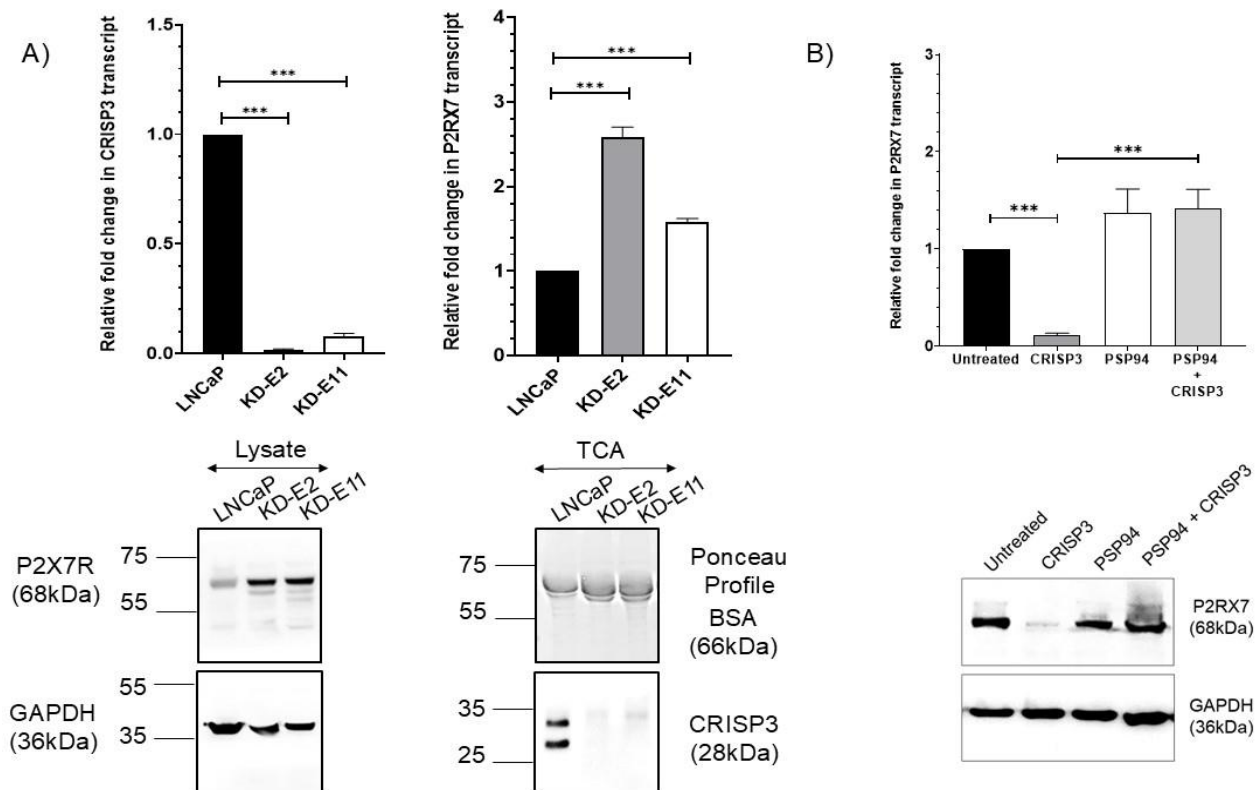


Figure 1: A) Expression levels of P2RX7 and CRISP3 in LNCaP cells and two CRISP3 knockdown clones of LNCaP (KD-E2, KD-E11) were compared by qRT PCR and immunoblotting. B) P2RX7 expression was evaluated in PC3 cells (either untreated or CRISP3 treated or PSP94 treated, with or without CRISP3) by qRT-PCR and immunoblotting. Significance of the difference between deficient groups calculated by unpaired student's 't' test *p<0.001.

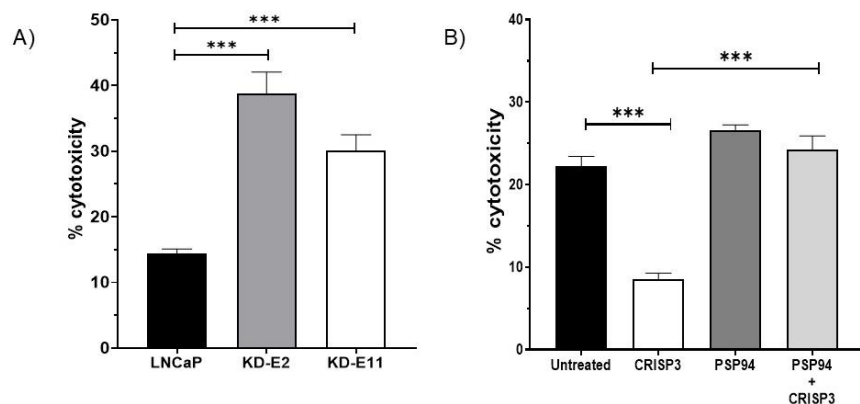


Figure 2: Cytotoxicity (%) on treatment with 2mM ATP in (A) LNCaP and CRISP3 knockdown clones (KD-E2 and KD-E11) and (B) PC3 cells either untreated or pre-treated with the indicated proteins as determined by LDH assay. Data was plotted as mean % cytotoxicity $\pm$ SEM. Statistical significance was determined using unpaired student's 't' test where *** represents $p \leq 0.001$ for the indicated comparisons.

2.6 Delineating the Role of Human β -Microseminoprotein in Male Reproduction (Partly Funded by Indian Council of Medical Research)

Principal Investigator : **Dhanashree Jagtap**
 Project Associate : B Kulkarni, Bhakti Pathak, Priyanka Parte, D Modi
 Collaborators : R Gajbhiye, V Kulkarni, Anushree Patil, Deepti Tandon
 A Phadke, SRL Dr Avinash Phadke Labs
 Duration : 2023-2025

Beta-microseminoprotein (β -MSP, also known as PSP94) is secreted by the epithelial cells of the prostate and is found in abundance in human seminal plasma and is also present on the spermatozoa. Its abundance in semen and its presence on the spermatozoa suggest its role in male fertility which is not yet understood. The aim of the study is to delineate the role of β -MSP in male reproduction. Men attending infertility clinics of ICMR-NIRRH and SRL Avinash Phadke Lab were recruited in the study. Spermatozoa from normozoospermic and asthenozoospermic men were used for immunoprecipitation of β -MSP binding proteins using anti- β -MSP antibody developed in the lab (Fig. 1). MS/MS analysis showed 240 (18.4%) unique proteins present in normozoospermic samples (Fig. 2A) while 253 (27.3%) unique proteins were found in asthenozoospermic samples (Fig. 2B). Further analysis of the data is in progress.

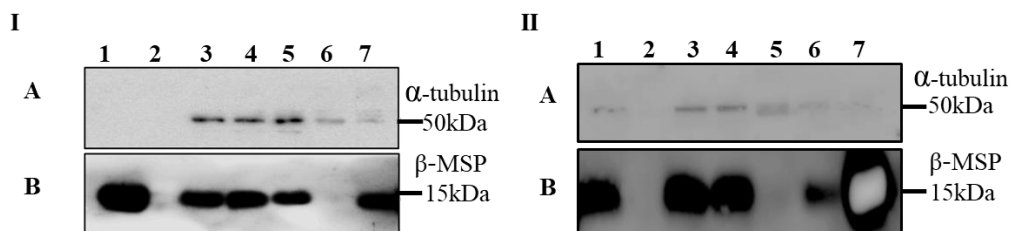


Figure 1: Western blot of immunoprecipitation of β -MSP from (I) normozoospermic and (II) asthenozoospermic spermatozoa. (A) Anti- α -tubulin (1:500) was used as loading control and (B) anti- β -MSP (1:2000) was used to detect the elute of the immunoprecipitated normozoospermic and asthenozoospermic spermatozoa lysate. (I) Normozoospermic spermatozoa: lane 1: β -MSP standard (100 ng), lane 2: Marker, lane 3: Input, lane 4: Control flow through, lane 5: Test flow through, lane 6: Control elute, lane 7: Test elute; (II) Asthenozoospermic

spermatozoa: lane 1: Input, lane 2: Marker, lane 3: Control flow through, lane 4: Test flow through, lane 5: Control elute, lane 6: Test Elute, lane 7: β -MSP Standard (500ng).

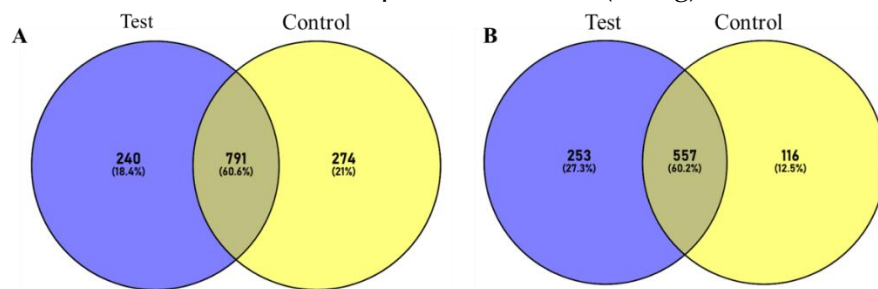


Figure 2: Proteomic analysis of β -MSP binding proteins in spermatozoa lysates. Venn diagram showing the presence of (A) 240 unique β -MSP binding proteins in normozoospermic samples and (B) 253 unique β -MSP binding proteins in asthenozoospermic samples.

2.7 Unravelling the Sperm Epigenetic Landscape in Infertile Men with Clinical Varicocele (Partly Funded by ICMR-NIRRH Core Grant)

Principal Investigator : **Dipty Singh**

Project Associates : Deepshikha Arya, Nafisa Balasinor, R Gajbhiye, Kushaan Khambata, Deepti Tandon

Collaborator : P Pawar, Lokmanya Tilak Municipal General Hospital, Mumbai, P Kothari, Nair Hospital

Duration : 2020-2025

Varicocele is reported to be associated with male infertility. Currently, it is managed by antioxidant treatment or varicocelectomy and/or assisted reproductive techniques (IUI/IVF/ICSI). Treatment modalities for varicocele improve semen parameters, yet more than 50% men remain infertile. Though varicocele affects spermatogenesis via several distinct mechanisms, elevated oxidative stress has been implicated as a key factor in varicocele-induced male infertility. High oxidative stress during spermatogenesis may affect sperm mitochondrial functions, which can in turn lead to aberrant epigenetic modifications in spermatozoa. The epigenetic modifications occurring during spermatogenesis in the germ cells are very crucial for normal sperm function and fertilization as they regulate gene expression. In view of the crucial role of sperm epigenome in its functionality, this case control study aims to investigate the epigenetic modifications of sperm in infertile men with clinical varicocele. Group I includes apparently healthy fertile men and Group II includes infertile men with clinical varicocele- i) before and after 3 months of antioxidant treatment; ii) before and after 3 months of varicocele repair. Healthy fertile men (n=25) and 40 infertile men with clinical varicocele (Grade I-III) have been recruited. Varicocele patients were followed-up and semen samples (n=20) were collected after 3 months of treatment. Semen samples were analyzed for basic semen parameters as per WHO (2021) standards. Varicocele group had significantly lower semen parameters compared to controls, which were improved in a subset of men of both the treatment modalities. However, it was noted that varicocelectomy helped better in improving sperm parameters compared to antioxidant treatment. Previously we had reported reduced MMP, high iROS, and high mtDNA copy number in men with varicocele, suggesting mitochondrial dysfunctions. Further the methylation status of mitochondria D loop and genes (promoter region) involved in mitochondrial functions were analyzed by pyrosequencing. Altered DNA methylation of mitochondria D loop and mitochondrial structure and function genes UQCRC2, MIC60, TOM22, and LETM1 were observed in varicocele group (Fig. 1).

DNA methylation levels were restored after varicocele treatment; however, the restoration was not consistent at all CpG sites (Fig. 2). Both the treatment modalities helped in restoring DNA methylation levels of mitochondrial genes but the restoration is nonhomogeneous across the studied CpG sites. This study suggests that varicocele treatment improves sperm quality and sperm mitochondrial function partially in men with varicocele. Assessment of histone retention in spermatozoa in all groups is underway.

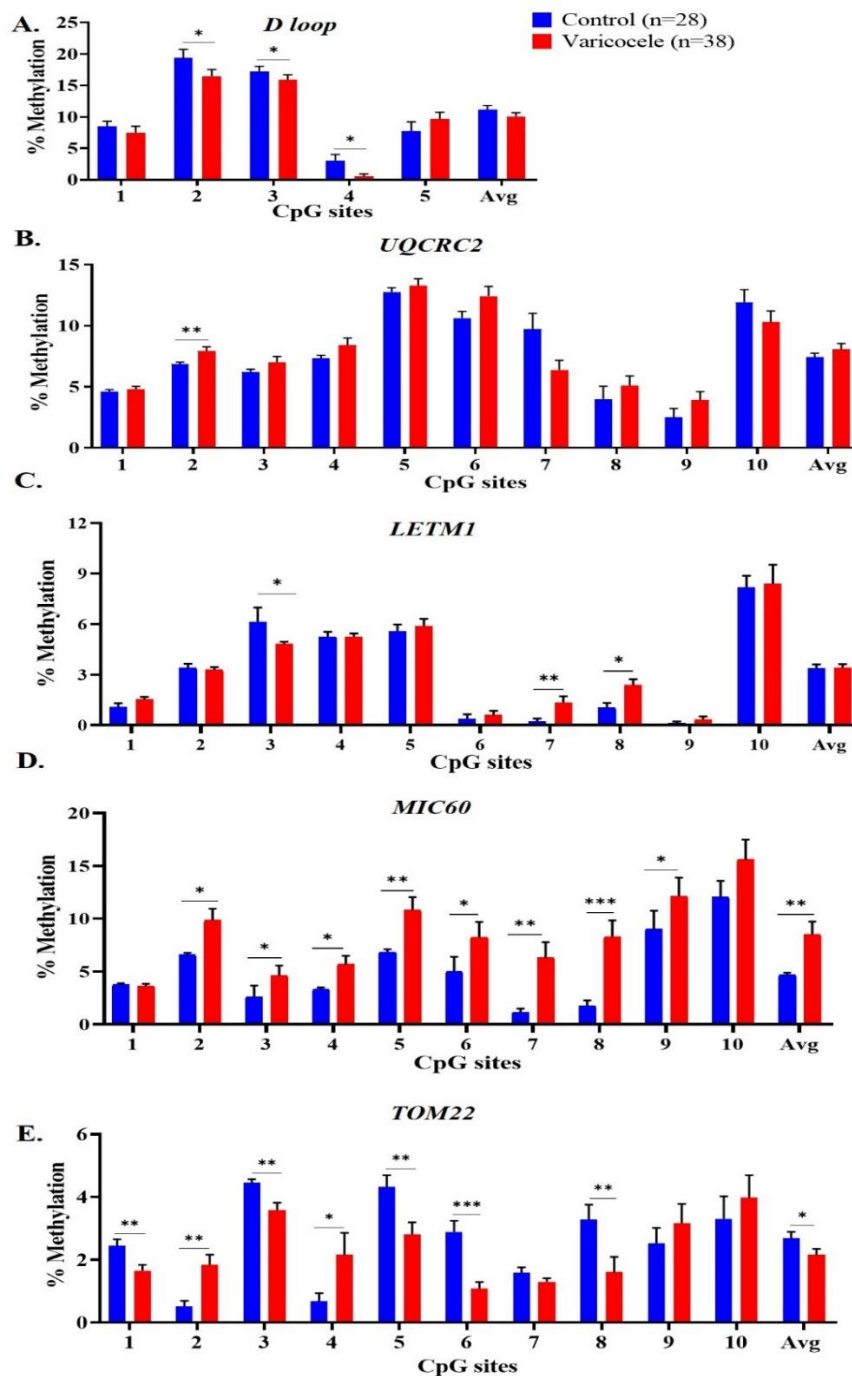


Figure 1: Methylation status of sperm mitochondria structure and function genes (A) D loop, (B) UQCRC2, (C) LETM1, (D) MIC60, (E) TOM22, in control and varicocele groups. All results are represented as mean $\pm$ SEM. *p < 0.05, **p < 0.01 and ***p < 0.001

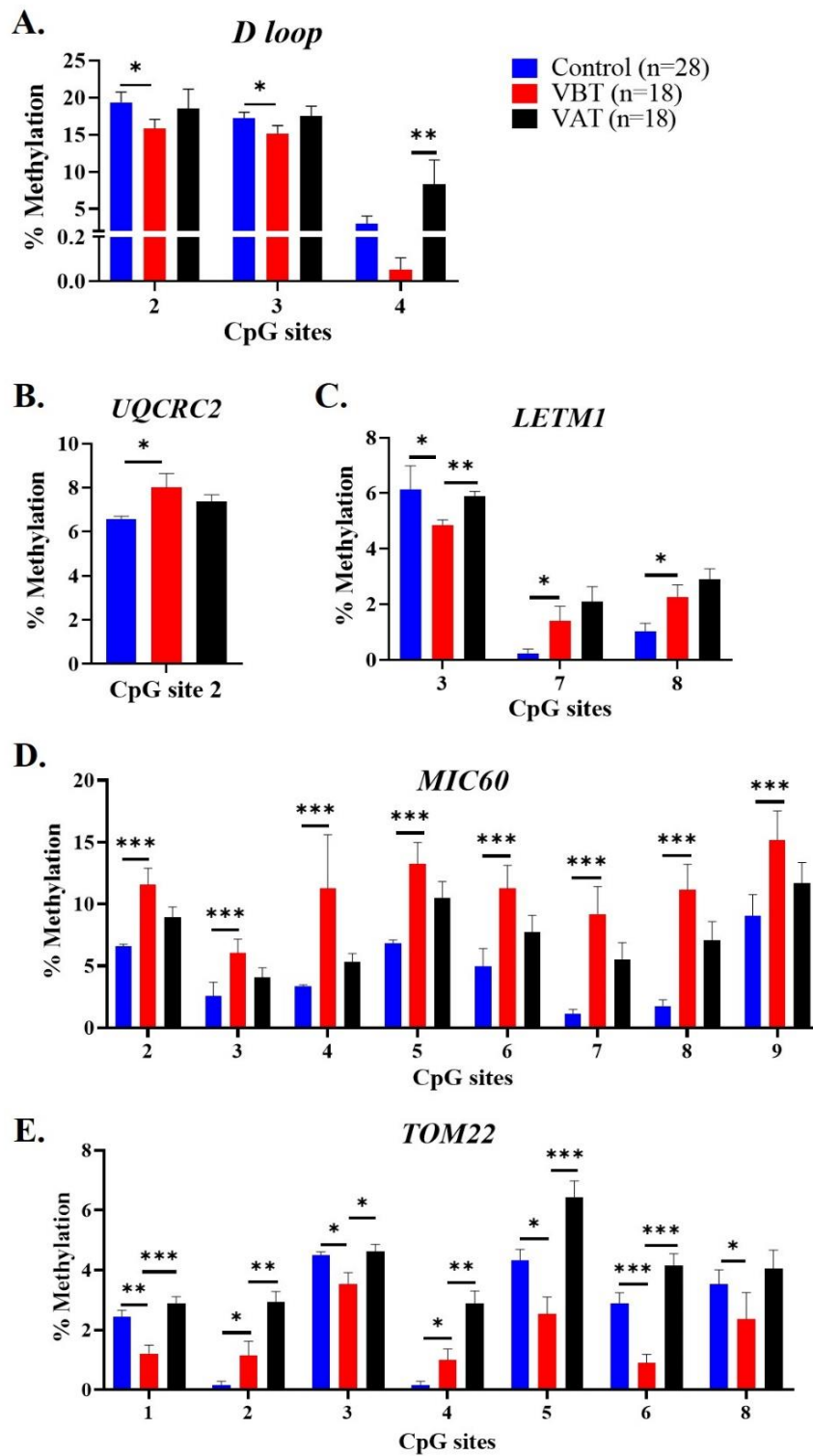


Figure 2: Methylation status of CpG sites within sperm mitochondria structure and function genes (A) D loop, (B) UQCRC2, (C) LETM1, (D) MIC60, (E) TOM22 in varicocele group before (VBT) and after treatment (VAT) as compared to the control group. All results are represented as mean $\pm$ SEM. *p < 0.05, **p < 0.01 and ***p < 0.001.

2.8 Functional Significance of Testis Specific Histone H2B Variant (TH2B) in Sperm and Early Embryonic Development *(Partly Funded by Department of Biotechnology)*

Principal Investigator : **Priyanka Parte**
 Co-Principal Investigator : Nafisa Balasinor
 Project Associates : A Patankar, Isha Singh, DVS Sudhakar, Kairavi Joshi, D Gaikwad, M More
 Collaborators : R Gajbhiye, Suchitra Surve
 Duration : 2018-2024

The epigenetic landscape of testis specific histone variants TH2B and TH2A was profiled in the murine sperm and of TH2B in human sperm. Heterogeneity in the epigenetic landscape of TH2A and TH2B was seen which is intriguing as TH2B and TH2A are reported to be present in the same nucleosomes to promote open chromatin. TH2A was highly enriched with mitochondrial functions or mitochondrial encoded genes while TH2B was enriched around transcription start site (TSS) and gene ontologies associated with it were meiosis, embryo development, RNA pol II transcription and spindle assembly (Annual reports 2018-2021).

Altered expression of TH2B associated genes in infertile individuals with sperm chromatin compaction defects indicates involvement of TH2B in transcriptional regulation of these genes in post meiotic male germ cells. Data indicates that the altered transcriptome may be a consequence or cause of abnormal nuclear remodeling during spermiogenesis. An important role for TH2B in meiosis and its phosphorylation in sperm motility was shown by this study. TH2B was also enriched at developmentally important HOX cluster. A 26% evolutionary conservation was observed between human and murine TH2B-associated genes. These conserved genes were also found to be crucial for embryogenesis (Annual report 2021-2022, pp. 27-29). Seven conserved TH2B associated embryonically important genes were validated in fertile human sperm by ChIP-qPCR. Mutants of most of these genes are known to show embryonic lethality.

Therefore, TH2B dynamics in oocyte and murine preimplantation embryos was profiled in order to decipher the contribution of paternal TH2B to the development of the early embryo (Annual report 2022-2023, pp. 43-45). Towards this, MII oocytes, 2 cell and 8 cell embryos were collected by mating C57BL6N/J female and DBA/2J male mice. These were then subjected to ultra-low input native chromatin immunoprecipitation sequencing (ULI-ChIP) to profile the dynamics of TH2B genome-wide. In the reporting year the data was analyzed.

Data analysis revealed that TH2B deposition varies between male and female gamete but is rapidly redistributed in 2-cell embryos after fertilization (Fig. 1). TH2B was also found to be enriched at ZGA genes, and associated with H2A.Z, and H2AK119ub1, and in LTRs indicating potential involvement in developmental programs (Fig. 2). These findings highlight the unique properties of TH2B chromatin in gametes and preimplantation embryos. This study is now completed. To summarize, the study sheds

light on our understanding of the role of paternal TH2B in sperm function and in the development of the pre-implantation embryo.

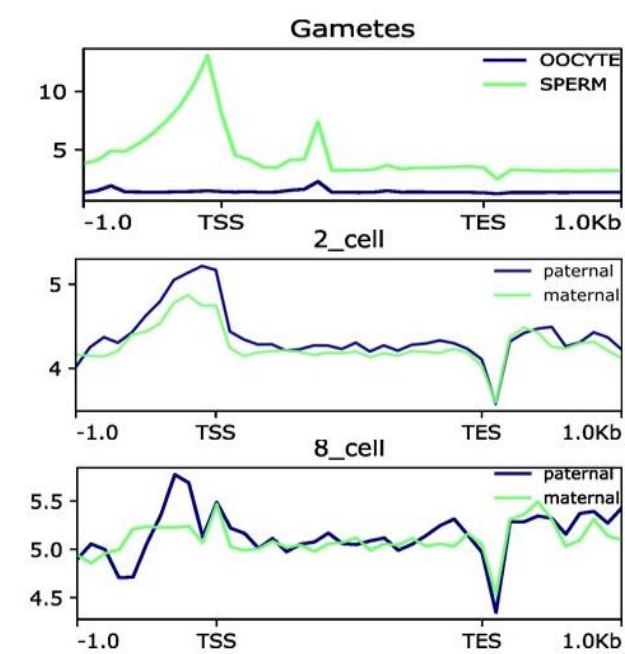


Figure 1: Profile plots depicting TH2B signals across all the protein encoding genes in gametes and parental alleles of early embryos; TSS- transcription Start Site, TES- Transcription End Site.

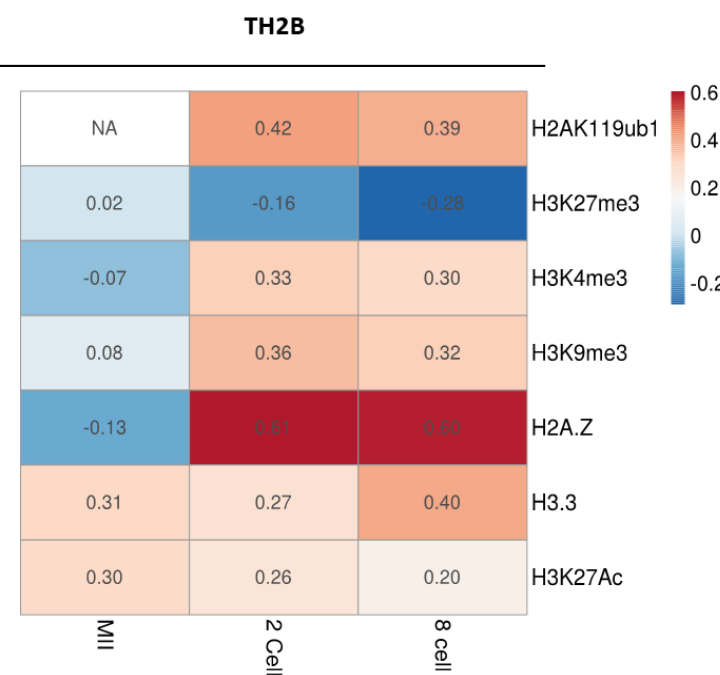


Figure 2: Heatmap showing correlation of TH2B peaks with other epigenetic marks in MII oocytes, 2-cell and 8-cell embryos.

2.9 Therapeutic Potential of EGCG for Improving Sperm Quality, Fertility and Pregnancy Outcomes in a Murine Model of Endocrine Disruption *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : **Dipty Singh**
 Co-Principal Investigator : Kumari Nishi
 Project Associates : Anushruti Singh, Deepshikha Arya, Shobha Sonawane
 Duration : 2023-2026

The exposure of endocrine disruptor chemical (EDCs) such as cypermethrin (CYP), widely used as insecticide, during adulthood can lead to detrimental effects on male reproductive system. Epigallocatechin-3-gallate (EGCG) is a major polyphenol found in green tea and a potent anti-oxidant, has protective role against damage caused to male reproductive system. But evidence for the EGCG improving sperm quality, fertility and reproductive outcomes is scanty. In the present study, CYP dose (50 mg/kg bw/day) was selected based on available studies (Li et al., 2013; Elbetieha et al., 2001). EGCG dose (10 mg/kg bw/day) was chosen based on three generation reproductive toxicity study

(Isbrucker et al., 2006). Adult male wistar rats (n=20) were randomly distributed in 2 groups: Group 1: Vehicle control (corn oil) (n=6); Group 2: CYP (n=14). The CYP (50 mg/kg bw/day) was gavaged for 30 days. CYP exposed rats were further divided into 2 groups: Group 2a: Vehicle control (saline) (n=7); Group 2b: EGCG (10 mg/kg- bw/day) (n=7). Further, EGCG was gavaged for 30 days. Thereafter animals of all the groups were sacrificed for histopathological, biochemical and molecular assays. Body weights of rats were improved by EGCG exposure (Fig. 1A). The caudal sperm count and sperm motility significantly reduced in CYP treated group as compared to control. These parameters were restored by EGCG treatment (Fig. 1B, 1C). Serum testosterone levels declined in CYP -treated group and significantly recovered by EGCG (Fig. 1D). Also, the estradiol levels were significantly elevated in CYP -treated group and restored by EGCG (Fig. 1E).

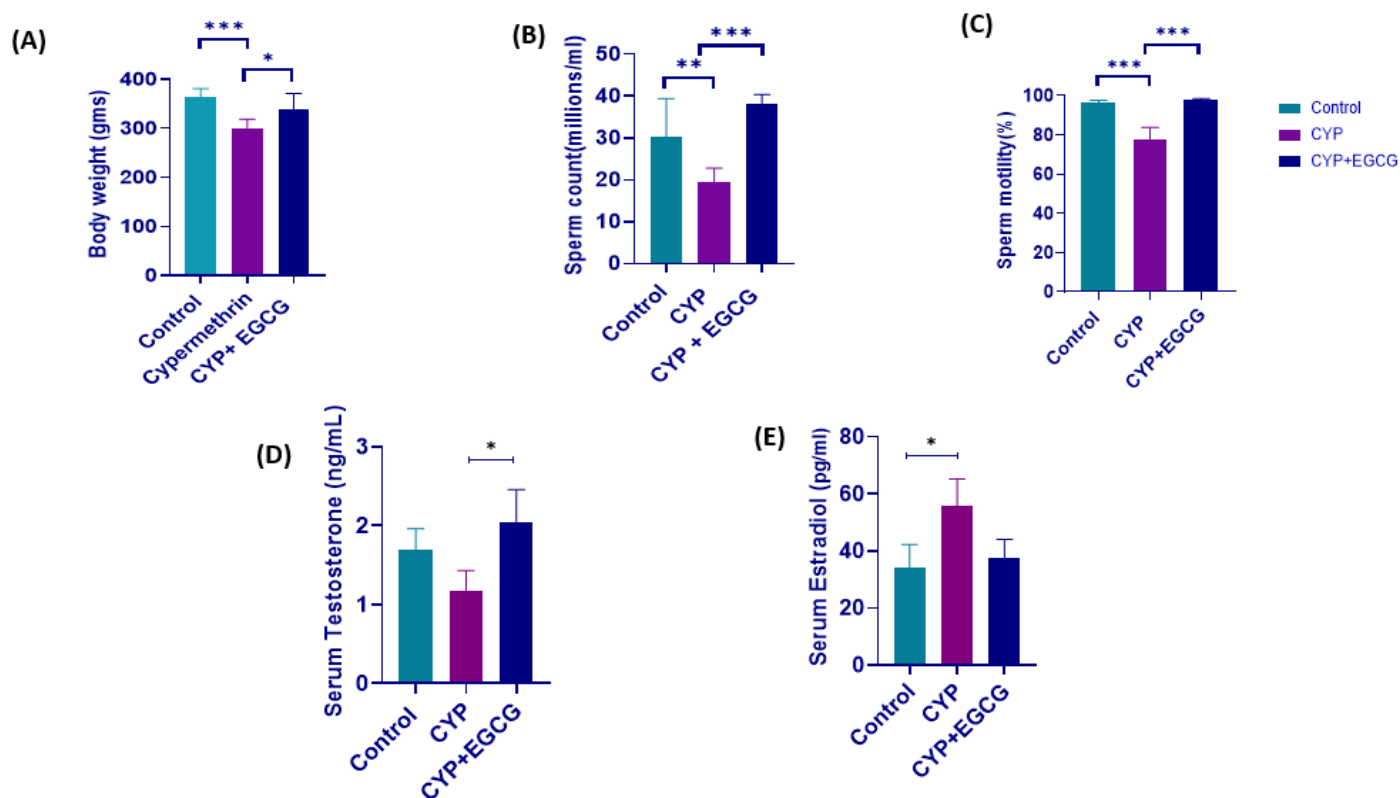


Figure 1: Effect of EGCG supplementation on body weight and reproductive parameters in CYP exposed adult male rats: A) Body weight; B) Sperm count; C) Sperm motility; D) Serum testosterone levels; E) Serum estradiol levels. n=6/group. *p < 0.05, **p < 0.001, ***p < 0.0001.

Histopathological changes in testis were also observed in CYP treatment group. These included seminiferous tubules, disorganized structure and increased inter-tubular and intra-tubular spaces. Further treatment of EGCG, restored the damage in seminiferous tubules caused by CYP treatment (Fig. 2A). Histopathological changes observed in kidney and liver of CYP exposed rats were also reversed by EGCG supplementation (Fig. 2B, 2C). Study indicates the ameliorative potential of EGCG. Further studies are underway to unravel molecular mechanisms of EGCG on spermatogenesis.

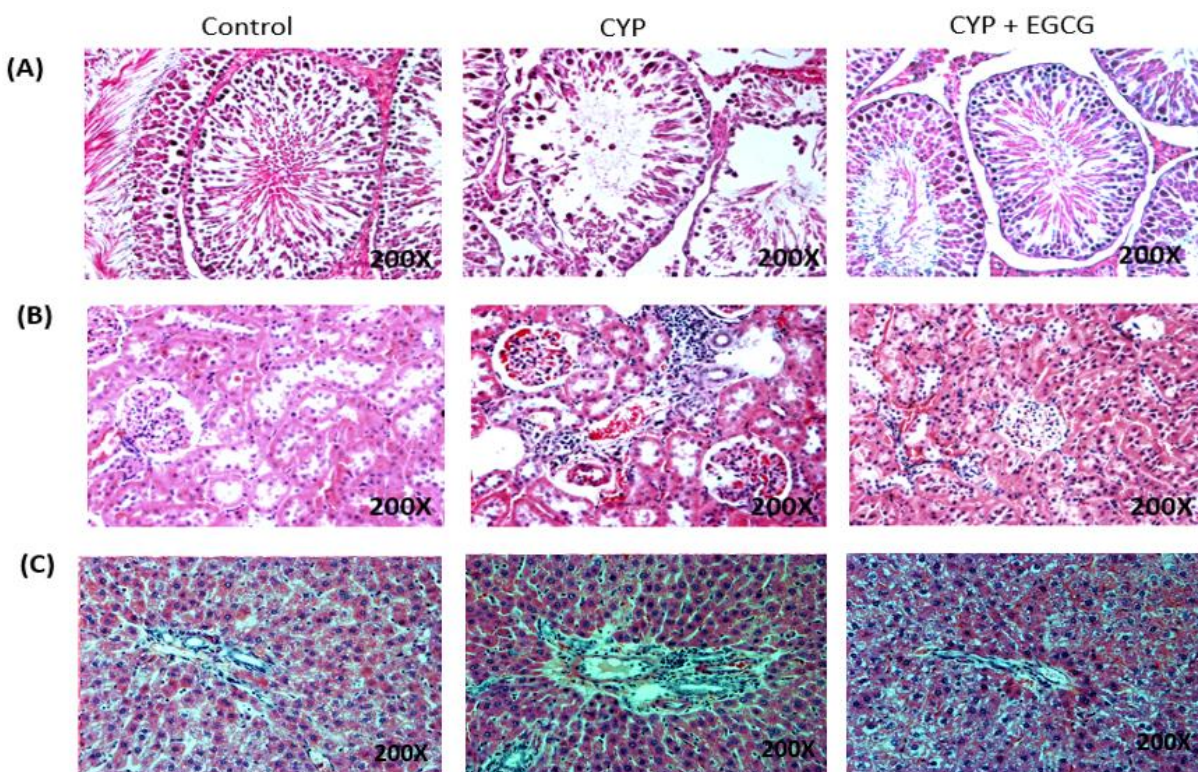


Figure 2: Histopathological changes in control, CYP and CYP+EGCG groups: A) Testis B) Kidney C) Liver. (Magnification: 200X).

2.10 Design and Development of a Microfluidic Chip for Sperm Selection / Sorting based on Chemotaxis (Partly Funded by Department of Biotechnology)

Principal Investigator	: Priyanka Parte
Project Associates	: Shraddha Gandhi, A Patankar, Kairavi Joshi, Smita Yevate, D Gaikwad, M More
Collaborator	: V Gundabala, IIT-Bombay
Duration	: 2021-2024

A growing body of evidence is available implying the role of sperm not just in fertilization but also in implantation, embryo development and placentation. Selection of sperm is therefore imminent to the success of *in vitro* fertilization (IVF). This will help bring down the cost associated with IVF by reducing repetitive IVF attempts and enhance the IVF success rate. In this study, we proposed to develop a microfluidic device to sort good quality sperm based on chemotaxis. The study is being conducted in collaboration with IIT-Bombay. In the previous report, we had described our attempts at modifying the device design to overcome the shortcomings of the prototype developed (Annual Report 22-23, pp. 47-49). The modifications and simulations were done in Comsol Multiphysics 5.5 version. After successful simulation, the device design was drawn in CleWin4 software and printed on a photomask. The device design was printed on silicon wafer using soft lithography and this was used to cast the device in Polydimethylsiloxane (PDMS). However, the modified design failed to generate a gradient even upto 3h. As a back-up, we also worked on another design and did stationery and time dependent

study in Comsol Multiphysics 5.5 version. The gradient generation in the microfluidic device was predicted by simulation. Linear concentration profile of the chemoattractant was predicted by numerical simulation. Further this device was tested for its ability to generate a stable gradient using FITC dye. But it took a very long time to form a gradient. Hence the design dimensions of the main channel and side channels were modified several times and for each modification simulation experiment was run at different mesh sizes (coarse, normal, finer) and in both stationary study and time dependent study to finally achieve the design that worked successfully (Device V2.7). The Device V2.7 showed a good correlation between the concentration profile generated from time dependent (TD) and stationary study (Fig. 1). V2.7 was therefore tested for its ability to generate a stable gradient using FITC. A gradient of the dye was seen within 15 minutes and it is stable for up to one hour. Presently it is being tested for its sorting ability using murine sperm.

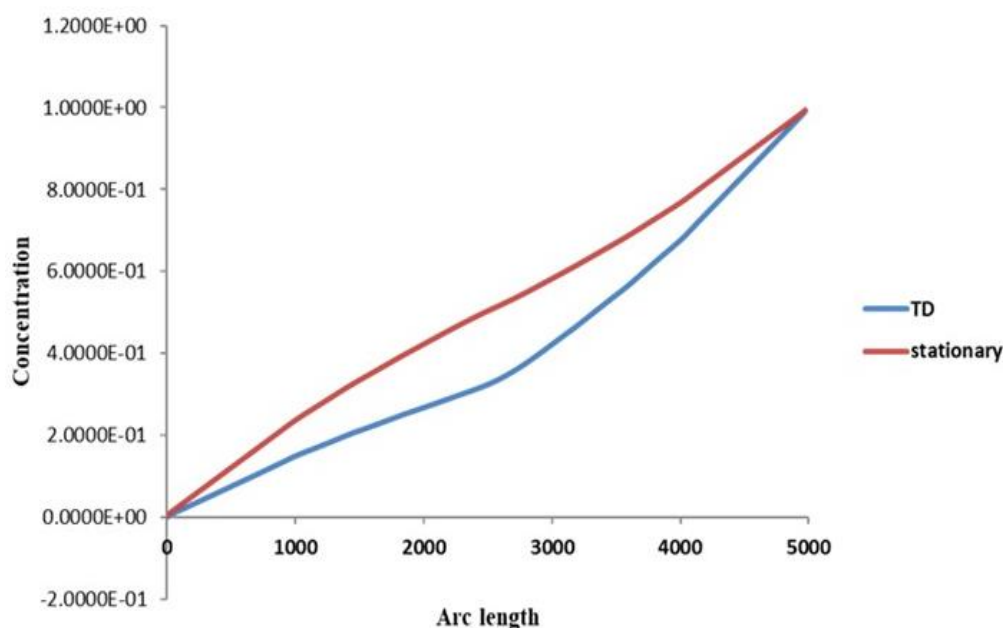


Figure 1: Concentration gradient profile after COMSOL simulation of the device V2.7 design in time dependent (TD) and stationary study

2.11 Investigation of Potential Chemotactic Metabolites in the Follicular Fluid

Principal Investigator : **Priyanka Parte**
 Project Associates : D Panchal, Aishani Bose, MT More
 Collaborator : Grishma Desai, Nowrosjee Wadia Maternity Hospital, Mumbai
 Duration : 2019-2024

Our previous research demonstrated that oviductal fluid collected during ovulation (OV-OF) exhibits a stronger chemoattractive effect on sperm compared to pre-ovulatory oviductal fluid (PreOV-OF). Thus, we employed liquid chromatography-tandem mass spectrometry (LC-MS/MS) to identify the potential sperm chemoattractants present in the OV-OF. The M-PLEX protocol, chloroform: methanol-based separation method was initially used to separate the hydrophilic and hydrophobic metabolites from both PreOV-OF and OV-OF (Annual report 2022-2023, pp. 45-47).

The present report focuses on a metabolite identified in the hydrophilic fraction. The hydrophilic metabolites from PreOV-OF and OV-OF were identified using hydrophilic interaction liquid chromatography-mass spectrometry (HILIC-MS/MS). The MS data revealed the presence of various metabolites known to function as odorants, odorant receptor agonists, bacterial/leukocyte chemoattractants, or fertility regulators. Metabolites exclusively present or exhibiting significantly higher abundance in OV-OF were prioritized for further investigation to elucidate their role in sperm chemotaxis during ovulation. The levels of X771.472 an estrous specific metabolite, were shown to be significantly higher in the OV-OF fluid by 4.868 fold as compared to the pre-ovulatory phase and with significant statistical difference (p-value 5.7 e-5 and q-value - 0.00168) (Fig. 1A). Independent investigations have reported that X771.472 may positively influence sperm motility in individuals with asthenozoospermia, potentially enhance fertility, and reduce ovarian pathological changes associated with premature ovarian failure. Given its potential to enhance sperm motility, the role of X771.472 in inducing sperm chemotaxis was explored using a microfluidic system. To begin with, several concentrations of the metabolite were explored using rat sperm to arrive at a concentration that could be used to study its chemotactic ability. Sperm motility was observed to be maintained at 1 and 10nM X771.472 for 45 min (Fig. 1B).

Sperm chemotaxis was assessed in response to gradients of X771.472 using our microfluidic device. Sperm chemotaxis parameters were evaluated on exposure of sperm to 0 (media control), or gradient concentrations of 1nM, 10nM, or 100nM X771.472. The percentage of sperm exhibiting a directional bias towards the ascending concentration were significantly higher in a 10nM X771.472 gradient compared to the media control (Fig. 2A). Additionally, significant increase in straight line velocity (VSL) was also observed at this gradient concentration (Fig. 2B). Analysis of the VSL distribution revealed that the sperm population exposed to gradient of 10nM X771.472 exhibited a higher proportion of cells with a VSL in the 80-120 $\mu\text{m/s}$ range compared to the media control and other X771.472 concentrations (Fig. 2C). The chemotactic population can be well appreciated with the shift in the peak for 10nM X771.472 as compared to media control.

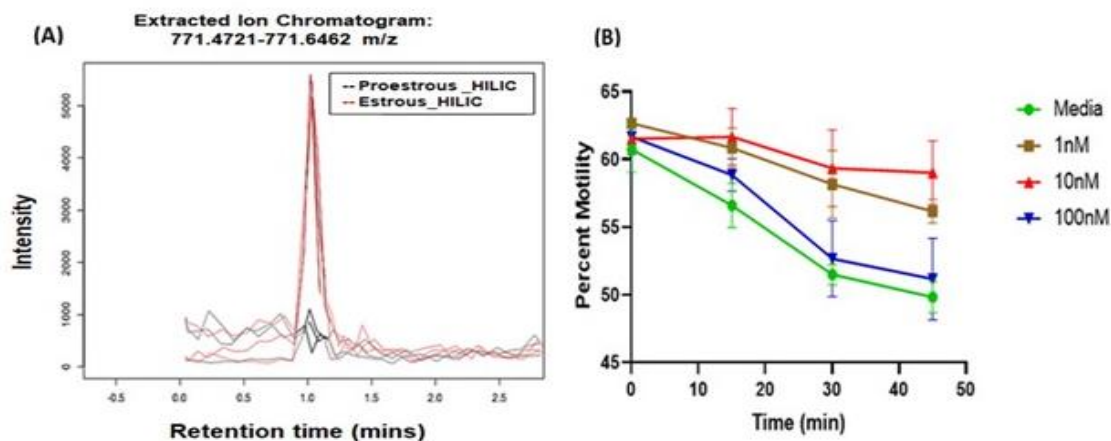


Figure 1: Identification of X771.472 in OV-OF using LC-MS and its effect on sperm motility. Extracted ion chromatogram (EIC) for X771.472 obtained through comparative metabolomic analysis of OV-OF(estrous) and PreOV-OF (proestrous) using XCMS online software. (A); Sperm motility in response to X771.472 exposure. The figure depicts percent motility of capacitated sperm incubated without or with 1 nM, 10 nM, and 100 nM of X771.472 for 15, 30, and 45 minutes (B).

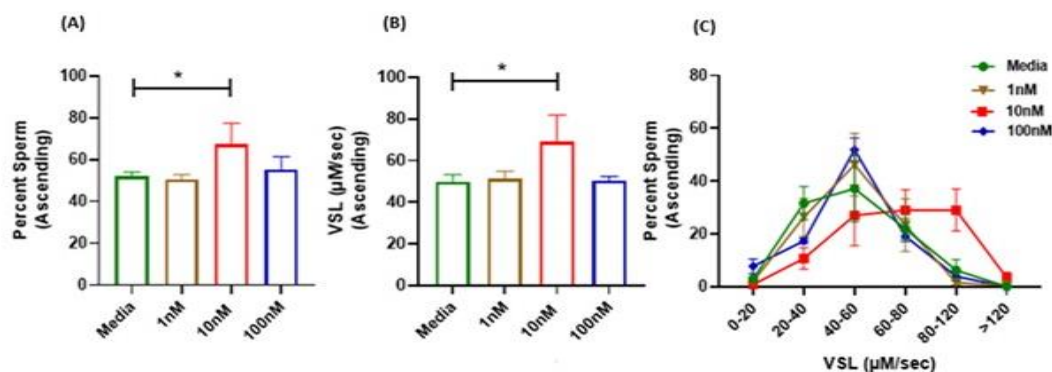


Figure 2: Sperm chemotaxis in response to gradient concentrations of X771.472. Sperm directionality represented by the percentage of sperm entering the test zone in the ascending direction of the gradient (A); their mean VSL $\pm$ SD (B); and VSL frequency distribution (C), in response to gradient concentrations of X771.472 ($n = 3$). ‘*’ $p < 0.05$.

2.12 Identification and Characterization of Genetic Factors Associated with Multiple Morphological Abnormalities of Sperm Flagella (MMAF)

Principal Investigator : DVS Sudhakar
 Co-Principal Investigator : R Gajbhiye
 Collaborators : Dipty Singh
 Duration : 2022-2025

Male infertility is a multifactorial and clinically heterogeneous condition affecting approximately 7% of the male population. Ben et al (2014) defined a severe form of asthenoteratozoospermia which is characterised by multiple morphological abnormalities of the sperm flagella (MMAF). Individuals with MMAF show sperm morphology abnormalities, aberrant flagellar phenotypes (no flagella, short flagella, coiled flagella, bent flagella, and/or irregular flagella) and seriously impaired sperm motility. MMAF is a genetically heterogeneous phenotype. Various independent studies have identified ~30 genes whose pathogenic variants induce MMAF and thus male infertility. However, the frequency of MMAF phenotype and the underlying genetic cause of MMAF among Indian infertile men is unknown. Hence, this study is primarily aimed at the identification and characterization of genetic causes associated with MMAF in infertile men from India. We recruited a total of 18 asthenozoospermic men with suspected MMAF phenotype. After semen analysis, a total of 13 individuals were found to fit with the MMAF classification criteria (at least 5% of spermatozoa with bent, absent, coiled and absent flagella). We studied the sperm flagellar ultrastructure in these individuals using the Transmission Electron Microscope (TEM imaging). We identified various sperm flagellar ultrastructure defects such as disrupted 9+2 arrangement of the microtubules, disrupted ODF and absent central pair. After whole exome sequencing (WES), raw data and intermediate files for all 13 samples were obtained. WES data of all 13 samples was analysed using an in-house bioinformatics pipeline during the current reporting period. We identified novel, pathogenic variants in three candidate genes in three infertile men with MMAF phenotype. Currently, we are validating these variants by Sanger sequencing. Further, we are performing functional assays using the cellular model system to understand the correlation between genotype and phenotype.

3. MICROBES, PATHOGENS AND REPRODUCTIVE HEALTH

3.1 Evaluating the Inflammatory, Microbiome Profile and Co-infections in Women Diagnosed with Treatment Failure, Relapse or Recurrent Bacterial Vaginosis (Funded by Indian Council of Medical Research)

Principal Investigator : **Deepti Tandon**
Co-Principal Investigators : V Bhor, Kiran Munne, Clara Aranha
Project Associates : Anushree Patil, Shahina Begum, Rachna Dalvi
Collaborator : K Mali, N Mayadeo, Jyotsana Divedi, KEM Hospital
Duration : 2023-2026

This prospective study, a collaboration between NIRRCH and KEM hospital aims to assess the proportion of cases with recurrent, relapse, remission or treatment failure in 427 symptomatic women with bacterial vaginosis (BV), identified from a screened pool of 1067 participants. The study seeks to evaluate co-infections, longitudinal changes in the vaginal microbiome, inflammatory profiles, and factors influencing adherence to treatment among women experiencing relapse, recurrence, or treatment failure following standard BV treatment. Recruitment is being conducted at two ICMR-NIRRCH family welfare clinics, ICMR NIRRCH infertility clinic, and KEM Hospital, Mumbai. Fig. 1 illustrates the design to recruit and follow-up women with BV for identifying recurrent, relapse, remission, and treatment failure cases. Total 292 patients have been recruited. Based on Nugent scoring at first visit, 117 (40.06%) patients were classified as BV, 87 (29.79%) as intermediate and 88 (30.13%) as normal. The patients were prescribed with the standard antibiotic treatment under syndromic management at the time of recruitment (F0). Syndromic management includes Kit 1 composed of azithromycin (1.0gm) and cefixime (400 mg) for cervicitis, Kit 2 composed of secnidazole (1 gm) and flucanazole (150 mg) for vaginal discharge. The Kit 6 had 400 mg cefixime (single dose), metronidazole (400 mg) and doxycycline (for 14 days) for lower abdomen pain. 117 BV patients were followed for six time points (F1 to F6) at different intervals for 7 days, 1 month, 3 months, 6 months, 9 months and 1 year. BV patients followed up so far are 82.9% (n=97), 63.24%(n=74), 48.71%(n=57), 27.35%(n=32), 7.69%(n=9), and 0.85%(n=1) respectively from F1 to F6. At baseline (F0), STI co-infections were assessed using the FTD-Urethritis plus (RUO) multiplex PCR kit, capable of detecting seven common STIs. Among these, *Mycoplasma hominis* was prevalent in 27.61%(n=29), *Ureaplasma parvum* in 42.85%(n=45), and *Ureaplasma urealyticum* in 17.14%(n=18), while *Trichomonas vaginalis* was detected in 10.47%(n=11), *Mycoplasma genitalium* in 1.90%(n=2), and *Chlamydia trachomatis* in 3.80%(n=4). Notably, *Neisseria gonorrhoeae* was absent in all BV patients. Among the recruited patients, candida coinfection was observed in 47.26% (138) of samples at baseline (F0). Identification of candida species, based on colony characteristics, revealed the predominance of *Candida albicans* in 46.37% (64) of cases alongside non-albicans species, notably *Candida krusei* in 62.31% (86) and *Candida glabrata* in 11.59% (16). Less frequently encountered species were *Candida tropicalis* in 1.44% (2) and *Candida dubilinsis* in 0.72% (1). To track the dynamics of inflammatory cytokines and microbiome profiles in recurrent, relapse, treatment failure and remission cases of BV, seven key cytokines (IL-10, IFN-gamma, IL-8, IL-1 β , IL-12, IL-6, and TNF-alpha) and microbiome profiling using 16sRNA sequencing are under process. These are being done at F0 (baseline, pre-treatment), F1 (immediately post-treatment) and at the time of

diagnosis with recurrent, relapse, treatment failure and at the time of diagnosis with remission cases to see the longitudinal changes in inflammatory and microbiome profiles.

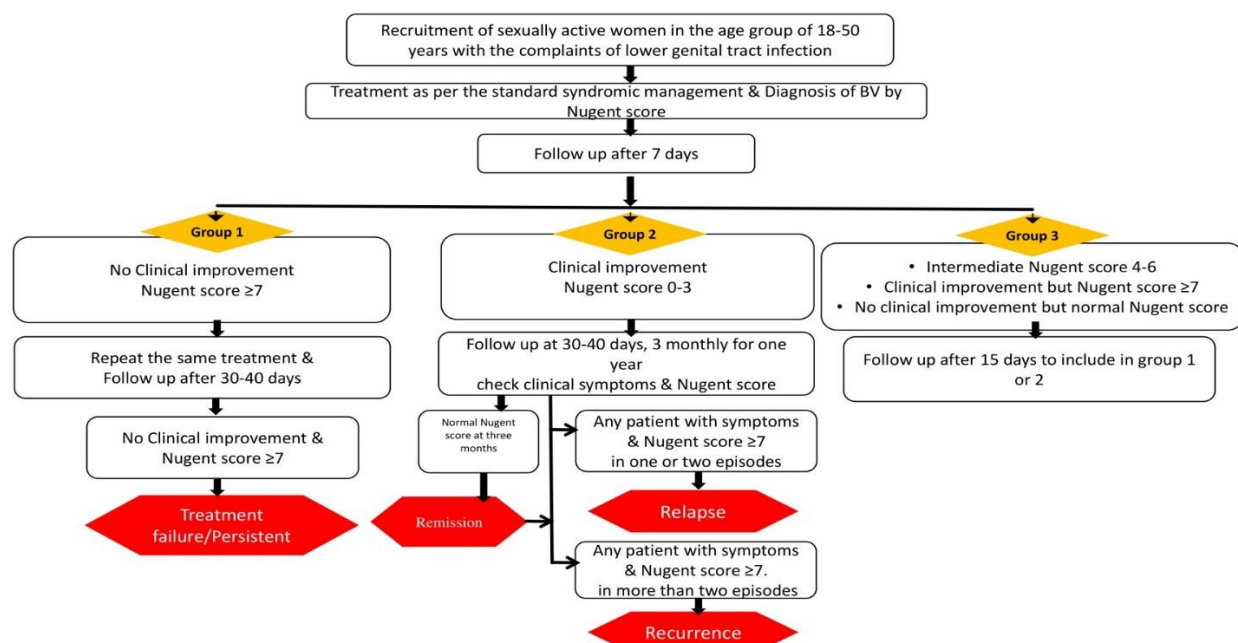


Figure 1: Flow chart to depict recruitment and follow-up of women with BV for identifying recurrent, relapse, remission, and treatment failure cases.

3.2 Integrated Analyses of Genomic Scale Metabolic Models and Omics Profiles to Capture the Host-Pathogen-Environment Interplay of *Candida sp* (Partly Funded by Science and Engineering Research Board)

Principal Investigator	: Susan Thomas
Co-Principal Investigators	: Taruna Madan, KV Venkatesh
Project Associates	: Kshitija Rahate, Shuvechha Chakraborty
Collaborator	: K Raman, IIT - Madras
Duration	: 2021-2024

Candida spp are opportunistic pathogens existing in humans as commensals under healthy host conditions. They have the ability to cause superficial (candidiasis) as well as deep-seated infections (candidemia) in every organ of the human body. The increasing burden of *Candida* infections worldwide has placed this pathogen at prominent place in the fungal priority pathogens list released by World Health Organisation in 2022. Increasing resistance to limited array of antifungal drugs available to effectively tackle these infections makes *Candida* spp a significant public health challenge. The present study aims to understand the host-pathogen interactions at the global level using multi-omics analyses. In the reporting year, the in vitro model of host-*Candida* interactions in the vaginal environment generated using the human vaginal epithelial cell line (A-431) and *C. albicans* (CAL) in the previous year was validated by PCR, biochemical assays and ELISA (Fig. 1&2). RNA-sequencing and

LC-MS/MS techniques were used to generate the transcriptomic, proteomic and metabolomic profiles of the host (A-431) and pathogen (CAL) grown in co-culture and monocultures (control) for 3 hrs and 6 hrs. Integrated analysis of the multi-omics data is being performed to gain insights into the host-pathogen interactions. This data will further be integrated into the genome-scale metabolic models of human (RECON3D) and *C albicans* (iRV781) to develop an integrated human-Candida metabolic model specific to the vaginal niche. Such a model can help identify potential targets for drug development. Arginine metabolism was identified as a significant pathway during host-Candida infection, confirmed through in vivo studies. A deletion mutant *C albicans* defective in arginine metabolism was developed which showed attenuated virulence in vitro and in vivo; it also improved the survival percentage when used as vaccine in mice (80%) compared to mock vaccinated control (50%). A provisional patent has been filed for this mutant strain. A provisional patent (202411019977) is filed for intravenous besifloxacin hydrochloride, a repurposed drug. Besifloxacin hydrochloride reduces fungal load in mouse kidneys infected with *Candida albicans* compared to a vehicle control group. Through an in silico drug repurposing pipeline, we found that DNA topoisomerase II, the target of the FDA-approved anti-bacterial drug Besifloxacin, shared sequence homology with DNA topoisomerase II of *C. albicans*. To validate this in vivo, we used a murine model of systemic candidiasis. Intravenous administration of this drug reduced the fungal load by 83% in the mouse kidneys. A combination of besifloxacin with fluconazole also showed a positive synergy resulting in 80% inhibition of microbial growth in vitro. A provisional patent (202411019977) for this novel intravenous formulation of Besifloxacin has been filed at ICMR for its anti-Candida activity.

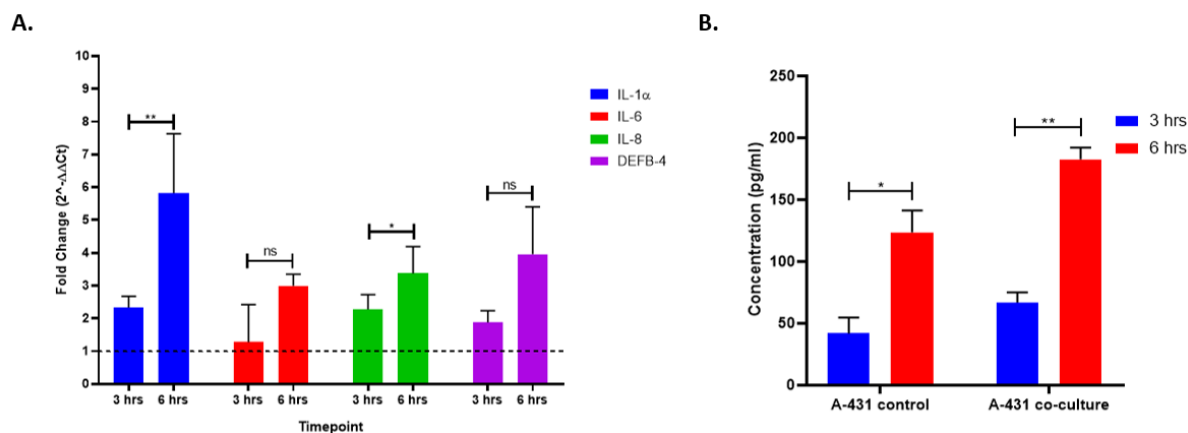


Figure 1: Host response to 3-hour and 6-hour co-culture: A. Expression of cytokine genes IL-1α, IL-6, CXCL8 (IL-8) and DEFB-4 (β-defensin) were upregulated in A-431 cells co-cultured with CAL compared to A-431 monocultures; B. Expression of TNF-α was higher in co-culture supernatant compared to supernatant from A-431 monocultures.

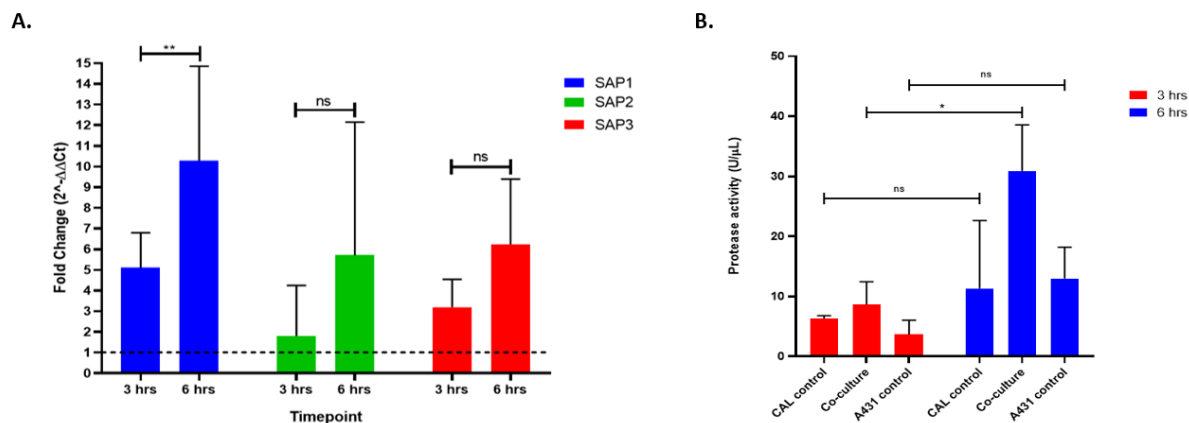


Figure 2: Pathogen response to 3-hour and 6-hour co-culture: A. Expression of virulence genes (SAP1, SAP2 and SAP3) were upregulated in CAL co-cultured with A-431 compared to CAL monocultures; B. Secreted protease activity was higher in co-culture supernatants compared to supernatant from CAL and A-431 monocultures

3.3 Recent Maternal HCMV Infection in Early Pregnancy within a Prospective Cohort and Association with Congenital Transmission and Adverse Pregnancy Outcome *(Partly Funded by Department of Biotechnology & Team Science Grant- DBT/Wellcome Trust India Alliance)*

Principal Investigator : **V Patel**

Co-Principal Investigator : V Bhor

Project Associates : Harsha Palav, Varsha Padwal, Shilpa Velhal, Sapna Yadav, Varsha Kalsurkar, Gauri Bhonde

Collaborators : Purnima Satoskar, Ira Shah, Forum Shah. Nowrosjee Wadia Maternity Hospital and Bai Jerbai Wadia Hospital for Children

Duration : 2020-2025

Human Cytomegalovirus (HCMV) infection, leading to >90% seroprevalence in Indian women of reproductive age, is the largest contributor to congenital infections worldwide. We assessed the impact of maternal HCMV infection status across trimesters in women with and without Bad Obstetric History (BOH) and consequent impact on congenital transmission (cCMV) as well as pregnancy outcome in a public health setting. In this prospective study, participants were recruited from Nowrosjee Wadia Maternity Hospital (NWMH) in their first (upto 12 weeks) or second trimester (13-20 weeks) and were followed upto delivery i.e. third trimester (28 weeks and above). Blood and saliva samples were collected during each time point and cord blood was obtained after delivery. Further, neonates born to these pregnant women were tested for detecting cCMV transmission using saliva samples collected within 72 hours of birth, before or post 1 hour of breast feeding. If HCMV positive neonates will be followed at Bai Jerbai Wadia Hospital for Children (BJWHC) for a period of one year. HCMV infection status of 83 pregnant women, with (n=45) and without BOH (n=38), was determined by ELISA (IgM,

IgG and IgG avidity) for all TORCH pathogens along with HCMV specific nested PCR. Data sets were analyzed using descriptive statistics to determine associations between maternal infection status, pregnancy outcome and cCMV in 49 mother-neonate dyads. Using an integrated approach i.e. serology along with HCMV PCR, the infection status of the participants was identified. We observed 10 cases of pregnancy losses and 18 cases of cCMV (with 11 symptomatic births followed by 1 neonatal death) with evidence of HCMV infection in all 28 cases. Our findings highlighted the importance of IgG avidity and PCR based screening to detect HCMV infection during pregnancy. Pregnancy loss associated highest with BOH and concurrent HCMV infection. Signatures associated with adverse pregnancy outcome, including congenital HCMV infection, were high PCR positivity (first trimester) and high rates of concurrently assessed anti HCMV IgM and intermediate avidity IgG ($p=0.0813$, 0.0274). Additionally, recent HCMV infection (with intermediate IgG avidity), observed mainly in the BOH group in first and second trimesters and not recurrent infection (with IgM positivity), was associated with neonatal saliva positivity and adverse outcomes including neonatal death ($p=0.0507$). Exposure to other TORCH pathogens, while present, did not include IgM positivity or low/intermediate IgG avidity. Our research underscores the significance of implementing early, integrated screening for maternal HCMV infection during pregnancy, especially in resource-limited public health settings with high HCMV seroprevalence.

Prospective pregnancy cohort, n=83 (Control group: n= 38. BOH group: n= 45); 52 mother-neonate dyads

✓ Superiority of independent IgG avidity and PCR based maternal HCMV screening over IgM alone.

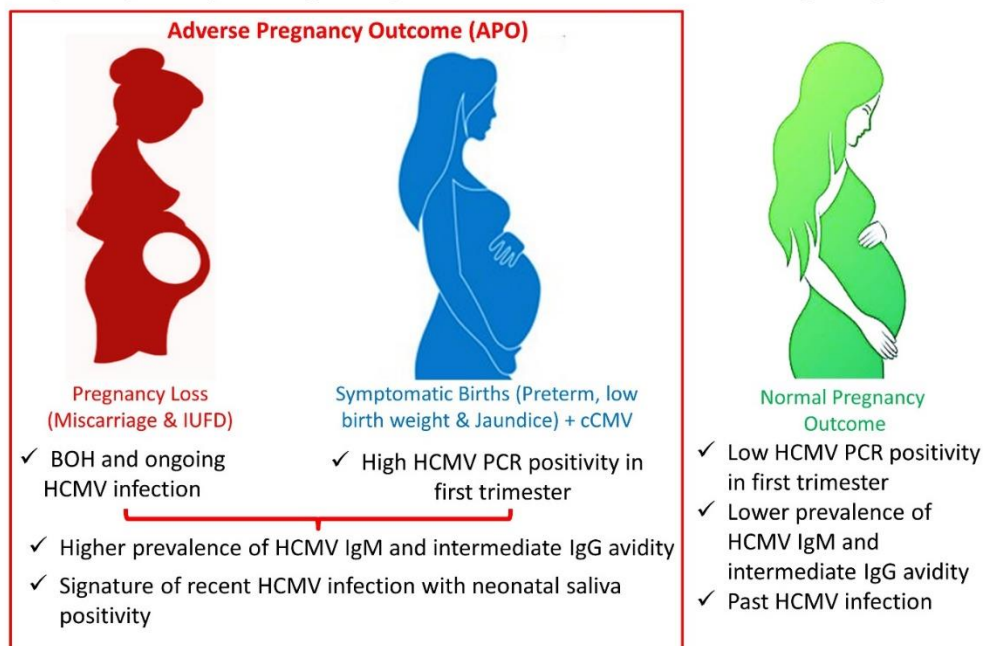


Figure 1: HCMV infection status within different pregnancy outcome groups.

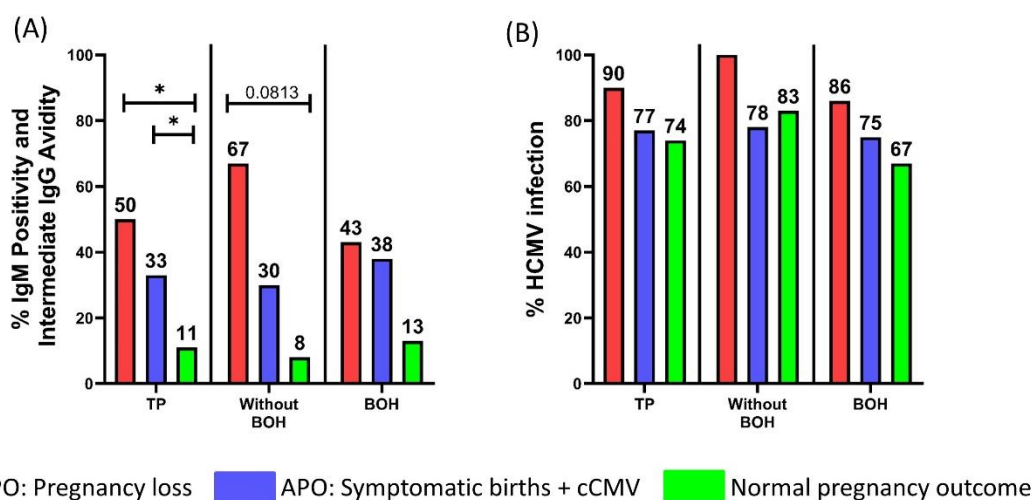


Figure 2: Distinct HCMV infection signatures associated with pregnancy outcomes. (a) Integration of occurrence of IgM positivity or intermediate avidity during pregnancy in participants who had pregnancy loss, symptomatic births and normal pregnancy outcome. (b) HCMV infection status by integrated approach i.e. IgM positivity or intermediate avidity and HCMV nested PCR positivity. TP: total participants and, BOH: Bad Obstetric History and APO: adverse pregnancy outcome. Comparisons between groups was evaluated by Fisher's exact test. $p < 0.05$ was considered significant.

3.4 Gut Dysbiosis in HCMV infected Pregnant Women with Bad Obstetric History

Principal Investigator : V Bhor

Co-Principal Investigator : V Patel

Project Associates : Jyoti Batgire, Gauri Bhonde, Kalyani Karandikar, P Devadiga, Harsha Palav, Varsha Padwal, Shilpa Velhal

Collaborators : Purnima Satoskar, Nowrosjee Wadia Maternity Hospital

Duration : 2021-2025

Human cytomegalovirus (HCMV) infection is associated with bad obstetric history (BOH) and adverse pregnancy outcomes. Reports on specific host factors that determine susceptibility to HCMV infection in pregnant women have overlooked the involvement of the gut microbiota, which are known to influence susceptibility to infection via immune dysregulation. We previously reported the role of gut dysbiosis in influencing susceptibility to HCMV infection as well as the severity of infection in infants with neonatal cholestasis. In the present work, we undertook an investigation of the gut microbiome composition of pregnant women with BOH and HCMV infection. During the reporting period, 40 pregnant women with or without BOH and HCMV infection and 10 non-pregnant women without HCMV infection were recruited from Wadia Maternity Hospital. Paired blood and stool samples were collected. 16S rRNA sequencing of the V3-V4 region in stool samples revealed an increase in

abundance of proteobacteria and actinobacteria as well as bacteroidetes in pregnant women compared to non-pregnant women and this appears to be a pregnancy associated signature (Fig. 1). BOH was associated with reduced actinobacteria, bacteroidetes and increased proteobacteria compared to controls. HCMV infection was also associated with a greater increase in proteobacteria and reduction in actinobacteria, bacteroidetes, with the extent of change being higher in BOH compared to controls (Fig. 1). At the genus level, two distinct microbiome signatures, one specific for women with BOH while the other specific for women infected with HCMV were observed (Fig. 2) a. HCMV specific signature comprised of increased *Lactobacillus*, *Clostridium* spp. and reduced *Prevotella* spp. The BOH specific signature comprised of increased abundance of *Ruminococcus* and *Dorea* and reduced *Faecalibacterium* spp. The exact significance of the changes in gut microbiome composition of pregnant women, especially those with BOH without HCMV infection, is not very apparent. However, the pronounced increase in proteobacteria in pregnant women with HCMV infection is indicative of the heightened pro-inflammatory condition and may contribute to the dysregulated immune responses associated with adverse pregnancy outcomes in these women.

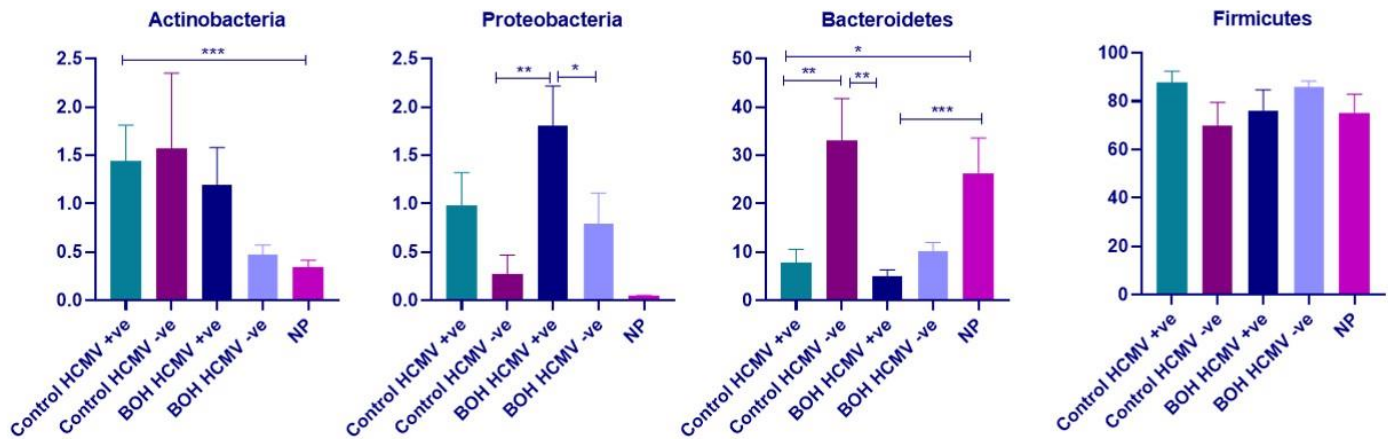


Figure 1: Phylum level changes in the gut microbiome profile of HCMV infected pregnant women with BOH (n=10) compared to those with BOH without HCMV infection (n=10) and corresponding controls without BOH but with (n=10) and without HCMV infection (n=10) as well as non-pregnant women (NP, n=10). Data represented as mean± SEM. Statistical significance was calculated by Mann-Whitney U-test; *, $p < 0.05$; **, $p < 0.01$, ***, $p < 0.001$; and ****, $p < 0.001$.

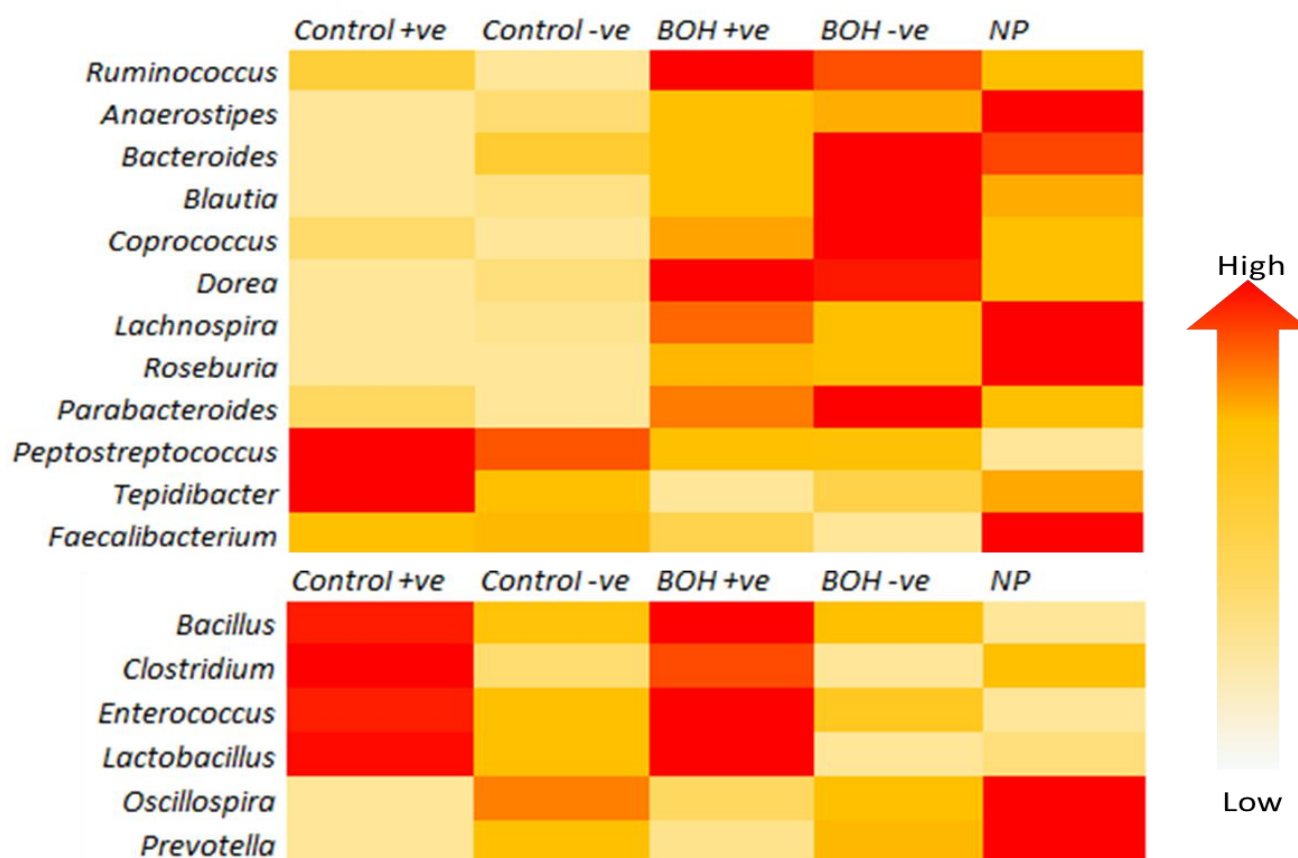


Figure 2: Genus level changes in the gut microbiome profile of pregnant women with BOH and HCMV infection (BOH +ve, n=10); with BOH without HCMV infection (BOH -ve, n=10) and corresponding controls i.e. pregnant women without BOH with (control +ve, n=10) and without HCMV infection (control -ve, n=10) as well as non-pregnant women (NP, n=10). Colour indicates high (red) to yellow (low) range of relative abundance of the individual taxa.

3.5 Exploring the Association of Cervicovaginal Microbiome with Transient and Persistent High-Risk HPV Infection and Cervical Precancerous Lesions

Principal Investigator : **Kiran Munne**

Co-Principal Investigator : Anushree Patil, V Bhor

Project Associates : Anamika Akula, Deepti Tandon, Shahina Begum

Collaborators : Sharmila Pimple, Professor and Physician Department of Preventive Oncology, Tata Memorial Hospital, Mumbai
S Biswas, Professor and Head, Department of Microbiology, Tata Memorial Hospital, Mumbai

Duration : 2023-2026

Persistence of the Human Papillomavirus (HPV) is essential for development of high-grade CIN and cervical cancer. Factors that correlate with higher persistence of HPV include age, parity, immunodeficiency, smoking, oral contraceptives and Chlamydia trachomatis infection. Emerging evidence indicates that cervicovaginal microbiota plays a substantial role in the persistence or regression of the virus and subsequent disease. This prospective observational cohort study was planned with an objective to study the association of cervicovaginal microbiome with transient and persistent high-risk HPV infection. A cohort of HR-HPV positives and negatives from a previously completed study on screening of cervical precancers and cancers by molecular HPV (n=90) method are being followed for persistence or clearance of HPV infection and changes in vaginal microbiota. Total sample size will include 30-HPV persistent, 30- HPV transient and 30-HPV negative women). The study has been initiated and total 5 participants have been recruited from the camp at Dahanu site. Their socio-demographic and clinical history have been recorded in CRF. Based upon the HPV reports (previous and after 1 year), the participants have been classified as persistent HPV (n=1), transient HPV (n=2) and HPV negative group (n=2). Cervico-vaginal microbiota will be characterized by metagenomic analysis in the samples of women with transient and persistent HPV infection and HPV negative cases. Microbial profiles will be analyzed for association with viral clearance or persistence.

3.6 Gut Microbiome Signatures of HIV-TB Coinfection

Principal Investigator	: V Bhor
Project Associates	: P Devadiga, Nandini Kasarpalkar, Shilpa Bhowmick, V Patel, Taruna Gupta, Nupur Mukherjee, Kiran Munne
Collaborators	: Vidya S Nagar, Priya Patil, Grant Medical College and JJ Group of Hospitals Jayanthi Shastri, Sachee Agrawal, TN Medical College and BYL Nair
Duration	: 2021-2025

Tuberculosis (TB) is a predominant comorbidity among individuals living with HIV (PLHIV), significantly affecting disease progression and treatment outcomes. Dysbiosis of the gut microbiome has been independently associated with both HIV and TB and is likely to influence the course and treatment outcomes of HIV-TB coinfection. In order to gain a better understanding of the link between gut dysbiosis and disease pathogenesis, we carried out investigation of the gut microbiome composition of HIV-infected individuals, distinguishing between those solely infected with HIV and those concurrently affected by latent or active TB. A total of 60 ART naïve HIV infected individuals were recruited at Integrated Counselling and Testing Centers (ICTC) and ART centers at J J Hospital and Nair Hospital, Mumbai along with 35 age- matched controls. Paired blood and stool samples were collected. All individuals were screened for latent TB infection (LTBI) using interferon gamma release assay (IGRA) and categorized into those with and without LTBI. The gut microbiome composition of all study participants was determined by deep sequencing of the V3-V4 region of 16S rRNA. The results revealed a noteworthy reduction in alpha diversity among HIV-infected individuals without concurrent TB infection, indicating a less varied microbial landscape in their gut. Within the cohort of

HIV-TB coinfection cases, those with active TB exhibited the lowest alpha diversity, underscoring the impact of active TB on the gut microbiome. Intriguingly, individuals with latent TB exhibited alpha diversity similar to uninfected controls (Fig. 1A), hinting at a potential resilience of the gut microbiome in this subset of coinfection. Furthermore, beta diversity of the HIV infected individuals with and without LTBI was found to be different (Fig. 1B) implying differences in the composition of the gut microbiome in these two groups of HIV - infected individuals. Beyond alterations in diversity metrics, a distinct gut microbiome profile emerged among HIV-infected individuals coinfecting with both latent and active TB, emphasizing the intricate interplay between these pathogens and the gut microbial community. Further work on the longitudinal analysis of the gut microbiome composition of the HIV infected individuals with LTBI will be undertaken to determine whether anti-retroviral treatment can result in restoration of the gut microbiome similar to the restoration of CD4+ T cell counts. This in turn may open avenues for probable targeting the gut microbial ecosystem, for enhancing treatment efficacy and improving health outcomes in this vulnerable population.

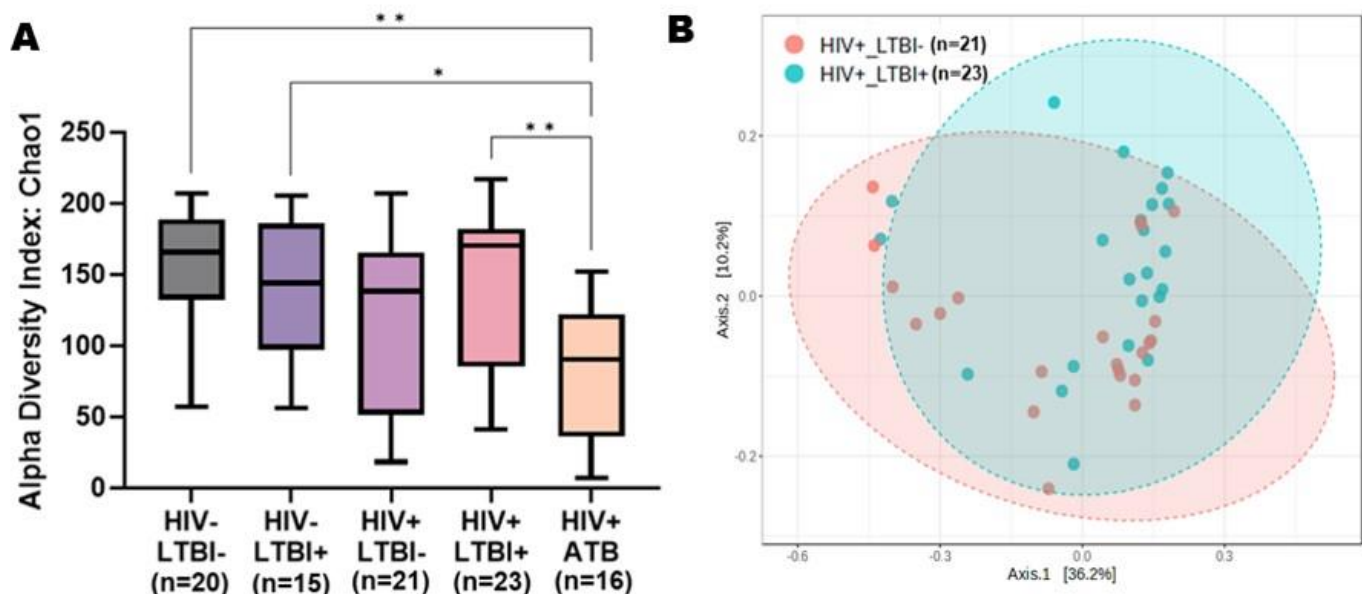


Figure 1: Gut microbiome dysbiosis in individuals with HIV-TB coinfection (A) Alpha diversity analysis for individuals with HIV infection alone (n=21) or HIV infection along with either LTBI (n=23) or active TB (n=16) compared to uninfected controls (n=20) and controls with LTBI (n=15) (*p < 0.05; ** p < 0.01). (B) Beta diversity analysis for HIV infected individuals with (n=23) and without LTBI (n=21) by Jensen-Shannon Divergence index. Significance computed by PERMANOVA (F-value: 2.1141; R-squared: 0.046861; p-value: 0.042).

3.7 Viral Reservoir Dynamics in a Prospective HIV-1C Cohort (Partly Funded by DBT India Alliance Wellcome Trust- Team Science Grant)

Principal Investigator : V Patel

Co-Principal Investigator : Jayanta Bhattacharya, IAVI-THSTI

Project Associates	: Nandini Kasarpalkar, Snehal Kaginkar, Shilpa Bhowmick, P Gurav, Tejaswini Pandey, Sapna Yadav, Varsha Padwal, Namrata Neman, S Musale, Varsha Kalsulkar, Sayantani Ghosh
Collaborators	: Jyoti Sutar, Gita Nataraj, Kavita Joshi, Nayana Ingole, Jayanthi Shashtri, Sachee Agrawal, Sushma Gaikwad
Duration	: 2020-2025

HIV has become a manageable disease due to successful roll out of anti-retroviral therapy (ART). Though ART is successful in reducing disease transmission by reducing plasma viremia, it does not achieve cure due to the presence of long lasting viral reservoirs which persist and can even amplify with time. This study aims to investigate the reservoirs (reservoir dynamics) and their modulation by chronic immune activation or immune cell exhaustion in an Indian cohort. For this study, we recruited 230 participants from KEM and Nair hospital and follow up samples were also collected from some of these participants. We observed that in spite of extended ART and CD4 count rebound, CD4/CD8 ratio in therapy receiving individuals was not restored. Similarly, HIV proviral burden in the naïve group was reduced significantly but remained persistent in ART group with a trend of higher proviral burden in 2nd line ART group (group having a history of an ART failure). Central memory CD4⁺ T cells have been known to be long lasting reservoirs due to their higher survival ability. Significantly higher CD4⁺ T cell (total and CM subset) activation was observed in therapy naïve group which dampened in response to ART but was not restored to seronegative levels. In contrast, PD-1 dysregulation while observed in the CD4⁺ T cell compartment within therapy naïve individuals seemed to be restored in ART receiving participants. We observed a positive correlation between conventional activation markers and immunomodulation marker PD-1 in both Naïve and on ART group. PBMC proviral load showed a positive correlation with HLADR+CD38+CD4⁺T cells in the ART naïve group but not with PD-1. PBMC proviral burden was not found to be correlated with CD4 counts either in naïve group or on ART group that showed CD4 rebound in response to ART. To understand if activation/immunomodulation drives seeding of the reservoirs, we associated activation/ exhaustion with PBMC proviral load. We found positive correlation between activation of CD4⁺ T cells and HIV copies in the naïve group and no correlation in ART group. HIV proviral burden was not found to be correlated with PD-1 in either of the groups. Similarly, we did not observe any correlation between absolute CD4 count with HIV proviral burden in either of the groups. From the individuals where corresponding proviral burden of CM cells were available, we observed enrichment in the CM subset indicating it as a major HIV-1 reservoir. We further would like to explore the compartmental quasispecies which lead to viral rebound upon treatment interruption and if compartment specific distribution of quasispecies having drug resistant mutations.

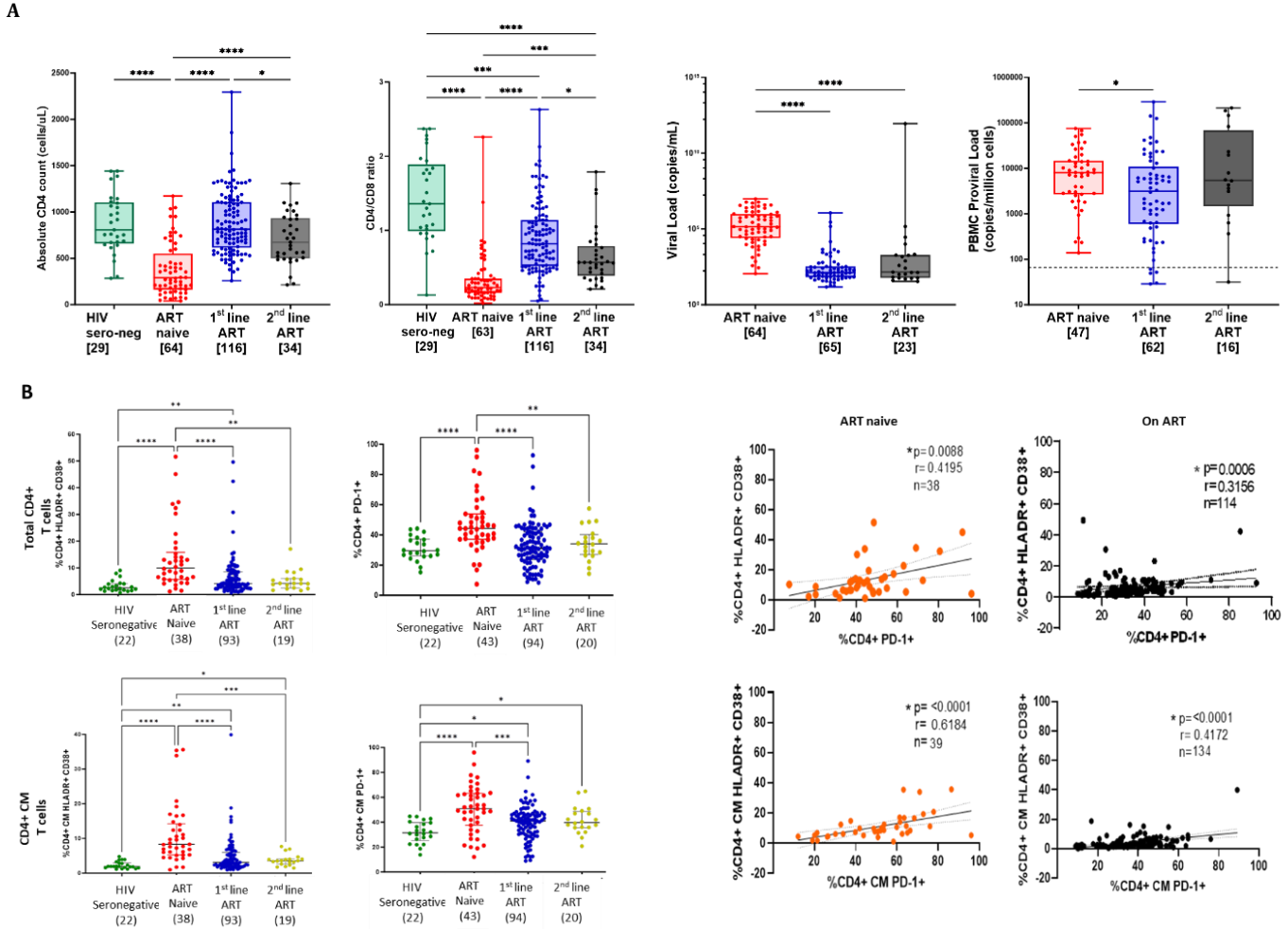


Figure 1: Ex-vivo monitoring of immune restoration in putative reservoirs A) Immune signature in the HIV infected groups and dynamics of proviral burden across disease progression: Clinical and virological characteristics of study population (from left to right) Absolute CD4+ T cell counts, CD4/CD8 ratios, plasma viral load and HIV proviral burden in PBMC. Comparison between groups was calculated by Kruskal-Wallis one-way ANOVA non-parametric test, (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$). B) Increased and persistent activation of CD4+ T cells in the infected groups: (upper panel-from left to right) Frequency of activated and PD-1 expressing total CD4+ T cells. Correlation between frequencies of PD-1 expressing cells with activation in total CD4+ T cells in ART naïve group and ART receiving group. (lower panel) Frequency of activated and PD-1 expressing CD4+ CM subset. Correlation between frequencies of PD-1 expression with activation in CM subset in ART naïve group and in CM subset of ART receiving group. Comparison between groups was calculated by Kruskal- Wallis one-way ANOVA non-parametric test, (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$). p and r values for associations were determined by Spearman's correlation test, with linear regression shown as a line.

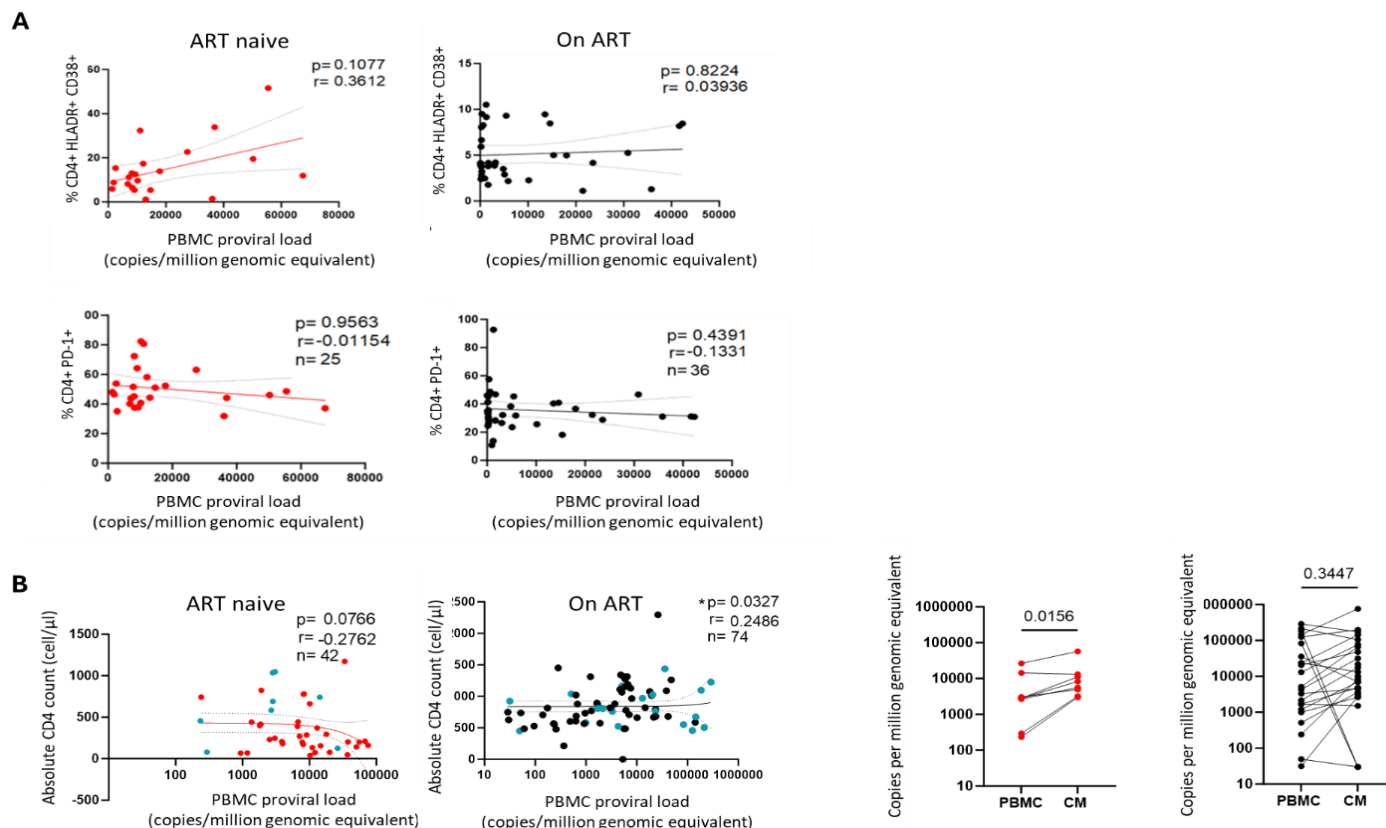


Figure 2: Correlation of functional signatures and proviral load in CD4+ T cell compartments A) Association of activation/immunomodulation profile of the putative reservoirs with proviral burden: (Upper panel) Correlation of PBMC proviral load with activated CD4+ T cells in ART naïve and ART receiving group. (Lower panel) Correlation of PBMC proviral load with PD-1 expressing CD4+ T cells in ART naïve and ART receiving group. B) Association of CD4 count with HIV proviral burden. Correlation between PBMC proviral load with absolute CD4+ T cell counts in ART naïve and ART receiving group. HIV proviral burden in PBMC and matched CM subset (from the same individual) is plotted for ART naïve and ART receiving group. p and r values for associations were determined by Spearman's correlation test, with linear regression shown as a line.

3.8 Immune Status Against SARS-CoV-2 among COVID-19 Vaccinated Adults in India: A Health Facility-Based Multicentric Serial Cross-sectional Survey (Partly Funded by Indian Council of Medical Research)

Siteprincipal Investigators : **Ragini Kulkarni, Kiran Munne**

Co-Principal Investigator : L Sankhe

Project Associates : M Sadawarte, S K Mishra

Collaborators : B Hengne, Medical Superintendent, Subdistrict hospital, Dahanu
A Gadag, Medical Officer, Ashagad PHC

Duration : 2023-2023

Prior infection with different SARS-CoV-2 variants, vaccination with different types and doses of COVID-19 vaccines and a combination of both have made the population immunity to SARS-CoV-2 more complex. Neutralizing antibody studies can provide insights into vaccine performance against new and emerging variants of concern and their subvariants. Estimating the level of protection in the different population subgroups, especially vulnerable groups, with different vaccine doses is vital. This multicentric study led by ICMR NIE, Chennai was planned with an objective to estimate the proportion of individuals, positive for neutralizing antibodies against different variants of SARS-CoV-2, among those who received two or three doses of COVID-19 vaccine in India. The study was conducted among individuals of age above 45 years who received two primary doses / three doses of COVID-19 vaccine visiting OPD at SDH Dahanu, PHC Ashagad and Grant Medical College and JJ hospital, Mumbai. Blood samples were collected from 160 individuals (SDH-Dahanu n=117; PHC-Ashagad n=03; JJ Hospital n=40). These samples were collected from individuals who received (1) two primary doses and (2) three doses of COVID-19 vaccine across each of the following three groups: a. age >60 years b. age 45-60 years with known co-morbidities (diabetics >10 years or with complications, heart/kidney/liver disease on treatment, solid tumors, hematolymphoid malignancies, patients on prolonged corticosteroids/ immunosuppressive medication) c. age 45-60 years without co-morbidities mentioned in group (b) The information on demographic details, vaccination status, clinical/treatment details for comorbidities, history of COVID-19 vaccination were collected for each individual enrolled in the study. All data were entered in an Open Data Kit (ODK) application on mobile phones by the survey team. All 160 sera samples were transported to ICMR-NIV, Pune for conduction of various serological assays (MNT, PRNT 50, IgG antibodies against S1-RBD of SARS-COV-2). Results of IgG antibodies against S1-RBD of SARS-COV-2 for all 160 sera samples tested positive. Test reports for COVID-19 S1-Receptor binding domain (RBD) IgG test (CLIA) were prepared for each participant and sent to their respective contacts through WhatsApp application.

3.9 Longitudinal Cohort Study of Lactating Women to Assess Impact of SARS-CoV-2 Exposure and Vaccination on Systemic and Vertically Transferred SARS-CoV-2 Specific Immunity in the Mother-Infant Dyad. (Partly Funded by Indian Council of Medical Research)

Principal Investigator : V Bhor
 Co-Principal Investigator : V Patel
 Project Associates : Gauri Bhonde, Sindoor Balan, Hajra Ansari, P Devadiga, Pranita Nikam, Dhanashree Jagtap
 Collaborator : Purnima Satoskar, Nowrosjee Wadia Maternity Hospital
 Duration : 2023-2025

Lactation signifies a unique physiological transition for women, influencing their susceptibility to SARS-CoV-2 infection. Maternal immunity plays a pivotal role in safeguarding neonates from COVID-19. Hence, understanding the transmission of immunity from mother to infant is crucial for determining neonatal protection against COVID-19. The present study aims to explore the nature and

mode of transmission of SARS-CoV-2 specific maternal immunity, considering both, history of natural infection and vaccination. During the reporting period, 61 pregnant women admitted at Wadia Maternity Hospital, Mumbai, for delivery were recruited as study participants. All the study participants were vaccinated against SARS-CoV-2, with the majority having a history of natural infection. Peripheral blood, cord blood and breast milk samples were obtained from these women, post-delivery. Immunophenotyping data revealed higher counts of CD4+ and CD8+ T lymphocytes, NK cells, B cells, and eosinophils in cord blood compared to peripheral blood. Monocyte and neutrophil counts were slightly elevated in peripheral blood. However, no significant difference was observed based on vaccine dosage. ELISA demonstrated higher levels of anti-SARS-CoV-2 IgG in cord blood and peripheral blood compared to breast milk. Notably, none of the participants were seronegative. Overall, cellular immune responses were low to moderate, contrasting with robust humoral responses (Fig. 1). These findings suggest a decline in cellular immune responses with a notable humoral response. Further research with a larger sample size and longitudinal follow-up will be carried out to confirm these observations, which could inform vaccination strategies and contribute to understanding maternal-infant immunity against SARS-CoV-2.

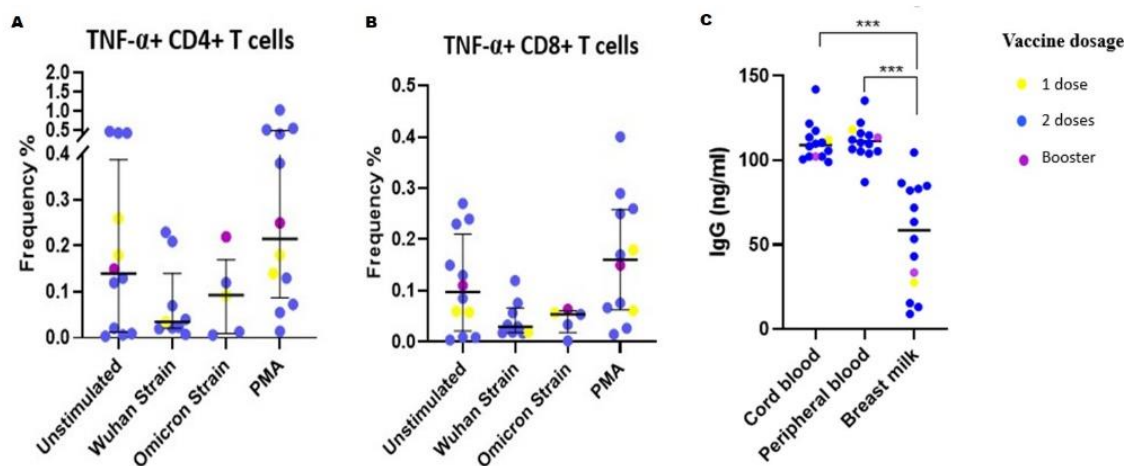


Figure 1: SARS-CoV-2 specific cellular and humoral immune responses. Representation of TNF- α production within (A) CD4+ T cells and (B) CD8+ T cells from cord blood of the study participants (n=13) on the basis of vaccine dosage, following stimulation with Wuhan and Omicron strains of SARS-CoV-2 peptide, alongside phorbol myristic acid (PMA) as the positive control and an unstimulated negative control. Statistical significance was calculated by Mann-Whitney U Test; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; and ****, $p < 0.0001$. (C) Levels of anti-SARS-CoV-2 specific IgG in cord blood, peripheral blood & breast milk of the study participants (n=14), based on the difference in dosage of vaccination. Statistical significance was calculated by Mann-Whitney U Test; *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; and ****, $p < 0.0001$.

3.10 Immune monitoring of Nipah Virus infected individuals (2023 outbreak) conducted at Maximum Containment Facility, Indian Council of Medical Research-National Institute of Virology, Pune

Principle Investigators : V Patel, Pragya Yadav

Associates : Rima R Sahay, Harsha C Palav, Anita M Shete, DY Patil, Sreelekshmy Mohandas, N Mohite, P Gurav, Rajlaxmi Jain, Y Joshi, Denna Prabhin

This work was carried out in response to an urgent request from ICMR HQ as part of the national response to the 2023 Nipah Virus (NiV) outbreak. Immune profiling of NiV infection survivors is crucial for understanding NiV pathogenesis, improving diagnostic and therapeutic strategies, and guiding public health efforts to prevent future outbreaks. Currently, limited data exist on the immune response to NiV infection. This study aims to elucidate the specific immune mechanisms involved in protection against NiV by analyzing the immune profiles of survivors from the 2023 Nipah outbreak in Kerala, India. Immune cell populations were quantified and compared between survivors (up to four months post-onset) and healthy controls. Key immune signatures common to all survivors included a previously undescribed persistent lymphopenia, particularly within the CD4+ Treg compartment, with a relative expansion of memory Tregs. Trends indicative of global leukopenic modulation were observed in monocytes and granulocytes, including an expansion of putatively immunosuppressive low-density granulocytes, recently noted in severe COVID-19 contexts. Altered mucosal homing was observed in integrin beta-7 (ITGB7) expressing subsets, alongside increased mobilization of activated T-cells (CD4+ and CD8+) and plasmablasts in the early phase of infection. Comparative analysis based on clinical presentation and outcome suggested that lower initial viremia, increased activated T-cell responses, expanded plasmablasts, and restoration of ITGB7 expressing CD8+ T-cells may be protective signatures. This longitudinal study delineates putative protective signatures associated with milder NiV disease and supports the development of immunotherapeutic interventions, such as monoclonal antibodies, to reduce early viremia and ameliorate pathogenesis.

Table 1: Summary of immune signatures from NiV survivors

Overall Immune Signatures of Nipah Virus (NIV) Cases
All monitored cases were Nipah viral RNA negative by 2nd week post infection (POD ≥ 15)
Lymphopenic profile observed in B-cells ^b , CD4+ and CD8+ T ^t -cells
Neutropenia ^t
Eosinopenia ^t
Elevated putative LDGs ^b
Increased Classical monocytes ^t
Depletion in CD4 Treg cells [*]
Increased count of memory Treg ^t was observed, therefore depleted count of Naive Treg cells [*]
Higher frequency of CD8+ EM T-cells [*]
Reduced frequency of Naïve CD8+ T-cells [*]
Expansion of Plasmablast cells (count and frequency) ^t
Reduction in Integrin β-7 expression in T-cells and B-cells [*]
[*] - non-parametric Mann-Whitney U test, p < 0.05; ^b - borderline significance, p ~ 0.05; ^t - trend

3.11 Longitudinal Cohort Study to Evaluate the Effect of Various Contraception Methods on the Composition and Diversity of the Vaginal Microbiota (Partly Funded by Indian Council of Medical Research)

Principal Investigator : **Deepti Tandon**
Co-Principal Investigators : V Bhor, Clara Aranha
Project Associates : S Chauhan, Shahina Begum, Kiran Munne, Sharmila Kamat
Collaborator : Vandana Bansal, Nowrosjee Wadia Maternity Hospital, Mumbai
Duration : 2019-2023

The study is being conducted to evaluate vaginal health status of women before and after using various contraception methods by diverse methods [vaginal pH, quantification of leukocytes, Nugent score, microbial culture and Amsel's criteria; to evaluate species-level composition of the vaginal microbial ecosystem in these women over a period of 24 weeks; to determine the vaginal inflammatory profile in these women over a period of time; and to investigate the association between the microbiome profile with clinical symptoms, Nugent score, Amsel's criteria and vaginal inflammation profile.

Under this prospective study 60 healthy, sexually active, non-pregnant women aged 18 to 45 years, using various contraceptive methods in a community clinic in Mumbai were recruited. The participants were divided into six groups based on their contraception method: intrauterine copper T 380A IUCD, condom, injectable DMPA, oral contraceptive (OC) pills, LNG IUCD, and a control group of tubal ligation with no active contraception. Follow-up assessments were conducted longitudinally at 90 and 180 days, evaluating the vaginal milieu using Gram stain, vaginal cytokine analysis, and vaginal microbiome analysis. Participants who did not complete the follow-ups were excluded. Additionally, baseline vaginal microbiome was mapped for 52 women, and cervical microbiome for 43 women. The cohort's mean age was 32.1 ± 6.1 years, with an average sexual activity frequency of 4 ± 2.3 times per month. Socioeconomic distribution varied, with 43.3% in the lower-middle class with Maharashtrian ethnicity predominated 66.6%. None reported smoking or alcohol addiction, while 1.7% reported smokeless tobacco use. Sanitary napkins were the preferred menstrual hygiene product for 83.3% women. The median parity was 3, with 36.7% currently breastfeeding. Fig. 1 represents cytokine levels assessed at different time points in all contraceptive groups. Deep sequencing of vaginal samples (16S rRNA V3-V4 amplicon) from participants generated 16749428 reads in the cohort's samples with an average of 108,060.8 reads per sample. The study found variations in the abundance of specific vaginal microbiome species in response to different contraceptive methods. The most prevalent species observed in the cohort was *Lactobacillus iners*, with an average relative abundance of 47.04%. *Gardnerella vaginalis* was the most abundant pathogenic anaerobe, accounting for 10.19% of the total. In the study, different contraceptive methods were assessed for their impact on vaginal health over time. Users of Copper IUCD380 A experienced a subtle shift towards intermediate Nugent scores, indicating changes in the vaginal microbiota composition, alongside elevated levels of pro-inflammatory cytokines. Specifically, there was an increase in the abundance of beneficial bacteria like *Lactobacillus iners* and *Lactobacillus gasseri*, while the presence of the pathogen *Gardnerella vaginalis* decreased. Condom usage initially led to higher intermediate Nugent scores but eventually resulted in an improvement in vaginal health, marked by decreased bacterial vaginosis (BV) prevalence. However, the use of condoms was associated with an increase in pro-inflammatory cytokines over time, suggesting a potential immune response. Users of Injectable DMPA exhibited fluctuating Nugent scores throughout the study duration. Despite this variability, there was an overall decrease in pro-inflammatory cytokines over time. Notably, *Lactobacillus gasseri* showed a significant increase in its abundance among DMPA users. OC pill users demonstrated improved Nugent scores and a decrease in the prevalence of BV. This

improvement was accompanied by an increase in *Lactobacillus iners* and a decrease in *Gardnerella leopoldii*. In contrast, non-users of contraception experienced an increase in BV prevalence over time. This was accompanied by a decrease in *Lactobacillus iners* and an increase in *Gardnerella vaginalis*.

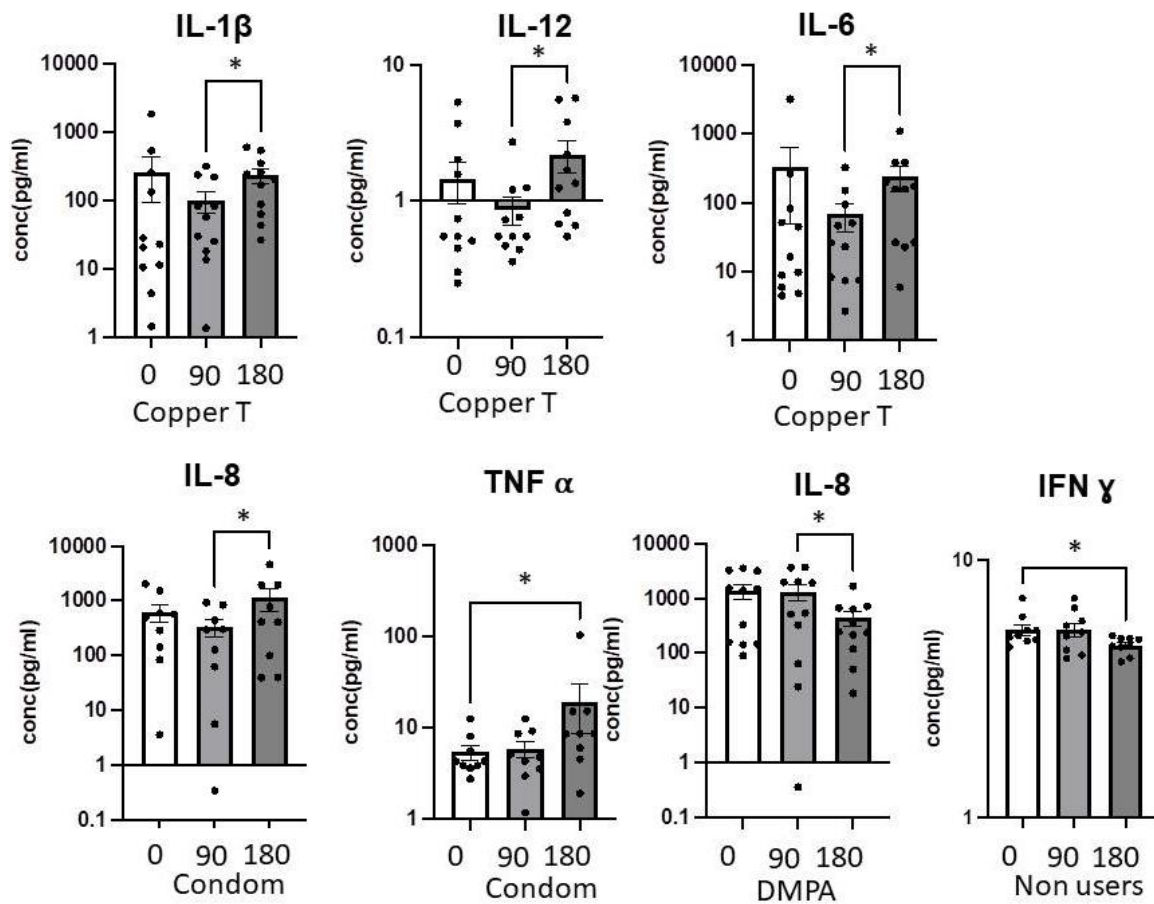


Figure 1: Box and Whiskers plot representing cytokine levels assessed at 0, 90 and 180 days for all groups with p - value (*) = < 0.05.

4. MATERNAL HEALTH

4.1 Understanding the Progress of Maternal Health and Outcomes among Indian Women: Findings from the NFHS

Principal Investigator : **P Kuppusamy**
Project Associates : RK Prusty, Deepali Kale
Duration : 2022-2023

High-risk pregnancies (HRP) place women and their offspring at the highest risk for morbidity and mortality. Maternal and medical factors increase pregnancy risk and complications during pregnancy and childbirth. It may require special medical care and monitoring by multi-disciplinary medical team. However, there is a lack of data on the prevalence of HRP in India. We conducted a study to assess the prevalence of HRPs among Indian women, which is defined through various risk factors. This study analysed a total of 23 853 currently pregnant women's data extracted from India's National Family Health Survey-5 (NFHS-5). The factors that can contribute to HRPs were considered as follow: maternal risks (age, height, BMI), lifestyle factors (smoking, tobacco and alcohol), health risk (anemia, diabetes, hypertension, asthma, thyroid, heart disease, cancer, kidney disorder), birth outcome risk (high birth order, short/long birth spacing, adverse birth outcomes, and caesarean delivery). This study found that the prevalence of HRPs among Indian women was 49.4%. Further, 33% of pregnant women had any one high-risk factor, and 16.4% of women had multiple high-risk factors. The leading states of HRP in India were Meghalaya (67.8%), Manipur (66.7%), Mizoram (62.5%), Telangana (60.3%) and Ladakh (60%). The top states with multiple-HRP were Meghalaya (33%), Mizoram (27.1%), Telangana (26.6%) and Andhra Pradesh (26.2%) (Fig. 1). The most leading contributing factors of HRP were short birth spacing (31.1%), adverse birth outcomes reported in last birth (19.5%), Caesarean delivery (16.4%), longer birth spacing (15.8%), history of last birth with preterm (14.1%), comorbidities (6.4%), higher BMI (>30 kg/m²) (4.7%), and lifestyle risk (2.8%). Logistic regression analysis showed that women with no education (adjusted odds ratio (aOR) = 2.02; 95% confidence interval (CI) = 1.84-2.22) and the poorest wealth quintile (aOR = 1.33; 95% CI = 1.04-1.29) had significantly higher odds of having HRP than those with higher education and the highest wealth quintile, respectively. This study demonstrates that nearly half of all pregnant women in India had any one or more of high-risk factor(s). Further, the risk was higher in vulnerable population such as no education and poorest wealth quintile. The Northeastern states such as Meghalaya, Manipur and Mizoram had higher frequency of high-risk pregnancies. Public health authorities should ensure regular health check-up throughout pregnancy and delivery in pregnant women. Since short birth spacing contributes to major share of HRP prevalence, public awareness to follow an appropriate time period from one birth to next birth through policy and programmes is required. Regional specific health issues particularly the life-style risk of smoking, use of tobacco and alcohol in northeastern states can be addressed through socio-behavioral interventions.

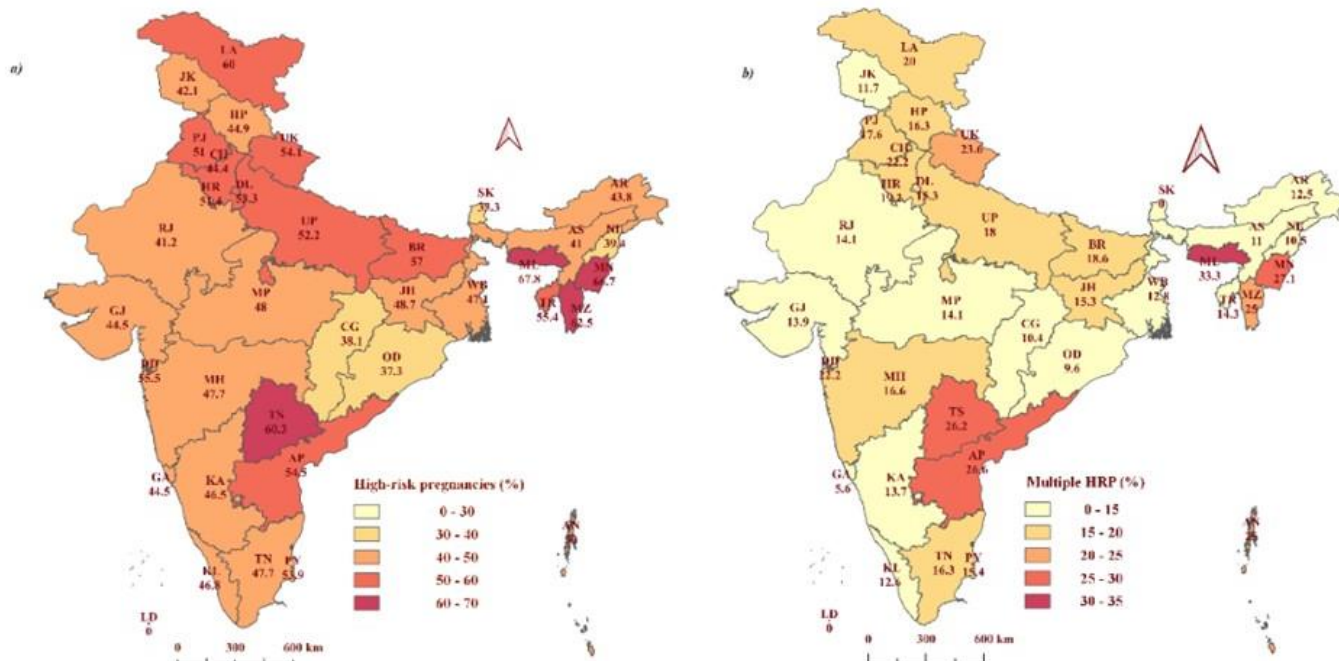


Figure 1: Prevalence of high-risk pregnancies (a) and multiple high-risk pregnancies (b) among Indian women during 2015-21

4.2 Impact of Mukta Shukti Bhasma and Saubhagya Shunti in Reversal of Bone Mineral Density among Lactating Women Consuming Traditional Diet Foods in Maharashtra: A Randomized Controlled Preliminary Clinical Study (Partly Funded by CCRAS, Ministry of AYUSH)

Principal Investigator : **Lalita Savardekar**

Project Associates : S Timmanpyati, Vandana Bansal , Sheetal Mohite, D Singh, A Jain, Daksha Shah, Mangala Gomare, Vaishali Chandans, Municipal Corporation of Greater Mumbai

Collaborators : R Ramdeo, A Podar, Central Ayurveda Research Institute
K Choudhary, R. Govind Reddy, Saylee Deshmukh, Pallavi Mundada, Central Council for Research in Ayurvedic Sciences

Duration : 2023-2026

Lactation affects endocrine profile, bone dynamics and mental health status. There is a physiological decline in the bone mineral density post-delivery which reverses subject to nutritional status. Traditional diet foods are known to be energy dense foods rich in calcium, proteins, iron, fats etc. The present study is undertaken i) to document traditional dietary food practices, food taboos and cultural beliefs among postpartum & lactating women ii) to formulate a dietary recommendation for lactating women representative of different regions of Maharashtra (following 'Deshvichar' as per Ayurveda) as Phase I while the phase II will attempt to assess the clinical efficacy of *Mukta Shukti Bhasma* and *Saubhagya Shunthi Churna*.

As part of Phase I study, 10 focused group discussions (FGDs) were conducted in Konkan region (3), Nashik (3), Pune (3), and Marathwada region (1) Initially, 130 participants were screened for eligibility across all FGDs. Out of these, 64 participants were recruited for the final FGD sessions, while 16 participants were found to be ineligible. Among the eligible participants: 25 were unwilling to participate and 25 were unavailable for the FGD sessions. A total of 73 traditional recipes were collected across the 10 FGDs conducted. Additionally, there were 5 recipes pending collection. Among the collected recipes, macro and micro nutrition calculations were completed for 50 recipes, while 23 were pending. Traditional recipes received included 8 kalvan/kadha recipes, soups, 10 vegetable meals, 5 ladoos, 8 porridges, 6 chutneys, 2 churans, 3 special masalas, 1 bhakari, 1 ghavan and 1 papad recipe.



Figure 1: Focus Group Discussions at Kalyan

Figure 2: Focus Group Discussions at Bone Health Clinic, Naigaon

4.3 Transgenerational Effects of Paternal Hypertension on Fertility and Pregnancy Outcome: An Epigenetic Approach

Principal Investigator	: Kumari Nishi
Co-Principal Investigator	: Dipty Singh
Project Associates	: Reshma Gaonkar, S Mandavkar
Duration	: 2022-2025

Nitric oxide (NO) is a highly reactive free radical that acts as a potent vasodilator of vascular smooth muscle and regulates blood pressure. N ω -Nitro-L-Arginine-Methyl Ester (L-NAME), an inhibitor of nitric oxide is used to induce hypertension in animal models (pharmacological "NO-deficient hypertension" model) which targets the nitric oxide synthase (NOS) pathway. The L-NAME model of male hypertension was developed by using a dose of 10 mg/kg bw (L10) and 20 mg/kg bw (L20) for 3-weeks in wistar rats The control group was given drinking water (L0) (Annual report 2022-2023, pg. 70-72). In present study male rats were sacrificed at day 60 post L-NAME treatment and spermatozoa collected after the completion of a spermatogenic cycle in testis and transit through epididymis. A significant decrease in serum phosphorus and calcium levels was observed in both L10 and L20 animals as compared to L0 animals. The direct bilirubin levels were also found to be significantly

increased in L10 group animals. The Glucose (GLU), Triglyceride (TRIG), Cholesterol (CHOL) and High Density Lipoprotein Cholesterol (HDLC) were found to be significantly reduced in both treatment groups compared to control (Table 1). No significant difference in the levels of Serum glutamic pyruvic transaminase direct (SGPTD), Serum Glutamic-Oxaloacetic Transaminase (SGOTD), Creatinine (CRE), Uric Acid (UA), Albumin (ALB) and Protein (PRO) were observed between different groups. The serum catalase activity in both the L10 and L20 groups was similar to that of the control (Fig. 1A). A significant decrease in SOD activity was observed in L20 $p<0.01$, while a non-significant decrease was observed in L10 as compared to control after 60 days of L-NAME treatment (Fig. 1B). The nitric oxide levels after 60-days of the L-NAME treatment termination in treated groups L10 ($27.64 \pm 1.979 \mu\text{M}$) and LN20 ($30.47 \pm 5.833 \mu\text{M}$) were observed to be the same as the control ($27.80 \pm 0.3778 \mu\text{M}$) (Fig. 1C). No change in estradiol levels was observed in the treatment groups compared to control (Fig. 1D). While a significant increase was observed in the levels of serum testosterone in L10 ($6.66 \pm 0.905 \text{ ng/ml}$; $p<0.05$) and L20 ($p<0.05$) groups, compared to control L0 group ($4.26 \pm 0.48 \text{ ng/ml}$) (Fig. 1E). Intra-testicular testosterone (iTt) levels were also assessed in treatment and control groups. A significant increase in iTT levels was observed in both L10 ($p<0.01$) and L20 ($p<0.05$) animals as compared to control L0 animals (Fig. 1F).

Table 1: Serum biochemical parameters at day 60 after termination of L-NAME treatment. Values are mean $\pm$ SD. One-way ANOVA. * $p<0.05$, ** $p<0.01$ Treatment vs Control

Serum biochemical parameter	L0	L10	L20
SGPTD (U/L)	74.70 ± 7.951	58.27 ± 8.391	63.78 ± 5.440
SGOTD (U/L)	175.7 ± 3.955	132.6 ± 24.19	191.3 ± 22.75
PHOS(mg/ dl)	8.672 ± 0.734	$5.247 \pm 0.6234^{**}$	$6.410 \pm 0.1079^{*}$
BID(mg/ dl)	0.087 ± 0.004	$0.06 \pm 0.0009^{**}$	0.08250 ± 0.0025
CRE(mg/ dl)	0.5917 ± 0.036	0.47 ± 0.053	0.522 ± 0.047
GLU(mg/ dl)	128.9 ± 8.641	$76.35 \pm 0.95^{**}$	$84.5 \pm 8.628^{**}$
TRIG(mg/ dl)	283.9 ± 32.56	$150.5 \pm 17.67^{**}$	$171.4 \pm 9.364^{**}$
CHOL(mg/ dl)	95.83 ± 4.415	$39.50 \pm 3.50^{**}$	$72.75 \pm 7.631^{*}$
HDLC(mg/ dl)	60.30 ± 3.903	$34.50 \pm 2.10^{*}$	52.56 ± 4.725
UA(mg/ dl)	1.08 ± 0.08	0.96 ± 0.088	1.0 ± 0.18
CA(mg/ dl)	9.4 ± 0.5	$5.45 \pm 0.35^{**}$	8.12 ± 0.74
ALB(g/ dl)	2.856 ± 0.1413	2.297 ± 0.2761	2.706 ± 0.2094
PRO(g/ dl)	8.976 ± 0.4739	6.833 ± 0.7029	8.068 ± 0.579

Abbreviations: ALB – Albumin, BID – Bilirubin Indirect, CA – Calcium, CHOL – Cholesterol, CRE –Creatinine, GLU – Glucose, HDLC – High Density Lipoprotein Cholesterol, PHOS – Phosphorus, PRO – Protein, SGOTD – Serum Glutamic-Oxaloacetic Transaminase, SGPTD – Serum Glutamic Pyruvic Transaminase Direct, TRIG – Triglyceride, UA – Uric acid

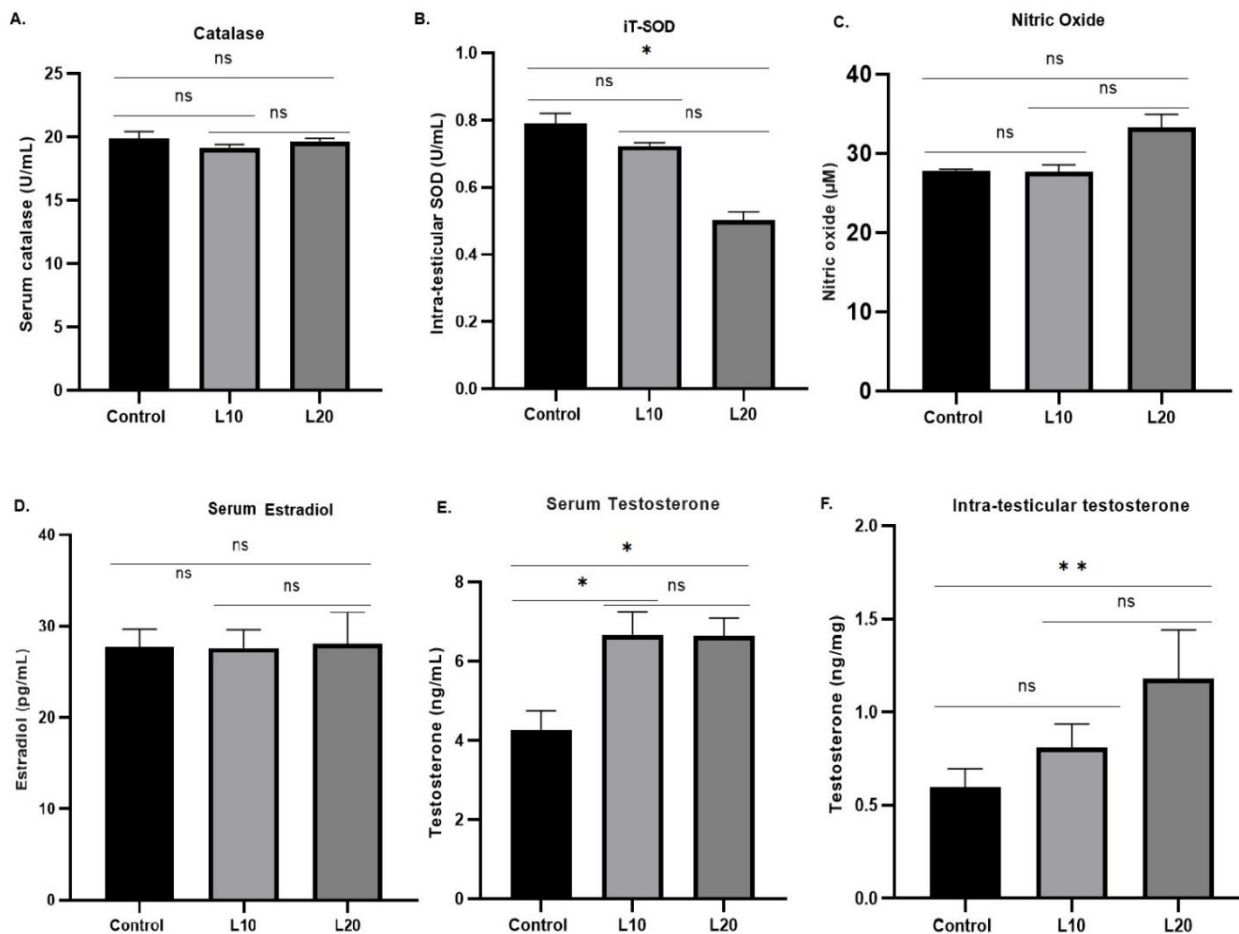


Figure 1: Effect of L-NAME on serum catalase (A), intra-testicular superoxide dismutase (B), intra-testicular nitric oxide (C) level, serum estradiol levels (D), serum testosterone (E) and intra-testicular testosterone levels (F) at day 60 after termination of L-NAME (L10: 10 mg/kg bw; L20: 20 mg/kg bw) treatment. * $p < 0.05$, ** $p < 0.01$, Values are mean $\pm$ SEM. (n=6 in each group)

4.4 Implementation Research to Explore Operational Feasibility, Acceptability and Cost-Effectiveness of using IV Ferric Carboxy Maltose (FCM) in Management of Iron Deficiency Anemia (IDA) among Pregnant Women through Sub-district Health System in Maharashtra (Partly Funded by Department of Health Research)

Principal Investigator	: Beena Joshi
Co-Principal Investigator	: Deepti Tandon
Project Associates	: Ragini Kulkarni, Shahina Begum, Kiran Sangwan, P Sanap and I Mashal
Collaborators	: B Hengne, SDH, Dahanu K Bhoje, Jawhar Cottage Hospital
Duration	: 2022-2024

The study aims to estimate the improvements in haemoglobin and ferritin indices post treatment with IV Ferric Carboxy Maltose (FCM) vs IV Iron Sucrose (ISC) for treating moderate to severe iron deficiency anemia in pregnancy. It would also document pregnancy and neonatal outcomes and estimate health system costs; out of pocket expenditure (OOPE) and Quality of life of women treated for anemia in pregnancy to analyse cost-effectiveness of using IV Ferric Carboxy Maltose vs standard of care (IV Iron Sucrose). Eligible 280 pregnant women diagnosed with Iron - deficiency anemia were enrolled randomly (1:1) and treated with IV Ferric Carboxy Maltose or IV Iron Sucrose with follow-up at 4 weeks post infusion and 6 weeks postpartum. In the group receiving FCM, mean rise in hemoglobin was 1.61 ± 1.04 and in the group receiving iron sucrose, mean rise in Hb was 1.59 ± 1.08 as compared to their baseline Hb. Mean rise in both groups was found statistically significant ($p < 0.001$). The mean rise in Hb from baseline (8.84 ± 0.63) to 6 weeks postpartum (10.21 ± 1.34) and at the time of delivery (10.42 ± 0.78) was significantly higher in FCM group than mean rise in Hb from baseline (8.78 ± 0.67) to 6 weeks postpartum (10.00 ± 1.28) and at the time of delivery (10.00 ± 1.28) in ISC group with (p value < 0.001). Serum ferritin levels were significantly higher at 4 weeks post IV and 6 weeks postpartum in FCM group compared to ISC group. There was no significant difference among the two groups in terms of pregnancy outcomes. The proportion of preterm birth was 5.7% in FCM group and 4.3% in ISC group. However, low birth weights were reported more among ISC group i.e. 32.6% as compared to 30% in FCM group. No side effects were reported in IV FCM group. However, there were minor drug related side effects in the ISC group. OOPE for complete course of IV FCM was Rs. 178 and that for IV Iron Sucrose was Rs. 352. This was excluding the cost of both injections as that was provided from the health system free of cost and IV FCM was being supplied through project funds. The difference was mainly due to multiple visits need to complete the full course of IV Iron Sucrose. The health-related Quality of Life measured using EUROQol 5D 5L- Utility scores derived were: 0.976 for FCM and 0.974 for IV Iron Sucrose, (1 being in full health state). The analysis shows that IV FCM facilitates improvement in QALYs gained, reduces the number of adverse events, increases the numbers who move from severe / moderate anemia to mild or non anemic state compared to IV Iron Sucrose. Incremental cost-utility ratio (ICUR) value of Rs. 32,153.86 indicates that IV FCM is a cost-effective intervention at current price of FCM at Rs. 3030 for 1000 mg.

4.5 Machine Learning Algorithms Trained on Voice to Predict Psychological Distress and Postpartum Depression *(Partly Funded by ICMR-AI Cell)*

Principal Investigator : **Susan Thomas**

Co-Principal Investigator : Shahina Begum

Project Associates : Ulka Gawde

Collaborators : TS Jaisoorya, S Ganjekar, Paulomi Sudhir, Shobha Meera, National Institute of Mental Health and Neuro Sciences (NIMHANS)

Duration : 2023-2025

This project aims at identification of voice biomarkers for prediction of psychological distress and postpartum depression. In the reporting year, voice datasets of 45 participants have been processed for

further analysis. Machine learning algorithms such as support vector machines (SVM), random forests, naïve Bayes, artificial neural networks, k-nearest neighbor (kNN), c5 and CART are being explored for prediction. The recruitment of individuals as per the inclusion and exclusion criteria of the study is ongoing.

4.6 Omics of Placental Exosomes in Early Onset Preeclampsia: An Approach towards Identifying Predictive Biomarkers (Phase-II) *(Partly Funded by Department of Biotechnology)*

Principal Investigator : **Nafisa H Balasinor**
Co-Principal Investigators : Taruna Madan, DK Das
Project Associates : Aishwarya Rao, Uma Shinde, Tejashree Sontakke
Collaborators : N Mayadeo, Seth GS Medical College & KEM Hospital, Mumbai
Vandana Bansal, Geeta Balsarkar, Nowrosjee Wadia Maternity Hospital, Mumbai
Duration : 2020-2024

Preeclampsia (PE) is a placental disorder leading to high risks for mother and fetus, especially in Early Onset Preeclampsia (EOPE) before 34 weeks of gestation. Early prediction of EOPE is crucial for preventive care. Placental exosomes, which contain trophoblast-derived proteins and nucleic acids, appear in maternal serum by 6 weeks of gestation and have altered compositions in placental disorders. Analyzing these exosomes through comparative OMICS could reveal biomarkers for early EOPE prediction, offering a non-invasive method to improve maternal and fetal outcomes. Previously (Annual report 2022-2023, pp. 75-76). The proteome analysis of EOPE-derived circulating placental exosomes at term stage of pregnancy identified total 208 proteins, out of which 26 were differentially abundant compared to the placental exosomes from healthy controls. The total identified proteins revealed significantly enriched biological processes such as complement and coagulation cascade, hemostasis, lipid transport and metabolism along with involvement of innate immune system. In all, 1139 participants at different gestational ages have been recruited. 50 EOPE cases were identified after follow-up of participants. Small RNA sequencing (RNAseq) was performed on circulating placental exosomes from 6 preeclampsia and 6 control samples in early pregnancy (8-10 weeks). Differential gene expression analysis revealed 22 upregulated and 50 downregulated miRNAs in preeclampsia. Notably, hsa-miR-181-5p and hsa-miR-203a-3p were differentially expressed in both the groups [Group I (8-10 weeks of gestation) and Group IV (at the time of delivery) pregnant women's] (Fig.1). These findings align with previous reports of these miRNAs` dysregulation in preeclampsia in other populations. This is the first study from the Indian population. These results will be validated using qPCR and probe-based assays with additional samples. A total of 355 Differentially Methylated CpGs (DMCs) (cut-off >5%) were obtained from Whole Genome Bisulfide Sequencing (WGBS) from normal and PE pregnant women, of which, majority were of mitochondrial origin. Screening of all DMCs of DMGs involved in placental mitochondrial dysfunction like oxidative stress and oxidative phosphorylation using UCSC browser (Fig. 2). Therefore, DMCs of the mitochondrial genes like MT-TL1, MT-CO2, MT-RNR2, MT-CO3, MT-CO1, MT-NDL4 were selected for validation by pyrosequencing along with their respective expression profile by RT-PCR in the PE (n=20) and control (n=20) study population.

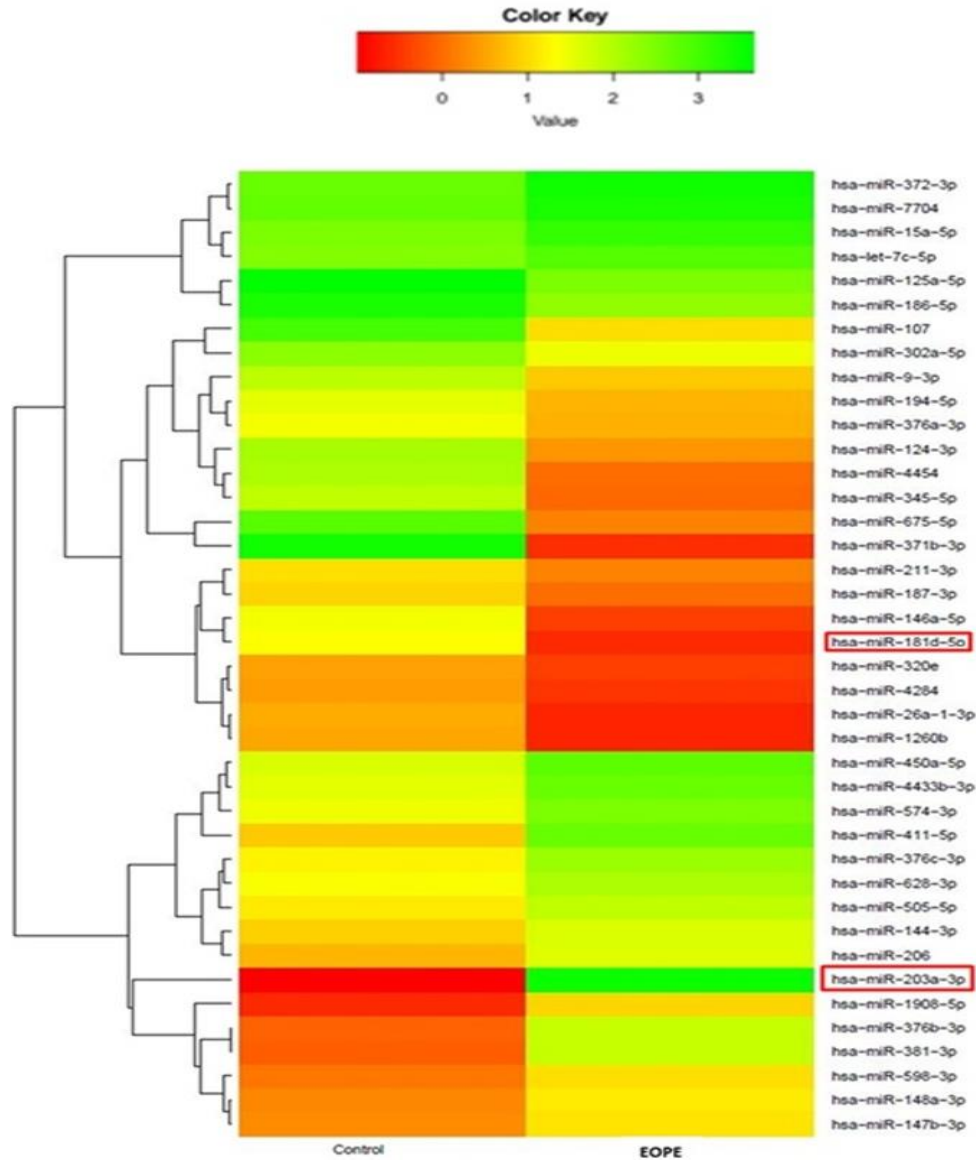


Figure 1: Heat map showing the expression matrix of significant dysregulated miRNAs identified in circulating placental exosomes of preeclampsia and control samples of group I (8-10 weeks) pregnant women (n=6) shortlisted based on the p value. miRNA's highlighted in red box, hsa-miR-181-5p and hsa-miR-203a-3p were differentially expressed in both the study groups [Group I (8-10 weeks of gestation) and Group IV (at the time of delivery) pregnant women's].

Figure 2: DMGs identified in EOPE cases, involved in oxidative stress and oxidative phosphorylation using UCSC browser.



4.7 Aberrant Paternal Imprinting: A Risk Factor for Preeclampsia

Principal Investigator : **Nafisa H Balasinor**
 Co-Principal Investigator: Anushree Patil
 Project Associates : Sweta Nair, Kumari Nishi, Zakiya Ansari
 Collaborators : Vandana Bansal, Nowrosjee Wadia Maternity Hospital, Mumbai
 Himangi Warke, Seth GS Medical College & KEM Hospital, Mumbai
 Duration : 2016-2024

Preeclampsia is a pregnancy-specific disorder with the symptoms of hypertension and proteinuria. In the absence of proteinuria, it is detected by elevated liver enzyme levels and end-organ damage. The major underlying cause of preeclampsia is shallow placentation due to incomplete spiral artery remodelling. The paternal genome plays an important role in the development of the placenta. Experiments in mice by Surani et al (1984) and McGrath and Solter (1984) showing the non-equivalence of parental genomes in terms of contribution towards embryonic and placental development also unravelled the phenomenon of genomic imprinting. Imprinted genes are those genes which are expressed in a parent-of-origin specific manner due to differential methylation on DNA. Imprinted genes play important roles in placental growth and development. Several imprinted genes have been found to show aberrant methylation and expression in the placentae of preeclamptic women. However, the association of sperm epigenetic status with preeclampsia has not been investigated till date. Hence, the objectives of the present study were to measure the global methylation levels in the spermatozoa of partners of women experiencing preeclampsia; to measure the methylation levels of imprinted genes and the imprinted chromosome 19 miRNA cluster (C19MC) in the spermatozoa and; to quantify the expression levels of the imprinted genes and the C19MC miRNAs in the placental villi. Participants were recruited into two groups: Case group (14 couples) in which the female partner was experiencing early-onset preeclampsia (preeclampsia onset at ≤ 34 weeks of gestation) and control group (25 couples) in which the female partners had normal pregnancy with no medical issues. The clinical characteristics of the two groups have been presented in Table 1. The sperm parameters (concentration, motility, morphology and chromatin compaction) were not significantly different between the two groups. Methylation analysis of differentially methylated regions (DMRs) of imprinted genes was carried out by pyrosequencing. DLK1-GTL2 IG-DMR was hypomethylated while, PEG3, DMR, PEG10 DMR and KvDMR were hypermethylated in the case group spermatozoa and placental villi. C19MC DMR was hypomethylated in the placental villi of cases. Global DNA methylation did not differ between the two groups. In the case group placental villi, gene expression of DLK1, PHLDA2, CDKN1C, PEG3 and IGF2 was upregulated. The expression of PHLDA2 and CDKN1C was not associated with birth weight after adjusting for clinical variables. C19MC miRNAs, hsa-miR-520a-5p, hsa-miR-518a-5p and hsa-miR-527 were upregulated in the placental villi of cases (Fig. 1). The target mRNAs (TMs) of these miRNAs were associated with molecular functions of transcription factor activity and, enzyme- and receptor-binding. The expression of TMs was downregulated in the preeclamptic placental villi (Fig. 2). The target TWIST1 is known to repress the expression of pro-inflammatory cytokines, TNFA, IL1B and CADM3 (Cell Adhesion Molecule 3, an adhesion protein). Reduction in CUL3 expression is known to cause vasoconstriction and hypertension. VCAM1 and ACAA2 are associated with response to hypoxia. TRAF2 is involved in response to nitric oxide. DAB2IP is associated with cell migration. The study concludes that sperm DNA methylation is associated with preeclampsia and with aberrant expression of some of the imprinted genes in the placenta.

Table 1: Clinical characteristics of participants. Data are expressed as mean $\pm$ SEM unless otherwise mentioned. BMI, Body Mass Index; CS, Caesarean Section; V, Vaginal; M, Male; F, Female; IUFD, Intra-Uterine Fetal Death; IUGR, Intra-Uterine Growth Restriction; NA, Not Applicable; * $p < 0.001$, ** $p < 0.0001$.

Clinical Characteristics	Controls (n=25)	PE (n=14)
Maternal age (years)	28 $\pm$ 0.61	25.6 $\pm$ 1.0
Maternal Early Pregnancy BMI (kg/m ²)	23.3 $\pm$ 0.64	22.8 $\pm$ 0.87
Primigravidity (n, %)	10, 0.4	6, 0.43
Gestational age at delivery (weeks)	38.5 $\pm$ 0.23	34.1 $\pm$ 0.75**
Gestational age at onset of PE (weeks)	NA	31.4 $\pm$ 0.6
Systolic blood pressure (mm Hg)	118.4 $\pm$ 0.75	148.6 $\pm$ 2.7**
Diastolic blood pressure (mm Hg)	78.4 $\pm$ 0.75	95 $\pm$ 1.7**
Urine protein levels (n)	NA	7 (+), 1 (++) , 1 (+++) , 5 (++++)
Mode of delivery (n)	16 (CS), 9 (V)	7 (CS), 7 (V)
Birth weight (kg)	2.8 $\pm$ 0.07	1.6 $\pm$ 0.14**
Placental weight (g)	495.2 $\pm$ 7.8	354.6 $\pm$ 29.2*
Baby gender (n)	11 (M), 14 (F)	8 (M), 6 (F)
IUFD (n), IUGR (n)	NA	4, 3
Paternal age (years)	31.4 $\pm$ 0.6	30.9 $\pm$ 1.2
Paternal BMI (kg/m ²)	25 $\pm$ 0.81	25.7 $\pm$ 1.6

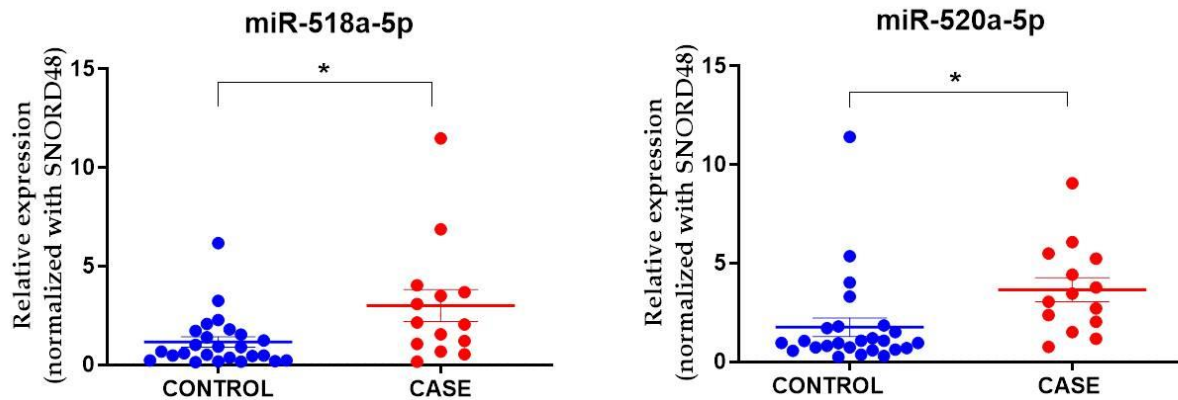


Figure 1: Gene expression levels of the C19MC DEMs, hsa-miR-518a-5p and hsa-miR-520a-5p. * p values < 0.05

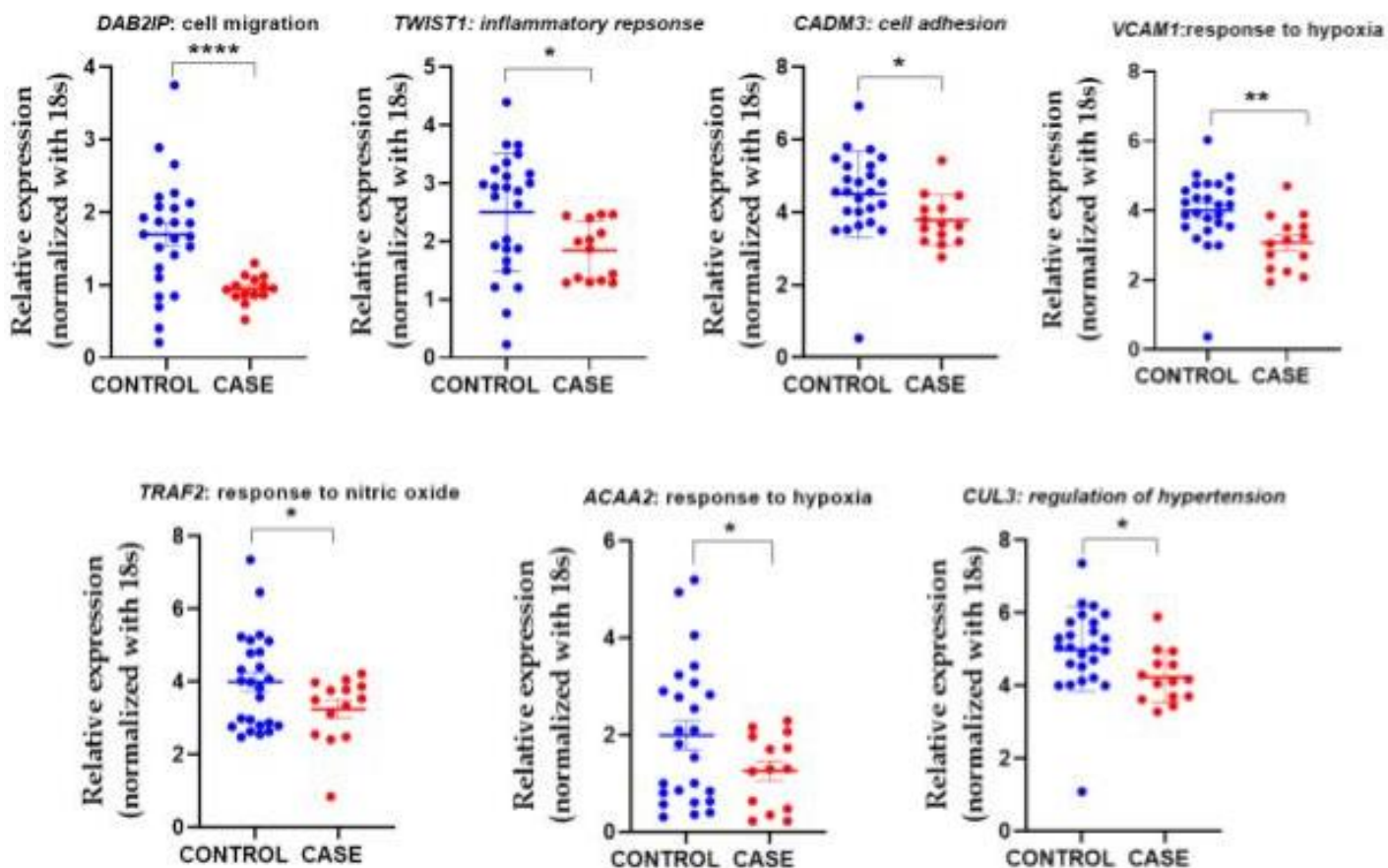


Figure 2: Gene expression levels of target mRNAs of the C19MC DEMs, hsa-miR-518a-5p and hsa-miR-520a-5p. hsa-miR-527 shares the same targets as hsa-miR-518a-5p. p values * <0.05 , ** <0.01 , **** <0.0001

4.8 Developing an Immunochromatography Based Strip Test for Analyzing PLGF Concentration for Prediction of Risk for Developing Preeclampsia

Principal Investigator : **Bhakti R Pathak**
 Project Associates : Ananya Breed, Shahina Begum, Deeksha Jadhav
 Collaborators : A Pawar, Nowrosjee Wadia Maternity Hospital, Mumbai
 Duration : 2017-2024

Placental Growth Factor (PLGF) is a member of Vascular Endothelial Growth Factor family (VEGF) and a key molecule in placental angiogenesis. Low levels of PLGF in circulation have been shown to predict onset of preeclampsia (PE) by multiple studies. Apart from circulation, presence of PLGF in the urine of pregnant women at different time points during gestation has been reported in literature. Urinary PLGF levels were found to rise and reach maximal levels at 28-30 weeks of gestation and decline thereafter. Some recent studies have reported lower circulatory PLGF levels in women who delivered small for gestational age infants (SGA). Our preliminary data of urinary PLGF levels from 81 healthy pregnant women showed significant association between low urinary PLGF levels and preterm delivered SGA infants (Annual report 2022-23, Pg.79-80). To increase the statistical power of the study

and to ascertain the observation obtained in 81 participants, we have recruited additional 134 healthy pregnant women (Maternal age ranging from 19-39 yrs with median age of 28 yrs). Random urine samples collected at 28-32 weeks of gestation were evaluated for urinary PLGF levels by ELISA. PLGF levels were further normalized by urinary creatinine. Participants were segregated into low PLGF (n=22) and normal PLGF (n=193) levels by applying 10th percentile cut off (Fig. 1). Out of total 215 participants, 21 women delivered SGA infants. Out of these 21, 6 women delivered preterm with SGA infants. In low urinary PLGF levels, 18.18% women delivered preterm with SGA whereas in normal PLGF levels 1.03% women delivered preterm with SGA infants (p value= 0.0011, Odds ratio 21.2). We used PLGF values and baby birth weights to plot ROC curve. Table 1 shows specificity and sensitivity of predicting SGA infants (A) or SGA with preterm delivery (B) at different cut offs. As per our study, at a tertiary care hospital located in Mumbai, urinary PLGF values below 10th percentile were able to predict preterm deliveries with SGA infants with 66.67% sensitivity and 91.39% specificity (AUC, 0.707).

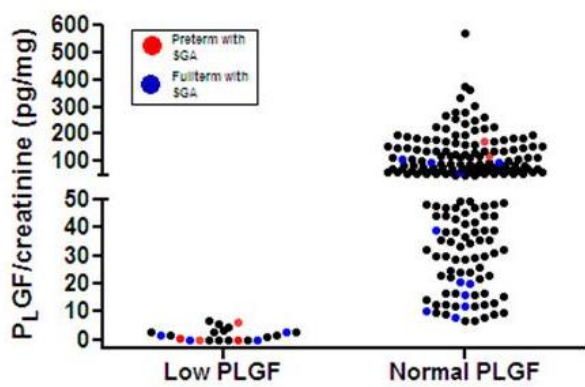


Figure 1: Scatter plot depicts ratio of urinary PLGF levels to Creatinine in healthy pregnant women at 28-32 weeks of gestation. SGA infants of our study cohort delivered either at preterm or full term are indicated.

Table 1: Sensitivity and specificity of predicting SGA (A) and SGA with preterm delivery (B) at different cut offs of Urinary PLGF.

A

Percentile cut offs (PLGF pg/ Creatinine mg)	Sensitivity	Specificity
25th (< 25.32 pg/ mg)	66.67%	79.38%
10th (< 6.674 pg/ mg)	38.10%	92.78%

B

Percentile cut offs (PLGF pg/ Creatinine mg)	Sensitivity	Specificity
25th (< 25.32 pg/ mg)	66.67%	76.08%
10th (< 6.674 pg/ mg)	66.67%	91.39%

4.9 Evaluation of Synergistic Impact of Nano-curcumin and Alpha-Linolenic Acid on Pathophysiology of Pre-eclampsia *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : V Dighe

Co-Principal Investigator : T Madan

Project Associates : A Tiwari, Shruti Desai, S Jadhav, P Salunke, M Ghosalkar

Duration : 2021-2024

Pre-eclampsia is pregnancy-induced hypertension associated with increased oxidative stress and proteinuria in mothers leading to fetal growth restriction. It involves higher maternal oxidative stress and inflammation with altered fatty acid metabolism. Curcumin and Alpha-linolenic acid (ALA) have anti-inflammatory and antioxidant properties respectively and have been investigated individually for their effects on pre-eclampsia. The present study aims to investigate the synergistic impact of Alpha-Linolenic Acid (ALA) and Nanocurcumin in a Lipopolysaccharide (LPS) induced preeclamptic rat

model. Earlier two generational reproductive toxicity assessments of Curcumin(C), Nano-curcumin (NC), Alpha-Linolenic Acid (ALA), and a combination of NC and ALA were carried out in female Wistar rats. In the reporting year, treatment-related effect on physiological parameters was undertaken. Progesterone was found to be significantly elevated at GD-20 of pregnancy in all the treated groups. Estradiol showed increased levels in treated groups at GD-20 of pregnancy. Follicle Stimulating Hormone was found to be increased in NC and NC+ALA dosed groups in GD-20 of pregnancy (Fig.1A-C). Oxidative stress parameters were assessed in the F0 pregnant rat. Malondialdehyde levels were quantified to estimate the lipid peroxidation, and it was found to be significantly reduced in all the treated groups. Catalase enzyme showed no change in treated groups as compared to control group (Fig. 1D&E). Histopathological examination of all the vital and reproductive organs by H&E staining showed normal tissue morphology as compared to the control group. Attempts were made to develop Lipopolysaccharide (LPS) induced pre-eclampsic female Wistar rat. Pregnant Wistar rats were given LPS by intraperitoneal injection from GD-12 to GD-20 with increasing doses each day from 20 μ g/Kg-BW to 100 μ g/Kg-BW. Blood pressure taken at GD18 showed significant elevation in systolic BP and Diastolic BP in the LPS treated group as compared to the vehicle control. Total urinary protein level in the LPS-treated group was found to be significantly higher as compared to vehicle control (Fig. 2). Further validation of the model is being carried out.

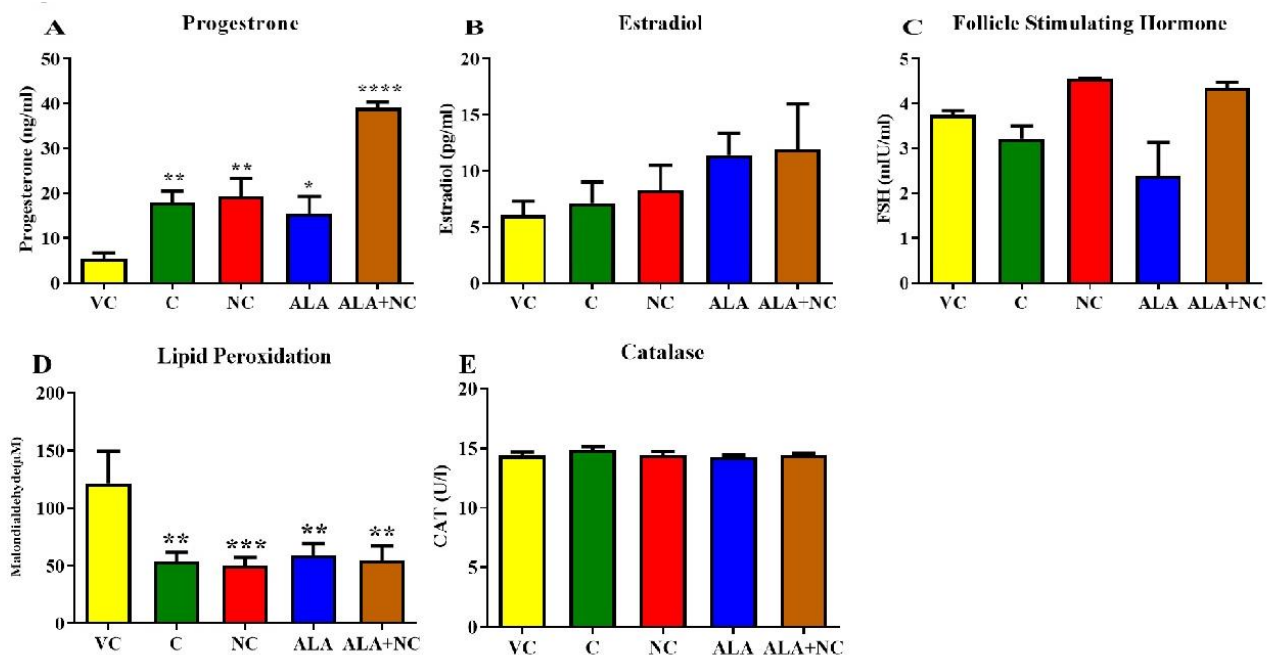


Figure 1: (A) Progesterone hormone was found to be significantly elevated in all the treated groups compared to the control group. (B) Estradiol levels were found to be increased in all the treated groups as compared to the control group. (C) FSH levels in NC and NC+ALA showed increase as compared to the other three groups while curcumin and ALA groups showed decrease in FSH levels as compared to the control group. (D) lipid peroxidation was found to be significantly reduced in all the treated groups as compared to control group. (E) catalase levels were found to be unchanged in all the groups. (Abbreviations: VC-Vehicle Control, C-Curcumin, NC-Nanocurcumin, ALA-Alpha Linolenic Acid) (Values are expressed as Mean $\pm$ SD. Statistical analysis was carried out by one-way ANOVA followed by a Sidak's multiple comparisons test. Treatment groups Vs Vehicle Control Group.)

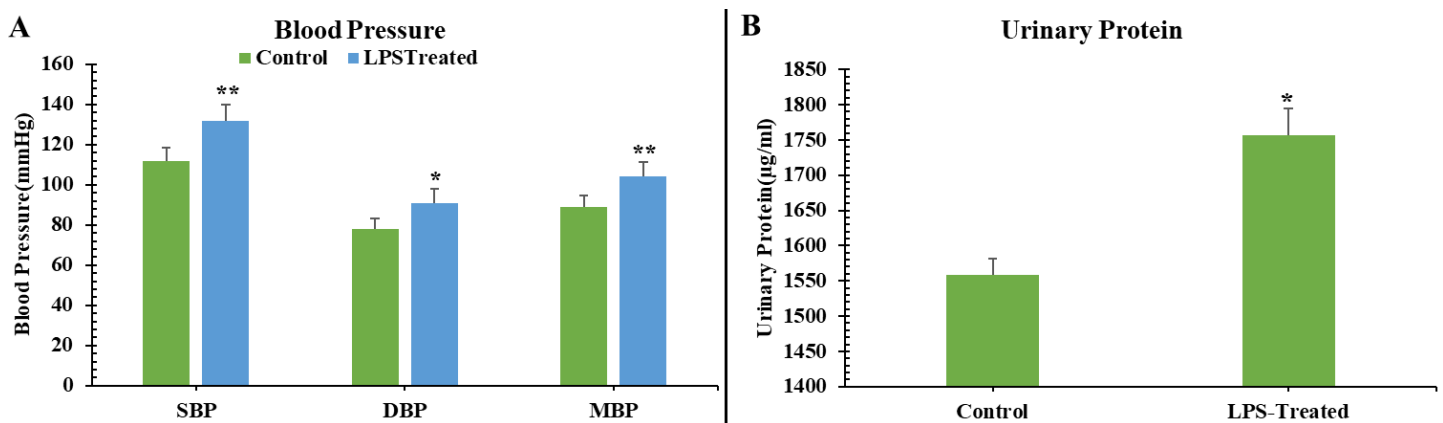


Figure 2: A: Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Blood pressure (MBP) show significantly elevated levels of blood pressure in the LPS-treated group as compared to the control group. B: Total urinary protein levels show significant elevation in the LPS-treated group as compared to the control group. Values are expressed as Mean $\pm$ SD. Statistical analysis was carried out by one-way ANOVA followed by a student's t-test. Treatment groups Vs Vehicle Control Group

4.10 Investigation of Therapeutic Potential of Candidate Recombinant Proteins in Trophoblast differentiation and Placental Spiral Artery Remodeling in Murine Models of Pre-eclampsia

Principal Investigator : **Taruna Madan**
 Project Associate : Hajra Gupta
 Duration : 2021-2025

Preeclampsia (PE) is a pregnancy-specific hypertensive disorder characterized by an imbalance of angiogenic-antiangiogenic factors, inflammatory and anti-inflammatory cytokines, and immune cell activation-tolerance. Surfactant Protein D (SP-D), a collectin expressed by the trophoblasts, modulates and regulates the inflammatory response, which is a critical etiological factor of PE. Data from SP-D KO mice show that sustained SP-D levels are critical during implantation and placentation. Moreover, significantly downregulated serum levels of SP-D are associated with the development of severe early-onset preeclampsia (EOPE). Hence, we aim to assess the immunotherapeutic efficacy of rfhSP-D in PE. Since hypoxia is an indispensable factor during placentation, *in vitro* experiments using a first-trimester trophoblast cell line (HTR8/SVneo), and *ex vivo* experiments were conducted in hypoxic conditions. *In vitro* rfhSP-D significantly upregulated the levels of angiogenic and invasion factors, (VEGF, PLGF, TGF β , MMP-9, N-cadherin, Vimentin) and significantly downregulated the levels of anti-angiogenic factors (sFlt1 and sEng) (Fig. 1) in HTR8 cells, possibly indicating its contribution to immune-mediated control of angiogenesis. rfhSP-D treatment significantly downregulated the levels of inflammatory markers, IL1 β , TNF α , and TLR4 (Fig. 1).

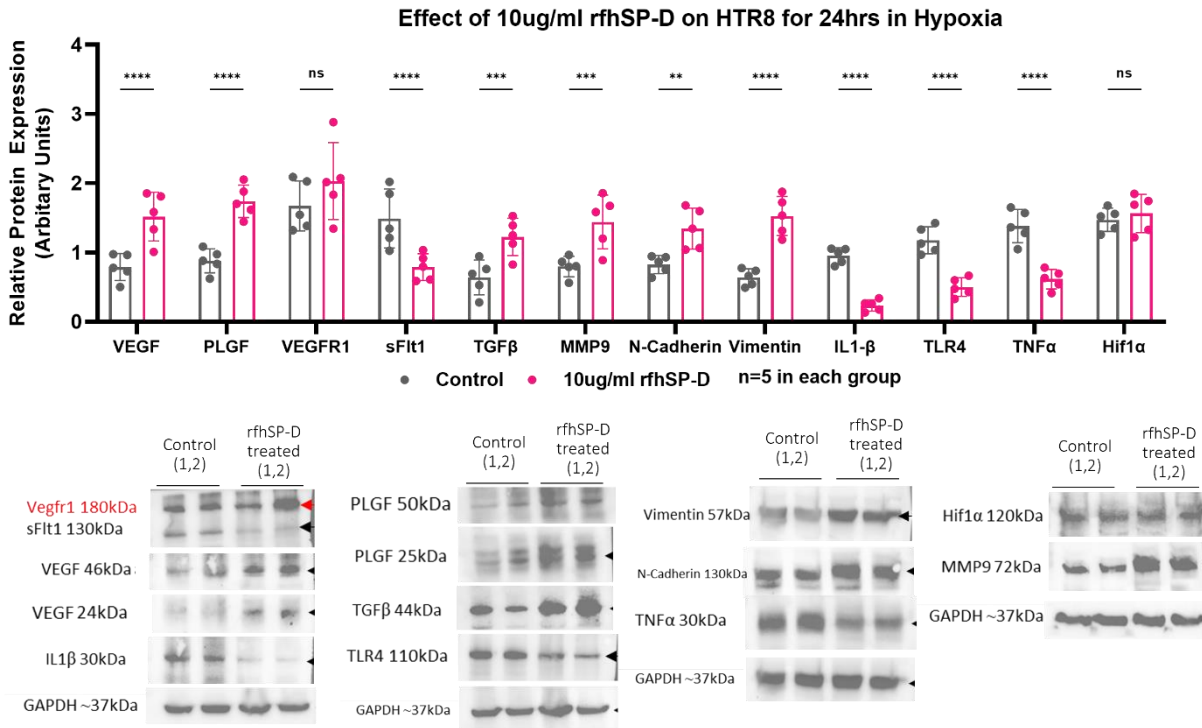


Figure 1: Effect of 10 μ g/ml rfhSP-D on the levels of angiogenic factors, invasion factors and inflammatory markers in HTR8 cells under hypoxia

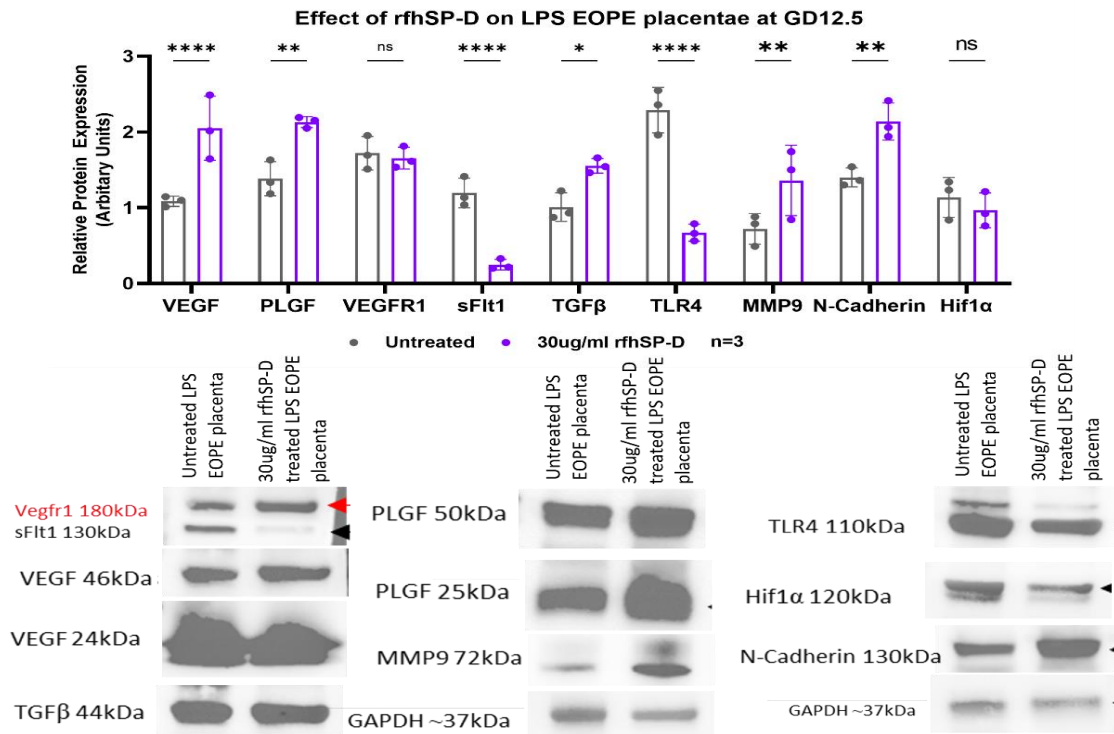


Figure 2: Effect of 30 μ g/ml rfhSP-D on levels of angiogenic factors, invasion factors and inflammatory markers in *ex vivo* explants of LPS EOPE mice placenta at GD 12.5 in hypoxia

To evaluate the therapeutic potential of SP-D in PE, an exposure to ultra-low dose lipopolysaccharide (ULD LPS) was used to mimic PE in HTR8 cells. The ULD LPS stimulation induced a significant pro-inflammatory response – by upregulation of TLR4, IL1 β , TNF α , pNF κ B; and anti-angiogenic response – by upregulation of sFlt1 and downregulation of VEGF, PLGF, MMP9, TGF, N-Cadherin, Vimentin in HTR8 cells under hypoxia. Additionally, it also demoted the migration capacity of HTR8 cells. The administration of low-dose LPS in pregnant mice at GD 5.5 produced hypertension, proteinuria, placental abnormalities, and kidney pathology. The LPS EOPE dams also exhibited lower placental and fetal weights. In an *ex vivo* culture of the LPS EOPE placentae from GD12.5, rfhSP-D treatment under hypoxia restored the inflammatory and angiogenic balance in the placental tissue explants (Fig. 2).

4.11 Evaluating the Role and Proteolytic Processing of Trop1 and Trop2 in Normal Placentation and Placental Pathologies *(Partly Funded by Department of Biotechnology)*

Principal Investigator : **Bhakti R Pathak**
 Project Associates : AS Pawar, Antara Banerjee, Ananya Breed, Madhulika Bajaj, D Modi,
 Collaborators : Pooja Bandekar, A Pawar, Nowrosjee Wadia Maternity Hospital,
 Mumbai
 Duration : 2021-2026

Trop1 [Trophoblast protein 1], more commonly known as EpCAM: (Epithelial Cell Adhesion Molecule) and Trop2 [Trophoblast protein 2], are transmembrane glycoproteins, initially identified through expression in the human placental trophoblast cells and were later found to be overexpressed in multiple cancers. However, their expression pattern in the placenta across gestation as well as specific function in the placenta remains largely elucidated. We previously had shown the differential expression patterns of EpCAM and Trop2 at specific gestational time points in the rat placenta (Annual report 2021-2022, pp. 78-79). Also, their expression patterns were determined and compared in the morphologically and functionally distinct rat placental zones (Annual report 2022-2023, pp.81-82). In this reporting year, the expression of EpCAM and Trop2 proteins was evaluated in the human placentas collected from the medically terminated pregnancies at the second trimester (13.5, 17.2, and 22 weeks of gestation) and placenta collected at term (38 weeks' gestation). The expression of both EpCAM and Trop2 was detected as early as 13.5 weeks' gestation in the human placenta and observed till term (Fig. 1). However, in rat placenta at GD9.5, Trop2 protein is undetectable and EpCAM is low but both these proteins show gradual increase with maximal levels at GD 19.5. GD 7.4 of rat placenta corresponds to 13.5 weeks of human placenta. Thus human placenta shows abundant Trop2 and EpCAM protein expression at early gestation (week 13.5), rat placenta does not show expression of these proteins early in gestation. The proteolytically cleaved forms of EpCAM (34kDa) and Trop2 (43kDa) were detected in the second and third-trimester human placenta. The rat placenta exhibits several key physiological relevant features that closely mirror the human pregnancy. Despite this, the species-specific differences between them such as the gestational length, gestation timescales, trophoblast subtypes, and their organization within the placenta are probably having an influence on the differences in the expression profile patterns of Trop2 and EpCAM between human and rat placenta. Trop2 was expressed in the syncytiotrophoblast and cytotrophoblast cells of the floating (term

placenta) as well as the anchoring villi (second trimester) human placenta (Fig. 2). Though a strong expression of Trop2 was observed in the proximal cytotrophoblasts of the cell columns of anchoring villi, its marked absence from the distal cytotrophoblasts hinted towards their silencing as an important feature of extravillous trophoblasts (EVT) differentiation. The EVTs residing within the maternal decidua lacked expression of Trop2. In the term placenta, where cytotrophoblast number is minimal with syncytiotrophoblasts being the predominant population, Trop2 staining was clearly apparent in them. Cytokeratin-7, a pan trophoblast marker, was used to mark all the trophoblast cell types and vimentin was used to stain the stromal compartment. Our data suggests that the regulated expression of Trop2 in distinct trophoblast populations might be associated with controlled placental invasion.

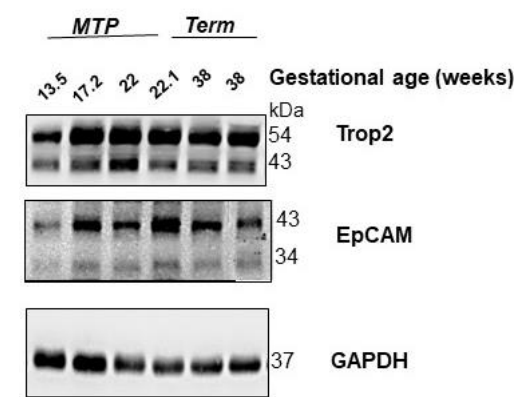


Figure 1: Expression of Trop2 and EpCAM in the cell lysates of the second and third-trimester human placenta. Two forms of Trop2 (full length and N-terminally cleaved form) were observed to migrate at ~54kDa and ~43kDa. Full-length EpCAM was detected at ~43kDa and cleaved form at ~34kDa. The expression of GAPDH served as the loading control. The molecular weights of the proteins are indicated at the right. MTP: Medically Terminated Pregnancies.

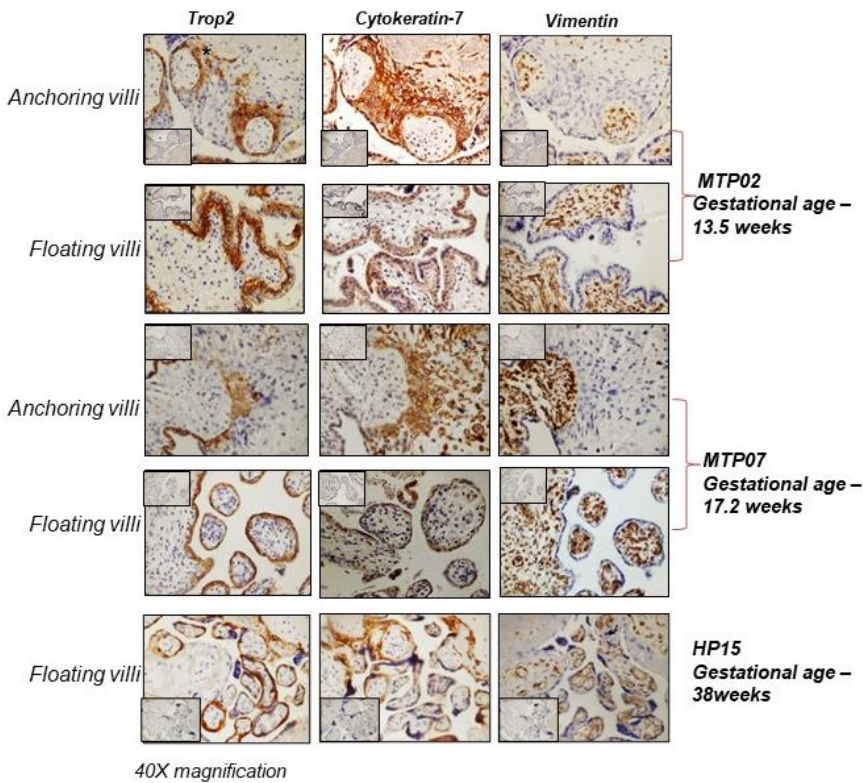


Figure 2: Immunohistochemical staining for Trop2 in the human placental sections from second trimester (13.5 and 17.2 weeks of gestation) and term (38 weeks) pregnancy. Images are at 40X magnification. Brown is the immunostaining of indicated proteins and blue for the hematoxylin-stained nuclei. Secondary control for the tested proteins is shown in the inset.

4.12 Idiopathic Recurrent Pregnancy Loss: Possible Association with Paternal Exposure to Endocrine Disruptors and Epigenetic Modifications in Sperm

Principal Investigator : **Dipty Singh**
 Project Associates : Delna Irani, Nafisa Balasinor, Anushree Patil, Deepti Tandon
 Collaborators : Vandana Bansal, Nowrosjee Wadia Maternity Hospital, Mumbai
 Padmaja Samant, KEM Hospital and GS Medical College, Mumbai
 Duration : 2018-2024

Recurrent Pregnancy loss (RPL) is a condition mainly attributed to defects in embryo and placenta development. It is described as two or more losses of consecutive clinically recognized pregnancies prior to 20th week of gestation. Around 1-2% women experience RPL globally, among which, ~50% cases are idiopathic (iRPL). Majority of the known RPL factors are of maternal contribution. This is a case-control study, including apparently healthy fertile couples and couples experiencing first trimester iRPL. A total of 54 fertile couples and 70 iRPL couples have been recruited in the study. During fertilization, spermatozoa contribute genetic and epigenetic factors such as chromatin packaged with protamines and histones; DNA methylome, micro-RNAs etc. Human sperm chromatin retains 5-15% nucleosomes which can play a key role in embryonic development. The retained nucleosomes have been reported to be significantly enriched at loci of developmental importance namely; imprinted gene, HOX gene and microRNA clusters etc. Any perturbations in the establishment and/or maintenance of any of these epigenetic marks may have a profound effect on embryo development and implantation. Besides paternal genetic factors, epigenetic factors via sperm could also be responsible for iRPL.

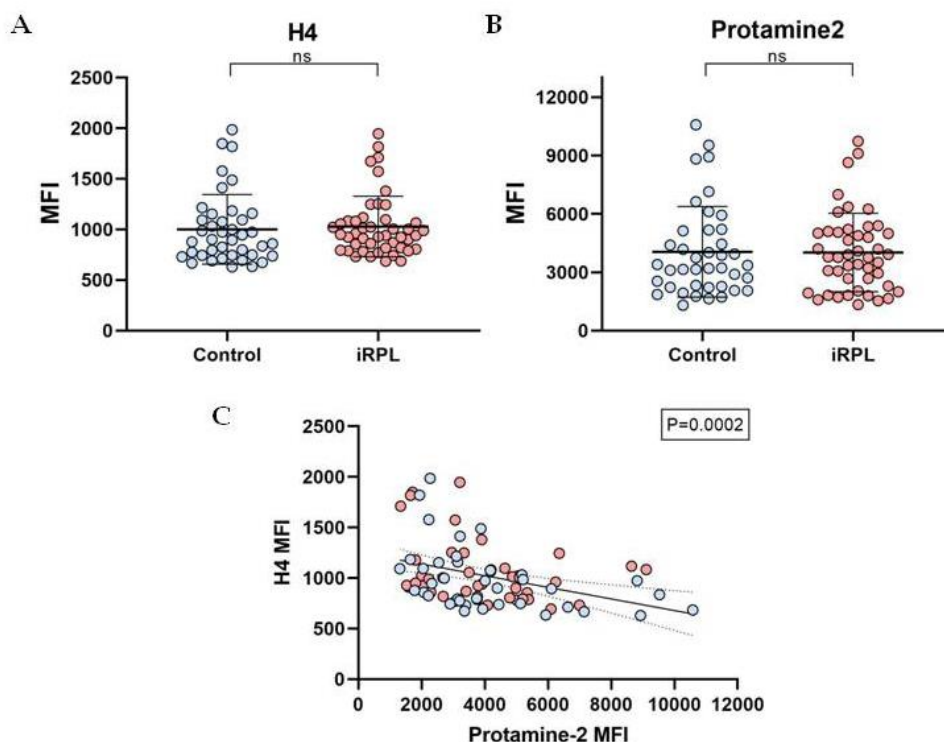


Figure 1: Levels of (A) core histone H4 and (B) Protamine-2 in sperm of study population (Mean $\pm$ SD, MFI- Mean Fluorescence Intensity, ns - non-significant). (C) Correlation between MFI values of sperm H4 and Protamine 2 (Individual data points and linear regression line are shown). Control (n = 40, Blue dots) vs. iRPL (n = 46, Pink dots).

Hence, we investigated alterations in retained nucleosome content of iRPL sperm (n=45) as compared to fertile sperm (n=40). We measured the relative core histone H4, Protamine-2 content and modified histones H3K4me3, H3K27me3, H3K9me3 and H4ac by flow cytometry. Enrichment of these modified histones at regulatory loci have either transcription activating or repressing roles and Protamine-2 condenses the sperm chromatin into compact structure. H4 and Protamine-2 levels were comparable in both groups (Fig. 1A&B) and showed significant negative correlation (Fig. 1C). The iRPL group was found to have significantly higher levels of sperm H3K4me3 as compared to the fertile control group (Fig. 2A). The other modified histones H3K27me3, H3K9me3 and H4Ac levels showed no alterations among the two groups (Fig. 2B,C&D). Sperm chromatin H3K4me3 has recently been reported to escape epigenetic reprogramming post fertilization wherein a subset of its marks (present homogenously in sperm) are retained in the pre-implantation embryo. Hence, any discrepancy in the sperm would reflect in embryo and placenta development by affecting the early gene expression transcriptome leading to early embryo loss.

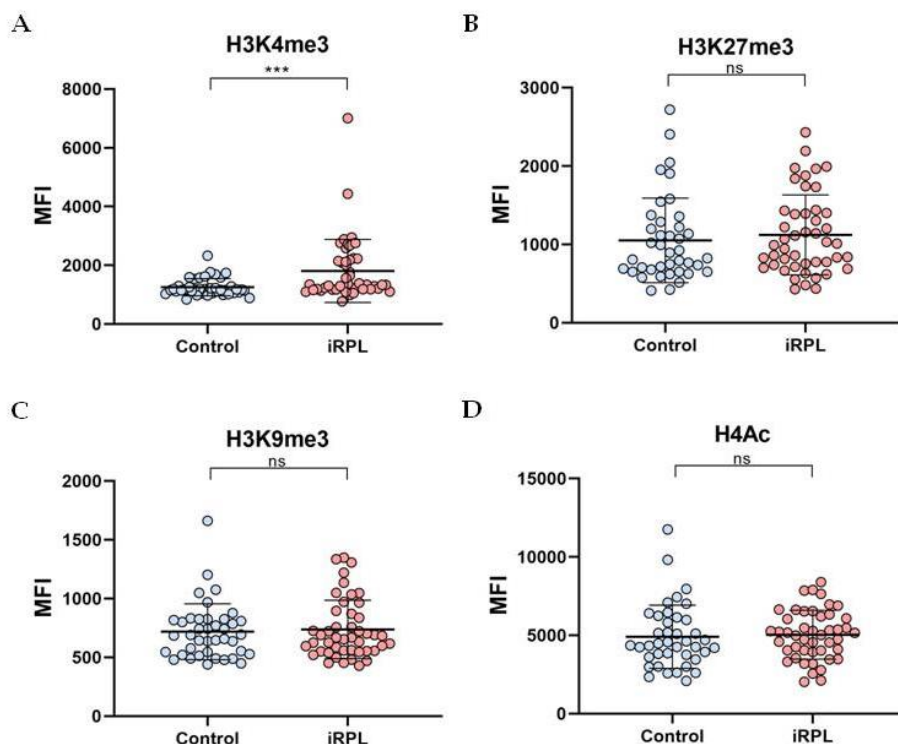


Figure 2: Levels of modified histones (A) H3K4me3, (B) H3K27me3, (C) H3K9me3 and (D) H4Ac in sperm of Control (n = 40) and iRPL (n = 46) groups. (Mean $\pm$ SD, MFI- Mean Fluorescence Intensity, ns - non-significant; ***p $\leq$ 0.001).

4.13 Investigating the Role of Endocannabinoid System in First Trimester Chorionic Villi of Women Experiencing Recurrent Spontaneous Abortions *(Partly Funded by SERB)*

Principal Investigator : **Kumari Nishi**

Project Associate : Sharon D'souza

Collaborators : Vandana Bansal, Nowrosjee Wadia Maternity Hospital,
Padmaja Samant, G.S. Medical College and KEM Hospital

Duration : 2023-2026

Recurrent Spontaneous Abortions (RSA) causes physiological and psychiatric trauma to women experiencing it. It is defined as two or more consecutive miscarriages within 20 weeks of gestation. RSA affects about 1-2% of females of reproductive age. Approximately 50% of incidences are due to chromosomal anomalies, while others remain idiopathic. Endocannabinoid system (ECS), a lipid signalling system, is involved in neuromodulation and also other physiological processes. It is also shown to be involved in spontaneous abortions. Several studies have indicated the involvement of endocannabinoids in the placental development. Our study aims to investigate the role of ECS (cannabinoid receptors i.e CB1 and CB2 (CBRs); regulatory enzymes involved in synthesis and degradation of endogenous ligands -Anandamide and 2-arachidonoylglycerol. This study is a case-control study including women experiencing RSA undergoing dilation and curettage procedure (n=25; cases) and women undergoing medical termination of pregnancy with no identifiable medical problem (n=25; control).

Presently, we are working on placental cell lines i.e. HTR/SV neo cell lines. Initial experiments with the cell lines involved determining the non-toxic concentrations of the receptor agonists and antagonists i.e. AM251, (a CB1 antagonist); HU308 and SRR144528 (CB2 agonist and antagonist) respectively using MTT assay. Fig. 1c shows concentration of agonists and antagonists of CB1 and CB2 receptors, ranging from 1-10 ng/ml plotted against percentage cell viability. However, the R2 values show low to moderate influence of the given concentration on cell viability, indicating the given concentration is non-toxic to HTR8/SV neo cell lines. Fig. 1d shows slight increase in proliferation with the increase in the concentration. However, R2 value signifies low influence. Further experimentations to study the role of endocannabinoids are still ongoing.

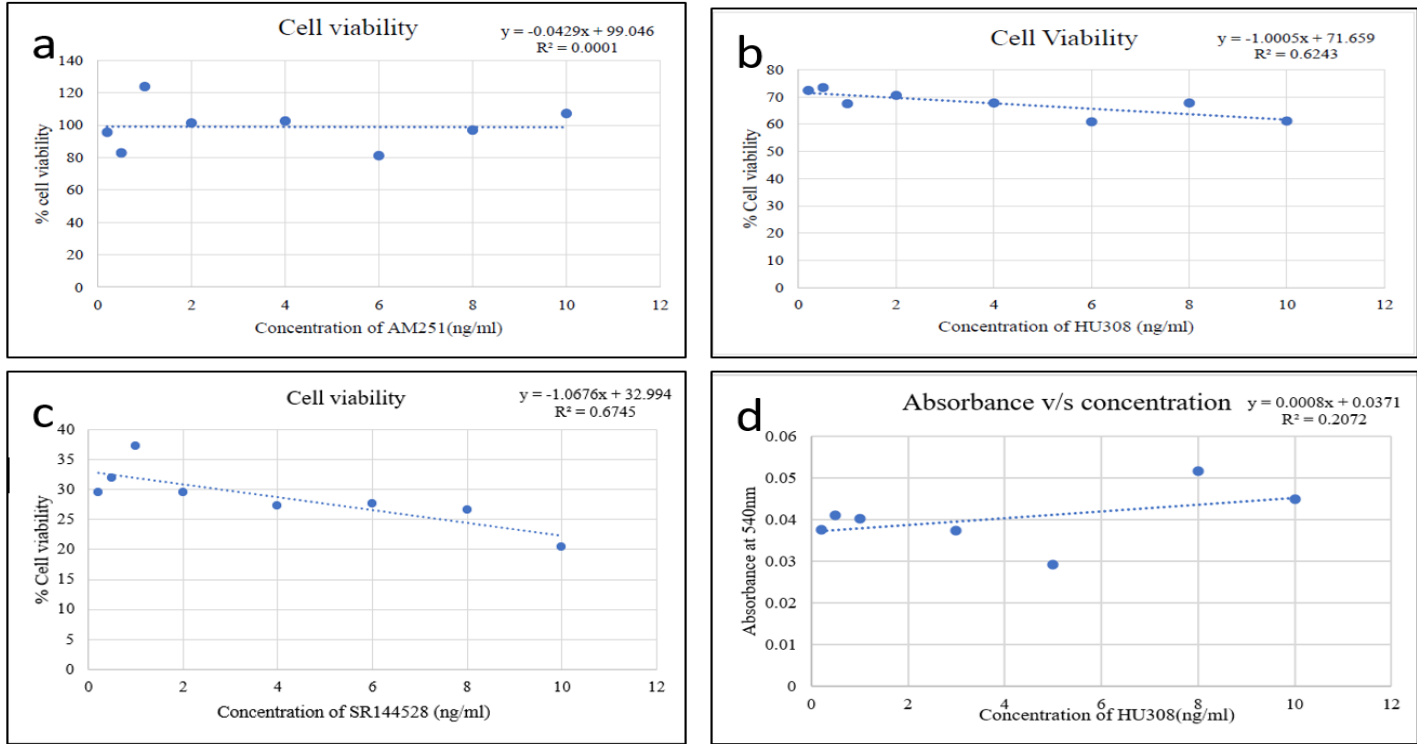


Figure 1: MTT assay showing concentration of respective agonist and antagonist against percentage cell viability (a, b, c). d: BrdU assay carried out using CB2 agonist (HU308).

4.14 Molecular Analysis of HLA-G in Pregnant Tribal Women and its Role in Infectious Etiologies Modulating Intrauterine Inflammation - A Prospective Cohort Study (Partly Funded by Indian Council of Medical Research)

Principal Investigator : **KC Itta**
Co-Principal Investigator : VM Bhor
Project Associates : Anushree Patil, Ragini Kulkarni, SK Mishra
Collaborators : B Hengne: Sub District Hospital, Dahanu, Palghar, PN Dhodi: Sub District Hospital, Kasa, Palghar, A Gadag: Primary Health Center, Ashagad, Dahanu block, Palghar, Smita Bari: Primary Health Center, Gholwad, Dahanu block, Palghar.
Duration : 2023-2026

The role of HLA-G in the host, viz. protecting the fetus from the mother's immune response and a simultaneously minimalizing effect on the mother's protective nature against pathogens, is still being explored. Identifying the genotype of the HLA-G is crucial in understanding its dual effect in pregnant women. The study aims to carry out molecular analysis of HLA-G in pregnant tribal women and associated infections in a cohort of pregnant women and its influence on pregnancy outcomes. During the study period, three hundred and twenty-two study participants (1st trimester- 166, 2nd trimester-99, and 3rd trimester -57) were recruited from four study sites in Dahanu block. About 91 % of the study participants were from Warli tribes with a mean age of 21.8 years. Ninety-two of these first-trimester samples were tested for soluble HLA-G levels (sHLA-G), and eighty-three were tested for the 14bp HLA-G genotype and infectious aetiologies (viruses, parasites, and bacteria) which cause intrauterine inflammation. The plasma levels of sHLA-G among the study participants ranged from < 10 to 1223.61 U/ml (IQR-22.9 (15.7-38.6). A majority (48%) of the samples were -14 bp/-14 bp (homozygous deletions) and 37% were -14 bp/+14 bp (heterozygous deletions). At least one infectious etiology was detected in 12.6% of the samples. Toxoplasma antibodies were detected in 5.7%, Cytomegalovirus, and Hepatitis C virus in 2.3%, and 1.1% of each were positive for Herpes simplex virus, Hepatitis B, Rubella virus, and Chlamydia. Plasma sHLA-G levels did not differ with the HLA-G 14 bp genotype. A total of 14 DNA samples were typed using Next-generation sequencing-based typing with full phasing over the whole HLA-G gene sequencing with 3'UTR. The majority of them were heterozygous and one was homozygous with G*101:01:01:01 genotype. A new allele (HLA-G*101:01:01:01 - SNP "G" to "A" at 1432 position) was identified and submitted to GenBank and IPD-IMGT/HLA database for official nomenclature by the World Health Organization Nomenclature Committee. Trimester-wise analysis of sHLA-G levels, HLA-G genotypes, and various infectious aetiologies with pregnancy outcomes are under investigation.

4.15 Trends, Patterns and Determinants of Sex - Selective Abortion in India: Using Nationally Representative Survey Data (Partly Funded by Indian Council for Medical Research)

Principal Investigator : **M Bhise**
Co-Principal Investigator : Shahina Begum, R Prusty
Duration : 2024-2025

Between 1980 and 2010, an estimated 3 to 12 million sex-selective abortions occurred, contributing to a skewed sex ratio of 109 boys for every 100 girls (ages 0-6) according to the 2011 census. Advances in medical technology, such as ultrasounds introduced in the 1970s, were misused for sex determination, leading to increased female feticide. Despite the 1994 Pre-conception and Prenatal Diagnostics Techniques Act aimed at curbing this practice, cultural preferences for male children persist. The decrease in fertility rates has heightened the desire for sons, especially in smaller families, further exacerbating sex-selective abortions. This study aims to analyze sex ratio at birth (SRB) patterns and socioeconomic factors over four decades (1981-2020) using data from five rounds of the National Family Health Survey (NFHS), India. The conditional sex ratio (CSR), an indirect indicator of sex-selective abortion, was calculated at parity levels. While the overall sex ratio was relatively stable over the study period, there were significant declines in the conditional sex ratio for second-born children when the first-born was female. Additionally, the sex ratio for third-born children varied based on the sexes of the previous children, suggesting potential sex-selective abortion practices. Socioeconomic factors such as education, wealth, and living in urban-rural areas further influenced these trends, due to knowledge, accessibility and utilization of abortion services. The fall in Conditional Sex Ratio provides evidence of sex-selective abortion in some communities/ socio demographic groups in India.

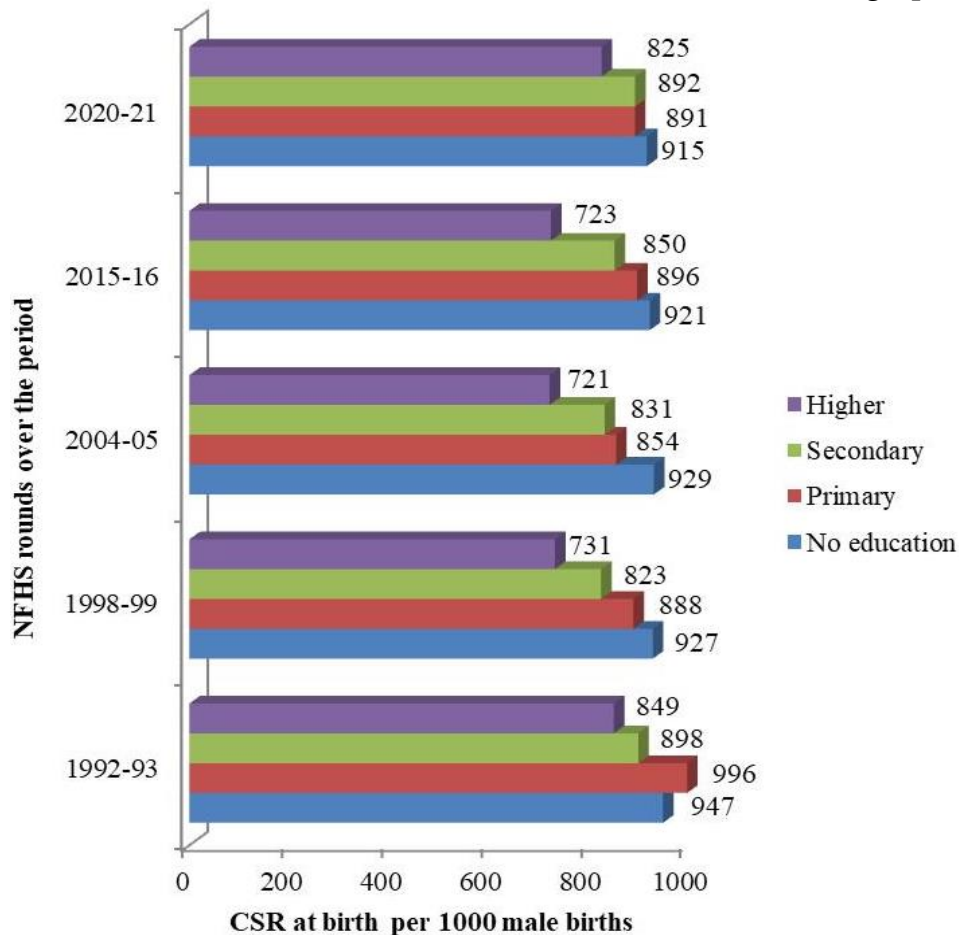


Figure 1: Conditional sex ratio of second order births where first born child was girl by the educational level of mother over the time

5. CHILD HEALTH RESEARCH

5.1 Effect of Maternal Gestational Micronutrient Deficiency on Offspring's Fertility and its Underlying Epigenetic Mechanisms in Germline

Principal Investigator : **Dipty Singh**
 Project Associates : Anushruti Singh, Nafisa Balasinor, Kumari Nishi
 Duration : 2021-2026

The Developmental Origin of Health and Disease (DOHaD) hypothesis explains the link between early fetal life exposure to nutritional deficiencies and emergence of various metabolic disorders such as obesity, type 2 diabetes and hypertension in adulthood. However, development of the origin of reproductive disorders due to early life nutrient insufficiencies are not well studied. Hence, this study aims to unravel the effects of maternal methyl donors (vitamin B12, folic acid and methionine) deficiency during gestation on offspring's reproductive development and fertility. For this, pregnant female B6 CBA tg OCT4-GFP mice were fed on AIN 76A control chow diet (CCD) or 40% methyl donors-deficient diet (MDD). The window period of maternal deficiency was from gestation day (GD) 5 till delivery. F1 offsprings were fed on CDD after weaning. The day of delivery was considered as post-natal day 0 (PND0). The pups were examined at PND0 and their sex was determined by checking AGD (anogenital distance). The live birth index of pups (at PND 0) was 100% in both the groups (Fig. 1A). But the viability index (at PND 60) was reduced by 38% in the MDD group due to pups' mortality (Fig. 1B). Glucose levels in F1 offsprings were similar between the groups at PND 30 and increased in the MDD/group at PND 75 as compared to CCD group (Fig. 1C). Caudal sperm count, sperm motility and serum testosterone levels were significantly reduced in the MDD group (Fig. 1D-F).

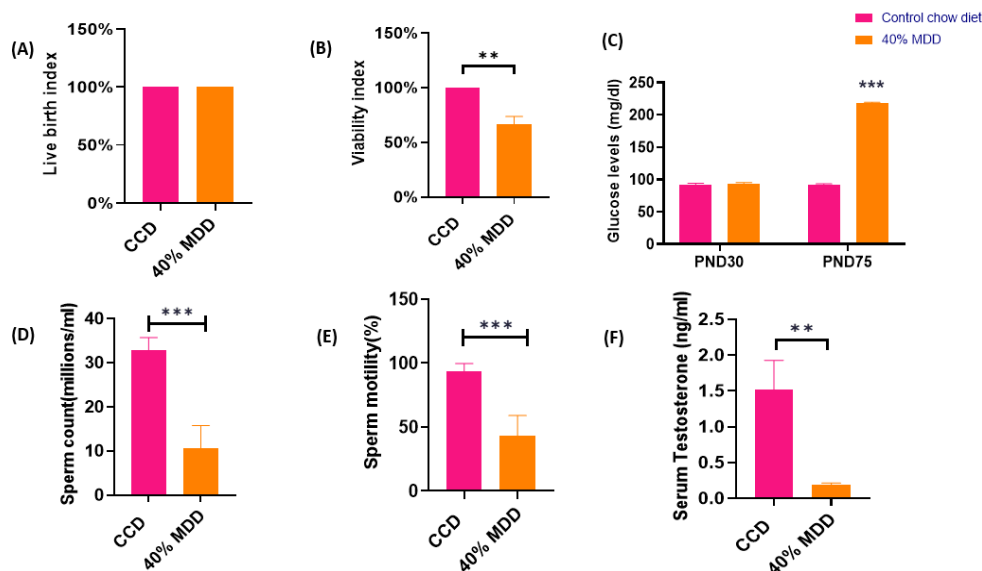


Figure 1: Developmental, metabolic and reproductive parameters of F1 offspring s of mothers fed CCD or MDD diets: A) Live birth index; B) Viability index; C) Glucose levels (mg/ dl) (at PND30 and PND75); D) Sperm count (millions/ ml); E) Sperm motility (%); F) Serum testosterone (ng/ ml). n= 3-6 per group. **p< 0.001, ***p<0.0001

Fertility index was reduced by 33.3% in the MDD group (Fig. 2A). Litter size was significantly decreased (Fig. 2B) and %POL was significantly increased in the MDD group (Fig. 2C). Some pups of MDD copulated in the second estrous cycle (Fig. 2D). CRL (crown rump length) and body weight of F2 fetuses of the MDD group were also found to be reduced (Fig. 2E). The present findings suggest that gestational methyl donor deficiency may have detrimental effects on offsprings' reproductive parameters and fertility. Further studies are underway to investigate epigenetic modifications in the primordial germ cells of F1 embryo.

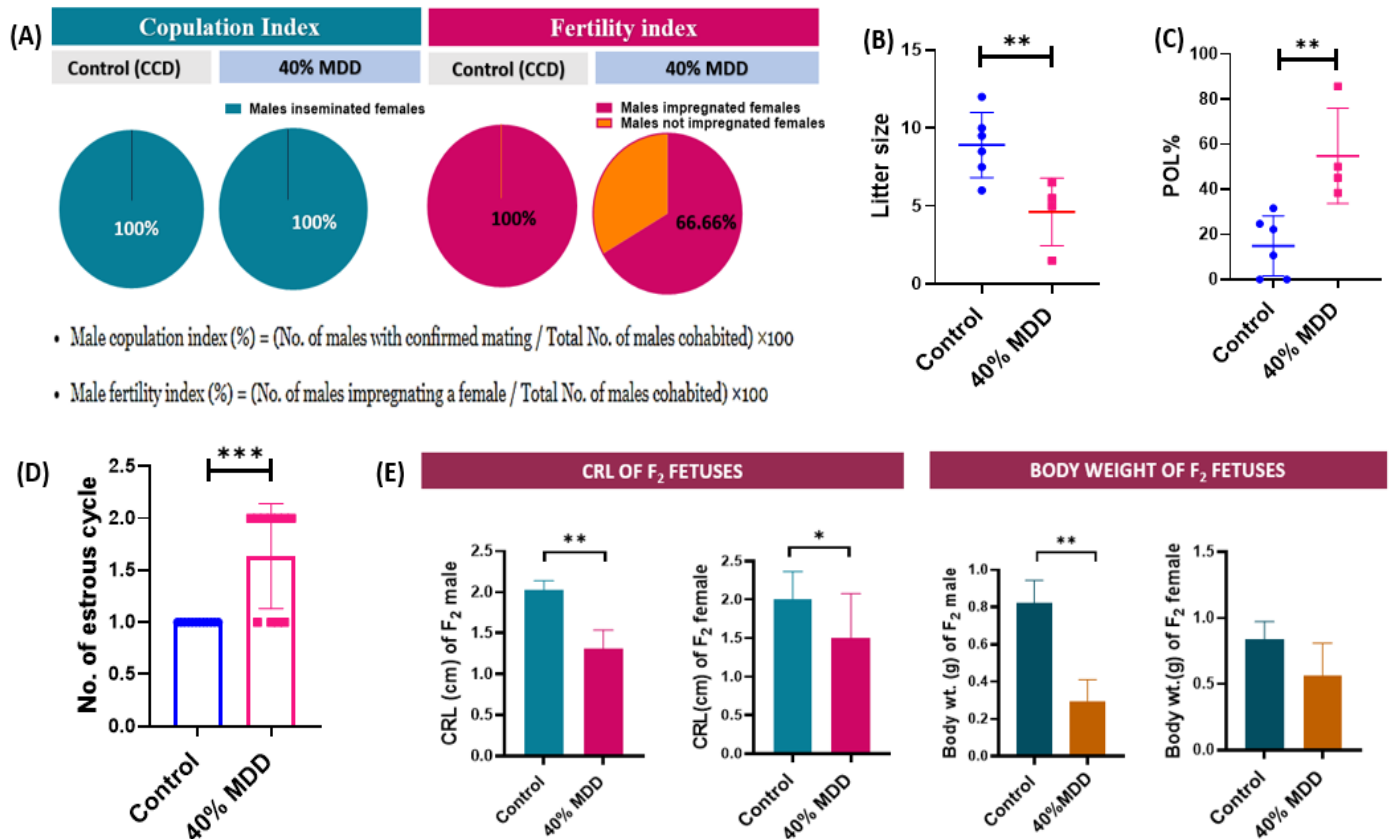


Figure 2. Fertility assessment of CCD and MDD groups: A) Copulation index and fertility index; B) Litter size; C) %POL; D) Number of estrous cycle taken to copulate; E) CRL of F2 fetuses and body weight of F2 fetuses. n=6 per group. *p<0.05, **p<0.001, ***p<0.0001

5.2 Comprehensive Genetic Evaluation of Fetus in Antenatally Detected Abnormal Pregnancies with Fetal Malformations: Outcomes, Benefits and Limitations - a Pilot Study (Funded by Department of Health Research)

Principal Investigator : **S Pande**
 Co-Principal Investigator : D Das
 Project Associates : Shaini Joseph, V Bhanothu, Neha Minde, H Gawade, Shiny Babu
 Collaborator : Vandana Bansal, Nowrosjee Wadia Maternity Hospital, Mumbai
 Duration : 2021-2024

The objectives of the study are to develop a pipeline for the genetic diagnosis of ultrasonography (USG) specific foetal malformation; to determine the frequency and pattern of genetic abnormalities in antenatally detected foetal malformations; to determine the efficacy of microarray in detecting genetic abnormalities; determining the efficacy of NGS in detecting genetic abnormalities; and to determine the percentage of denovo mutations in foetal malformations. Inclusion criteria were antenatal USG showing malformations of 12-24 weeks gestation age with suspicion of genetic abnormalities. Exclusion criteria were recurrent pregnancy loss, known genetic abnormalities in family, non-genetic causes. Fetus (muscle/skin), placenta, blood samples were taken from parents wherever applicable (also to rule out maternal cell contamination). A total of 102 samples have been collected during the study period, of which 46 were recruited during the reporting period. Parental consanguinity was reported in 15 of the collected samples. Histopathological examination of all the tested 77 samples were found to be negative for infections. Trisomies and chromosomal mosaicism were identified by karyotyping and FISH in seven samples. Pathogenic CNVs were identified in eight of the samples by Chromosomal Microarray Test. Whole exome sequencing (WES) was performed in remaining 67 samples. Pathogenic variants were detected in five samples. Likely pathogenic variants were detected in two samples. Variants of uncertain significance were detected in total 19 samples. Four samples had likely pathogenic variants as well as variants of uncertain significance. No pathogenic, likely pathogenic, or variants of uncertain significance were detected in 23 samples. The parents were called for post-test counselling. Till date, 63 patients attended the genetic counselling session. Six patients were unavailable for the counselling. Thirty-one patients are still pending for the counselling session.

5.3 Mission Program on Paediatric Rare Genetic Disorders (Mumbai Chapter) *(Partly Funded by Department of Biotechnology)*

Principal Investigator : **S Pande**
 Co-Principal Investigator : V Bhanothu
 Project Associates : Shaini Joseph, DVS Sudhakar, Suchitra Surve, Neha Minde, H Gawde, Shiny Babu
 Duration : 2022-2027

The objectives of the study are i) Recruitment of patients with pediatric rare genetic diseases, ii) Genomic analysis for diagnosis of rare genetic disorders, iii) Database development and analysis, iv) Functional validation of novel variants/novel genes, v) Development of affordable diagnostics/screening strategies for rare genetic diseases, vi) Lentiviral vector mediated gene editing for treatment of rare genetic diseases, vii) Awareness program in rare genetic diseases.

A total of 103 samples have been screened using conventional methods, including karyotyping, FISH, microarray, MLPA, and Fragile-X testing. The patients who were tested negative by conventional tests were referred to Centre for DNA Fingerprinting and Diagnostics (CDFD) for high throughput Whole Exome Sequencing (WES). Total 49 samples have been sent to the CDFD for WES. The samples have been sourced from various hospitals such as KEM Hospital, Sion Hospital, Nair Hospital, and B. J. Wadia Hospital. Additionally, we have received samples from different special schools across Mumbai, including ETC School, Vashi; SEC School, Agripada; and Jay Vakeel School, Kalachowki. WES data for

11 patients have been analyzed. Out of these 11 cases, pathogenic variants were found in 2 cases. In the remaining 9 patients, variants of uncertain significance (VUS) were detected, and further investigations are ongoing. We have also conducted several community awareness sessions on pediatric rare genetic disorders across Mumbai. The details of the awareness sessions are as follows: (i) Community awareness session for approximately 100 high school science/math teachers of Kendriya Vidyalaya from Gujarat and Maharashtra at the Genetic Research Centre (GRC), ICMR – NIRRH on 23rd August 2023. (ii) Awareness session conducted on 29th August 2023 for parents and teachers of special children at the Education and Training Service Centre for Persons with Physical Disabilities, Vashi. (iii) Awareness program conducted for Medical Officers of Palghar District, Maharashtra on 12th September 2023. (iv) Awareness session conducted at Sunshine School for Differently Abled Children, Vashi on 30th September 2023. (v) Awareness session for parents and teachers of Kindergarten School, Ghansoli Gaon on 9th October 2023. (vi) Lecture series conducted as a part of community awareness for 6 fetal medicine fellows from Wadia Hospital, Mumbai. (vii) Community awareness session conducted for faculty and parents from the Society for the Education of the Crippled (SEC Day School), Agripada on 22nd February 2024. (viii) Awareness session at DY Patil University, Navi Mumbai on February 23, 2024. (ix) Scientific program conducted on Rare Disease Day (February 29, 2024) as a part of awareness activities. (x) Awareness program for nursing students from Leelabai Thackersey College of Nursing on 7th March 2024 at ICMR – NIRRH, Mumbai.

5.4 Identification and Evaluation of Novel Metabolites with the Potential of Prenatal Diagnosis of Fetal Congenital Heart Diseases *(Partly Funded by Department of Science and Technology - Science and Engineering Research Board)*

Principal Investigator	: V Bhanothu
Project Associates	: S Pande, U Chaudhari
Collaborators	: Jayashree Mishra, Bai Jerbai Wadia Hospital for Children, Mumbai Vandana Bansal, Nowrosjee Wadia Maternity Hospital, Mumbai
Duration	: 2022-2025

This project aims to assess the potential of novel metabolites in the early diagnosis of fetal congenital heart diseases. Blood and urine samples were collected from 56 healthy pregnant women between 11 to 38 weeks of gestation and 17 pregnant women carrying fetus with Congenital Heart Diseases (CHD). As per our interim analysis, out of 13 fetal CHD cases, 23.8% of cases with Ventricular Septal Defects (VSD), 23.8% of the cases with Hypoplastic Left Heart Syndrome (HLHS); 15.38% of cases with Tetralogy of Fallot (ToF), and 38.46% of cases with other defects (1 double outlet right ventricle, 1 triventricular septal defect, 1 tricuspid atresia, 1 left atrial isomerism and 1 heart block) were recorded. Significantly higher levels of 3-Hydroxybutyrate ($p=0.01$; $df=19$) dimethylamine in cases compared to controls were detected. Further, the NMR data from IISER, Pune and LC-MS/MS data from NCL, Pune and IIT Bombay have been received and analysis is under progress. The study has potential to provide novel insights into the metabolomics of fetal CHD, as the Indian context varies with unique genetic makeup and geoethnic risk factors.

5.5 Molecular Profiling of Common Clinical Phenotypes Associated with Congenital Hypothyroidism (CH) *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : **V Bhanothu**
Co-Principal Investigator : S Pande
Project Associates : Isha Haria, Y Karbikar, Sudhakar DVS, Sudha Rao, Suchitra Surve
Collaborators : Sudha Rao, Jayashree Mishra, Bai Jerbai Wadia Hospital for Children
Vandana Bansal, Nowrosjee Wadia Maternity Hospital, Mumbai
Suchitra Surve
Duration : 2022-2025

Congenital hypothyroidism (CH) is a metabolic disorder caused due to the deficiency of thyroid hormones detected at the birth. The common etiology for CH involves gene mutations that lead to either dyshormonogenesis which involves lack of thyroid hormone synthesis or dysgenesis which is caused due to abnormal development of thyroid gland. However, there are only few cases of dysgenesis reported that have shown familial inheritance that include mutations in PAX8 and TSHR genes. In contrast to this, dyshormonogenesis shows stronger correlation with gene mutations, mostly involving those genes that produce proteins that are involved in eight complex steps of thyroid hormone synthesis and these include: SLC5A5, TPO, DUOX2 and TG. TDH has highest prevalence in South-Asian population. This project focuses on identifying pathogenic genetic variants in children with TDH presenting different clinical phenotypes. Blood samples from 45 index cases (Ages: 0-18 yrs) and their parents were collected. The whole exome sequencing (WES) analysis of 13 CH cases and Thyroid-Stimulating Hormone Receptor (TSHR) gene mutation analysis of three trios were performed. Our study is the first study to report 41 gene variants in eighteen genes. Out of which, 10 genes are reported to be pathogens. These include Thyroid Peroxidase (17.07 %), Dual Oxidase, (17.07 %), Thyroglobulin (9.76%), and Solute Carrier Family-5 Member-5, (4.87%). TSHR gene variant c.1349G>T/p.R450L (autosomal heterozygous), and other variants might contribute to clinically more severe TDH in children. One of the genes that was detected was EXCO7 that codes for a protein that plays role in regulating vesicles but no evidence has been found about its role in CH. Using bioinformatics analysis, it was found that the mutant has no major effect on physio-chemical property of the primary protein structure. Similarly, using Castp tool and MEGA11 tools it was found that the D172 residue is neither part of the active site nor of the conserved region. However, Polyphen-2 and Mutation tester did detect the variant as pathogenic. Further in-vitro studies are required to understand about the variant and its role in human diseases, specifically for CH. Gender-wise differences among TDH were observed. All cases showed elevated levels of TSH. This study may aid in developing a cost-effective molecular diagnostic panel, for the early detection of CH.

5.6 Population Based Birth Defect (BD) Surveillance in Linkage with Rashtriya Bal Swasthya Karyakram (RBSK) Programme in Rural Blocks of Palghar District in Maharashtra *(Partly Funded by Department of Health Research)*

Principal Investigator : **Suchitra Surve**
Co-Principal Investigator : Ragini Kulkarni

Project Associates : Priyanka Gawai, U Pachalkar
 Collaborators : S Bodade (Civil Surgeon), D Suryawanshi (District Health Officer), M Chavan (RCH Officer), P Pagi (RBSK Co-ordinator)
 Duration : 2020 – 2023

The present study was a population based study conducted in public healthcare facilities and communities through ASHAs. The study setting consisted of 7 blocks of Palghar district which are predominantly occupied by tribal population (Dahanu, Palghar, Talasari, Jawhar, Vikramgad, Wada, Mokhada). Data collection was done in 38 PHCs, nine rural hospitals and three Sub-district hospitals in Palghar district. A total of 4 rounds of visits were done in all the public healthcare facilities. During the preparatory phase of the study, a total of 1905 of 2211 (86%) ASHAs were trained for identification of birth defects. Pre and post assessment of ASHAs were done during the training program. Of the total 1901 ASHAs trained, assessment was done for 1023 ASHAs. Findings revealed a significant increase in the knowledge of participants with regard to prevention, risk factors and identification of BD after intervention as compared to before intervention. Also there was improvement in reporting of BDs after training program (70 BDs reported) through ASHAs. With respect to birth defects, a total of 402 birth defects were identified from April 2021 to August 2023. Table 1 represents blockwise distribution of birth defects. Highest percentage of birth defects was reported in Jawhar (21.6), Palghar (19.7), Dahanu (19.4), followed by Vikramgad (12.4), and Wada (11.9). Mothers of new borns with birth defects were aged between 20 to 25 years (53%), followed by 26 to 30 years (23.3%). Around 13% mothers were below 20 years at the time of delivery. In 44% of cases, Gestational Age (GA) at the time of delivery was 38 to 40 weeks in 34%, GA was 32 to 37 weeks. 57% new borns with birth defects were male child and 38.6% were female child. Majority of the children were low birth weight (54.2%) and 11.7% were very low birth weight. Only 25.4% new borns had equal to or greater than 2.5 kg weight. The percentage of cardiovascular defects like CHDs (17.2%) was highest, followed by musculoskeletal defects like Club foot (15.4%), and Orofacial defects like Cleft lip and palate (12.4%). Other major births reported were Hydrocephalous (4.6%), Neural tube defects (8.3%), Imperforate Anus (4%), Multiple defects involving one major defect (7%). Prevalence of birth defects was planned to be calculated from April 2021 to March 2023. However, it was calculated till February 2023 as the HMIS reports for total deliveries in Palghar district was available only till February 2023. Prevalence of birth defects in new borns in study area = Total number of birth defect cases (live birth/still birth)/total number of deliveries x 1000. Prevalence of birth defects in the new borns in the study area was 8.08.

Table 1: Block wise distribution of birth defects

Block	Total birth defects		Birth defects out of total deliveries (Block wise)		Prevalence/1000
	Frequency	%	Frequency	% (within block)	
Jawhar	87	21.6	5612	1.5	1.81
Palghar	79	19.7	11349	0.7	1.65
Dahanu	78	19.4	15257	0.5	1.62
Vikramgad	50	12.4	3739	1.3	1.04
Wada	48	11.9	5510	0.9	1.00
Talasari	31	7.7	3690	0.8	0.64
Mokhada	29	7.2	2711	1.7	0.60
Total	402	100	47868	0.24	8.39

5.7 Assessment of Neonatal Screening Approaches for Sickle Cell Disease and the Effect of Early Intervention in Management of the Disease in Tribal Populations (Partly Funded by Indian Council of Medical Research)

Principal Investigator	: Suchitra Surve
Coordinating Center	: ICMR-National Institute of Immunohaematology
Co-Principal Investigator	: Ragini Kulkarni
Project Associates	: Yugali V Kore, Aarati Patil, Jidnyasa Kore, Shweta Dube, A Gawad, S Solanki, Y Jadhav
Collaborators	: S Bodade, Palghar District; D Suryavanshi, District Health Officer; B Hengne, SDH Dahanu; P Dhodi, SDH Kasa
Duration	: 2019 - 2024

This multi-centric study, implemented in 7 sites across the country (Maharashtra -2 centers, Gujrat, Tamil Nadu, Odisha, Madhya Pradesh and Rajasthan) was undertaken to establish a new-born screening program for Sickle cell disease in tribal populations of seven different states of India for early detection, to assess the magnitude of the problem and to understand the barriers for undertaking such programme and to measure the benefit of early comprehensive care of affected babies. The study is being implemented at Dahanu block of Palghar District (Sub-district Hospital, Dahanu and Kasa, PHCs) through Model Research Health Unit, Dahanu. A total of 1505 samples were screened by HPLC. A total of 129 (12.6.%) heterozygous babies were detected. 08 (0.53%) babies were detected to have disease. Awareness and training activities were carried out including celebration of Sickle cell day and a role play followed by an awareness session about Sickle cell disease for parents of babies with sickle cell disease at Sub District Hospital, Dahanu. Since the start of the project 41 babies have been detected to have Sickle cell disease. Pneumococcal vaccine was given to these babies through Universal Immunization Programme (UIP). Typhoid vaccine and Meningococcal vaccine were given. Medicines such as Pentid, Folic acid, A-Z syrup were commenced in 21 babies with sickle cell disease. Hydroxyurea was commenced in 13 babies.

Table 1: New born screening data from Dahanu and Kasa

	Samples (April 2023 to March 2024)	Total samples
Total number of deliveries	2353	13469
Total live births undergone newborn screening by HPLC**	1510	7786
Normal	1305	6688
HbS heterozygous	129	661
HbS homozygous	8	41
Other Hemoglobinopathies**	42 (+26 Undermined)**	396

** Including other Hemoglobinopathies & undetermined result : 99

Other Hemoglobinopathies - S window with raise A2 , Unknown window, D window, C window, Raise A2, S window with unknown window = 01, S window with C window = 02, S window with Ao > F = 1) Undetermined result /results with unknown significance

5.8 Genetic and Biochemical Characterization of Mitochondrial Oxidative Phosphorylation (OXPHOS) Disorders in Children

Principal Investigator	: DK Das
Project Associate	: Debolina Saha
Collaborators	: Shilpa Kulkarni, Sonam Kothari, Bai Jerbai Wadia Hospital for Children, Mumbai
Duration	: 2021-2026

Mitochondrial Disorders (MD) are a wide group of disorders with variable age of onset and clinical presentations. The clinical presentations primarily affect those organs and tissues that have a high energy requirement like skeletal muscle, heart, brain, eyes etc. However in majority of the cases, MDs are multisystemic. Due to the wide spectrum of clinical manifestations and relatively poor genotype-phenotype correlation of MDs, a combinatorial diagnostic approach is preferred including laboratory tests, metabolite analysis, respiratory chain enzyme assays, histopathology and genetic analysis. The respiratory chain enzyme analysis on skeletal muscle biopsy has remained the gold standard for the deficiency analysis of mitochondrial complexes I-IV. The ideal tissue for investigation of MDs is one that contains larger amount of mitochondria. However, considering the invasive nature and the expense of a muscle biopsy, it is often difficult to obtain it from children for routine diagnostic purpose. Therefore, there has been an inclination towards developing alternative approaches to diagnose MDs. The objectives of the study are to classify mitochondrial disorders into biochemical and histopathological phenotypes and further identify genetic variations in mitochondrial and nuclear genomes. Till now, 43 pediatric patients suspected of MD and age matched 37 healthy controls were recruited for the study. Buccal swab samples were collected. Using spectrophotometric analysis, a significant decrease in the activities of mitochondrial Complex I, III and IV ($p < 0.05$) was observed in buccal swab samples of 35 patients (Fig 1). Further, analysis was carried out to identify number of patients who have isolated and multi-complex deficiencies. Out of 35 pediatric patients, 13 patients (30.2%) showed isolated complex deficiency and 22 patients (51.1%) had multi-complex deficiency. A total of 13.9% patients had isolated complex I deficiency and 11.6% with complex IV deficiency, whereas, only 4.6% patients had isolated complex III deficiency. However, isolated complex II deficiency was not observed in any of the patients. A comparative analysis between muscle biopsy and buccal swab samples ($n=4$) was also carried out and a concordance was observed in the results from buccal swab samples and muscle biopsies (Table 1). In order to check the ability of buccal swab as a sensitive and predictive tool for the diagnosis of MDs, ROC analysis was done. ROC analysis of Complex I had an AUC of 0.86 ($p=0.04$) for muscle biopsy compared to AUC of 0.70 ($p=0.02$) for buccal swab samples. Similarly, ROC analysis for Complex III & Complex IV in muscle samples showed AUC of 0.77 ($p=0.01$) and AUC of 0.80 ($p=0.08$) respectively. Similar concordance was observed in buccal swab samples with AUC= 0.77 ($p<0.01$) and AUC=0.72 ($p < 0.05$) in Complex III and IV respectively (Fig 2). A sensitivity of 78% was observed, suggesting that this approach can be used as a preliminary diagnostic technique prior to planning for invasive and expensive procedure of muscle biopsy.

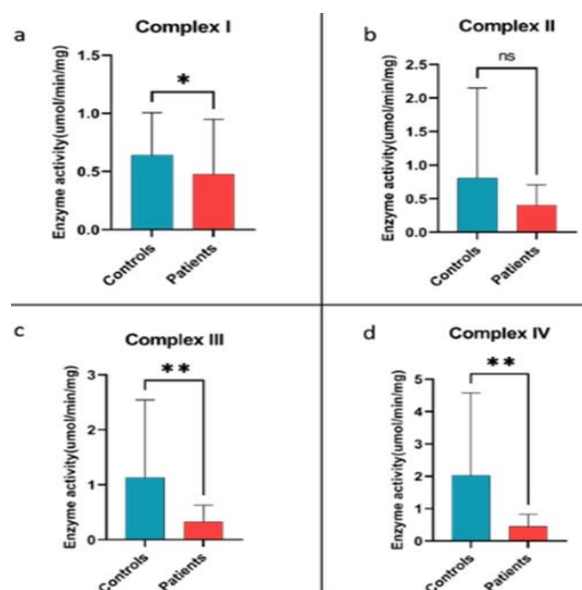


Figure 1: Mitochondrial enzyme activity in buccal swab samples from controls (n=37) and patients with mitochondria disorders (MDs) (n=43): (a) Complex I; (b) Complex II; (c) Complex III; (d) Complex IV

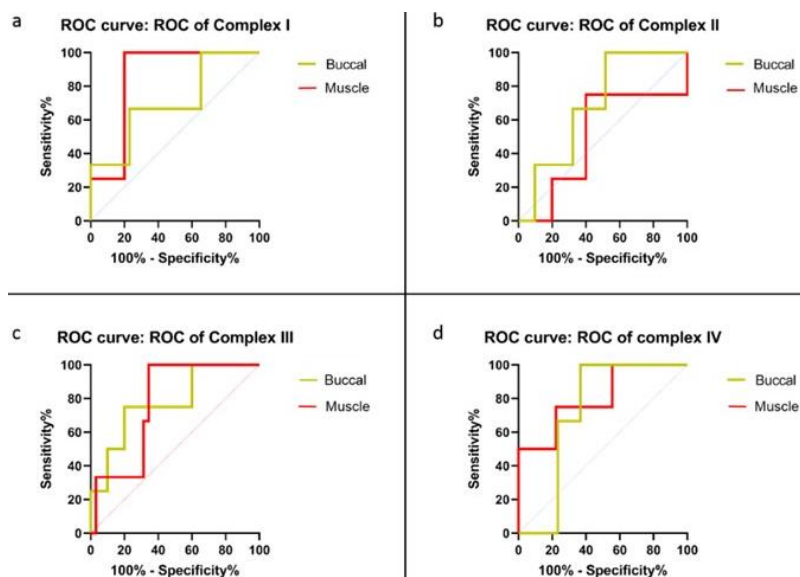


Figure 2: Receiver Operating Characteristic (ROC) curve of Complex I (a), Complex II (b), Complex III (c) and Complex IV (d) in 4 patients. Green line indicates ROC curve of buccal swab samples and red line indicates ROC curve of muscle biopsy samples.

Table 1: Comparative mitochondrial enzyme activities in muscle biopsy and buccal samples in patients P2 (a); P3 (b); P10 (c) and P19 (d)

Mitochondrial complex	Control enzyme activity ($\pm$ SD) (n=37)	Percentage deficiency in patients (Buccal Deficiency <40%, Muscle deficiency <30%)							
		P2		P3		P10		P19	
		Buccal	Muscle	Buccal	Muscle	Buccal	Muscle	Buccal	Muscle
Complex I	1.40 $\pm$ 0.83	N	N	N	N	N	8.20%	30.30%	N
Complex II	0.42 $\pm$ 0.23	27.20%	6.10%	40%	26.90%	N	N	N	N
Complex III	2.18 $\pm$ 1.92	12%	7.70%	3.30%	4.90%	N	N	13.20%	11.20%
Complex IV	2.68 $\pm$ 2.12	12.10%	N	12.40%	N	22.10%	4.35%	33.30%	8.25%

5.9 Exploring Clinical and Therapeutic Relevance of Novel Biomarkers among the Children Presenting with Idiopathic and Incomplete Precocious Puberty at Tertiary Hospital, Mumbai (Partly Funded by Indian Council of Medical Research)

Principal Investigator : **Suchitra Surve**

Co-Principal Investigators : Sudha Rao, Antara Banerjee

Project Associates : D Modi, Beena Joshi, Anushree Patil, Shahina Begum, S Pande, Deepti Tandon, Varsha Trayambake, Rachana Dalvi, Sharmila Kamat, Swati Kashikar, Shweta Bombe

Collaborator : Sudha Rao, Bai Jerbai Wadia Hospital for Children

Duration : 2021-2024

Precocious puberty (PP) is the early developmental onset of sexual characteristics, mostly defined as the attainment of breast stage II before the age of 8 years in girls and genital stage II before 9 years in boys, according to the sexual maturity rating (Tanner staging) method. Central Precocious Puberty (CPP), which mainly occurs due to the premature reactivation of GnRH pulse generator, leading to increased basal gonadotropin levels, is usually idiopathic in nature (ICPP) and may pose significant risks such as psychosocial stress, short stature, PCOS, diabetes mellitus-1, metabolic disorders in later life. However, some individuals present with incomplete puberty such as premature thelarche (PT), wherein the risk of disorder development is not significant and hence, a clear distinction is needed when managing these similar variants (ICPP and PT) of precocious puberty. Even though the GnRH-stimulated gonadotropin level test remains a gold standard for diagnosis of CPP, the cost-intensive and tedious nature of this test, combined with the lack of established cut-off values of the basal gonadotropin levels, may cause delay in initiation of treatment adversely affecting health outcomes. Increasing evidence points towards the utility of biomarkers such as Kisspeptin-10 (Kp-10), Neurokinin B (NKB) and Neuropeptide Y (NPY) biomarkers for the diagnosis of ICPP and PT. This study was planned to explore the clinical and therapeutic relevance of above-mentioned markers, 40 healthy age-matched controls who met the inclusion criteria, were recruited after screening of 250 girls. Out of the 86 precocious puberty cases, 57 girls met the inclusion criteria for PP. Of these 33 and 23 were confirmed ICPP and PT cases respectively. One remaining case is yet to be classified. Circulating levels of Kp-10, NKB, NPY in 40 prepubertal control participants, 33 ICPP cases and 23 PT cases are depicted in Fig. 1. A significantly higher level of Kp-10 was observed in ICPP cases ($p=0.0011$) and PT cases ($p<0.0001$) as compared to control participants but there was no significant difference among ICPP cases and PT cases ($p=0.7507$) as shown in the Fig 1a. Similar trends were noted for NKB levels (Fig 1b). For NPY, no significant difference between ICPP and PT cases and control cases was observed (Fig 1 c).

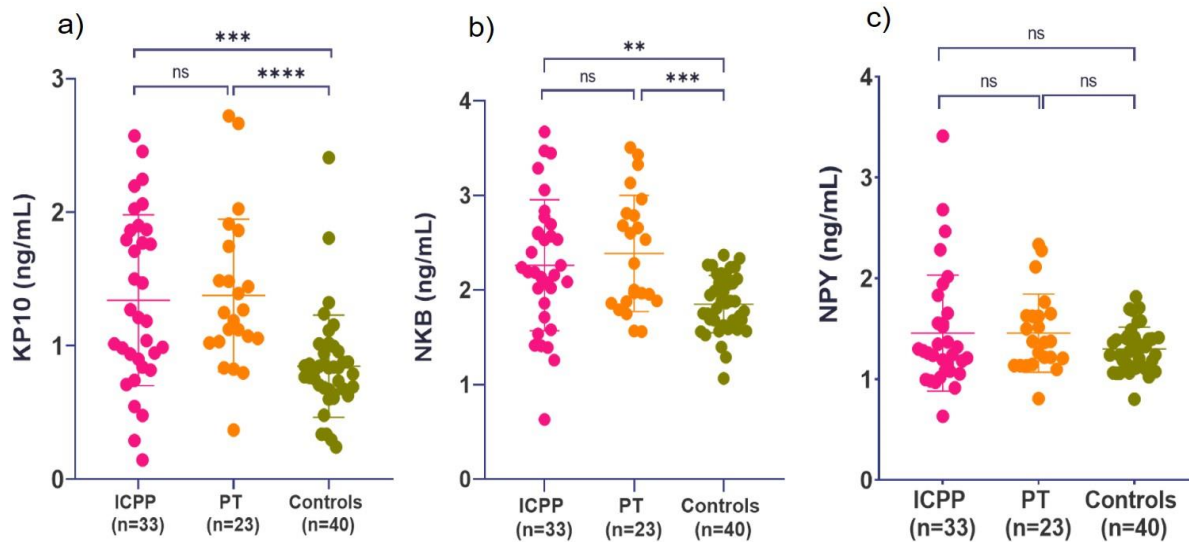


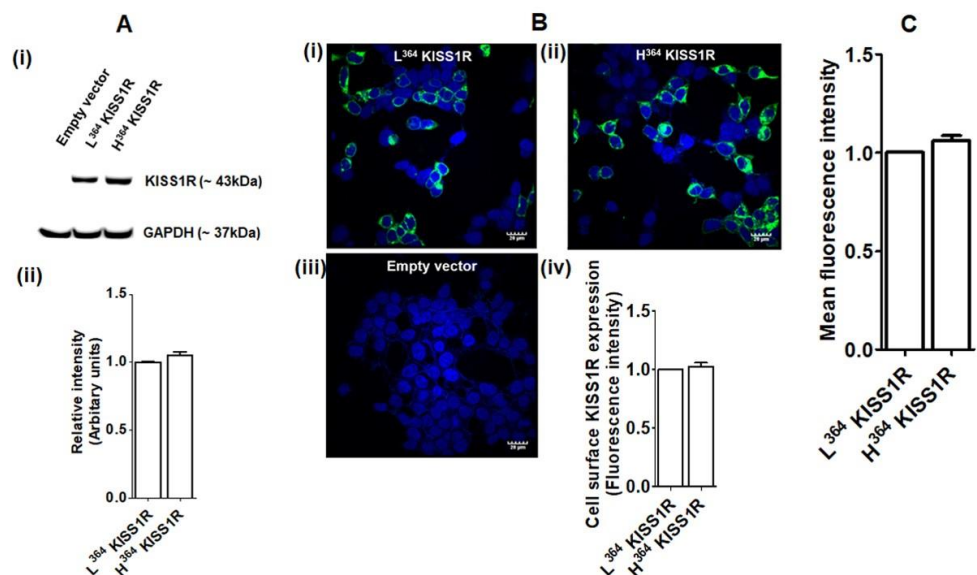
Figure 1: Estimation of Kisspeptin-10 (a), Neurokinin B (b), and Neuropeptide Y(c) levels. Data represents mean±SEM values where each dot represents a control participant and each square represents an ICPP case and each triangle represents a PT case. *Kit detection range 0-100ng/ml *The samples were processed in batches taking into consideration validity of the kits.

5.10 Role of Kisspeptin Mediated Signalling in Onset of Puberty (Partly Funded by Science and Engineering Research Board, Department of Science and Technology)

Principal Investigator : **Antara Banerjee**
 Co-Principal Investigator : Suchitra Surve, Bhakti Pathak
 Project Associate : Swati Kashikar
 Clinical Collaborator : Sudha Rao, Bai Jerbai Wadia Hospital for Children
 Mumbai
 Duration : 2021-2024

The neuropeptide kisspeptin-1 (KISS1) signals through its cognate G-protein coupled receptor, the kisspeptin-1 receptor (KISS1R); heralding the onset of puberty. Activating mutations in KISS1 or KISS1R are therefore implicated in idiopathic central precocious puberty. Functional studies on such naturally occurring mutations can provide a genotype-phenotype correlation. The H364 variant in KISS1R (homozygous) was identified in a girl with idiopathic central precocious puberty by whole exome sequencing. In vitro studies were carried out with the L364 KISS1R and H364 KISS1R constructs, in order to gain mechanistic insights into KISS1R dysfunction due to the H364 substitution that contributed to the pathophysiology of ICPP. Determination of total (Fig. 1A), cell surface KISS1R expression by confocal microscopy (Fig. 1B) and flow cytometry was carried out (Fig. 1C). The total as well as cell surface expression of H364 KISS1R was found to be slightly higher as compared to L364 KISS1R but not statistically significant.

Figure 1: (A) (i) Western blot depicting the total KISS1R expression of L364 KISS1R and H364 KISS1R twenty four hours post transient transfection in CHO cells revealed using an anti-KISS1R antibody (upper panel); GAPDH served as a loading control (lower panel). (A,ii) Densitometric analysis (mean $\pm$ SEM of 3 independent experiments) of the ratio of the levels of KISS1R normalized to GAPDH levels; the ratio obtained for L364 KISS1R was considered as one.



(B) Visualization of cell surface KISS1R expression by indirect immunofluorescence using an anti-KISS1R antibody. Confocal microscopy images (i-iii, Scale bar=20 μ M) demonstrates KISS1R (green) with nuclei stained with DAPI (blue). (B, iv) Graph depicts the mean $\pm$ SEM of the fluorescence intensity of the cell surface KISS1R expression across 30 cells. (C) Graph representing the mean $\pm$ SEM of three independent experiments for cell surface expression of L364 KISS1R and H364 KISS1R determined by flow cytometry; (B&C) the values obtained for L364 KISS1R were considered to be one.

Further, the effect of this receptor variant on kisspeptin-10 (Kp-10) evoked signalling responses were ascertained. It was observed that at the higher doses of Kp-10, an augmented signaling response was observed through H364 KISS1R as compared to L364 KISS1R in MAPK signaling response as well as IP1 production (Fig. 2). Thus, elevated levels of Kp-10 acting through H364 KISS1R most likely contributed to the manifestation of ICPP, providing further evidence that dysregulation of Kp-10/KISS1R axis impacts the onset of puberty. The functional characterization of this variant in KISS1R has been deposited in ClinVar (RCV003483648.1). Screening of a total of 32 exomes was carried out in the cohort of girls (n=58) with ICPP and the observed variants in KISS1/KISS1R are noted in Table 1. Functional studies for the variants will be undertaken.

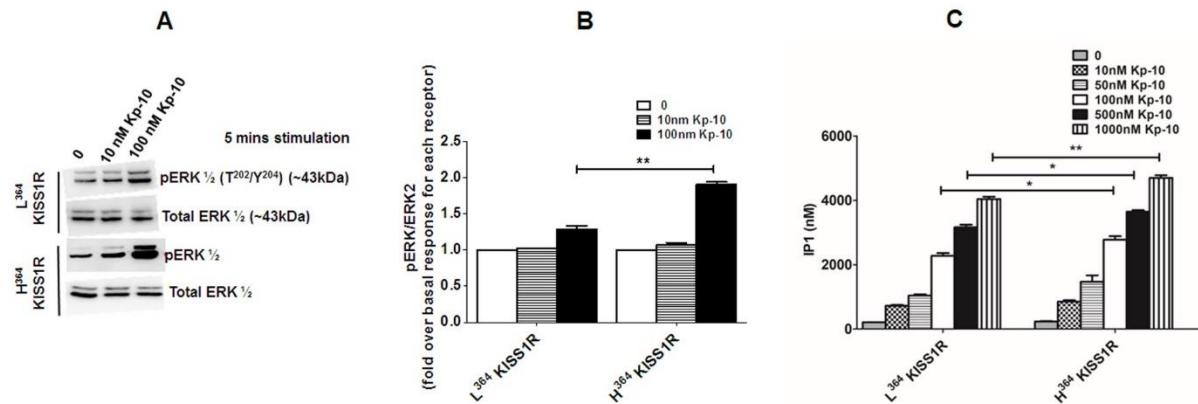


Figure 2: (A) Western blot of phospho-ERK1/2 levels (~43 kDa) normalized to total ERK1/2 levels (~43 kDa) in unstimulated condition (0) or post stimulation of L364 KISS1R or H364 KISS1R with either 10 nM Kp-10 or 100 nM Kp-10 for 5 minutes at 37°C. (B) Densitometric analysis (mean±SEM of three independent experiments) of the ratio of the levels of phospho-ERK1/2 to total ERK1/2 (pERK/ERK) plotted as a fold over basal response for each receptor. (C) Graph depicting the mean±SEM of three independent experiments of the levels of inositol phosphate production in unstimulated condition (0) or post stimulation of L364 KISS1R or H364 KISS1R with increasing doses of Kp-10, 10, 50, 100, 500 or 1000 nM Kp-10 for one hour at 37°C. *p < 0.05, **p < 0.01 with respect to L364 KISS1R; One-way ANOVA, Tukey's post hoc test.

Table 1: Variants in KISS1/KISS1R in girls with ICPP

Variant	SNP identifier	Number of cases harbouring the variant
L364H KISS1R	rs350132	31
P81R KISS1	rs4889	9
E20K KISS1	rs12998	5
Q36R KISS1	rs35431622	3

5.11 Delineation of the Role of Isoforms of Kisspeptin in Mammalian Reproduction (Partly Funded by Science and Engineering Research Board)

Principal Investigator : **Antara Banerjee**
 Project Associates : Aishwarya Chakraborty, Dhanashree Jagtap, B Kulkarni
 Duration : 2022-2024

Kisspeptins are neuropeptides that play a central role in mammalian reproduction by inducing puberty and regulating fertility. These neuropeptides are synthesized initially as a pro-peptide that undergoes cleavages to form four isoforms in humans. The kisspeptin isoforms in humans are kisspeptin-54 (Kp-54), kisspeptin-14 (Kp-14), kisspeptin-13 (Kp-13) and kisspeptin-10 (Kp-10). All four kisspeptin isoforms have a common decapeptide sequence towards the C-terminal. The smallest isoform, kisspeptin-10, can completely activate the Kisspeptin receptor (KISS1R) independently like the others. Several studies have been carried out to elucidate the role of Kp-54 and Kp-10, but there is lack of data on Kp-13 and Kp-14. In this study, we aim to carry out structural and functional characterization of the kisspeptin isoforms. In the reporting year, we carried out signaling studies post stimulation of KISS1R with various kisspeptin isoforms, Kp-10, Kp-13 and Kp-14 which were synthesized in-house by solid phase peptide synthesis and Kp-54 that was procured commercially. Activation of KISS1R leads to activation of phospholipase C that cleaves PIP2 to form IP3 which further gets processed to IP1. IP1 production was estimated in FK-31, a KISS1R expressing stable clone of CHO cells. FK31 was stimulated with the different isoforms of kisspeptin for one hour. Results revealed that Kp-10 and Kp-13 stimulation resulted in the highest IP1 production (Fig. 1). A multitude of phospho-kinases get activated post KISS1R activation which was delineated using a Proteome Profiler Human Phospho Kinase Array kit. Interestingly, Kp-13 induced phosphorylation of the substrates, namely, ERK, CREB and p53 was higher than that observed for other isoforms of kisspeptin (Fig. 2). Currently, validation of these targets as well as effect of these isoforms on other signaling cascades is ongoing.

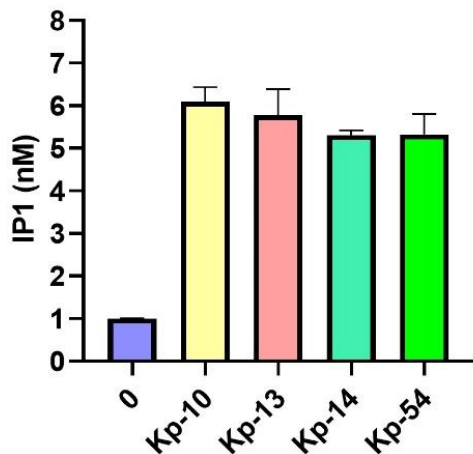


Figure 1: Inositol phosphate (IP1) levels (mean±SEM) post stimulation of KISS1 receptor expressing cells with vehicle (0) or 1mM each of kisspeptin isoforms for 1h using competitive ELISA. The values obtained for vehicle-treated cells were considered as 1.

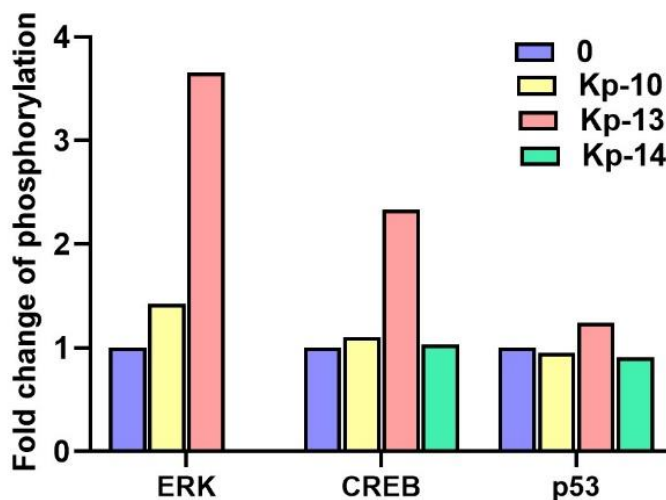


Figure 2: Fold change in the phosphorylation of ERK, CREB and P53 induced by kisspeptins in CHO cells stably expressing KISS1R. The values obtained for vehicle treated cells were considered as 1.

5.12 Determining the Prevalence and Risk Factors Associated with Precocious Puberty among Pre-pubertal Girls in Mumbai

Principal Investigator : **Suchitra Surve**
Co-Principal Investigator : Beena Joshi (Taken charge of PI since October 9, 2023)
Project Associates : Beena Joshi, Dipty Singh, Anushree Patil, Shahina Begum, Deepti Tandon, Varsha Tryambake, Rachana Dalvi, Sharmila Kamat
Collaborator : Sudha Rao, Bai Jerbai Wadia Hospital for Children, Mumbai
Duration : 2023-2025

The study is being implemented in a community based Child Health Clinic of ICMR-NIRRH. Screening is ongoing among five schools in vicinity of clinic, for which awareness sessions with parents have been taken. The girls in the age group of 6-9 years are being screened after taking appropriate assent and parental consent. Data in CRF and mother questionnaire are also being recorded. Each participant is being followed up at every three-month interval for noting further pubertal changes. The total 202 girls have been screened so far from these schools and 39 early puberty cases (Premature Thelarche) have been detected which are being evaluated at the collaborating B J Wadia hospital for Children. The endocrine disruptors will also be evaluated among diagnosed cases.

5.13 Study of Kisspeptin Receptor Oligomerization and its Functional Significance *(Partly funded by Board of Research in Nuclear Sciences)*

Principal Investigator : **Antara Banerjee**
Co-Principal Investigator : Bhakti Pathak, Dhanashree Jagtap
Project Associate : Vidhi Rathod
Collaborator : Vidita Vaidya, Tata Institute for Fundamental research, Mumbai
Duration : 2023-2026

G-Protein Coupled Receptors (GPCRs) form higher order homo di/oligomers. The oligomerization regulate the functions of GPCRs by expanding the repertoire of interacting partners and signaling pathways. The human kisspeptin-1 receptor (KISS1R) belongs to the family of GPCRs and plays a pivotal role in mammalian reproduction, however, information about its di/oligomerization status is lacking. The present study aims to delineate the homo di/oligomerization potential of KISS1R using in vitro model systems. Towards the same, Flag and HA epitope tagged KISS1R constructs were transiently co-transfected in CHO cells, followed by their detection using the respective anti-tag antibodies by western blotting. Co-immunoprecipitation studies were carried out post co-expression of Flag KISS1R and HA KISS1R constructs (1:1 ratio) in CHO cells. Immunoprecipitation with anti-Flag antibody followed by immunoblotting with anti-HA antibody (Fig. 1A) and vice versa (Fig. 1B) was carried out. Receptor dimerization was found to be constitutive in nature as the dimers could be detected in the absence of the cognate ligand (kisspeptin-1). Co-localization studies were carried out post transient co-expression of Flag KISS1R and HA KISS1R constructs (1:1 ratio) in CHO cells. Confocal imaging using fluorescently tagged anti-Flag and anti-HA antibodies provided a visual proof of localization of KISS1R monomers (Fig. 2) in the endoplasmic reticulum (ER) as evidenced by their

co-localization with calnexin (ER marker). Further, FRET studies are being carried out to confirm the formation of KISS1R di/oligomers.

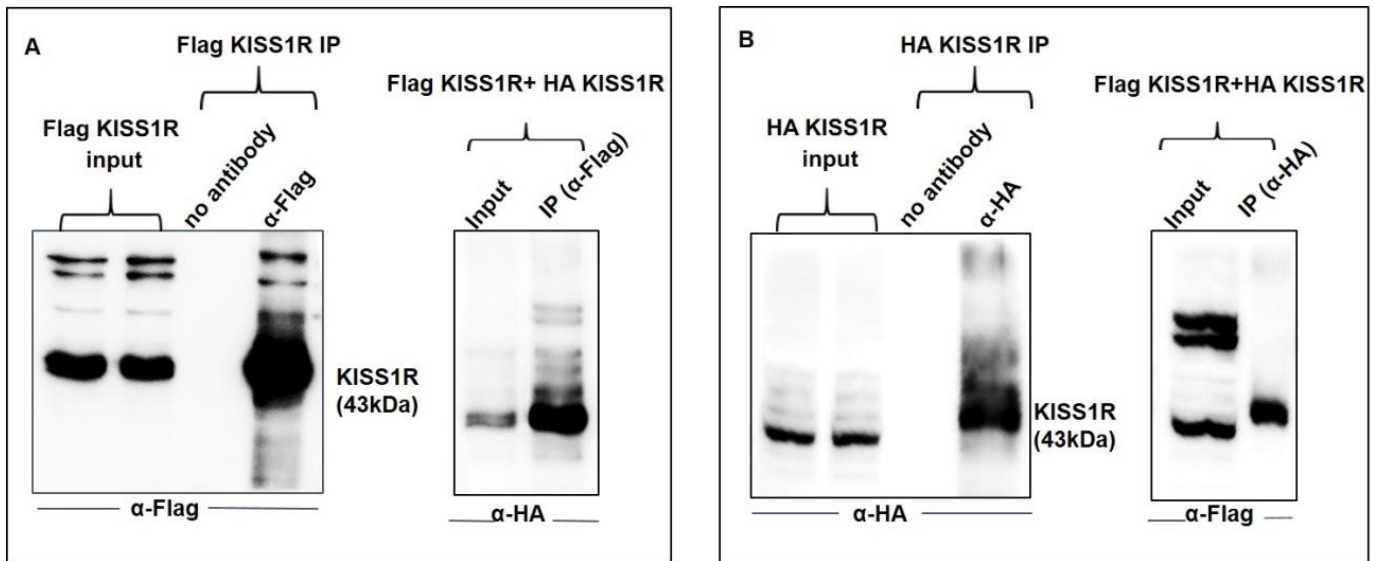


Figure 1: (A) Flag and HA tagged KISS1 receptors form di/oligomers as detected by coimmunoprecipitation experiments. Western blotting has been performed using anti-Flag and anti-HA antibodies as depicted in the image. Immunoprecipitated band of Flag KISS1R (Lane 4) is specific as determined using a 'beads only' control wherein no anti-flag antibody is added (Lane 3). In lane 7, both Flag as well as HA tagged KISS1 receptors have been co-transfected followed by immunoprecipitation with anti-flag antibody. Upon probing the blot with anti-HA antibody, the band of KISS1R is observed corresponding to KISS1R di/oligomers. (B) Reciprocal experiments were carried out by performing immunoprecipitation using anti-HA antibody.

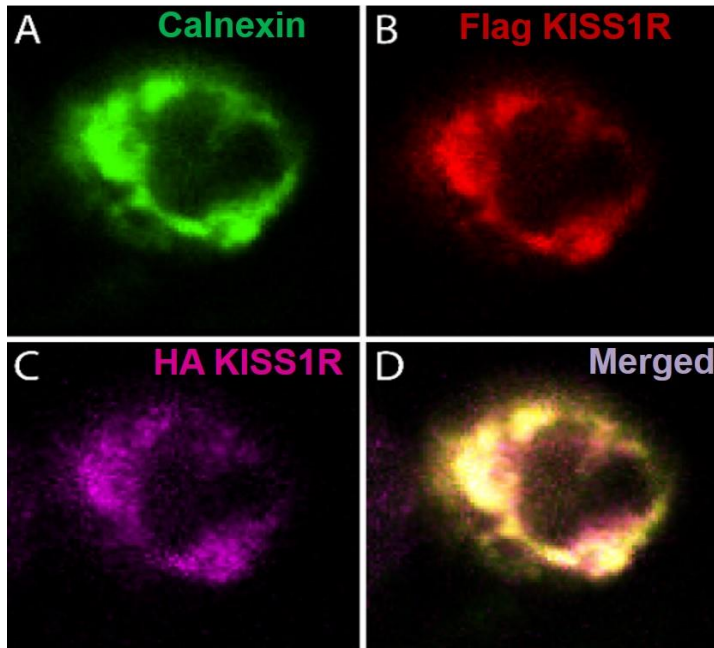


Figure 2: Visualization of Flag and HA tagged KISS1 receptors by colocalization studies. Direct immunofluorescence has been performed using anti-Flag alexa 594 (Panel B) and anti-HA alexa 633 (Panel C) fluorescent antibodies as depicted in the image (60X magnification; 3X zoom). Calnexin staining (Panel A) is carried out to visualize the endoplasmic reticulum. Merged image (Panel D) reveals the co-localization of Flag and HA tagged KISS1 receptors and their presence in the endoplasmic reticulum.

5.14 Investigating the Role of Microdeletion Syndrome in Neuronal Functions using Induced Pluripotent Stem Cells

Principal Investigator : **DK Das**
Co-Principal Investigator : S Pande
Project Associate : B R Shekhar
Duration : 2023-2028

Copy number variations (CNVs) across the human genome lead to numerous genetic disorders involving majorly cognitive and psychiatric issues. These regions harbor many genes or a critical region of genome which collectively impart serious effects on the pathology of the disorders. Various microdeletions affecting neuro-developmental and neuro-psychiatric disorders are of our interest in this project. The objective of the study is to generate iPSCs from patients with microdeletion syndrome and differentiate them into cortical neurons. Structural and functional defects in neurons derived from patients will be assessed. We previously reported that a deletion of 7q35-36.1del encompassing CNTNAP2 gene in two affected siblings with schizophrenia. (Annual report 2022-23, p.104) iPSCs were generated from the two sisters and differentiated to neurons. It was observed that the average neurite length in patient neuron increased by 47.64%. Among other variables, the soma area and volume were reduced by 43.74% and 20.26% respectively. Although, the neurite length in the patient neuron increased, neurite branching was found to be decreased by 15.69%. Dendritic arborisation is a crucial process for synaptic connection and is assessed by dendritic branch number. This analysis revealed that dendrite branch number was reduced by 18.24% in patient neurons and dendritic length was also shortened by 50.82% (Fig. 1a). Further spine morphology was analysed using Imaris spine classification extension and MATLAB. Altogether, total number of all four types of spines were decreased in patients' neurons (stubby: 41.09%; mushroom: 11.83%; long thin: 20% and filopodia: 59.31) (Fig. 1b). However, the contributions of each four types of spines to the total number of dendritic spines were variable. It was observed that there was no significant change in stubby form (52.05 % in control and 53.7% in patient) whereas percent contribution of mushroom type was found to be reduced from 18.5% in control to 5.67 % in patient, while long thin form was reduced from 72.5% in control to 36.55% in patient. In contrast to the other types, filopodia spine percentage was found to be increased in patient (22.75% in patient and 15% in control). To identify molecular pathology in patient's neurons, transcriptomics of mature iPSCs derived neurons was studied. All the differentially regulated genes in both the patients (7144) were taken into account to identify enriched pathways. The pathway analysis identified some of the important processes such as ECM receptor interaction, Glutamatergic synapse etc (Fig. 2a). Upon prioritisation top 7 upregulated and downregulated genes were taken along with CNTNAP2 for further validation. These 14 genes were then analysed in Genemania for interactive pathway. This analysis revealed that CNTNAP2 is co-expressed with 8 genes namely PADI2, LHX2, TTR, LARGE1, HOXB1, GSG1L, MAPT and EPHB6. The expression of these genes was validated using RT-PCR (Fig. 2b).

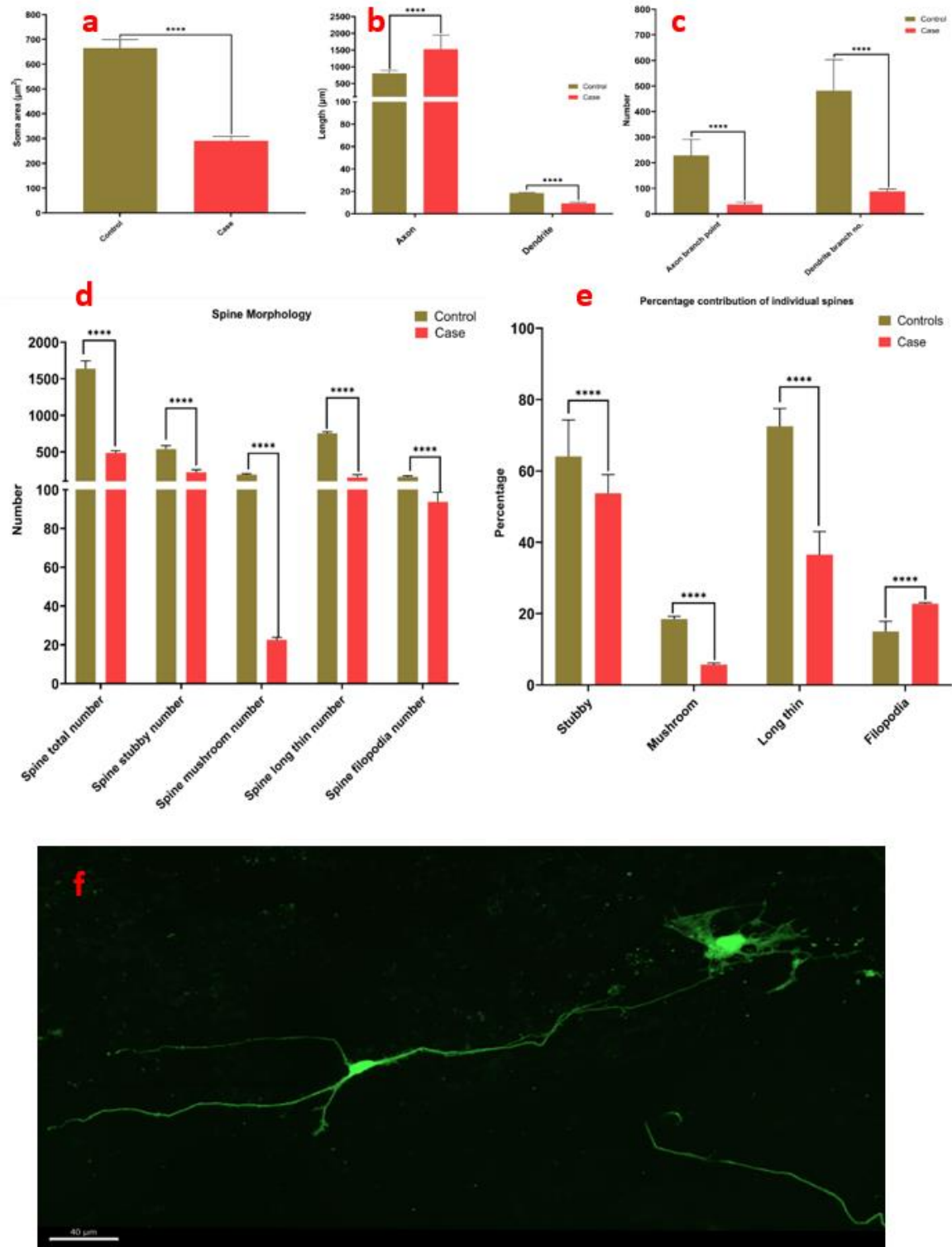


Figure 1: Morphometry of iPSCs derived neurons cultured for 120 days. a. Soma area of matured neurons; b. axon and dendrites length; c. Number of branch point of axon and dendrites; d. Spine morphology in cases and control. Analysis of dendritic spine characteristics (n= 40, Two-way ANOVA was used for statistical analysis $P = 0.0001$); e. percent contribution of four types of dendritic spine; f. eGFP transfected cultured neurons (Z- series projection captured at intervals of $0.3\mu\text{m}$ depth with 60X magnification).

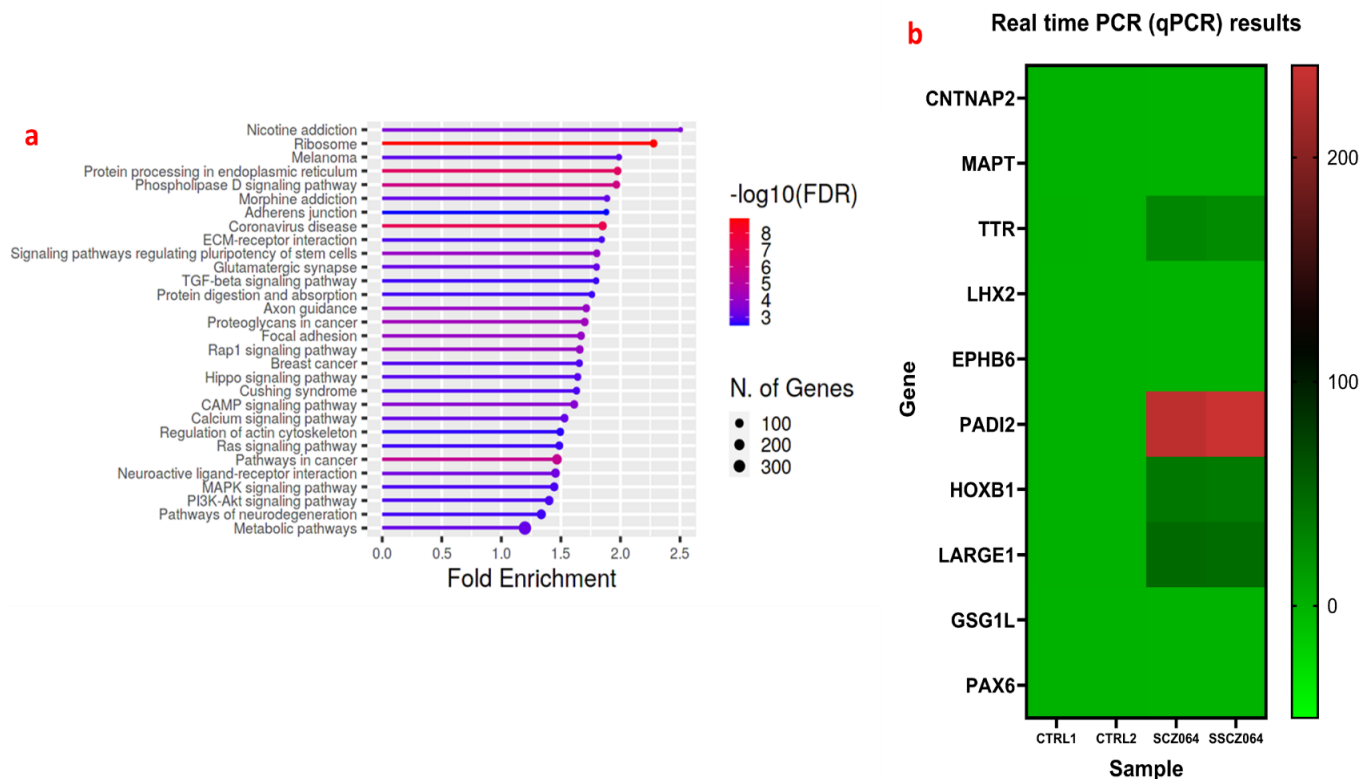


Figure 2: Transcriptome analysis of iPSCs derived matured neurons. a. Top enriched pathways showing significant number of genes involved; b. Realtime PCR results of top upregulated and down regulated genes that showed interaction with CNTNAP2 depicted using heatmap.

6. REPRODUCTIVE CANCERS

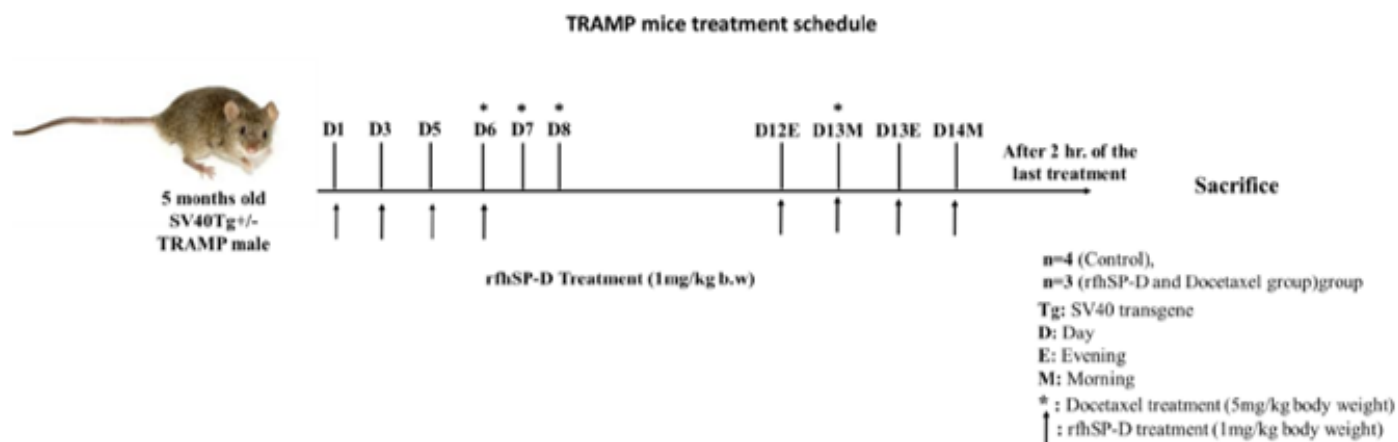
6.1 Investigating the In Vitro and In Vivo Potential of rfhSP-D to Inhibit Prostate Cancer Metastasis and Mechanistic Involvement of GRP78

Principal Investigator : **Taruna Madan**
Project Associates : R Subedi, SM Metkari
Duration : 2021-2024

Surfactant Protein D (SP-D) is among the most studied soluble Pattern Recognition Receptor (PRR). It is involved in host defense against pathogens and allergens, and immunomodulation. Previous studies from our group reported induced apoptosis in the tissue explants from patients of metastatic prostate cancer (Annual report 2017-18). Furthermore, our research (Annual report 2021-22) has shown that treatment with rfhSP-D results in a concentration-dependent reduction in the migration of PC3 and LNCaP cells. Additionally, we observed that rfhSP-D treatment leads to a decrease in the cell invasion, and an increase in the expression of GRP78, a chaperone (Annual report 2012-23).

Hereafter, the study administered rfhSP-D treatment to TRAMP mice according to the protocol outlined in Fig. 1a. The results showed that rfhSP-D treatment caused an increase in necrotic cells and a decrease in viable cells in the prostate tissue. Interestingly, similar effects were also observed in the prostate tissue of TRAMP mice treated with docetaxel (Fig. 1b). In addition to its effects on prostate tissue, treatment with rfhSP-D increased the number of circulatory NK-cells, MDSCs, and inflammatory monocytes. Furthermore, rfhSP-D treatment was associated with a reduction in body weight, which was comparable to the effects observed in the Docetaxel group (Fig. 2). In summary, the in vitro and in vivo experiments strongly support the potential of rfhSP-D as an anti-cancer and anti-metastatic agent.

a



b

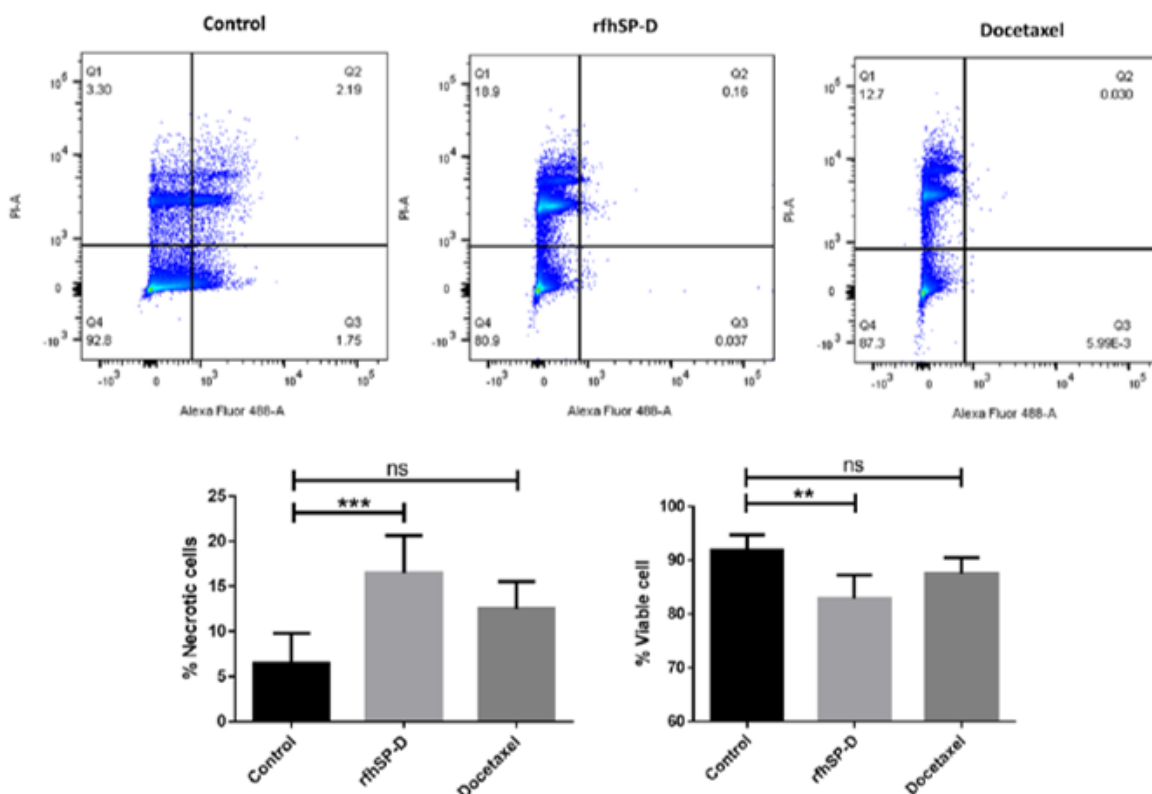


Figure 1: (a) rfhSP-D and Docetaxel treatment schedule for TRAMP mice. (b) Increase in cell death in prostate tissue of TRAMP mice treated with rfhSP-D and Docetaxel

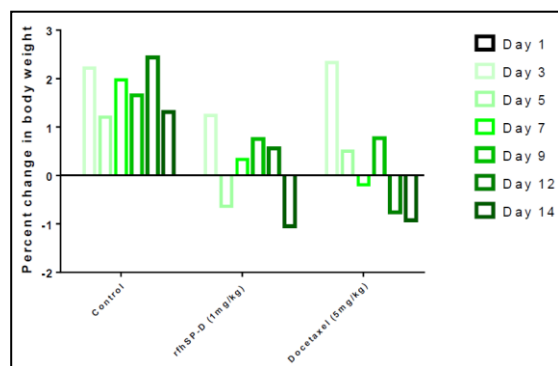


Figure 2: Changes in the body weight of TRAMP mice treated with rfhSP-D and Docetaxel (positive control). Body weight was measured every alternate day since the start of the rfhSP-D administration.

6.2 Investigating the Key Elements in Estrogen Signaling and their Contribution to Prostate Cancer

Principal Investigator : **Geetanjali Sachdeva**

Project Associates : Junita Desouza, S M Metkari, V Patel, U Chaudhari

Collaborators : G Bakshi, S Menon, M Pal, N Sable, Tata Memorial Hospital, Mumbai
S Patwardhan, A Joshi, G Fernandes, GS Medical College & KEM Hospital, Mumbai

Duration : 2021-2027

GP-1 (G-Protein coupled Estrogen Receptor 1) a membrane receptor, is reported to bind estrogen. GP-1 is reported to have a cell context dependent role; in some cancers it has pro-tumoral functions while in others it has anti-tumoral functions. GP-1 functions have been gaining relevance in the pathophysiology of prostate cancer (PCa), the second most common cancer diagnosed in men. GP-1 activation by G1 (an agonist) leads to the inhibition of cell proliferation in different prostate cancer cell lines in-vitro and in-vivo. Clinical studies, although few, have reported GP-1 protein expression to be high in grade 2 and 3 tumors followed by a decrease in grade 4 tumors. Further, GP-1 expression is found to be lower in primary tumors compared to metastatic cases. Thus, GP-1 is postulated as a potential therapeutic target. Previously we demonstrated that GP-1 silencing in PC3, an androgen independent cell line, led to increased migration and invasion (Annual report 2021-2022, pp 98). Further, we demonstrated higher GP-1 expression at the high-grade intraepithelial neoplasia (HGPIN) stage compared to respective age-matched control TRAMP mice (Annual report 2022-2023, pp 113). Thus, targeting GP-1 at an early stage may be beneficial in prostate cancer. In the reporting year, RT² profiling was carried out to identify GP-1 regulated tumor metastasis associated molecules. A dysregulation in the expression of 16 metastasis associated genes was found. Out of which, 8 were significantly upregulated and 8 were significantly downregulated (Fig. 1). Further, the activity of MMP-9, which was found upregulated was validated using zymography. We also designed a study to administer TRAMP mice with G1 at HGPIN stage to understand its effects on cancer progression. We found a significant reduction in tumor size when mice were administered 2 and 4 mg/kg body weight G1, compared to vehicle or 0.5 mg/kg body weight G1 dose (Fig. 2). On histological analysis, the prostates of 2 and 4 mg/kg body weight G1 administered animals depicted HGPIN features while vehicle control depicted Poorly Differentiated Carcinoma (PDC). Thus, G1 administration prevented PDC development in TRAMP mice.

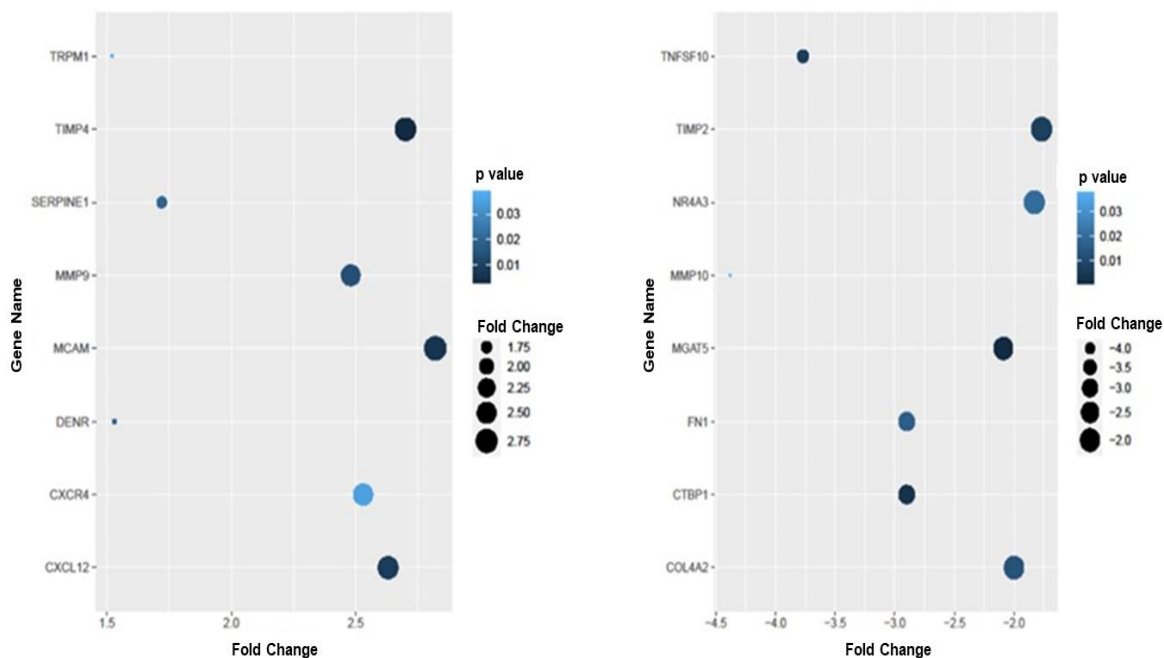


Figure 1: Bubble plot depicting significantly dysregulated genes A) genes displaying an upregulation in their expression and B) genes displaying a downregulation in their expression as identified by RT 2 profiler array.

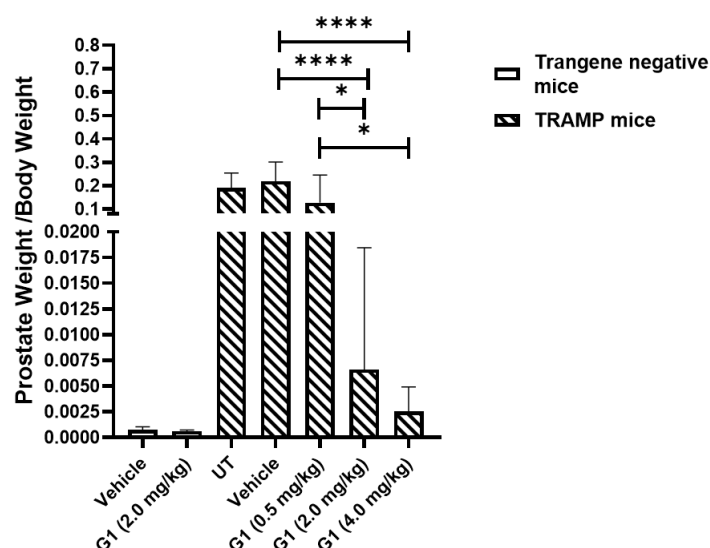


Figure 2: G1 prevents prostate cancer progression in TRAMP mice. Graph depicts prostate weight / total body weight at 5 months of age post administration of G1 at different concentrations (0.5, 2.0 and 4.0 mg/kg body weight). Each group had at least 5 animals. UT denotes animals that were not treated whereas 'vehicle' presents data from animals treated with DMSO. The data were analyzed using one-way ANOVA and Tukey Post-hoc test.

* denotes significance $p < 0.05$. **** denotes significance $p < 0.0001$.

6.3 Utility of Estimating Serum PSP94 Levels in Management of Patients with Raised PSA in Clinical Setting: A Multicentric Study (Partly Funded by ICMR-Intramural)

Principal Investigator : **Dhanashree Jagtap**

Co-Principal Investigators : A Arora, Bhakti Pathak, Antara Banerjee

Project Associates : B Kulkarni

Duration : 2024-2027

Prostate cancer (PCa) screening is done by digital rectal examination and Prostate Specific Antigen (PSA) test. PSA is one of the major proteins secreted by the prostate and serum concentration of PSA is used worldwide to diagnose PCa. However, PSA test has low specificity for PCa since PSA also increases in non-malignant conditions such as benign prostatic hyperplasia (BPH) and prostatitis. Various approaches to increase the specificity of PSA are being studied. Prostate Secretory Protein of 94 amino acids (PSP94) has emerged as a promising serological marker along with PSA for differential diagnosis of BPH and PCa. We have developed specific, sensitive and cost-effective in-house ELISA for measuring serum PSP94 concentrations. We had tested novel diagnostic strategy of using serum PSP94/PSA ratio in our earlier retrospective study using limited number of biopsy confirmed PCa and BPH cases. Results indicated that serum PSP94/PSA ratio had increased specificity over identical PSA sensitivity. Our studies in patients with lower urinary tract symptoms revealed that on the basis of PSA alone, 100% of participants in PSA range of 4-20 ng/ml were recommended for biopsy whereas if ratio of PSP94/PSA had been used, ~50% of prostate biopsies could have been avoided. The aim of the study is to ascertain the utility of estimating serum PSP94 levels in management of patients with raised PSA in clinical settings at multiple centers across India. Human seminal plasma (5mL) was used to purify PSP94 using a standardized protocol (Fig. 1). Peak 1 obtained on RP-HPLC when resolved on 10% SDS-PAGE followed by silver staining and immunoblot using anti-PSP94 (1:3000) confirmed it to be PSP94 (Fig. 1). This will be used as immunogen for raising for polyclonal antibodies for further study.

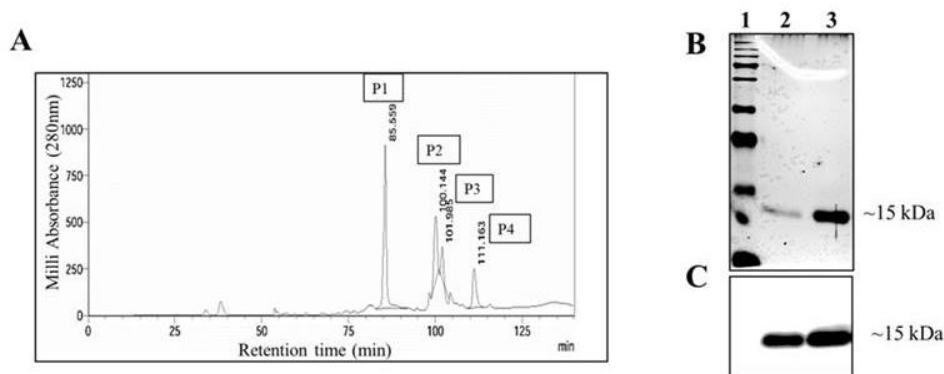


Figure 1: Purification of PSP94 from human seminal plasma. Bound fractions eluted from phenyl sepharose column were loaded onto RP-HPLC (C18 column) which showed four peaks (A). Peak 1 (P1) having retention time of 85.5 min was resolved on 10% SDS PAGE followed by silver staining (B) and was further immunoblotted with anti-PSP94 antibody (1:3000) (C); lane 1: Marker, lane 2: PSP94 standard (20 ng) and lane 3: Peak 1 (85.5 min). Protein band of ~15 kDa was observed corresponding to PSP94.

6.4 Role of Toll-like Receptors and TLR Agonists in Modulating Response to Chemotherapy in TNBC Patients *(Partly funded by DBT-BIOCARE)*

Principal Investigator : **Nupur Mukherjee**
 Co-Investigator : Taruna Madan
 Project Associate : Rushigandha Salunke
 Collaborator : Shalaka P Joshi, Tata Memorial Hospital, Mumbai
 Duration : 2019-2024

Triple Negative Breast Cancer (TNBC) is a subtype of breast cancer (BC) that lacks hormone receptors (ER/PR/Her2). Based on current studies, TNBC is now considered to be a highly immunogenic subtype of breast cancer, making it a good candidate for treatment with immunotherapeutic approaches. Members of TLR (Toll-like receptor) family of pattern recognition receptors (PRR) have been previously associated with immunoregulatory roles and chemotherapy response in TNBC and other cancers. Previously, we reported differences in TLR expression across TNBC tumors and cell lines with significant differences in TLR4 expression in TNBC tumors having high Tumor-infiltrating lymphocytes (TILs) and low density of TILs. To further evaluate the immunomodulatory potential of TLR4 within TNBC-Tumour Micro Environment (TME), we examined its correlation with expression of pro-inflammatory cytokines such as TNF, IFNG, IL1B, IL6 and anti-inflammatory cytokines such as TGFB3, TGFB2, TGFB1, IL13 and IL10 (that are known to be associated with TLR4 signaling pathway) in TNBC-TCGA tumors (n=180). Our analysis revealed the strongest correlation of TLR4 transcript expression with IL10 ($r=0.47$), an anti-inflammatory cytokine and IFNG ($r=0.47$), a pro-inflammatory cytokine (Fig. 1A). A weak correlation was observed between TLR4 and IFNG ($r=0.15$) in TNBC tumor samples (n=10) analysed in the study (Fig. 1B). On further segregating the TCGA-TNBC cohort into CD45 (PTPRC) high / CD45-moderate/ CD45 low tumors, a different pattern for association of TLR4 with pro- and anti-inflammatory cytokines was found. The CD45+ high TNBC tumors (representative of TIL enriched (TNBC) showed the strongest association of TLR4 expression with both anti-

inflammatory cytokines like IL10 ($r=0.52$), and proinflammatory cytokines like IL1B ($r=0.38$) cytokines. In CD45+ moderate TNBC tumors (representative of moderate TIL TNBC), highest correlation of TLR4 expression was observed with anti-inflammatory cytokines like TGFB1 ($r=0.4$) and TGFB3 ($r=0.4$). While in CD45+ low TNBC tumors (representing low TIL TNBCs), a strong correlation of TLR4 expression was observed with immunosuppressive cytokines such as IL10 ($r=0.5$), TGFB 1($r= 0.5$), and TGFB3 ($r= 0.6$). This implicates a potential immunomodulatory role of TLR4 in regulating tumor-immune microenvironment that differentially responds in immunologically active (TIL/CD45 high) or cold (TIL/CD45 low) TNBC tumors. On further comparing the survival probability of TNBC patients with respect to TLR4 expression in TCGA-TNBC datasets, tumors with high TLR4 and IFNG expression had prolonged survival compared to patients with low expression of IFNG/TLR4 (Fig. 2A). Further analysis showed TNBC tumors with high TIL count along with high TLR4/IFNG expression had better probability of survival compared to those with low TLR4/low TIL count/ low IFNG expression (Fig. 2B). Taken together, our data highlights the potential role of TLR4 in regulating TNBC immune microenvironment and its prognostic importance in TNBC patients.

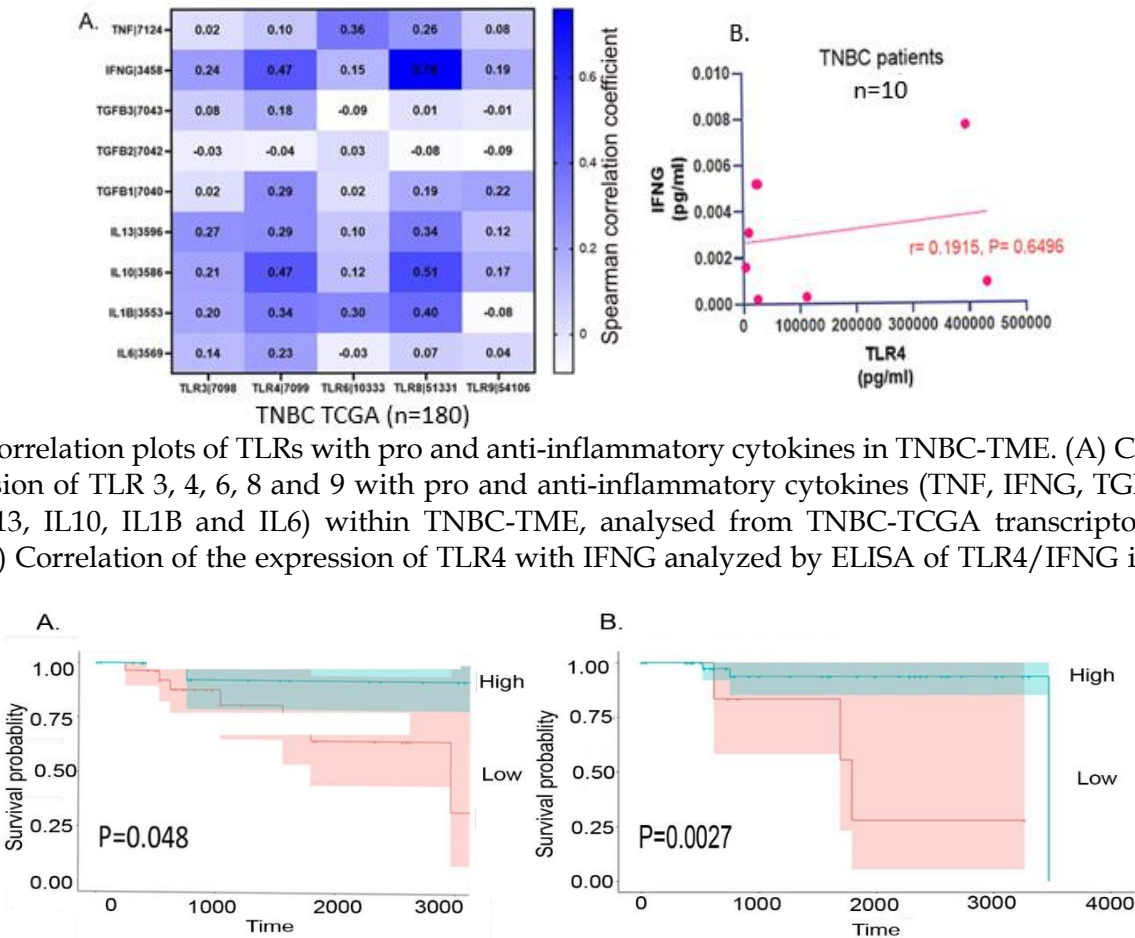


Figure 2: Kaplan-Meyer analysis of survival probabilities of TNBC patients with (A) high IFNG expression along with high TLR4 expression (B) high IFNG and TLR4 expression along with high CD45 expression (representing TIL dense TNBC tumors) as analysed from TNBC TCGA transcript dataset of TNBC patients (n=180).

6.5 Identification of Circulating microRNA Signatures as Diagnostic Markers for Early Stage and Metastatic Breast Cancer *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : **Sadhana M Gupta**
Project Associate : Shreya Thakkar
Collaborators : S Mehta, Saifee Hospital, J Anam, Surgical Speciality Oncology Hospital; V Maniar, Mumbai Oncocare Hospital
Duration : 2021-2024

The aim of the study is to identify circulating microRNA in the serum samples of breast cancer (BC) patients to identify markers for diagnosis of early stage and metastatic breast cancer. 120 BC and 30 normal healthy controls have to be enrolled for this study. The participants were divided into 4 groups, according to their molecular subtypes i.e. Luminal A (ER+, PR+ and HER2-), Luminal B (ER+, PR- and HER2), HER2 positive and Triple Negative (ER-, PR- and HER2-). So far, 90 BC and 30 healthy controls have been recruited. The NGS analysis of 32 serum samples (23 BC and 9 healthy controls) revealed that out of 1324 differentially abundant miRNAs, 30 miRNAs displayed statistically significant difference. Of these, 14 miRNAs were upregulated and 16 were downregulated in BC, compared to healthy women. Furthermore, miRTarBase database was used to identify the targets of all the differentially expressed miRNAs. The enrichment analysis of all the target genes indicated their enrichment in cancer-related pathways such as Wnt, Akt, Hippo, p53, and VEGF pathways. Significantly differentially abundant miRNAs (hsa-miR-4306, hsa-miR-200a-3p, and hsa-miR-125b-5p) were validated by real-time PCR. We report that hsa-miR-4306 ($p < 0.0001$), hsa-miR-200a-3p ($p = 0.0002$), hsa-miR-125b-5p (Fig. 1A, B, C) were significantly down-regulated in the sera of BC as compared to healthy controls, confirming the NGS data. These microRNAs were further validated in the breast tissues of 25 BC and 25 adjacent normal tissues by real-time PCR. The analysis showed significant downregulation in the expression of miRNAs-hsa-miR-4306 ($p = 0.0387$), hsa-miR-200a-3p ($p = 0.0378$), hsa-miR-125b-5p ($p < 0.0478$) (Fig. 1D, E, F) in BC tissues as compared to adjacent normal tissue. The target gene identification of selected miRNAs was carried out using miRTarBase. Out of all the target genes, we selected the genes associated with Wnt and Hippo pathways, reported to be involved in cancer metastasis and progression. The selected genes for hsa-miR-4306 was GSK3 β , for hsa-miR-200a-3p, YAP1 and β -catenin and for has-miR-125b was TAZ. The expression analysis of the target gene was carried out in 25 BC tissues and 25 normal adjacent tissues. We found that GSK3 β ($p = 0.0310$), YAP1 ($p = 0.0495$), β -catenin ($p = 0.0324$) and TAZ ($p = 0.0166$) (Fig. 1G-J) were significantly upregulated in BC tissues as compared to adjacent normal tissues. A second batch of 28 samples was sent for NGS and all the 60 samples were analyzed in subtype specific manner. In Luminal A subtype, out of 10 significantly expressed miRNA, 2 were upregulated and 8 were downregulated. Total 58 miRNAs were significantly expressed in Luminal B, out of which 15 were upregulated and 43 were downregulated. In HER2 patients, 23 miRNAs were significantly expressed; out of which, 15 were upregulated and 8 were downregulated. In TNBC, total 40 miRNAs were significantly expressed. Out of these, 9 were upregulated and 31 were downregulated. GO enrichment and KEGG analysis were carried out for all miRNAs (Fig. 2). Significant cancer-related pathways will be determined and genes associated will be validated. Novel miRNAs identified will be annotated and added to the miRBase database.

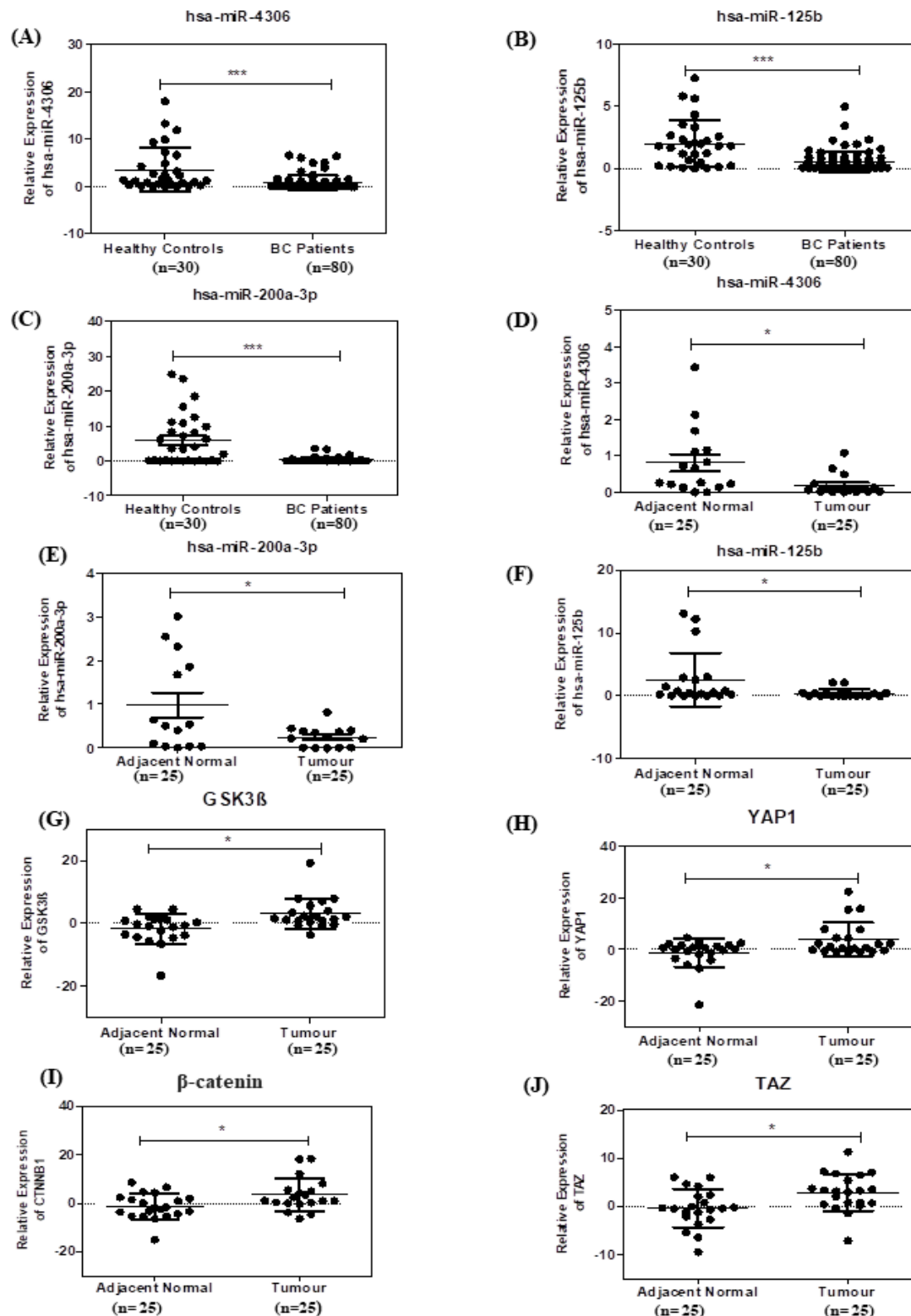


Figure 1: Relative levels of miRNAs hsa-miR-4306, hsa-miR-125b and hsa-miR-200a-3p in the sera (A-C) and tissues (D-F) of BC and controls. Relative expression of genes GSK3 β , YAP, β -catenin and TAZ is shown in panels G-J. * $p < 0.05$, *** $p < 0.001$

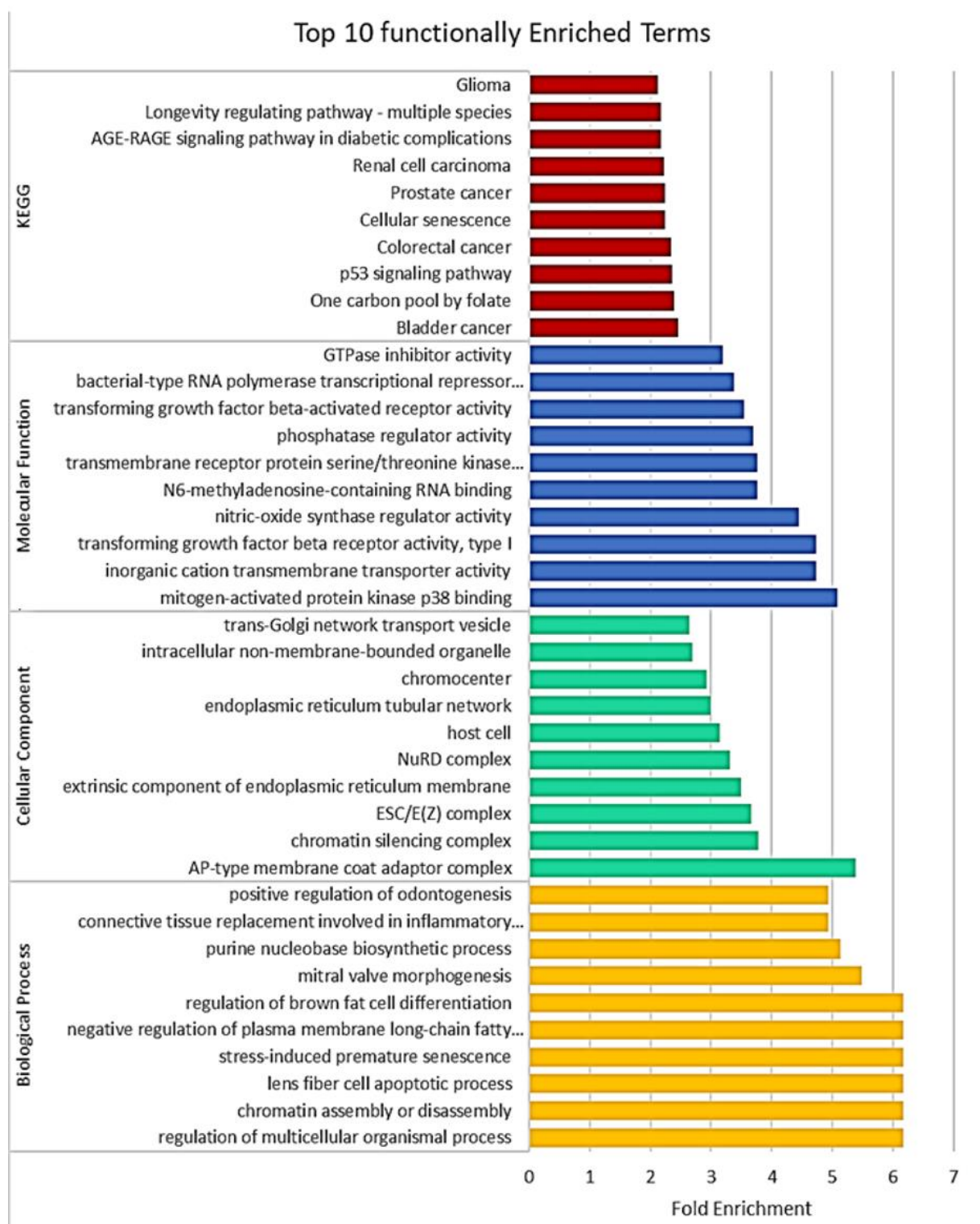


Figure 2: KEGG and Gene Ontology (GO) analysis of miRNA target genes. Abbreviation: KEGG- Kyoto Encyclopaedia of Genes and Genomes. Enriched terms were filtered based on p-value less than 0.05, and top 10 significantly enriched terms in each category were plotted against fold enrichment.

6.6 Analysis of Molecular Cargo and Paracrine Effects of Extracellular Vesicles Secreted by Ovarian Cancer Cells

Principal Investigator : **Bhakti R Pathak**
Project Associates : Meghali Borkotoky, Ananya Breed, Dhanashree Jagtap, A Banerjee
Duration : 2021-2027

Majority of the ovarian cancer cases are diagnosed at an advanced stage with disease spread in the peritoneal cavity in the form of ascites. Tumor cell derived extracellular vesicles (EV) cargo play a pivotal role in intercellular communication, fostering tumor spread and metastasis. Despite this understanding, extensive characterization of EV cargo for its potential diagnostic / prognostic / therapeutic utility in ovarian cancer remains limited. Hence, this study seeks to characterize the proteomic and transcriptomic profiles of EVs derived from ovarian cancer cell lines and assess their paracrine effects. Comparison of proteomic profiles of EVs liberated from 2D and 3D grown EVs was undertaken in the reporting year.

While traditional 2D cell cultures have been widely employed in studies of cancer cells, it is well-documented that they do not faithfully recapitulate the in vivo conditions. 3D cultures bridge the gap between 2D cell culture and animal models. In the previous year, we reported morphological and molecular characterization of EVs derived from 2D and 3D OVCAR4 cultures via TEM (Transmission Electron Microscopy) and immunoblotting respectively. Upon subjecting them to label-free quantitative proteome identification, EVs from 2D and 3D grown OVCAR4 cells yielded total 2597 and 2476 proteins respectively. Of these, 1489 proteins were upregulated in 3D derived EVs and 915 proteins were upregulated in 2D derived EVs. These lists of proteins were subjected to Gene Ontology (GO) Analysis. Response to wounding, small molecule metabolic process, vesicle mediated transport and peptide metabolic processes are some of the biological processes found to be enriched in 3D cultures. These pathways define the ways in which 3D culture and in turn in vivo tumors differ from the conventional 2D culture. The comparison also sheds light on major pathways to focus on while using 3D culture as preclinical models.

On the other hand, EV proteome of 2D grown OVCAR4 cells was enriched in lipid modification, lipid biosynthetic processes, intracellular protein transport and catabolic processes (Fig. 1). Further, 212 proteins in 2D EVs and 91 proteins in 3D EVs were found to be exclusive to the respective condition. Out of them, 27 proteins of 2D derived EVs and 23 from 3D derived EVs were found to be significantly upregulated. Three proteins of 3D-EV cargo were taken for validation by immunoblotting. All 3 proteins were detected by immunoblotting in the EVs of OVCAR4 cells grown in 2D as well as 3D condition but only one of them (labelled as 3D-EV1) was differentially upregulated in 3D derived EVs than 2D derived EVs not just in OVCAR4 but also in OVCAR5 cells. Interestingly, literature indicated that overexpression of 3D-EV1 is correlated with poor prognosis of cancer patients. The candidate proteins from comparative analysis will further be validated in animal model of ovarian cancer.

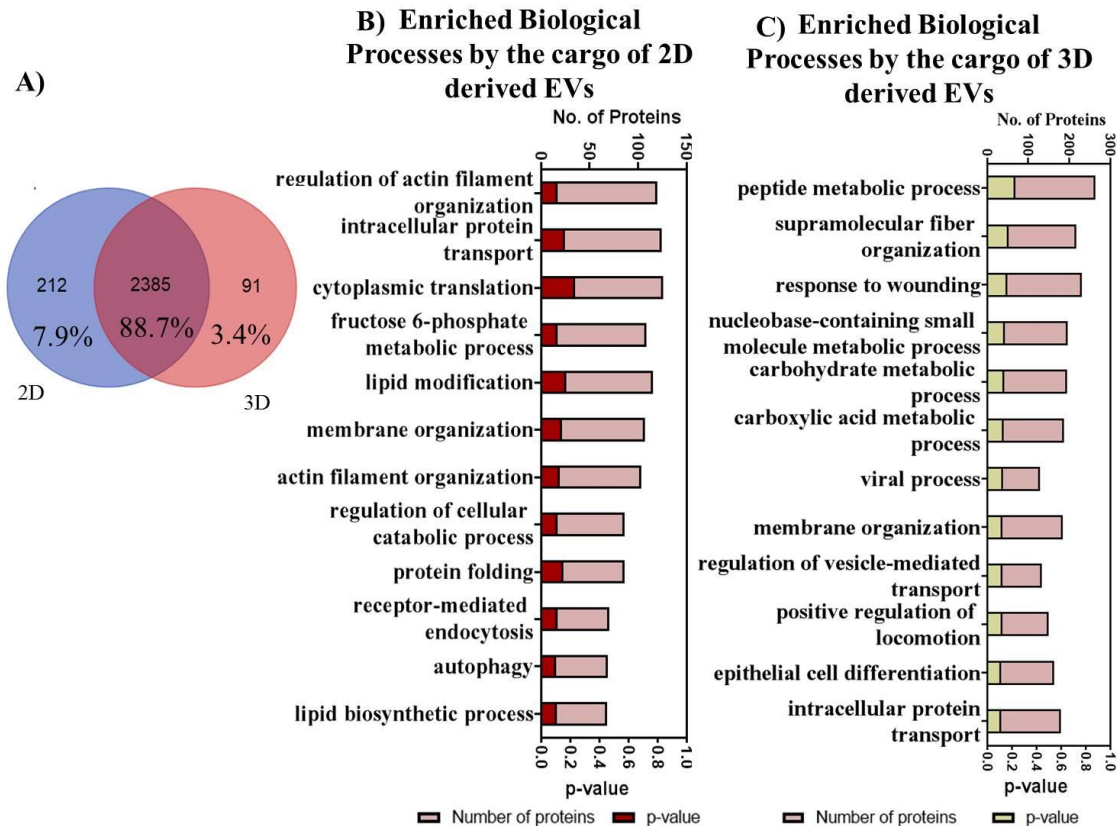


Figure 1: Global proteomic analysis of EVs derived from 2D and 3D grown cells of OVCAR4: (A) Venn diagram representing common and unique proteins present in the EVs derived from 2D and 3D grown OVCAR4 cells. 7.9% of total identified proteins were exclusively present in EVs derived from 2D grown cells and 3.4 % were exclusive to EVs derived from 3D grown cells of OVCAR4 (B) and (C) Bar graph represents biological processes (Gene Ontology analysis) that were enriched in EV proteome of 2D (915 proteins) and 3D (1489 proteins) grown OVCAR4 cells. Top 12 biological processes are represented based on p-value (right Y-axis) and number of proteins (left Y-axis)

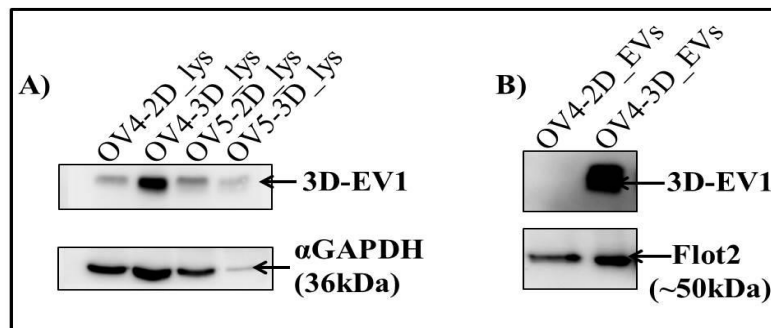


Figure 2: Detection of 3D-EV1 protein in the lysates of 2D and 3D given OVCAR4 and OVCAR5 cells (A) Total proteins from OVCAR4 and OVCAR5 cells grown under 2D and 3D condition were tested for 3D-EV1 protein which is upregulated in 3D culture conditions of both the cell lines. GAPDH was shown as a loading control for cell lysates (B) Immunoblot showing upregulation of 3D-EV1 protein in EVs derived from 3D grown OVCAR4 cells. Flotillin 2 was used as a loading control for EV proteins

6.7 Assessing Trop2 Expression and its Correlation with the Anti-Trop2 Immune Status in Ovarian Cancer Patients

Principal Investigator	: Bhakti R Pathak
Project Associates	: Ananya Breed, B Kulkarni, Madhulika Bajaj, Dhanashree Jagtap
Collaborators	: Amita Maheshwari, B Rekhi, Tata Memorial Hospital, Mumbai
Duration	: 2017-2024

Ovarian cancer is often diagnosed at an advanced stage where patients often show presence of ascites. Trop 2 is a transmembrane glycoprotein which is expressed in normal tissues but upregulated in many cancers including ovarian cancer. Overexpression of Trop2 in ovarian cancer is associated with poor prognosis. Till date, there exists no report on the expression of Trop 2 in the ascitic cells. We have evaluated Trop2 expression in the ascitic cells by qRT PCR and western blotting (n=39). Though Trop2 is reported to be overexpressed in ovarian cancer, we observed wide variation in Trop2 transcript levels in the ascitic cells. This could either be due to frequency of tumor cells in the ascitic fluid or due to the actual variation in Trop2 levels in the ascites cells. When we referred the histopathological reports of the patients to identify those showing fewer tumor cells, 13 out of 39 were having scanty tumor cells in their ascitic fluid. All these patients showed Trop2 transcript below median indicating that low Trop2 transcript levels were most likely due to lesser abundance of malignant cells. Hence, Trop2 transcript level in ascitic cell pellet correlates with the abundance of tumor cells shed in the ascitic fluid. Immunohistochemical (IHC) analysis for Trop2 in ascitic cell blocks (n=37) was also carried out to evaluate Trop2 positive cells and to quantitate their abundance in the ascitic fluid.

For IHC analysis, paraffinized ascitic cell blocks of recruited patients were obtained from Tata Memorial Hospital. Sections were immunostained for Trop2 and then evaluated and scored by a pathologist from Tata Hospital. All the patients showed strong membranous Trop2 staining with staining intensity of +3. Trop2 was specifically detected only in malignant cells and even the patients with very few tumor cells showed strong Trop2 positivity. Almost 86% patients showed more than 70% Trop2 positive tumor cells. Fig. 1 indicates representative cases with high and low frequency of malignant cells when grouped as per their transcript level. As shown in the figure, low abundance of Trop2 positive cells in the cytoblocks correlates with low transcript levels. Our data suggests Trop2 can be used as tumor specific histopathological marker for diagnosis of malignant ascites. Further, patients were categorized as per Trop2 transcript levels below 25th percentile and above 25th percentile as low and high Trop2 in ascites respectively. 6 out of 29 (20%) patients in high Trop2 transcript showed chemoresistance whereas only 1 out of 10 (10%) low transcript group patients showed occurrence of chemoresistance (Fig. 2). Relative risk of developing chemoresistance in lower Trop 2 group was 0.48.

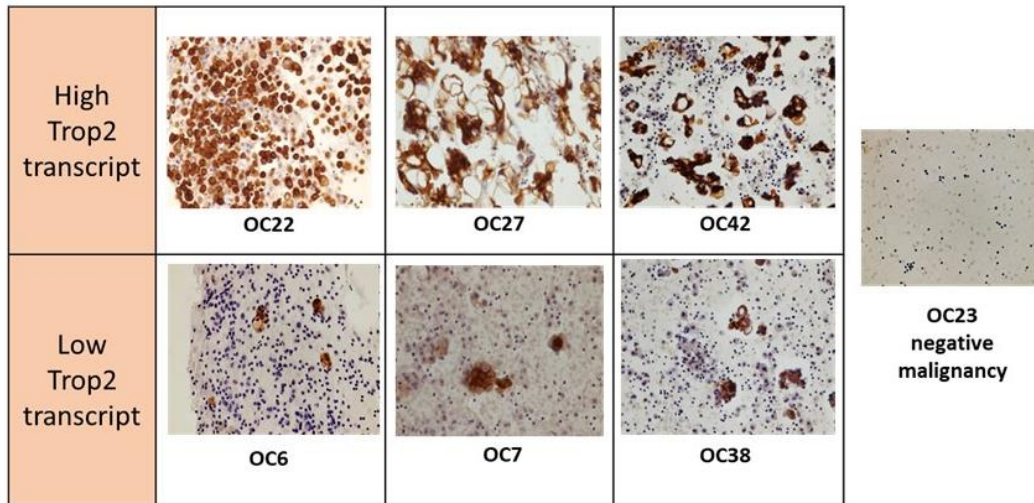


Figure 1: IHC staining of ascitic cell block of ovarian cancer patients showing representative images of cases with high and low Trop2 transcript groups. A patient negative for malignancy served as negative control and showed absence of Trop2 positive cells

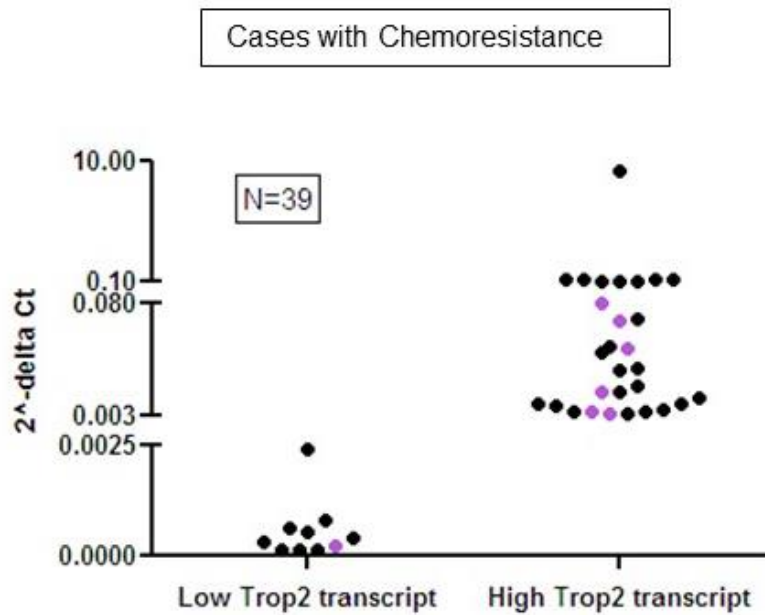


Figure 2: Scatter plot depicting the Trop2 transcript levels in the ascitic fluid cells of ovarian cancer patients. The 39 malignant cases were segregated employing 25th percentile as a cut-off and distribution of seven known chemoresistant cases were indicated with purple dots.

7. HTA AND DRUG DISCOVERY

7.1 Assessment of RMNCAH+N Service Delivery Costs, Work Patterns and Efficiency of Primary Healthcare Teams at Ayushman Bharat-Health and Wellness Centres *(Partly Funded by UNICEF)*

Principal Investigator : **Beena Joshi**
Project Associates : AK Padhan, Tejal R Varekar , Avantika Handore, S Gaikwad
Collaborators : S Prinja, PGIMER, Chandigarh
Duration : 2023-2026

India's efforts to achieve Sustainable Development Goals and Universal Health Coverage through the Ayushman Bharat – Health and Wellness Centres (AB-HWCs) program are crucial for national development and have global implications. Understanding the financial and efficiency components is essential for effective implementation and sustainable progress towards the goals. The study aims to understand the cost implications of the transformation of primary health centres into Health and Wellness Centres (HWCs). The impact of service expansion on human resources is assessed through time devoted for each services provided. It will capture the costs of delivering primary healthcare services including reproductive, maternal, neonatal, child, and adolescent health (RMNCAH+N) services through Health and Wellness Centres and assess the efficiency of health centres based on pre-defined inputs and outputs. The study is a multicentric study carried in Madhya Pradesh, Rajasthan, Maharashtra, Meghalaya, Jharkhand, and Tamil Nadu. In each state two districts were selected based on the proportion of functional AB-HWCs satisfying advanced functionality criteria (AB-HWCS providing all 12 expanded range of services). For Maharashtra, the two selected districts are Palghar and Nanded. A simple random selection was done to select 2 PHC-HWC and 4 SC-HWC in both the districts. A total of 12 facilities will be surveyed to acquire cost and efficiency data. The state and district permissions for the facilitation of the study were obtained and the project staff – two Junior Project Research Fellows (JPRFs) candidates were selected for data collection under the project. Training was provided to both the JPRFs for the data collection tool and process.

7.2 To Estimate the Cost of Diagnosis of Infertility and its Management including In Vitro Fertilization (IVF) and Quality of Life among Infertile Couples *(Partly Funded by Department of Health Research)*

Principal Investigator : **Beena Joshi**
Co-Principal Investigator : S Prinja, PGIMER, Chandigarh
Project Associates : Akshita Vikani, Prerana Patil, P Utekar,
Neelam Motwani, N Moon, JNMC, Wardha
Aasini Maria Georgina, Saranraj S, SRIHER, Chennai
Deeksha Bharti, A Kumar, PGIMER, Chandigarh
Belinda Grace, Anfal M, Government Medical College, Trivandrum
S Siddique, Abida Jammeel, MAMC, Delhi

Site Investigators / Co-ordinators	: Oshima Sachin, HTA In DHR, New Delhi Bhavani Shankara Bagepally, ICMR-NIE, Chennai B Soman, SCTIMST, Trivandrum
Co-Investigators	: Sukhpreet Patel (Ex-Consultant), Deepshikha Sharma, PGIMER, Chandigarh
Site Collaborators	: Renu Tanwar, MAMC, New Delhi Vanita Suri, PGIMER, Chandigarh Radha V, SRIHER, Chennai Anitha M, Ramesh P, Government Medical College, Trivandrum Deepti Shrivastava, JNMC, Wardha
Duration	: 2023-2024

Efforts are being made to include IVF in government health schemes like Pradhan Mantri- Jan Arogya Yojana (PM-JAY), necessitating cost assessments. Our objectives were to estimate health system costs of diagnosis and treatment of infertility including IVF, to estimate Out-of-pocket expenditure incurred by infertile couples including IVF services and to assess quality of life among couples accessing services for diagnosis and treatment of infertility including IVF. We identified three public and two private tertiary health facilities that were willing to participate in the study. Primary data was collected from 30 patients undergoing IVF treatment and 100 patients undergoing infertility treatment (particularly diagnosed with single cause such as PCOS, endometriosis, tubal factor, uterine factor and male infertility) at each site along with health system costing. Health Related Quality of Life (HRQoL) of these patients was assessed using five-dimensional Euro-QoL questionnaire (EQ-5D-5L) and Visual Analogue Scale (VAS). The quality-of-life measures for couples undergoing IVF was slightly reduced compared to the ones who were not receiving IVF. The average Out-of-Pocket Expenditure (OOPE) for IVF treatment was Rs.1,09,671 at public hospitals and Rs. 2,30,668.5 at private hospitals, with 88.5% incurring catastrophic health expenditure. The median OOPE for infertility treatment was Rs.11317 (IQR: 4801, 19513) with 25% incurring catastrophic health expenditure. The health system cost of providing one IVF cycle was Rs. 81,332 ($\pm$ 12,949) and infertility management for one year in the public facilities ranged between Rs. 6,822 to Rs. 11,075. Infertility management in private settings was higher than public facilities. The following recommendations were made based on study findings, the IVF package for consideration under Pradhan Mantri Jan Arogya Yojana (PM-JAY) could be considered at Rs. 81,332 for one IVF cycle. Currently, OPD expenses are not covered under PM-JAY. As the majority of expenditure for infertility treatment including IVF is OPD based, this consideration needs to be made for including IVF in the PM-JAY package. Since 25% of couples undergoing infertility treatment face catastrophic expenditure, this cost could also be considered for reimbursement under PM-JAY.

7.3 Feasibility, Acceptability and Costs of Providing Comprehensive Preconception Care services to Young Couples in Maharashtra *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator	: Beena Joshi
Co-Principal Investigator	: Ragini Kulkarni

Project Associates	: Saniya Qureshi, Purvi Pujara, P Gharat, A Bagul, B Prakshale, Shivani Gaikwad, Anusaya Pawane, D Devaraye, A Kayastha, V Saiyad, Damini Khunepimpre, Yamini Jagtap, Prerna Patil, SPawar, S Shelar
Collaborators	: Geetanjali Sachdeva, Deepti Tandon, Suchitra Surve, S Pande, Bhavya MK
Duration	: 2023-2026

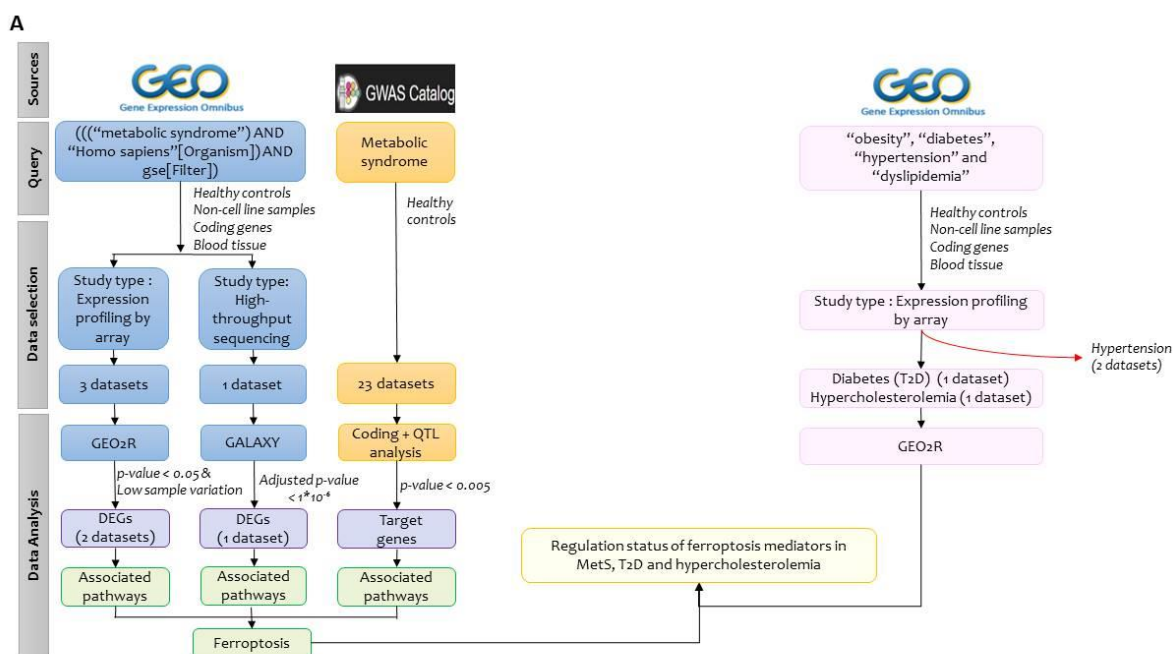
The objective of study is to assess feasibility and acceptability of providing comprehensive PCC package to young couples belonging to tribal, rural, urban slum and non-slum populations. Couples who married in the last 2 years, permanent resident available for follow up for at least 1 year and not having any living child were eligible for enrolment. The project aims to create awareness, screen, counsel and treat couples to ensure health of mothers prior to conception. Situational analysis was conducted from May 2023 -March 2024 in which 143 In-Depth Interviews (of health care providers at study site), 20 Focus Group Discussion (each of 2 young females ,2 young males and 1 mother in law at all 4 study sites) were conducted and facility assessments were done using a checklist. It was found that most of the health care providers were not aware about the preconception care package and lacked training regarding the same. Drugs to treat thyroid disorders, psychotropic drugs and contraceptives like Chhaya and Antara at study sites which are considered to be essentials for preconception cares (PCC) services were not available at most facilities. Required IEC materials for PCC were not available at most of sites, though Vatsalya Programme is in implementation phase in our state. Weekly Iron Folic Acid supplementations (WIFS) were not being distributed among adolescent population and reproductive age group female as per programme requirement. Lots of misconception regarding menstruation, fertile period and conception were found among general population. After several sensitization meetings with stakeholders, the enrolment was initiated at the Subcentre PHCs and urban health post level. Total enrolment during reporting period was 179 (71 in tribal, 47 in rural, 40 in urban slum and 21 in Urban non-slum). Most of the study participants were from upper lower socioeconomic status followed by lower middle. Among them 141(78.7%) wanted to conceive, 55 (30.7%) participants were under-weight, 15 (8.3%) overweight and 109 (57.5%) were having normal BMI. 56 anaemia cases were found in which 04 were severely anaemic and 02 had sickle cell trait, 05 had β thalassemia trait. Menstrual abnormalities were found in 23 participants of which 14 were known cases of PCOS, 21 had RTI/STI symptoms. Infertility (according to WHO definition) was found to be in 34 participants. The major interventions were 1. distribution of folic acid and IFA supplementation to those wanting to conceive. 2. distribution of contraceptives to those who didn't want pregnancy. 3. treating morbidities like anaemia, menstrual disorders & referral services to higher facilities for diagnosis and management of infertility. 4. genetic counselling (sometimes teleconsultation) was offered through GRC, NIRRCH for cases of consanguinity, BOH, short stature, sickle cell & thalassemia. The study is still ongoing.

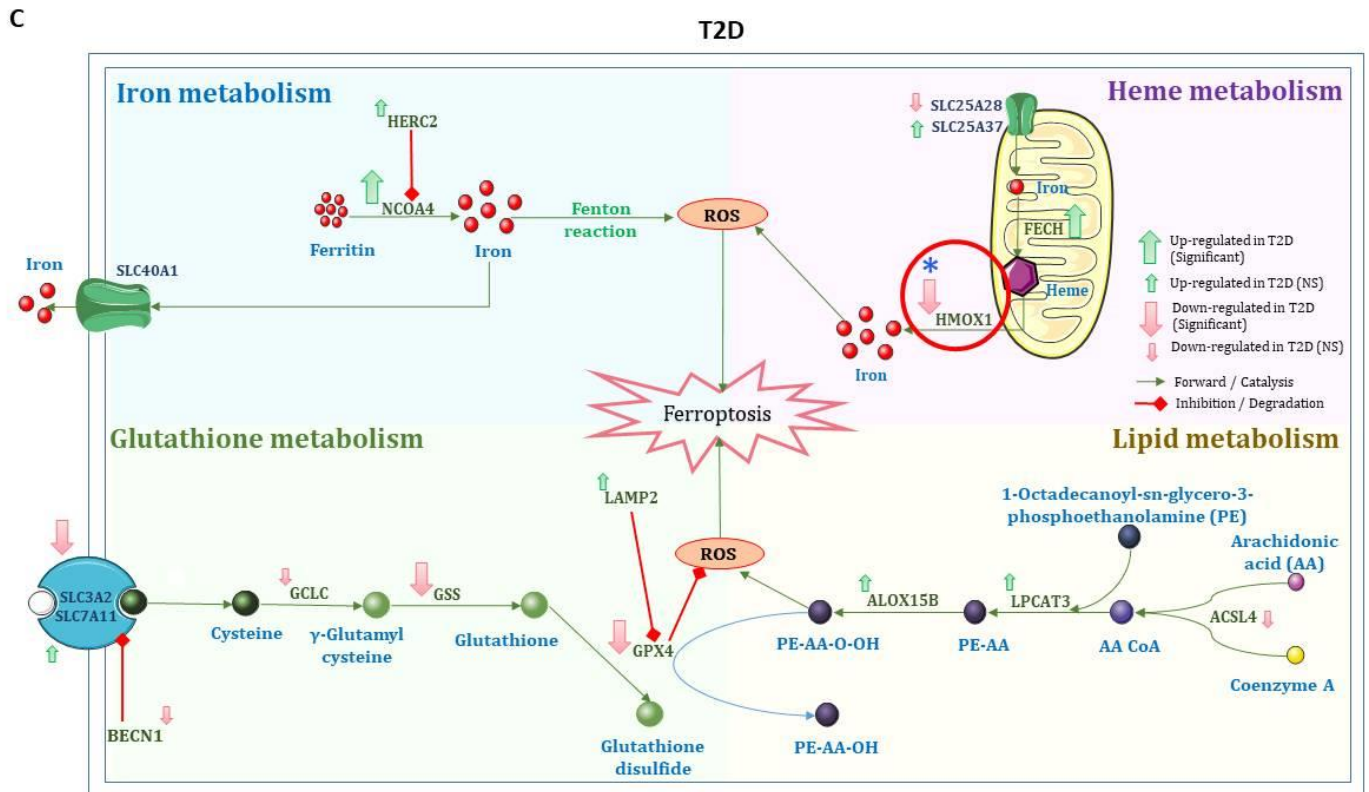
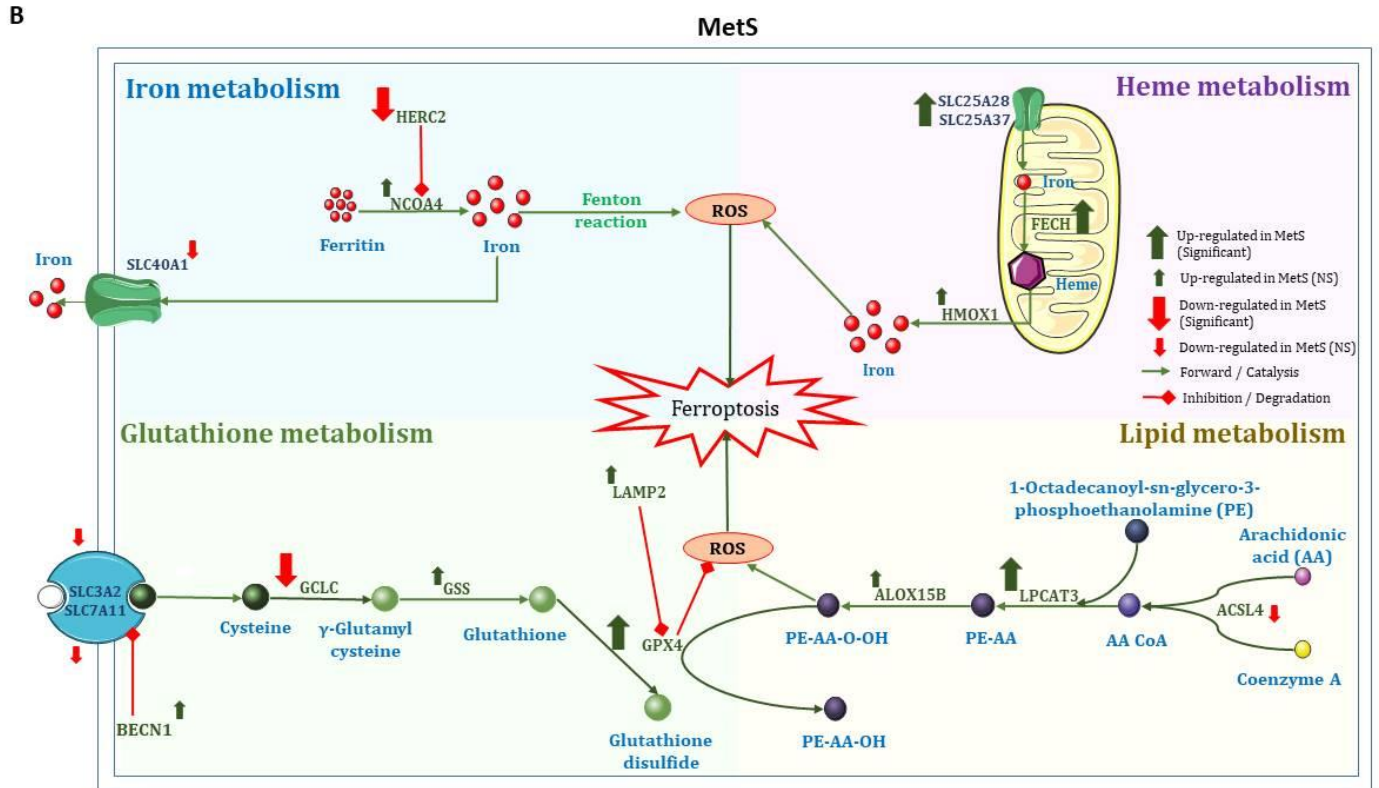
7.4 Identification of Enriched Biochemical Networks and Polypharmacological Targets for Metabolic Syndrome *(Partly Funded by Science and Engineering Research Board, Department of Science and Technology - STAR)*

Principal Investigator : **Susan Thomas**

Project Associate : Indra Kundu
Duration : 2021-2024

Metabolic Syndrome (MetS) is a cluster of metabolic abnormalities triggered by the interplay of obesity, insulin resistance and inflammation. Individuals with MetS are at higher risk of developing Type-2 Diabetes (T2D) and Cardiovascular Diseases (CVDs). Over the last decade, there has been emerging evidence on the role of ferroptosis (iron-dependent cell death) in T2D and CVDs. In the reporting year, we investigated and compared the expression status of ferroptosis mediators in MetS, hypercholesterolemia and T2D through meta-analysis of GWAS, RNA-seq and microarray datasets. 4342, 112 and 6080 genes identified from microarray, RNA-seq and post-GWAS analyses respectively were subjected to pathway enrichment analysis (Fig. 1a). 122 pathways were commonly identified to be enriched from all three analyses. Many of these pathways such as lipid metabolism, atherosclerosis, signaling of VEGF, MAPK, mTOR, PPAR and glycosphingolipid are well known for their role in MetS. In addition to the well studied pathway, we found ferroptosis and mitophagy to be enriched from all three analyses. Four cellular metabolism processes including glutathione, lipid, heme and iron regulate Ferroptosis pathway. The results of the current study indicate that in case of MetS, ferroptosis is due to i) increased glutathione mediated lipid peroxidation, ii) increased degradation of stored cellular iron (ferritin) along with less export of iron outside cell, and iii) increased degradation of heme in mitochondria (Fig. 1B). Individuals with T2D exhibited similar metabolic patterns to those with MetS (Fig. 1C). However, in cases of hypercholesterolemia, the ferritin degradation is reduced and the expression of iron exporter genes is increased indicating the cellular iron is not as high as in MetS (Fig. 1D). Based on these findings, we report the role of excess cellular iron in the progression of hypercholesterolemia to MetS for the first time. The findings of this study will be clinically validated by omics analysis of blood samples from individuals with MetS and its components (an on-going cross-sectional study).





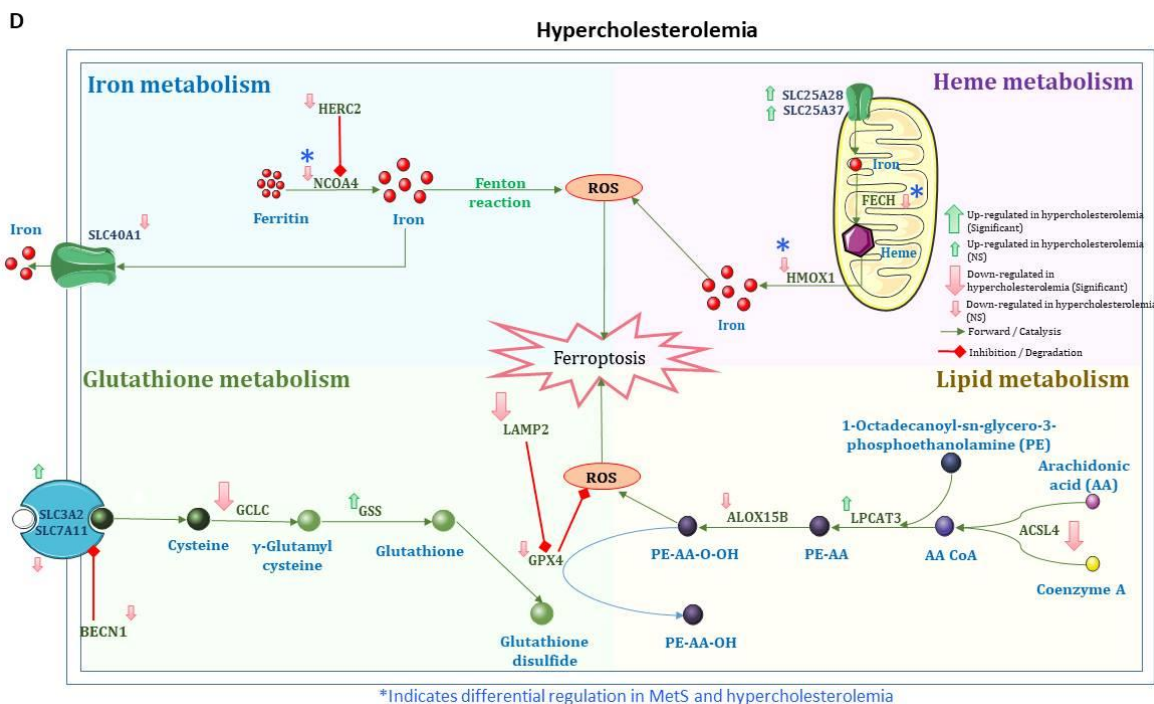


Figure 1: a) Overall schema for data collection and meta-analysis. b-d) Putative association of excess iron, ferroptosis, and mitophagy in b) MetS c) T2D and d) hypercholesterolemia. The up and down arrows indicate the expression status of the genes in MetS, T2D and hypercholesterolemia samples as compared to healthy controls. Size of the arrow indicates the significance of regulation.

7.5 Multi-omics Based Machine Learning Models for Detection of Metabolic Syndrome and its Components

Principal Investigator : **Susan Thomas**

Co-Principal Investigator : M Sudhakar

Project Associates : Karishma Desai

Collaborators : Taruna Madan
J Menon, Amrita Institute of Medical Science, Kochi

Duration : 2022-2027

Metabolic Syndrome (MetS) is characterised by presence of atleast three components of different components that include obesity, hyperglycemia, hypertension, high triglycerides (TG) and low high density lipoprotein cholesterol (HDLc). The incidence of MetS and its individual components has been consistently rising over the years, significantly adding to the burden of non-communicable diseases. To date, research in the field of MetS has been unable to elucidate the molecular mechanisms linked to MetS development from its individual or combination of components. The study aims to address this research gap by conducting a cross-sectional study in Kerala, India. The study design encompasses recruiting treatment-naïve individuals with the various combinations of MetS components. The study design and protocol have been approved by the ethics committee and the study has been initiated at

Amrita Institute of Medical Sciences. Treatment-naive individuals are being recruited into four major groups. Individuals without any MetS components are recruited under the healthy group. Individuals with any one component of MetS are recruited in the second group, third group consists of individuals with any two components of MetS and individuals with any three components of MetS are recruited in the fourth group. Group 2-4 are further divided into subgroups based on the presence of specific MetS component/s. This leads to formation of 15 subgroups for this study with 30 participants to be recruited per subgroup. The overall sample size of the study is 450. The study is currently at the stage of participant recruitment. Blood samples from these individuals will be subjected to omics analysis to identify underlying molecular networks involved in the pathophysiology of MetS. Identification of molecular networks operational in various MetS phenotypes will aid in better stratification of individuals based on risk of MetS development. In addition, a ML based risk prediction model for MetS trained on Indian data is not available currently. The study will help in development of such model for Indian population.

7.6 Evaluation of Drug-Cytochrome P450 Enzyme Interaction through Fluorometric High Throughput Screening Assays (Partly Funded by Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH)

Principal Investigator : **V Dighe**
 Project Associate : Amruta Gadade
 Duration : 2021-2024

Cytochrome superfamily members are identified as the most critical drug-metabolizing enzymes due to their ability to metabolize a wide range of pharmaceuticals. In the ongoing study, ayurvedic formulations are being examined for their potential herb-drug interactions (HDI) with key human CYP isoforms CYP1A2, CYP2C9, CYP2D6, and CYP3A4. Using preclinical (in vitro) and clinical (in vivo) interaction studies.

Table 1: In-vivo biochemical assay (Fluorometric assays) on liver microsomes.

Test compound	Extracts	CYP2C19		CYP2D6		CYP3A4		CYP1A2	
		The inhibitory activity is normalized with known inhibitor <u>miconazole</u> (30µM)		The inhibitory activity is normalized with known inhibitor <u>quinidine</u> (10µM)		The inhibitory activity is normalized with known inhibitor <u>ketoconazole</u> (10µM)		The inhibitory activity is normalized with known inhibitor <u>α-naphthoflavone</u> (10µM)	
Ayush GG	WE	0.545±0.0470	NI	0.710±0.037	NI	0.207±0.013	NI	1.560±0.234	NI
	ME	1.123±0.0871	NI	0.101±0.006	NI	0.112±0.024	NI	1.165±0.084	NI
Laksh Guggulu	WE	0.139±0.0980	NI	0.713±0.376	NI	0.390±0.030	NI	0.469±0.005	NI
	ME	0.095±0.0261	NI	0.411±0.0989	NI	0.184±0.033	NI	0.159±0.019	NI
Dhatri Lauha	WE	0.189±0.062	NI	0.152±0.0002	NI	0.304±0.0001	NI	0.180±0.001	NI
	ME	0.066±0.001	NI	0.061±0.0036	NI	0.114±0.046	NI	0.159±0.002	NI
Haritaki Churna	WE	0.049±0.0001	NI	0.420±0.018	NI	0.088±0.038	NI	0.117±0.001	NI
	ME	0.030±0.0134	NI	0.400±0.055	NI	0.028±0.001	NI	0.110±0.001	NI
Kanchanara Guggulu	WE	2.405±1.752S	NI	1.338±0.719	NI	3.845±0.001	NI	0.939±1.212	NI
	ME	0.131±0.0409	NI	0.706±0.153	NI	0.076±0.030	NI	1.441±1.831	NI

Note: WE: Water Extract, ME: Methanolic Extract NI: Non-inhibitory

In the reporting year, cytotoxicity of various ayurvedic formulations-water and the methanolic extract was assessed at different concentrations using the HepG2 (liver) cell line. All formulations were found to be safe and non-cytotoxic at concentrations ranging from 0.50 to 200 mg/ml. Herbal Drug Interactions (HDI) of five herbal formulations -water and methanolic extracts with CYP isoforms CYP1A2, CYP2C9, CYP2D6, and CYP3A4 were evaluated using a commercially available assay kit. The fluorometric assay results indicated that all ayurvedic formulations did not exhibit inhibitory activity unlike known inhibitors like Miconazole, Quinidine, Ketoconazole, and α -naphthoflavone (Table No: 1). The assay values were normalized with their respective inhibitors as recommended in the kit protocol. The values indicate that both the aqueous(WE) and methanolic (hydro-alcoholic) extracts (ME) of all five ayurvedic formulations are safe for use.

7.7 Exploring the Therapeutic Potential of Peptides Targeting Lysophosphatidic Acid Receptors in Ovarian Cancer *(Partly Funded by Department of Biotechnology)*

Principal Investigator : **V Dighe**
 Co-Principal Investigator : Taruna Madan
 Project Associates : Bhavana Bhat, Yugandhara Jirwankar, Akanksha Nair, S Jadhav, P Salunke
 Duration : 2022-2025

Ovarian cancer is one of the deadliest cancers affecting women worldwide. Many molecules get elevated in the microtumor environment of ovarian cancer patients. Among them, an onco-lipid Lysophosphatidic acid (LPA) is elevated in the ascitic fluid and serum in women with ovarian cancer. LPAR2 and LPAR3 are overexpressed in ovarian cancer cells and LPA -LPAR interaction activates the signaling pathways leading to cell proliferation, invasion, and metastasis in ovarian cancer. Hence, the present study aims to explore the therapeutic potential of the peptides targeting LPAR3 in ovarian cancer. Last year we reported identification of LPAR3 binding peptides by in-vitro panning. Full-length recombinant LPAR3 (rLPAR3) protein was used as a bait to carry out three rounds in vitro panning using Ph.D. -12 mer phage library. After NGS sequencing of the phage pools, Pep1-XQMXXXYXQSXX and Pep2-TXXRXXVXSXXA peptides were obtained with higher frequency count suggesting their enrichment after in-vitro panning. In the current year, we checked the specificity of the phages displaying the LPAR3 binding peptide sequences (LPAR3 Pep1 phage) by phage ELISA and cell-based ELISA. To achieve this, a bacteriophage plaque assay was performed to isolate individual phage clones (LPAR3 Pep1 phage). An amplified phage pool of third-round in-vitro panning was used for bacteriophage plaque assay to obtain individual phage clones. The sequence of the individual phages was confirmed by Sanger sequencing. LPAR3 Pep1 phage was employed for the phage ELISA. rLPAR3 was coated as bait on a polystyrene plate, LPAR3 Pep1 phage, and phage without the insert, a negative control, was immuno-assayed using the M13 phage antibody. The phage ELISA confirmed the specificity of the identified peptides specific to the LPAR-3 (Fig. 1). To confirm the binding specificity of the phages to human ovarian cancer cell line, OVCAR3 which overexpressed LPAR3, cell-based ELISA was performed. Phage binding assay using cell-based ELISA confirmed the specificity of the identified LPAR3 Pep-1phage to the OVCAR3 cells where an abundant expression of LPAR3 was reported (Fig. 2). Investigation on specificity of the commercially synthesized peptides in-vitro using cell lines and in-vivo are under progress.

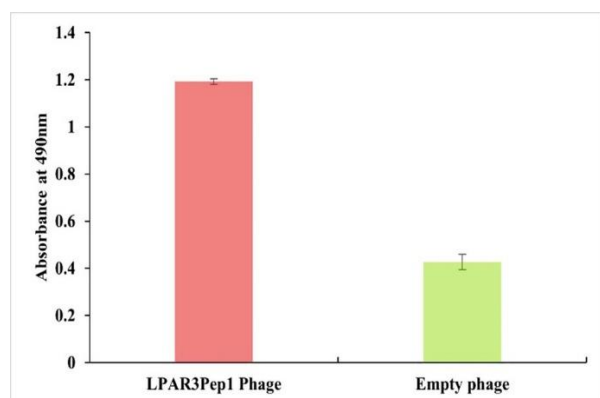


Figure 1: LPAR3Pep1 phage and the phage without the peptide insert (empty phage) were used to confirm the specificity of rLPAR3. The results showed that the respective phages of LPAR3 Pep1 are specific to rLPAR3 compared to the empty phage

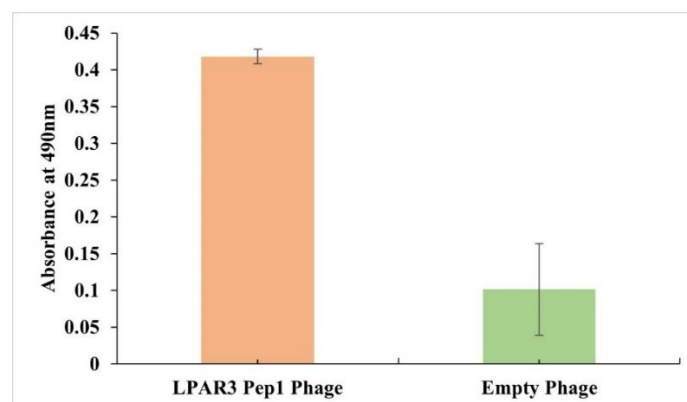


Figure 2: Cell-based ELISA: LPAR3 Pep1 phage and the empty phage (phage without the peptide insert) were used to confirm the specificity of binding of LPAR3 Pep1 phage to OVCAR3 cells. The results showed that the LPAR3 Pep1 phage binds to OVCAR3 as compared to the empty phage.

7.8 Sertoli and Leydig Cell Homing Peptides as Molecular Steering for Testicular Targeted Drug Delivery *(Partly Funded by Department of Health Research)*

Principal Investigator : **V Dighe**

Co-Principal Investigator : Taruna Madan

Project Associates : Yugandhara Jirwankar, Akanksha Nair, P Salunke, Sudhir Jadhav

Duration : 2021-2024

In the reporting year, previously identified Leydig cell homing peptides (LCHP) were characterized. The homing potential of FITC-tagged LCHP1 and LCHP2 to TM3 (mouse Leydig cells) was analyzed qualitatively and quantitatively using confocal microscopy and flow cytometry respectively. TM4 (Mouse Sertoli cells) and H9C2 (rat embryonic cardiomyocytes) were used as control/non target cells. Confocal microscopy Fig. 1(a –c) revealed higher uptake of LCHP1 and LCHP2 in TM3 cells compared to TM4 and H9C2 cells, indicating a specific affinity of LCHP1 and LCHP2 for Leydig cells. Quantitative uptake analysis via flow cytometry (Fig. 1d & e) showed that LCHP1 uptake in TM3 cells was significantly higher than in TM4 and H9C2 cells at 100 μ M and 200 μ M concentrations. LCHP2 demonstrated significantly higher uptake in TM3 cells than in TM4 cells at concentrations of 50 μ M, 100 μ M, and 200 μ M. However, H9C2 cells displayed an equivalent uptake of LCHP2 at 200 μ M and higher uptake at 50 μ M and 100 μ M, likely due to auto-fluorescence, as unstained H9C2 cells also exhibited elevated fluorescence intensity. To purify the molecular targets of the LCHP1 and LCHP2 on the surface of Leydig cells, affinity chromatography was performed using membrane proteins of TM3 cells and testis tissue. After the affinity purification, the affinity eluates were run on SDS-PAGE (Fig. 2a). In eluates from LCHP1 and LCHP2, affinity chromatography, a specific band around 27kDa (lanes 2 and 5) and 85kDa (lanes 3 and 6) was observed in SDS-PAGE. No such specific bands were observed in the eluate from control (lanes 4 and 7) but a few bands around 70kDa were present in all the samples, which could be the proteins binding non-specifically to the agarose medium. The specific bands obtained from LCHP1 and LCHP2 affinity chromatography were subjected to in-gel trypsin digestion,

followed by mass spectrometry for protein identification. No protein in the range of molecular weight of 27 kDa was obtained from in-solution digested eluate of LCHP1, whereas peroxiredoxin-2 Prdx2 protein (21.8 kDa) and peroxiredoxin-1 (22.2 kDa) were found from TM3 and testis membrane proteins affinity purification, respectively. The results suggest Peroxiredoxin 2 (Prdx2) protein (Q5M9N9), and/or peroxiredoxin-1 (P35700) as potential targets of the LCHP1 peptide in Leydig cells and testis. LCHP2 found to target junction plakoglobin (Q02257), also known as plakoglobin or gamma catenin, was plakoglobin reported to be present in adherens junctions and desmosomes. Literature suggests its expression at basal seminiferous tubules, concentrated at Sertoli cell-Sertoli cell junctions rather than Sertoli cell-germ cell junctions in the testis, akin to alpha-catenin. Although the presence and function of junction plakoglobin in adult Leydig cells aren't well-documented, even low-level presence in Leydig cells could make it more accessible to LCHP2 peptides because of its presence in the interstitial compartment. Moreover, western blotting of the eluate validated the presence of the eluate protein (Fig. 2b).

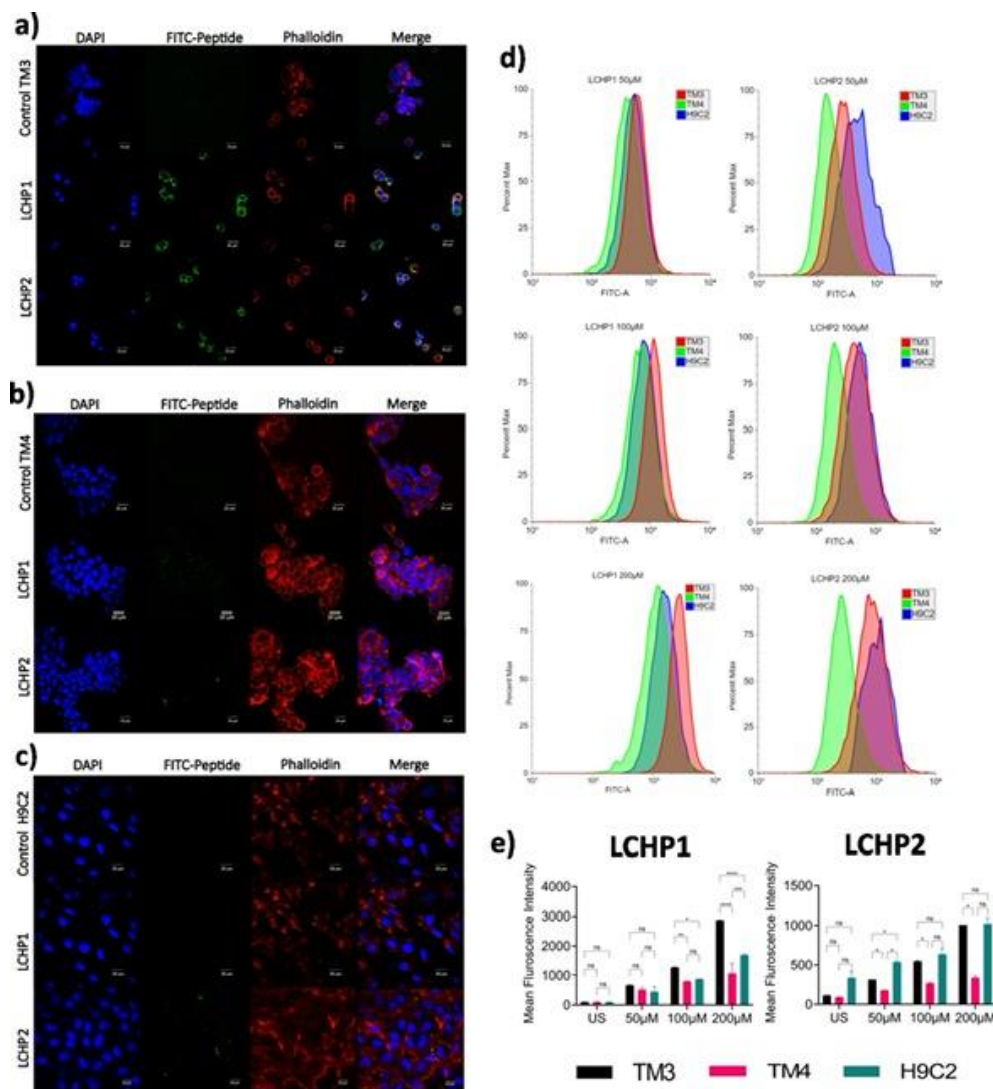


Figure 1: In-vitro uptake of LCHP1 and LCHP2 peptides by TM3, TM4 and H9C2 cells. Confocal micrographs of LCHP1 and LCHP2 treated TM3 (a), TM4 (b) and H9C2 (c) cells. d. Histograms of the quantitative uptake

measurement of LCHP1 and LCHP2 uptake at 50 μ M, 100 μ M, and 200 μ M by flow cytometry. e. Statistical analyses of the quantitative uptake of LCHP1 and LCHP2 by TM3, TM4, and H9C2 cells. Data represent mean $\pm$ SD; (n = 3) * p < 0.05, ** p < 0.001, and **** p < 0.0001 assessed by Two-way ANOVA, followed by Tukey's multiple comparison test.

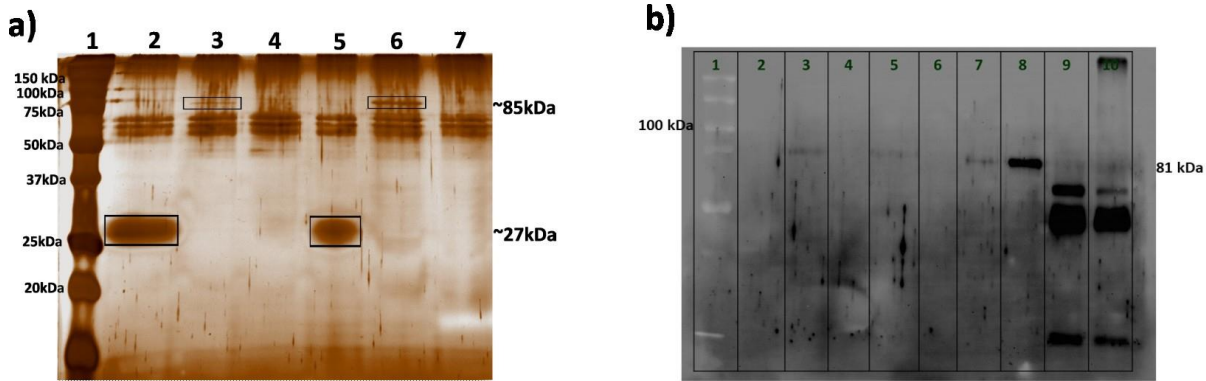


Figure 2: a) Silver stained SDS-PAGE of the affinity eluate. Lanes 1. protein molecular weight marker, 2. LCHP1 affinity eluate from TM3 membrane proteins, 3. LCHP2 affinity eluate from TM3 membrane proteins, 4. No-peptide affinity eluate from TM3 membrane proteins, 5. LCHP1 affinity eluate from testis membrane proteins, 6. LCHP2 affinity eluate from testis membrane proteins, and 7. No-peptide affinity eluate from testis membrane proteins. b) Immunoblotting of affinity eluate with antibody against function plakoglobin (gamma catenin). Lanes 1-9 represent 1. protein molecular weight marker, 2. LCHP1 affinity eluate from TM3 membrane proteins, 3. LCHP2 affinity eluate from TM3 membrane proteins.

8. HEALTH CARE RESEARCH

8.1 Understanding Availability of Essential Diagnostic in Healthcare Systems Identifying Barriers and Facilitators (ICMR Multicentric Study) *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator	: Beena Joshi
Co-Principal Investigators	: Ragini Kulkarni, Shahina Begum
Coordinator	: Kamini Walia, ICMR
Project Associates	: Sakshi Rane, Iswarya Reddy
Duration	: 2022-2024

The project aims to assess the availability of essential diagnostics in alignment with the National Essential Diagnostics List (NEDL) and the Framework for Diagnostics in India (FDI) across various levels of healthcare facilities. Its primary objectives are to identify the barriers and facilitators influencing test availability and utilization; evaluate the presence of necessary infrastructure and operational facilities and to understand the mechanisms employed for diagnostic service delivery, through PPP (public private partnership) or state-run. This cross-sectional study assessed availability of essential diagnostics at 290 health facilities i.e 10 DHs, 120 SDH/RHs, 101 PHCs and 59 HSCs across 10 districts in Maharashtra, namely Pune, Gadchiroli, Nagpur, Akola, Latur, Parbhani, Ratnagiri, Nandurbar, Nashik and Mumbai Suburban. An ODK tool was developed for data collection purpose and Instruction Manual was created to ensure uniformity and accuracy in data collection. All the data was transferred to ICMR HQ. Data collection was initiated in July 2023 at the UPHC/PHC/HSC level and progressed to CHC/RH/SDH/DH levels from January 2024. As of March 2024, data collection in four districts, namely Mumbai Suburban, Pune, Nashik, and Akola was completed. Preliminary observations showed that approximately 70% of the diagnostic tests are done through PPP and remaining 30% are done in-house. For urban areas, PPP was done with Krsnaa Diagnostics Pvt Limited and for rural areas it is Hindustan Labs Limited (HLL). However, HLL also has its presence in some urban health facilities. One Major drawback in PPP is that routine tests such as CBC also requires more than 6 hours of turnaround time. It also highlights critical infrastructure deficiencies at UPHC/PHC level due to poor condition of the buildings, demolishment or ongoing construction work that affects the overall quality of service delivery. Lack of proper maintenance of washrooms due to inadequate water supply and leakage issues leading to reduced possibility of urine/stool tests. Biomedical waste management is neglected at some facilities due to lack of training/awareness. Moreover, challenges such as manpower shortage and inadequate regular training for lab technicians and radiographers, limited equipment availability, and supply chain problems at RH/PHC/HSC are significant hurdles that lead to unavailability of essentially required test. Basic test kits such as UPT/VDRL/Dengue Kits frequently run out of stock at some health facilities. Record maintenance and IT integration have been strengthened at various tiers of healthcare system. Internal quality assurance is done by MO/RMO but infrequently. External quality assurance is frequently done by Kayakalp/LaQshya. None of the labs have obtained NABL Accreditation as of March 24. The study is ongoing. Final results will provide a comprehensive picture on the availability and uptake of essential diagnostics.

8.2 Acceleration Efforts to End TB in India *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : **Bhavya M K**
Co-Principal Investigator : Beena Joshi
Project Associates : Deepti Tandon, Manoj Singh, Vinita Rajgar, Vimal Garasiya
Collaborators : State TB Unit, Dadra Nagar Haveli
Duration : 2023-2025

The study is a multi-center task force study of ICMR in collaboration with the Central TB division. Each of the selected ICMR institutes is allocated a district in a state/union territory and a close collaboration is established with the State Tuberculosis Officer (STO). The study site for ICMR NIRRCH is Dadra and Nagar Haveli district of Dadra Nagar Haveli and Daman and Diu Union territory. The first phase focused on rapid situational analysis to know the program gaps and challenges of the current TB program in Dadra Nagar Haveli. Baseline data from all the facilities and TB unit in Dadra Nagar Haveli were collected. All the health facilities were mapped. The patients registered in the last six months and patients registered prospectively, at the respective TB Units, were followed for treatment compliance and their contacts were screened. Basic information (mapping of the infrastructure, facilities, and staff for TB under the State TB program) about the district has also been collected. Qualitative data was collected using In-Depth Interviews (IDI) and Focus Group Discussions (FGDs). IDIs were conducted among Health Care Workers (Medical officers, ANM, ASHA, MO, MPW) using a validated questionnaire. FGDs at the patient level, were conducted to understand the challenges faced by them in availing the treatment and their experience with NTEP. The translation of the Informed Consent Form (ICF), Participant Information Sheet (PIS), and Questionnaires were done in Marathi/Gujarati/Hindi language and consent was obtained from the participants. Migration of patients was one of the major challenges faced by the health system. The community had basic awareness of TB. Stigma and fear of job loss restrict individuals from seeking treatment. In the second phase community-based intervention strategies were implemented. Main focus of the intervention was community-based screening of high-risk populations, contact tracing, spreading awareness, and providing services as per National TB Elimination Program guidelines. The identified high-risk population for the study was of TB patient contacts and patients with NCDs. 27,696 of such cases were identified for the first active case finding. Screening camps were conducted with the help of handheld X-ray machines. A total of 16,665 people were screened (till 31st March 2024), including 9,528 males and 7137 females. Out of this, 1,274 people showed symptoms of TB, with 836 being males and 438 females. Out of the total screened, 7 were identified as TB suspects, and 3 were confirmed to have TB. The project also emphasized raising awareness about TB in the community. We held awareness sessions along the screening camps in schools, industries, and in high-risk communities. In schools, these sessions helped students learn about TB. In industries, workers were taught how to keep their workplaces safe from TB, especially in crowded conditions. A special screening and awareness camp was organized for inmates in a sub-jail. The project is ongoing.

8.3 Development of Primary Health Care Models for Palliative Care, Elderly Care and Mental Health in Maharashtra *(Partly Funded by Department of Health Research)*

Principal Investigator : **Ragini Kulkarni**
Co-Principal Investigator : Kiran Munne
Project Associate : Bhavya MK
Collaborators : District Health Officer and Civil Surgeon Palghar
Duration : 2023-2025

The study is a multi-center MRHRU-based study to develop primary health care models for palliative care, elderly care, and mental health. The study aims to assess the current scenario of mental health, geriatric, and palliative care concerning the extent and pattern of morbidities in selected geographical areas. SWOT analysis is being conducted to identify the strengths and gaps, if any, in the healthcare delivery system. The study explores existing best practices and assess their suitability and adaptability in the public health care system concerning palliative care, elderly care and mental health. The staff received training from DHR regarding the REDCAP APP into which the quantitative data from the household survey is being uploaded. The first training for the data entry for the community survey was conducted on May 18, 2023, and the refresher training for REDCAP APP regarding its use in offline mode was conducted on August 1, 2023. Both the trainings were attended virtually by the scientists and field workers involved in the I-PEM project. In the formative phase of the project, data are being collected from the selected facilities and community. The facility-based data collection has been completed for selected PHCs (Ashagad and Gholwad) and Health and Wellness Centres (Vaki, Saravali, Gholwad, Narpad and Bordi). Data have been collected by the study team from the HMIS and other relevant records of HWCs and the related PHCs in a structured form. For the community-based data collection, household door-to-door survey was conducted for general health status profiling including mental health, palliative, and geriatric care of the community. ASHA workers from the respective HWCs helped the field workers during household surveys. This project has a target population of 25000 participants. All the members of each household from selected HWCs were interviewed and the data were collected using the RedCAP app. Total population covered till 31st March 2024 was 19373 from 4010 households. Household data is being collected from selected Health and wellness centers, namely HWC Golwad (1), Bordi (4), Narpad, Vaki and Saravali (1). Among the population, 192 needed elderly care, 18 needed mental health care services, and 38 were identified for palliative care. For the SWOT analysis of the health system, in-depth interviews of medical officers (n=2), community health officers (n=3), staff nurses (n=2), and ANMs (n=4) from selected PHC and HWCs have been completed. The major issue faced by healthcare providers are lack of proper training to identify mental health issues among patients. There is need for proper training and timely hand holding. In the next phase of the study, the delivery packages will be developed based on review of national and international best practices. These packages will be further customized as per the data emerging in the formative phase, focusing on local needs for the palliative, elderly, and mental health care services.

9. MODEL RURAL HEALTH RESEARCH UNITS (MRHRUs)

Government of India, in June 2013, approved the scheme for 'Establishment of Model Rural Health Research Units (MRHRUs) in the States' during the 12th Plan period as a path-breaking initiative to develop/strengthen the health research infrastructure in the country for the "Promotion, Coordination and Development of Basic, Applied and Clinical Research". The objectives of the scheme are to transfer technology to rural areas for improving the quality of health services, to ensure an interface between researchers, health systems, communities in rural areas, and to improve the geographical spread of health research infrastructure in the country.

9.1 Model Rural Health Research Unit, Dahanu, Maharashtra

Nodal Officer : **Ragini Kulkarni**

Member Secretary : Kiran Munne

MRHRU Dahanu continued to provide timely diagnostic support for SARS-CoV-2, Dengue and Chikungunya, Leptospirosis, Influenza, Sickle cell disease & Thalassemia to Palghar district. During 2023-24, a total of 1694 samples were tested for the presence of SARS-CoV-2 and 218 (12.9%) samples were detected positive for SARS-CoV-2 virus. Referred clinical samples (n=12) were tested using combo real time RT-PCR for SARS CoV-2, Influenza A & B. All samples were found negative for influenza viruses. Total 3208 suspected dengue fever samples were tested by IgM ELISA among which 621 (19.4%) were positive for DENV. A total of 179 suspected blood samples were received for chikungunya diagnosis. Out of these, 38 (21.2%) were found positive. A total of 09 samples were tested for Leptospira IgM antibodies using Leptospira IgM ELISA kit (Panbio, USA), all were tested negative for Leptospira IgM. Besides diagnostic support, various research projects continued in the area of nutrition, reproductive, maternal and child health, hemoglobinopathies, NCDs and common cancers, infectious diseases, contraception, serosurveys, Injuries and falls.

Ongoing projects

1. Integrated palliative, elderly and mental health care (I-PEM) funded by DHR
2. Assessment of neonatal screening approaches for Sickle Cell disease and the effect of early intervention in management of the disease in tribal population, funded by ICMR
3. Molecular analysis of HLA-G in pregnant tribal women and its role in infectious etiologies modulating intrauterine inflammation- A prospective cohort study, funded by ICMR
4. Implementation research to explore operational feasibility, acceptability and cost-effectiveness of using IV Ferric Carboxy Maltose (FCM) in management of iron deficiency anemia (IDA) among pregnant women through sub district health system in Maharashtra, funded by ICMR
5. Immune status against SARS-CoV-2 among COVID-19 vaccinated adults in India: A health facility-based multicentric serial cross-sectional survey, funded by ICMR.
6. Population based birth defect (BD) surveillance in linkage with Rashtriya Bal Swasthya Karyakram (RBSK) programme in rural blocks of Palghar district in Maharashtra, funded by DHR

7. A national model to measure burden and map quality of care for type 2 diabetes mellitus in rural populations in India, involving medical colleges through primary health care setup- a feasibility study, funded by ICMR
8. Validation of novel serum biomarkers in prediction of early onset preeclampsia among pregnant women and correlation with maternal and neonatal outcomes in a tribal district of Palghar, Maharashtra, funded by ICMR
9. Assessing the feasibility of point of care device in community-based screening of Sickle cell Disease and Thalassemia in tribal district of Palghar, Maharashtra, funded by ICMR

9.2 Model Rural Health Research Unit, Vani, Maharashtra

Nodal Officer : **R Gajbhiye**

9.2.1 Establishment of Model Rural Health Research Units (MRHRUs) under the Umbrella Scheme of Development of Infrastructure for Promotion of Health Research *(Funded by the Department of Health Research)*

Nodal Officers: : **R Gajbhiye**
K Aher, Deputy Director of Health Services , Nashik
Sarika Patil, Government Medical College, Dhule

Project Associates: : Suchitra Surve, H Munshi

MRHRU Staff : Savita Tapase, M Mali, Ht Chavan, Prajakta Suryawanshi, J Chaudhary,
Trunali Barde, A Bagul

Duration : 2024-2026

This is the second MRHRU in the state of Maharashtra. The sanction for the MRHRU was received on 31.03.2023 and a tripartite MOA was signed between the Department of Health Research, Government of India, ICMR-NIRRH, Mumbai and Public Health Department, Government of Maharashtra on 10.05.2023. The MRHRU has been made functional in the Trauma Care Center building provided by the District Health System, Nashik.

The MRHRU serves as an interface between ICMR-NIRRH, Mumbai as the research and mentor institute, Shri. Bhausaheb Hire Government Medical College & Hospital, Dhule as the linked medical college and the Directorate of Health Services, Government of Maharashtra as the facilitator. The MRHRU will cater to research activities not only in the Nashik district but also in the adjoining Dhule, Jalgaon and Nandurbar districts.

During the reporting year, MRHRU, Vani focused on service, research and outreach components. The service component included hematology and nutrition Clinics that were inaugurated by Dr Bharati Pawarji, MoS Health & Family Welfare and Tribal Affairs, Government of India on March 13, 2024 during the Foundation Stone Laying Ceremony of the new infrastructure of MRHRU, Vani.

The research component was initiated with the formation of the Local Research Advisory Committee (LRAC) and the first LRAC meeting was conducted on February 14, 2024.

9.2.2 ICMR National Snakebite Project (INSP) on Capacity Building of Health System on Prevention and Management of Snakebite Envenomation Including its Complications *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : **R Gajbhiye**
Co-Principal Investigator : H Bawaskar
Project Associates : H Munshi, Smita Mahale, ICMR-NIRRH,
A Yadav, M Vitthalrao Bansode, S Shambharkar, Kanna Madavi,
Public Health Department, Maharashtra
A Mahapatra, S Palo, Regional Medical Research Center,
Bhubaneswar
Duration : 2021-2023

The study was conducted in four blocks across two states: Shahapur in Thane and Aheri in Gadchiroli (Maharashtra), and Khordha in Khordha and Kasipur in Rayagada (Odisha). It aimed to address snakebite incidents, especially in rural and tribal areas. The study analyzed 1415 retrospective snakebite case records, revealing a higher incidence in males (65%, n=919). The most affected age group was 30-40 years (25.4%, n=360), with 14% (n=199) of victims below 20 years. The bite site was documented in 57% (n=806) of cases, mostly on lower extremities (88.2%, n=711). Time from bite to hospitalization was recorded in 27% (n=383) of cases, with 25.3% (n=97) admitted within one hour, 35.5% (n=136) within 1-2 hours, and 18.3% (n=70) after six hours. To understand community perspectives, 28 focus group discussions (FGDs) were conducted, split evenly between male and female participants. Project Technical Officers were trained in conducting FGDs to ensure high-quality data collection. Additionally, 248 medical and community health officers received specialized training in snakebite management, including basic life support and CPR using medical manikins. Healthcare workers, including nurses, pharmacists, and lab technicians were also engaged through 338 interviews to assess their knowledge and preparedness. The study assessed 34 healthcare facilities, including 26 Primary Health Centers, three Rural Hospitals/Community Health Centers, and five Sub-District/District Hospitals, for snakebite management readiness. Information, Education, and Communication (IEC) materials, such as protocols, booklets, posters, brochures, and snake identification charts, were developed in multiple languages (English, Hindi, Marathi, and Oriya) to ensure broad accessibility and impact. The intervention significantly improved snakebite management outcomes. The case fatality rate decreased by 30.8%, reflecting improved medical response and increased awareness. Documentation practices saw a 22.8% increase in recording bite sites and a 37% improvement in documenting the time from bite to hospitalization, essential for timely and effective treatment. The proportion of victims reaching health facilities within one hour of the bite increased from 25.3% to 39.2%, a 54.9% improvement, highlighting the effectiveness of training programs and IEC materials. First aid administration increased by 102.5%, demonstrating enhanced community awareness and preparedness, while the administration of anti-snake venom (ASV) test doses decreased by 34.2%, indicating more judicious use and potentially improved diagnostic

accuracy and treatment protocols. The study emphasizes the need for continued capacity building among medical officers and community health workers to manage snakebite cases effectively. The success of the training programs and IEC material dissemination suggests that such initiatives can significantly improve outcomes and should be scaled up to other high-burden areas. The insights gained from this study are crucial for shaping the National Action Plan for Prevention and Control of Snakebite Envenoming (NAPSE) in India. The comprehensive data collected provides a robust evidence base for formulating targeted interventions and policies to reduce the incidence and improve snakebite management. Future efforts should focus on sustaining and expanding these interventions to ensure that healthcare providers and communities continue to benefit from the knowledge and practices established by this study.

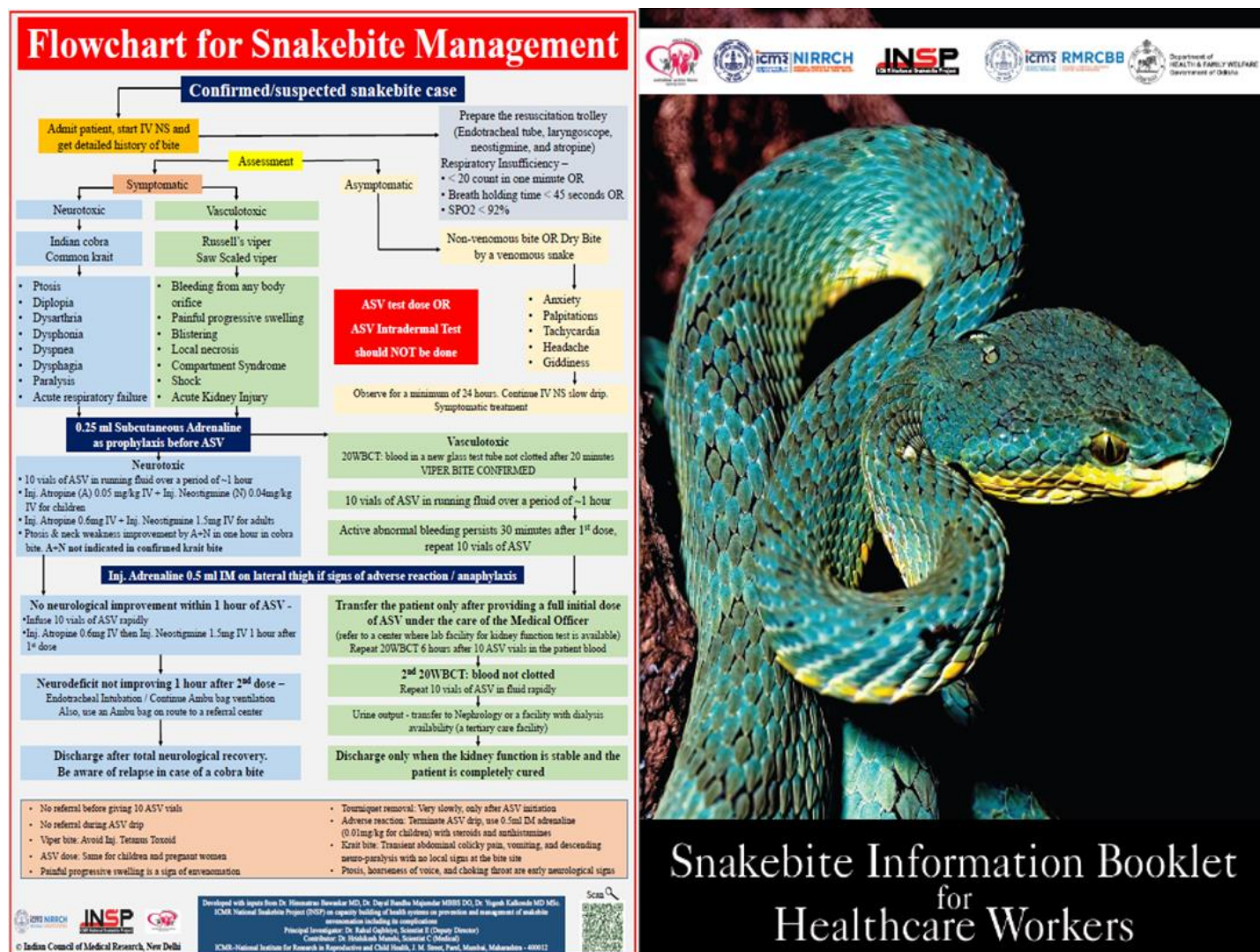


Figure 1: Flowchart for snakebite management for medical officers and snakebite information booklet for healthcare workers

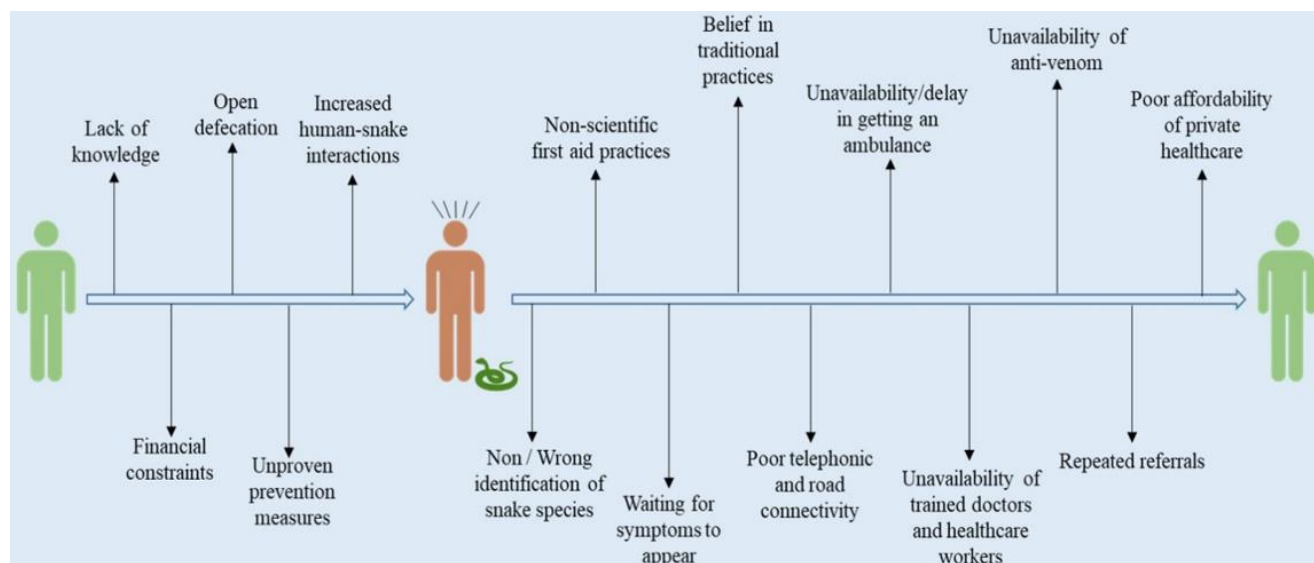


Figure 2: The barriers to prevention and barriers to effective management frameworks highlighting potential avenues for intervention. Developed based on the results of the Focus Group Discussions.

9.2.3 Nationwide Study to Estimate Incidence, Mortality, Morbidity and Economic Burden due to Snakebites in India *(Partly Funded by Indian Council of Medical Research)*

Principal Investigator : **R Gajbhiye**

Project Associates : Smita Mahale, HS Bawaskar, D Punde, Sadananda Raut, B Shinde, N Ishwarrao Bhosikar, B Pawar, S More, S Mane

Collaborators : Shital Narayan Rathod, Anjali Surykant Deshmukh,
Government Medical College Nanded
P Vasantrao Salve, Varsha Subhash Dange
Pimpri Chinchwad Municipal Corporation Pimpri, Pune

Duration : 2022-2024

The study was implemented in three districts in Maharashtra – Raigad, Pune and Nanded. The preparatory phase of the study involved capacity building training of ASHAs for data collection. The ASHA trainings in the study districts showed a commendable participation rate, with 78.9% of the 6862 ASHAs attending the training sessions. Raigad district had the highest attendance at 80.6%, followed by Pune at 78.3% and Nanded at 78.1%. The effectiveness of the training was evaluated using pre- and post-training questionnaires, which were completed by 80.3% of the attendees. Raigad and Nanded districts demonstrated the highest compliance rates for the evaluation, at 97.9% and 96.8% respectively, whereas Pune had a lower rate of 59.3%, likely due to logistical delays in administering the questionnaires. The incidence and case fatality rates (CFR) of snakebite cases varied across the districts. Raigad had the highest incidence at 34.1 per 100,000 people and a CFR of 1.6%, Pune had the lowest incidence at 2.3 per 100,000 but the highest CFR at 5.4%, and Nanded had an incidence of 22.6 per 100,000 and a CFR of 3.4%. About two-thirds of the snakebite cases were due to venomous snake species. The Big Four contributed to about 90% of all venomous cases. About 90% of the victims were

hospitalized for treatment, out of which about 80% were admitted at a Government facility including Medical College, District hospital, Taluk Hospital and Primary Health Centre. Economic analysis revealed significant financial burdens on snakebite victims and their caregivers. The average wage loss during treatment was Rs. 2637, and out-of-pocket expenses averaged Rs. 11262, totaling Rs. 13899 per snakebite case. These findings underscore the importance of training ASHAs and the need for strategies to reduce the economic impact on affected families. The findings of this study have several important implications.

Enhanced Training Programs: The high attendance and evaluation compliance rates indicate a successful engagement of ASHAs in training programs. This suggests that further investment in ASHA training could be beneficial in improving healthcare delivery and outcomes in rural areas.

Targeted Interventions: The variation in incidence and CFR across districts highlights the need for targeted interventions. Raigad, with the highest incidence but lowest CFR, might benefit from continuing its current strategies, while Pune, with the highest CFR, requires urgent intervention to reduce fatalities.

Economic Support: The significant financial burden on snakebite victims and their caregivers underscores the necessity for economic support mechanisms. This could include subsidized treatment costs, wage compensation, and financial aid programs to mitigate the economic impact on affected families.

Policy Development: The data provides a strong foundation for policymakers to develop evidence-based health policies. This includes improving logistical support for training programs, enhancing emergency response systems for snakebites, and integrating economic support strategies into health programs.

Future Research: The study highlights areas for future research, such as exploring the reasons behind the high CFR in Pune, assessing the long-term impact of training programs on healthcare outcomes, and evaluating the effectiveness of economic support interventions.



Figure 1: Ms. Ashwini Wanzolkar, District Coordinator, district Raigad conducting the training workshop for ASHAs at Uran block in Raigad district on May 11, 2022.

Ongoing projects:

1. Utilizing the Model Rural Health Research Units to improve snakebite management through rationalized antivenom distribution models in India: An implementation research project (*funded by the Department of Health Research, Government of India*) PI: R Gajbhiye; Co-PI: H Munshi
2. A situational analysis of the disease burden in the North Maharashtra Region. PI: R Gajbhiye; Co-PI: H Munshi
3. Strengthening implementation of antenatal screening and newborn management for Sickle Cell Disease at rural Hospital, Vani, Maharashtra. PIs: Suchitra Surve, R Gajbhiye; Co-I: H Munshi
4. Strengthening the National leprosy eradication program in Dindori, India. PI: R Gajbhiye; Co-PI: H Munshi

The outreach activities of MRHRU, Vani mainly focused on capacity building of communities and frontline health workers in the Dindori and Surgana blocks of Nashik District. Their details are described in Table 1.

Table 1: Outreach activities of MRHRU, Vani during 2023-2024

Date	Event / Activity	Resource person/s	No. of beneficiaries
25.08.2023	Training and awareness session on snakebite for community at Gram Panchayat Borgaon, Taluka Surgana	R Gajbhiye H Munshi	100
12.09.2023	Training for ASHAs on early detection and treatment of leprosy at PHC Nanashi	VM Katoch Kiran Katoch	60
27.09.2023	Informative session on snakebite prevention, first aid and management for ASHAs at MRHRU, Vani	H Munshi	70
27.09.2023	Role play and session on prevention and management of Sickle Cell Disease for ASHAs at MRHRU, Vani	Suchitra Surve	70
02.02.2024	Awareness rally and street play in Vani and Nanashi villages on occasion of World Leprosy Day	R Gajbhiye	100
07.03.2024	Awareness session for adolescent girls on women's health and endometriosis at Karmavir High School, Vani on occasion of Endometriosis Awareness Month	Savita Tapase	150
13.03.2024	Release of IEC material on snakebite prevention, first aid and management for medical officers, healthcare workers and community	R Gajbhiye H Munshi	-



Figure 1: Indicative snapshots of various activities organized by MRHRU Vani during 2023-24
A. Street play; B. Visit by Dr Vishwa Mohan Katoch, Former Secretary, DHR & DG ICMR and Dr Kiran Katoch, Former Director, NJIL & OMD Agra.; C. LRAC Meeting; D. Release of IEC material; E. Rally by school children on leprosy and F. Foundation Stone Laying of MRHRU, Vani

10. RESEARCH SUPPORT FACILITIES

10.1 Family Welfare Clinics

In-Charges : **Anushree Patil, Deepti Tandon**

Staff : Sunita Kale, Sunita Kharat, Sunita Kendre

The family welfare clinics located at Wadia hospital provide family planning services and serve as a model for integration of family planning services with other aspect of reproductive health care. Services offered routinely are contraceptive services, gynecological consultations, RTI/STI treatment, cancer screening. The women attending these clinics are then enrolled for clinical studies. These participants provide biological samples for basic research studies approved by the institutional ethics committee. The important feature of these clinics is a good rapport of the clinic staff with the women/couples attending these clinics. This results into high rate of follow-ups (more than 95%) for the project participant. Details of the services provided during year 2023-2024 are as below:

Table 1: Services provided by the clinic

Services	Number
Women who attended the clinic	1419
Women counselled for contraception	435
Women who accepted CuT-380	8
Women who accepted Oral Contraceptive Pills (OCPs)	7
Condoms distributed	5060
Women who accepted Injectable Contraception	6
Women who accepted Centchroman Contraceptive Pills (Chaya)	10
Women tested for RTI/STIs	142
Women who were tested by Papanicolaou test	38
Women treated for Anemia	49
Ongoing research projects from infertility clinic	15
Participants recruited for various collaborative research studies	100

10.2 Child Health Clinic

In-Charge : **Suchitra Surve**

Staff : Varsha Tryambake, Rachna Dalvi, Sharmila Kamat, Sarita Bhange

Child health services were initiated at Family Welfare Clinic located at Abhyudaya Nagar in 2015. The objectives of the clinic are growth monitoring and nutritional guidance, screening for disease and deficiencies, child development and mental health and health education services such as height, weight

monitoring and growth parameters, learning disorders and behavioral issues, counseling and referral and sex education are being provided. Details of the services provided during year 2023-2024 are as below:

Table 2: Child health services provided by the clinic

Services	Number
Total number of children who attended the clinic	1421
Total number of new children	640
Children treated for deworming	345
Children treated for anemia	151
Children who received dietary counseling	371
Children treated with Calcium and Vitamin D supplementation	512
Puberty counseling	17
Children recruited and followed up for research	202
Paediatric Endocrinology	40
Paediatric Nutrition OPD	22
Children referred from schools (growth + puberty)	338

Parents are advised mainly on new-born care and breastfeeding, growth and development of children, nutrition, issues related to menarche and puberty. In order to address issues related to precocious puberty, obesity, short stature. Pediatric endocrinology OPD is held once a month by Dr Sudha Rao, paediatric endocrinologist from Bai Jerbai Wadia Hospital for Children. Nutrition OPD clinic is held once in two months by Dr. Sanjay Prabhu, Medical Director from Bai Jerbai Wadia Hospital for Children. The linkages with schools have been established and children are referred for evaluation of growth and puberty.

10.3 Infertility and Reproductive Endocrinology Clinic

In-Charges : **Anushree Patil, Deepti Tandon**

Staff : Pratibha Kokate, Shobha Banage, Anamika Akula, A Hussain, Akshaya Rathod, Shalini Lambade

During the reporting period, clinical services were offered to infertile couples via the Infertility Clinic, specialized PCOS clinic, Specialized POI clinic and Andrology OPD. These services aided in managing the needs of infertile couples effectively. Telephonic consultations were also provided to support these couples. Additionally, monthly reports on Pre-Conception and Pre-Natal Diagnostic Techniques (PCPNDT) were compiled and submitted to the Municipal Corporation of Greater Mumbai.

Table 3: Services provided by the clinic

Services	Number
Infertility couple registered and consultation provided	228
Telephonic consultations	420
New infertile couples	228
Follow up patient visits for diagnosis, counseling and management	1730
New andrology cases detected	95
Ultrasound for serial follicular monitoring	242
Women hysterosalpingography (HSG) reports obtained and evaluated	110
Pregnancies reported	31
Couples referred for IUI	38
Couples referred for IVF	78
Couples counseled for adoption	26
Women diagnosed and treated for RTI/STI	142
Women who were tested by Papanicolaou test	38
Women diagnosed and treated for Anemia	67
Couples referred for genetic evaluation	54
Women referred to Preventive Oncology department (TATA Hospital)	6
Collaborator research projects	13
Participants recruited for various collaborative research studies of the institute	135

10.4 Multidisciplinary PCOS Clinic

In-Charge : **Anushree Patil**

Staff : Deepti Tandon, Pratibha Kokate, Shobha Banage, Anamika Akula, Akshaya Rathod, Shalini Lambade

Our Institute has a multidisciplinary team conducting research in clinical, epidemiological, genetic and bio-informatics aspects of PCOS. Metropolitan cities have increasing number of women of reproductive age being diagnosed with PCOS. 64% of women referred at the infertility clinic had PCOS. 55% were obese (BMI about 25) and 70% had waist hip ratio more than 0.8. This observation reiterated that PCOS is a cause of infertility and is increasing among adolescents. Recognizing that apart from medical management, PCOS needs a holistic care under one roof for weight reduction, diet, cosmetic and physiological issues, a model of multidisciplinary PCOS clinic was developed. This is one of its kind in India in a government health research institute. Women with PCOS are managed on a regular basis and once in a month a joint multidisciplinary clinic is conducted. A multidisciplinary team of eminent doctors like infertility specialist, dermatologist, psychiatrist, nutritionists and yoga experts provide holistic management to women with PCOS. Cohorts of adolescent and infertile women with PCOS are enrolled and followed at the clinic. Metabolic parameters are monitored. An electronic database is created of physical, hormonal, biochemical, ultrasound and emotional health parameters of the women with PCOS. Outreach education programme for adolescent school girls are also

conducted in school and colleges to increase awareness about the condition and to improve health seeking behavior and early diagnosis.

Table 4: Services provided by the clinic

Services	Number
PCOS cases detected	47
PCOS blood test done at Phadake lab	47
PCOS clinics conducted	8
Total clients attend the PCOS clinic	78
Ongoing research projects	7
Participants recruited for various collaborative research studies	84

10.5 Multidisciplinary Clinic for Premature Ovarian Insufficiency

In-Charge : **Deepti Tandon**

Staff : Pratibha Kokate, Shobha Banage, Anamika Akula, Akshaya Rathod, Shalini Lambade

A multidisciplinary clinic for Premature Ovarian Insufficiency (POI) was initiated from June 2022. It was conducted once in three months in the year 2023-2024. The clinic team is comprised of a gynecologist, an IVF expert, a clinical immunologist, an endocrinologist, genetic expert and basic scientist. The aim of the clinic is to evaluate the clinical spectrum, common autoimmune disorder; genetic factors and quality of life of women diagnosed with Spontaneous POI. Further the aim is to establish a longitudinal cohort for continuous monitoring of clinical features and metabolic parameters and improve management strategies.

Table 5: Services provided by the POI clinic

Services	Number
Number of POI cases detected	6
POI blood test at Phadake SRL lab	16
POI clinic conducted	3
Patients attended the POI clinic	23

10.6 Andrology Clinic and Laboratory

In-Charge : **R Gajbhiye**

Consultant Andrologists : P Kothari, R Shah, V Kulkarni

Staff : Shobha Banage, Pratibha Kokate, Anamika Akula, Akshaya Rathod, Shalini Lambade

During the reporting year, a total of 206 male infertility patients received treatment through Andrology Clinic. For surgery and other specialized investigations, we referred 35 patients to collaborating institutions in Mumbai. Total 24 OPDs were conducted and services included andrology examination, diagnosis, treatment and counselling. Apart from the clinical services, our team is actively involved in the research projects on male infertility. The well characterized clinical materials and clinical data were useful for the PhD students of institute. During reporting year, 2 PhD students submitted their PhD thesis from the collaborative work. One PhD student and one scientist received award also. Following study participants were screened and recruited for institutional research projects.

Table 6: Details of study participants recruited for collaborative research projects on male infertility

Name of the Scientist	No of participants screened	No of participants recruited
Periyasamy Kuppusamy	21	16
DVS Sudhakar	5	4
Dhanashree Jagtap	10	6
Deepti Singh	19	11
Kushan Khambata	32	11

10.7 Bone Health Clinic, Reproductive and Bone Health Unit, Naigaon

In-Charge : **Lalita Savardekar**

Staff : Neera Mehta, Kiran Chavan, Swaroopa Khedekar, V Prashant

The community based Bone Health Clinic is a unique model to address osteoporosis while attending to knee/ spine problems and improvement in physical activity / Quality of life by Yoga and stretching exercises. This multidisciplinary and comprehensive health care management may help in compliance of treatment for osteoporosis. In the reporting year, DXA was done in 28 new registered and 78 old registered clienteles. Repeat scans were done (total 103 scans). Total clinic attendees for the current year were 1589 attendees who were given various referrals as required for cardiac opinion, urology, physiotherapy, diabetologist and followed up for hypertensive treatment with physician. All clienteles were given monthly stock of routine calcium supplements, multivitamins, vitamin C and vitamin D. Regular follow ups were taken for all the registered clients via telephonic calls (>2000 calls) regarding intake of medicines. Spine OPD (Clinic consultation) were conducted with 19 OPD's with attendance of 195 clienteles. Endocrine OPD for non-communicable diseases (Diabetes Mellitus type II, Hypertension, thyroid disorders) were conducted with total 11 OPD's and 86 attendees in the current year. One knee camp for orthopedics consultations for osteoarthritis knees attended by 49 attendees.

10.8 Woman's Health Clinic, Reproductive and Bone Health Unit, Naigaon

In-Charge : **Lalita Savardekar**

Staff : Neera Mehta, K Chavan, Swaroopa Khedekar, V Prashant

The Woman's Health Clinic, community-based service cum research clinic located at BDD Chawl, offers services for minor ailments, gynaecological complaints, family planning needs etc. Routine health services include clinical examination, breast examination, cytology screening and contraception services. During was current year, Gynaecology consultations were provided to 117 women. Cervical cancer screening was done for 20 women. Services included Copper-T 380A insertions, Condoms distribution and any gynaecological complaints. These consultations included women who came with menorrhagia, incomplete abortion, PCOS, irregular menstruation, post-menopausal bleeding, urinary tract infections, Copper- T Users etc. A specialized gynaecology OPD was held with 9 OPD and 38 attendees.

10.9 Genetic Research Centre

In-Charge : **S Pande**

Staff : Shaini Babu

Genetic testing and conseling services were provided as follows:

Table 7: Services provided by the clinic

Services	Number
Genetic counseling	~700 cases (pre and post-test)
Karyotyping	~350 cases
FISH	~120
Molecular genetic test	~250

10.10 National Center for Preclinical Reproductive and Genetic Toxicology

In-Charge : **V Dighe**

Staff : S V Jadhav, Shilpa Kerkar, YN Kamble, P. S. Salunkhe, NB Shelar

The National Center for Pre-clinical Reproductive and Genetic Toxicity has a mandate of research, services and capacity building. Services to various academic bodies and industries are being undertaken following Organization for Economic Co-operation and Development (OECD) guidelines and Good Laboratory Practices (GLP). Following research projects were undertaken in collaboration with academic institutions during 2023-2024:

1. Acute and subacute toxicity of organo-selenium compound 3-# Diselenodipropionic acid (3-3 DSEPA) (*Funded by ACTREC Clinical pharmacology & Radiobiology lab, Mumbai*)
2. Evaluation of immunomodulatory and anti-cancer properties of Hydroxychavicol, a major constituent of Piper betel (*Funded by Institute of Chemical Technology, Mumbai*)
3. Preclinical study on efficacy, safety and toxicity and swarna prashan regimen as adjunct therapy in pediatric acute lymphoblastic leukemia (*Funded by the RARP-CCRAS, Mumbai*)
4. Developmental and reproductive toxicity studies and 28-day repeated dose oral toxicity studies for Cap. PCOSnil in Rats (*Funded by Acuere Biosciences Pvt. Ltd., Pune*)
5. Genotoxicity studies for Cap.PCOSNIL in rats (*Funded by Acuere Biosciences, Pvt. Ltd., Pune*)

10.11 COVID-19 Diagnostics Testing and Reporting

In-Charges : **V Patel, V Bhor, Kiran Munne**

Staff : K Shah, Namrata Neman, O Arekar

The COVID-19 diagnostic facility carried out testing of 5,643 samples by RT-PCR during the period April-June 2023. This activity was discontinued from July 2023.

10.12 Health Technology Assessment Resource Hub

In-Charge : **Beena Joshi**

Staff : A Padhan, Tejal Varekar and N Mungekar

HTA resource Hub has been functional with support from DHR HTAIn since 2018. In the reporting year two important projects were initiated and completed.

1. Estimating package costs for IVF for possible inclusion in PMJAY: This multi-centric study conducted across 5 centers in India collated health system costs, OOOPE and health related quality of life data for couples undergoing infertility treatment including IVF. The data generated could be also used for other HTA studies on the topic.
2. Estimating cost/ test of a Point of Care device Gazelle for diagnosing Sick Cell Anemia: The study was completed approved by the Technical Advisory Committee and Board. A policy brief has been developed and recommendation has been sent to Ministry.

The resource hub also sensitized the stakeholders of the state health department and has signed a MOU for collaboration on research and to provide technical guidance. The resource hub was assigned the responsibility of coordinating a session on HTA for new and emerging technologies for the National Consultative Workshop on HTA that was hosted by DHR in New Delhi in December 2023. Brainstorming with several experts and organizations was done and all discussions were synthesized and presented during the meeting. HTA resource Hub also was invited at Annual meeting of the Indian Council for Scientific Research to disseminate the work done by HTA. Also academic talks to students and entrepreneurs were held. The HTA resource Hub continues to take on new ideas from state and local health departments to conduct costing or costeffectiveness analysis.

10.13 Experimental Animal Facility

In-Charge : **D K Das, S M Metkari**

The institute has a well maintained animal facility distributed over three floors and houses different species of laboratory animals. The animals are maintained and well taken care of by qualified and trained staff everyday including weekends and holidays. The details of animals bred and supplied during the year are given as follows:

Table 8: Animals bred and supplied after due approval of IAEC during the year

Species	Animal Bred	Animals Supplied
Swiss Mice	647	88
Balb/c Mice	865	491
C57BL/6	1044	464
FVB-NJ	583	75
GFP- BL/6	353	NIL
GFP- FVB	411	05
Transgenic Mice WB/Rej/Kit	535	NIL
Transgenic Mice C57BL/6/ Kit/J	542	NIL
Transgenic Mice Mgat1 -/-	25	NIL
Transgenic C57BL/6-Tg (TRAMP)	167	30
Transgenic Mice B6:CBA Tg- Oct4	485	77
Wistar rats	1958	1343
Rabbits	NIL	04
Marmosets	14	00

10.14 Institutional Animal Ethics Committee

In-Charge : **DK Das, SM Metkari**

The Institute is registered for breeding and experimentation on laboratory rodents including non-human-primates with the Committee for the Control and Supervision of Experiments on Animals (CCSEA), Department of Animal Husbandry and Dairying, Ministry of Fisheries, Animal Husbandry and Dairying, Government of India (vide registration No. 78/GO/ReBi/SL/99/CPCSEA dated 11th March 1999) and this registration has been renewed periodically. The Institutional Animal Ethics Committee (IAEC) members including CPCSEA nominees critically review, approve and monitor research protocols on laboratory animals. The IAEC also conducts inspection of animal house facility periodically to ensure that animal welfare activities are stringently followed before, during and after animal experimentation. The institute upholds the principals of 3R's - Reduction, Refinement and Replacement principal for humane use of experimental animals in the scientific research. During the year 2023-24, two IAEC meetings were convened on August 28, 2023 and January 29, 2024 respectively. Total 14 animal study protocols were reviewed and approved by the IAEC.

10.15 ICMR-NIRRH Ethics Committee for Human Studies

In-Charge : **V Bhor**

Staff : Vaishali Bhogate, Zakia Ansari, A Hankare

During the reporting period, Prof Shubhada Chiplunkar and Dr Vikrant Bhor continued as chairperson and member secretary, respectively, for ICMR-NIRRH Ethics Committee for Human Studies. Dr

Suchitra Surve served as joint member secretary till October 8, 2023 and she was followed by Dr Bhakti Pathak from November 5, 2023 onwards. Dr Sadhana Gupta (affiliated- basic scientist) and Dr KV Ganapathy (community representative) joined as new members. The ethics committee secretariat staff remained unchanged with Ms Vaishali Bhogate, Ms Zakia Ansari, and Mr Anand Hankare. A total of 8 full board meetings were conducted during the reporting period and 51 new projects were reviewed. Among these, 35 underwent full board evaluation, 11 underwent expedited review and 5 were exempted from review. In addition to the review of new projects, 26 amendments and numerous continuing review reports, completion reports and a few protocol deviation reports were reviewed. Overall, the committee approved 48 new proposals, 26 amendments and granted extension for ongoing projects following review of continuing review reports and extension requests.

10.16 Library and Information Centre

In-Charge : **Prabhjeet Kaur**

Staff : Simmy Saji, Priya Menon, V Shinde, A Gode

Dr GM Phadke Memorial Library and Information Centre houses an exclusive collection of books, journals, reports etc. on subjects encompassing different aspects of reproductive health care. The library houses collection of manuals and books on basic techniques in molecular biology, immunology, cell biology, etc. To cater to specific requirements of the researchers at the Institute, the library subscribes to 45 online journals. These journals can be accessed via the institutional intranet. Apart from providing information services to all the staff and students of the Institute, the library also serves the users from other Institutions. It collates information for monthly/quarterly/annual reports on the significant achievements and publications of the Institute. The library staff is actively involved in updating and maintaining the institutional website and intranet. The library coordinates visits by students and staff from other institutions that are keen to learn about the research and facilities at the institute. Dr Prabhjeet Kaur acts as Central Public Information Officer and responds to applications filed/forwarded under the Right to Information Act 2005.

10.17 Communication Cell

Nodal Communication Officer : **Susan Thomas**

Staff : Priyanka Parte, Prabhjeet Kaur, Kumari Nishi, Bhavya MK,
Neha Minde, Priya Menon

The Cell is responsible for organizing activities based on important health days. They also manage social media handles of the institute including X (formerly Twitter), Facebook, LinkedIn, Instagram and YouTube; and update about latest publications and activities of the institute. It also provides help to the staff in disseminating their research using print and digital media.

10.18 Core Facilities

10.18.1 Confocal Imaging facility

In-Charge : **Dipty Singh**

Staff : Shobha Sonawane, Reshma Gaonkar

The facility provided assistance to staff and students of the Institute and other academic / research Institutes for co-localisation, FRET, live cell imaging, 3D imaging, on LASER Confocal System. From April 2023 to March 2024, 50 researchers used the facility from the Institute and other institutes.

10.18.2 Flow Cytometer and DNA Sequencing

In-Charge : **Srabani Mukherjee**

Staff : Sushma Khavale, Gayatri Shinde (Flow cytometry), Nanda Joshi (DNA sequencer)

These facilities provide services institutional projects and inter-institutional projects. During reporting year, 1175 samples were processed for flow cytometry and DNA sequencing was performed for 5939 samples.

10.18.3 Facility for Infectious Organisms

In-Charge : **V Patel**

Staff : Fiza Shaikh, Denna Prabhin

Infectious flow core facility has heavily been used both for intra-institution as well as Inter-institutional studies. We have BD Accuri and Symphony which are analyzers. BD FACS Aria Fusion is a cell sorter. Flow cytometers are being used to study immune cells from the infected or uninfected human, rat, mice blood as well as tissue samples addressing various infectious diseases (HIV, CMV, TB, COVID- 19), pre-eclampsia in pregnancy, ovarian cancer cells, drug toxicity studies. Sorter has been used to identify and segregate neuronal cells from mice brain, CD4+ T cell subsets from human blood, transfected cells in the cell line on the basis of reporter expression. Currently we are helping PIs from ICT, TIFR, Nair hospital by providing access to our flow cytometers and also guiding in data analysis.

10.18.4 Histology Work Station

In-Charge : **V Dighe**

Staff : P Salunke, M Ghosalkar

The histology workstation in the National Center for Preclinical Reproductive and Genetic Toxicology is a state of art facility equipped with an automatic tissue processor, automatic slide stainer, tissue embedder, microtome, and automatic cover slipper. This central facility is utilized by researchers in the institute as well as other academic and private institutions. In the reporting year, 1085 tissue samples were processed. Embedded and paraffin blocks were prepared. 5228 tissue blocks were sectioned, and 1259 slides were stained using haematoxylin and eosin staining.

11. PUBLICATIONS

11.1 Peer Reviewed Publications during 2023

1. Ahir-Bist S, Chavan V, Padmaja Samant M, Nanavati R, Mehta P, Mania-Pramanik J. Human leukocyte antigens class I and class II alleles associated with vertical human immunodeficiency virus transmission - an exploratory study from Mumbai, India. **Indian J Dermatol Venereol Leprol.** 2023 Jan-Feb;89(1):159. doi: 10.25259/IJDVL_654_19. PMID: 36331825. [IF: 2.9]
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3. Begum S, Battala M, Chalmiers MA, Prusty RK, Dixit A, Johns NE, Raj, A. Spousal concordance in attitudes toward Intimate Partner Violence (IPV) and its association with physical IPV against women: A cross-sectional study among young married couples in rural India. **Partner Abuse.** 2023 Jun. doi: 101891/PA-2021-0043. [IF: NA]
4. Bhadriricha H, Patel V, Patil A, Surve S, Desai M. Characterization of peripheral T helper 17 (Th17) cells phenotype in postmenopausal women with estrogen insufficiency. **Blood Cells Mol Dis.** 2023 Jan; 98:102702. doi: 10.1016/j.bcmd.2022.102702. Epub 2022 Sep 5. PMID: 36274341. [IF: 2.3]
5. Bhandari P, Prusty RK, Begum S. Association between intimate partner violence and nutritional status among Indian women: a latent class analysis approach. **Arch Public Health.** 2023 Aug 29;81(1):162. doi: 10.1186/s13690-023-01152-w. [IF: 3.3]
6. Bhanothu V, Munne K, Pande S, Singh P, Jagtap D, Aranha C, Gogoi D, Bhagat S, Gaonkar R, Kerkar S, Shah K, Mukherjee N, Bhor V, Patel V, Mahale SD, Sachdeva G, Begum S. The dynamics of SARS-CoV-2 infection in unvaccinated and vaccinated populations in Mumbai, India, between 28 December 2020 and 30 August 2021. **Arch Virol.** 2023 Jun 23;168(7):188. doi: 10.1007/s00705-023-05815-5. [IF: 2.7]
7. Bhide AR, Suri M, Katnoria S, Kaur S, Jirwankar YB, Dighe VD, Jindal AB. Evaluation of pharmacokinetics, biodistribution, and antimalarial efficacy of artemether-loaded polymeric nanorods. **Mol Pharm.** 2023 Jan 2;20(1):118-127. doi: 10.1021/acs.molpharmaceut.2c00507. Epub 2022 Nov 17. [IF: 4.9]
8. Bhojwani H, Begwani K, Bhor V, Bedi P, Balasinor N, Raut S, Joshi U. Synthesis and biological evaluation of benzamide-chalcone hybrids as potential c-Met kinase and COX-2 inhibitors. **Arch Pharm (Weinheim).** 2023 May;356(5): e2200405. doi: 10.1002/ardp.202200405. Epub 2023 Feb 8. PMID: 36752183. [IF: 5.1]

9. Bisht D, Sajjanar BK, Saxena S, Kakodia B, Dighe V, Thakuria D, Kharayat NS, Chanu KV, Kumar S. Identification and characterization of phage display-selected peptides having affinity to *Peste des petits ruminant's virus*. **J Immunol Methods**. 2023 Apr; 515:113455. doi: 10.1016/j.jim.2023.113455. Epub 2023 Mar 7. PMID: 36893896. **[IF: 2.2]**
10. Chaaithanya IK, Aranha C. Human monkeypox: A threat to dread in pregnancy? **J Med Virol**. 2023 Jan;95(1): e28170. doi: 10.1002/jmv.28170. Epub 2022 Oct 1. PMID: 36151576. **[IF: 12.7]**
11. Chaaithanya IK, Aranha C. Probiotics: An Armament for Vaginal Healthcare. **J Assoc Physicians India**. 2023 Aug;71(8):11-12. PMID: 37651257. **[IF: NA]**
12. Chakraborty S, Rahate K, Kumar C, Idicula-Thomas S. Expanding the therapeutic options for *Candida* infections using novel inhibitors of secreted aspartyl proteases. **Drug Dev Res**. 2023 Feb;84(1):96-109. doi: 10.1002/ddr.22015. Epub 2022 Nov 26. PMID: 36435973. **[IF: 3.8]**
13. Chaudhari UK, Hansen BC. Low serum creatinine, a surrogate marker of muscle mass, correlates with insulin sensitivity in nonhuman primates. **J Med Primatol**. 2023 Apr;52(2):100-107. doi: 10.1111/jmp.12633. Epub 2023 Jan 19. PMID: 36656041. **[IF: 0.7]**
14. Deshpande SSS, Bera P, Khambata K, Balasinor NH. Paternal obesity induces epigenetic aberrations and gene expression changes in placenta and fetus. **Mol Reprod Dev**. 2023 Feb;90(2):109-126. doi: 10.1002/mrd.23660. Epub 2022 Dec 21. PMID: 36541371. **[IF: 2.5]**
15. Dhivya kumari S, Chaudhari A, Brahmane MP, Das DK, Sathiyarayanan A, Yashwanth BS, Pinto N, Goswami M. Development and characterization of a new muscle cell culture system from *Clarias magur* (Hamilton, 1822). **Fish Physiol Biochem**. 2023 Dec;49(6):1295-1302. doi: 10.1007/s10695-023-01257-7. Epub 2023 Oct 25. PMID: 37878191. **[IF: 2.9]**
16. Doloi R, Gupta SM. MicroRNAs: The key players regulating the crosstalk between Hippo and Wnt/ β -catenin pathways in breast cancer. **Life Sci**. 2023 Sep 15; 329:121980. doi: 10.1016/j.lfs.2023.121980. Epub 2023 Jul 27. PMID: 37516428. **[IF: 6.1]**
17. Fernandes T, Patel V, Aranha C, Velhal S, Momin M, Mulcutkar M, Sawarkar S. pH-triggered polymeric nanoparticles in gel for preventing vaginal transmission of HIV and unintended pregnancy. **Eur J Pharm Biopharm**. 2023 Oct;191:219-234. doi: 10.1016/j.ejpb.2023.09.001. Epub 2023 Sep 3. PMID: 37669727. **[IF: 4.9]**
18. Gajbhiye RK. Endometriosis and inflammatory immune responses: Indian experience. **Am J Reprod Immunol**. 2023 Feb;89(2):e13590. doi: 10.1111/aji.13590. Epub 2022 Jul 1. PMID: 35751585; **[IF: 3.6]**

19. Gajbhiye RK, Chaaithanya IK, Munshi H, Prusty RK, Mahapatra A, Palo SK, Pati S, Yadav A, Bansode M, Shambharkar S, Madavi K, Bawaskar HS, Mahale SD. National snakebite project on capacity building of health system on prevention and management of snakebite envenoming including its complications in selected districts of Maharashtra and Odisha in India: A study protocol. **PLoS One**. 2023 Feb 17;18(2): e0281809. doi: 10.1371/journal.pone.0281809. PMID: 36800356 [IF: 3.7]
20. Gajbhiye RK, Munshi H, Bawaskar HS. National programme for prevention & control of snakebite in India: Key challenges & recommendations. **Indian J Med Res**. 2023 Apr;157(4):271-275. doi: 10.4103/ijmr.ijmr_2424_22. PMID: 36926753 [IF: 4.2]
21. Ganie MA, Chowdhury S, Suri V, Joshi B, Bhattacharya PK, Agrawal S, Malhotra N, Sahay R, Jabbar PK, Nair A, Rozati R, Shukla A, Rashid R, Shah IA, Rashid H, Wani IA, Arora T, Kulkarni B; PCOS Study Group. Normative range of various serum hormonal parameters among Indian women of reproductive age: ICMR-PCOS task force study outcome. **Lancet Reg Health Southeast Asia**. 2023 May 30; 15:100226. doi: 10.1016/j.lansea.2023.100226. PMID: 37614351 [IF: NA]
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23. Ganie MA, Chowdhury S, Suri V, Joshi B, Bhattacharya PK, Agrawal S, Malhotra N, Sahay R, Jabbar PK, Rozati R, Wani IA, Shukla A, Arora T, Rashid H. Prevalence, regional variations, and predictors of overweight, obesity, and hypertension among healthy reproductive-age indian women: nationwide cross-sectional polycystic ovary syndrome task force study. **JMIR Public Health Surveill**. 2023 Sep 6;9: e43199. doi: 10.2196/43199. PMID: 37672315 [IF: 8.5]
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27. Giri J, Modi D. Endometrial and placental stem cells in successful and pathological pregnancies. **J Assist Reprod Genet**. 2023 Jul;40(7):1509-1522. Doi: 10.1007/s10815-023-02856-2. Epub 2023 Jun 20. PMID: 37338750 [IF: 3.1]
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29. Hasan G, Shaikh S, Joshi B, Ganie MA, Shukla A, Vadhan H, Parab R, Sanap P, Mashal I. Addressing challenges during community based screening of women for Polycystic Ovary Syndrome (PCOS): A research experience from Maharashtra, India before and during COVID pandemic. **Indian J Community Med**. 2023 Jan-Feb;48(1):167-171. Doi: 10.4103/ijcm.ijcm_181_22. Epub 2023 Feb 1. PMID: 37082412 [IF: NA]
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11.2 Books

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3. Nishi K, Balasinor NH. Epigenetic regulation of placental function. In: Singh G, editor. Translational epigenetics, perinatal and developmental epigenetics. Volume 32. Academic Press; 2023. pp. 155-191. doi: 10.1016/B978-0-12-821785-6.00006-2.
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11.3 Papers / Posters Presented at Conference / Symposia

International

1. **25th European Congress of Endocrinology, Istanbul, Turkey, May 13-16, 2023**
 - **Raut S.** Delineating molecular mechanisms involved in hypo- and hyper-prolactinemia affecting male fertility
2. **42nd Annual Meeting of the American Society for Virology, Athens, Georgia, June 24-28, 2023**
 - **Palav H C.** A case for maternal screening of HCMV infection during complicated pregnancies: Integrated immune monitoring and association with adverse pregnancy outcomes
3. **8th European Congress of Virology 2023, Gdansk, Poland, May 4-7, 2023**
 - **Palav H C.** HCMV Infection status and immune monitoring in high risk pregnancy -association with adverse pregnancy outcome
4. **Epigenetics and Condensates in Lineage Decisions organized by EMBO, Dresden, Germany, September 28-30, 2023**
 - **Irani D.** Higher sperm H3K4me3 levels are associated with idiopathic recurrent pregnancy loss

National

5. **Genomics Analysis and Technology Conference; GATC-2023, InStem, Bangalore, April 7-9, 2023**
 - **Devadiga P.** Alteration of gut microbiome composition and function in people living with HIV

6. **XV Triennial & III International Conference of Indian Women Scientists' Association (IWSA), IWSA, Vashi, Navi Mumbai., June 11-13, 2023**
 - **Bhonde G.** Analysis of short-chain fatty acids in meconium samples of healthy newborns
7. **9th Annual Conference of the SMRM on Mitochondria in Biology and Medicine, Hyderabad, June 21-23, 2023**
 - **Arya D.** Effect of varicocele treatment on sperm mitochondrial functions and DNA methylation level in infertile men with clinical varicocele
8. **National conference of Indian association of Women's studies, Trivandrum, September 6-10, 2023**
 - **Bhavya M K.** Women is active or passive in environmental movements: A study on Athirappilly anti- dam movement Kerala.
9. **International Conference on Molecular Medicine, Reproduction and Endocrinology (ICMMRE-23) & 40th Annual Meeting of Society of Reproductive Biology and Comparative Endocrinology, Vadodara, September 14-16, 2023**
 - **Khambata K.** Estrogen receptors: shaping the sperm epigenome and beyond
 - **Mukherjee S.** Delving into the molecular mechanisms underlying poor oocyte quality in women with polycystic ovary syndrome
 - **Samant M.** Unveiling rare genetic variants in women with PCOS: A whole exome sequencing approach
 - **Singh A.** Effects of gestational methyl donor deficiency on fertility and reproductive outcomes of F1 mice offspring
 - **Singh D.** Potential contribution of sperm epigenome in recurrent pregnancy loss and varicocele associated male infertility
 - **Shinde U.** DNA methylation and expression of imprinted genes in circulating exosomes from women experiencing preeclampsia
 - **Shukla P.** Relation of mitochondrial DNA copy number and variants with the clinical characteristics and traits of polycystic ovary syndrome
 - **Sonawane S.** Ameliorative potential of epigallocatechin-3-gallate (EGCG) supplementation on steroidogenesis and spermatogenesis of cypermethrin exposed rats
10. **50th Annual Meeting of the Indian Immunology Society, Immunocon-50, AIIMS, New Delhi, October 5-8, 2023**
 - **Bhowmick S.** PD-1 expression and its interplay at different stages of HIV-TB coinfection
 - **Batgire J.** Gut microbiota derived metabolites from pregnant women with bad obstetric history exhibit altered macrophage polarization
 - **Devadiga P.** Gut microbiome dysbiosis is associated with altered gut homing potential of T lymphocytes in HIV infected individuals
 - **Kaginkar S.** To study if HIV-1B and HIV-1C differ in pathogenesis (viral and immune correlates)

- **Karandikar K.** Gut microbiota derived metabolites from HCMV-infected infants with cholestasis lead to *ex vivo* immune modulation in PBMCs
 - **Palav H C.** Integrated screening and anti-viral immune profile of HCMV infection in high risk pregnant women and its association with adverse pregnancy outcome
- 11. 15th The Cytometry Society Annual Conference and Workshops, 2023, AIIMS, Delhi, October 26-29, 2023**
- **Gurav P.** A comparative evaluation of immuno-dominant and cumulative HCMV specific cellular responses in the context of pregnancy
 - **Pandey T.** Studying the dynamics of recall T cell response post booster dose COVISHIELD/COVAXIN among healthy adult population
 - **Yadav S.** The interplay of sMAdCAM and sVCAM in cellular immune dysfunction responses accompanying HIV-1 infection
- 12. National HTA Consultative Workshop, New Delhi, December 7, 2023**
- **Joshi B.** HTA on new and emerging technologies
- 13. 19th National Research Scholars Meet, ACTREC, Navi Mumbai, December 7-8, 2023**
- **Panchal D.** The role of N-Formyl-L-aspartate in sperm chemotaxis
 - **Singh A.** Impact of maternal gestational methyl donor deficiency on reproductive development and fertility of mice offspring
 - **Miya V.** CRISP partnerships in controlling calcium expulsion
- 14. International Congress on Endometriosis, Endometriosis Society India, Dhaanodhanyo Auditorium, Kolkata, December 9-10, 2023**
- **Kuppusamy P.** Serum HE4 levels in Indian women with endometriosis: A preliminary study
- 15. 93rd Annual Session of the National Academy of Science (NASI) Symposium on 'India Secure @75' BARC, Mumbai, BARC, Mumbai, DAE Convention centre, December 3-5, 2023**
- **Arya D.** Genome wide sperm DNA methylation changes in infertile men with clinical varicocele
 - **Bhingardeve S.** DNA methylation and miRNA alliance- An emerging epimark of polycystic ovary syndrome
 - **Chakraborty AP.** Insights into the differential signaling barcodes evoked by isoforms of human kisspeptin.
 - **Dadachanji R.** Exploring association of thrombophilic gene variants with PCOS susceptibility and its related traits in Indian women.
 - **Naigaonkar A.** Metabolic coupling between oocyte and granulosa cells- links unraveled in PCOS
 - **Panchal D.** Unravelling the molecular mechanism/s of sperm chemotaxis mediated by N-formyl-L-aspartate
 - **b** Role of placental secretome in driving breast carcinogenesis during pregnancy.

- 16. National Conference on Social Work Research: Methodologies of the Peripheralized, Mumbai, January 8-9, 2024**
- **Bhavya M K.** Navigating feminist research in male-dominated spaces: A personal exploration
- 17. 19th Annual conference of the Indian Society of Bone and Mineral Research, Chennai, February 10-11, 2024**
- **Mehta N.** Mental health and Quality of life among menopausal women with osteoporosis and Musculoskeletal health disorders - A cross- sectional study
 - **Savardekar L.** Vertebral fractures among low income population: Association with bone mineral density and diabetes mellitus
- 18. REDRESS-2023, TIGS, Bengaluru, February 23, 2024**
- **D V S Sudhakar.** Genetic dissection of antenatally detected fetal abnormalities: uncovering promising candidate gene
- 19. International Conference on Reproductive Health: Innovations, Integration, and Implementation and 34th Annual Meeting of the Indian Society for the Study of Reproduction and Fertility (ISSRF-2024), CSIR-IICT, Hyderabad, February 23-25, 2024**
- **Bhanothu V.** Interim analysis of metabolomics data with potential of prenatal diagnosis of fetal congenital heart diseases in Indian women
 - **Bhanothu V.** Interim analysis of whole exome sequencing and thyroid-stimulating hormone receptor gene mutation in Indian families with thyroid dyshormonogenesis
 - **Bhanothu V.** Evaluation of different methods used in the detection of Female Genital Tuberculosis (FGTB) and gene polymorphism
 - **Bhor VM.** Delineating the interplay of the host vaginal milieu with pathogen & commensal membrane vesicles: implications for reproductive health
 - **Mukherjee S.** Dr. Subhas Mukherjee: The unsung hero of IVF
 - **Parte P.** Chemotaxis as mechanism for sorting good quality sperm for IVF/ICSI
 - **Patankar A.** Significance of Testis Specific Histone 2b (TSH2B) in meiosis and sperm function
 - **Singh D.** Sperm epigenome: A potential contributor in recurrent pregnancy loss and varicocele associated male infertility
 - **Tharayil SP.** Mitochondrial oxidative stress, dysfunction, and rare mitochondrial DNA variants: novel contributors in the pathophysiology of PCOS
- 20. National Public Health India Conference (NHPICON), New Delhi, February 24-26, 2024**
- **Surve S.** Paradigm shift in distribution of leprosy cases in high and low endemic districts of Maharashtra state, India
- 21. 8th World Cancer Congress 2024, JNU, New Delhi, March 18-20, 2024**
- **Mukherjee N.** Toll like receptors as therapeutic candidates in triple negative breast cancer

22. International Conference on Exploring Innovations in Life Sciences 2024 (ExILS 2024), Department of Botany and Zoology, Annasaheb Awate Arts, Commerce & Hutatma Babu Genu Science College, Manchar, Pune, March 23, 2024

- **D'souza S.** Investigating the role of endocannabinoid system in placental development: preliminary findings

11.4 Invited Lectures

- **Bhor VM:** Gut Microbiome-Immune System Crosstalk Influences Disease Severity in HCMV Infected Infants, GATC-2023, InStem, Bangalore, April 7-9, 2023
- **Mehta N:** Research -A Way Forward, Sharing of Experiences, Visit of 74 Students of from Leelabai Thackersey College of Nursing, SNDT Women's University, ICMR-NIRRH, April 18, 2023
- **Savardekar L:** Responsibilities of the Sponsor and the Investigators, Programme by CCRAS, Delhi, Online, April 19, 2023
- **Chaudhari U:** Insights in Utility of Animal Model for Human Diseases Research, One-Day Seminar on 'Current Trends and Future of '3Rs' in Laboratory Animal Experimentation', BARC Mumbai, April 24, 2023
- **Prusty RK:** Quantitative Research: Sampling Design, Measurement, and Scaling Techniques, PhD Lecture, National Institute of Design, April 26-27, 2023
- **Chaudhari U:** Inclusiveness of Veterinarians in Public Health for Preparedness of Next Pandemic: One Health Perspective, World Veterinary Day Technical Seminar Organized by Maharashtra Field Veterinarian, Panvel, Mumbai, April 29-30, 2023
- **Savardekar L:** Basics of Ethical Issues in Biomedical Research, Programme by ICMR-National Institute of Research in Tribal Health, Chhattisgarh, May 19, 2023
- **Pande S:** Genetics in Medical Practice, Wadia Hospital, Mumbai, June 8, 2023
- **Joshi B:** Reflections on Journey of HTA in India, HEOR and RWE Conclave 2023, Mumbai, July 28, 2023
- **Pande S:** Genetics of Infertility, Wadia Hospital, Mumbai, August 14, 2023
- **Pande S:** Genetics in Recurrent Pregnancy Loss, Wadia Hospital, Mumbai, August 21, 2023
- **Pande S:** Prenatal Genetic Diagnosis, Wadia Hospital, Mumbai, August 28, 2023
- **Pande S:** Preimplantation Genetic Testing, Wadia Hospital, Mumbai, September 4, 2023
- **Patil A:** PCOS, Indian Women Scientist Association (IWSA), Vashi, September 14, 2023
- **Bhor VM:** Microbiome Immune Axis in Health and Disease, Sophia College, Mumbai, September 15, 2023
- **Mukherjee S:** Demystifying Mechanism of Follicular Defect Leading to Poor Oocyte Quality in Women with Polycystic Ovary Syndrome, 11th ACE International Conference, Bengaluru, September 22-24, 2023
- **Bhor VM:** Gut Microbiota-Immune Cross Talk: Implications for Severity of HCMV Infection in Infants with Neonatal Cholestasis, 50th Annual Meeting of the Indian Immunology Society, Immunocon-50, AIIMS, New Delhi, October 5-8, 2023

- **Savardekar L:** ICMR Guidelines, Online Training Program for National Ayush Mission Ethical Committee Members, Online, October 7, 2023
- **Savardekar L:** ICMR Guidelines, Programme for Research Project Staff under SMART Program Organized by National Ayurveda Research Institute for Panchakarma, CCRAS, Ministry of AYUSH, Online, November 6, 2023
- **Pande S:** Genetics of Hereditary Breast and Ovarian Cancer, Wadia Hospital, Mumbai, November 19, 2023
- **Patel V:** Host-Pathogen Interplay in the Emergence and Re-Emergence of Viral Diseases, Popular Science Lecture Organized by Indian Women Scientists' Association, Changu Kana Thakur College of Arts, Science and Commerce, New Panvel, November 30, 2023
- **Bhor VM:** Decoding Metagenomics: Concepts, Tools and Applications, Indian Woman Scientists Association (IWSA)-Board for Radiation Nuclear Sciences (BRNS) sponsored Popular Science Lecture, SIES College, Mumbai, December 16, 2023
- **Pande S:** Genetics in Fetal Medicine, USG course, Mumbai, December 18, 2023
- **Savardekar L:** EC Structure and Responsibilities, Programme by Association for Research in Homoeopathy (ARH), Airoli, Online, January 10, 2024
- **Mukherjee S:** Alteration in Follicular Angiogenesis Contributing to Pathophysiology of Polycystic Ovary Syndrome, International Conference on Molecular Signalling, 2024, Department of Animal Biology, School of Life Sciences, University of Hyderabad, February 1-3, 2024
- **Joshi B:** Utility of Real World Evidence in Health Technology Assessment, 17th Annual Conference of Indian Society for Clinical Research (ISCR), Hyderabad, February 2-3, 2024
- **Mukherjee S:** Epigenetic Landscape in the Follicular Microenvironment of Women with Polycystic Ovary Syndrome, 21st All India Congress of Genetics and Genomics (AICGG) International Symposium Environmental Toxicogenomics: Ecosystem Health and Sustainability - Challenges and Way Forward, Kolkata, February 5-7, 2024
- **Mukherjee S:** Demystifying Mechanism of Follicular Defect Leading to Poor Oocyte Quality in Women with Polycystic Ovary Syndrome, NIBMG, Kalyani, February 8, 2024
- **Banerjee A:** Invited Member of Board of Studies- PG Department of Biotechnology, St Xavier's College, Mumbai, Virtually, February 22, 2024
- **Banerjee A:** Research Methodology Workshop, MGM Institute of Health Sciences, Navi Mumbai, February 26, 2024
- **Pande S:** Genetic Basis of Ultrasound Abnormalities, Wadia Hospital, Mumbai, March 5, 2024
- **Mehta N:** Osteoporosis and Mental Health: Exploring the Link, Visit for TYBSc & FYMSc Students from Leelabai Thackersey College of Nursing, SNTD Women's University, ICMR-NIRRH, March 7, 2024
- **Savardekar L:** Woman: Healthy Foods for a Healthy Family, International Women's Day 2024, Lalit Kala Kendra, Kamgar Kalyan Mandal, Naigaon, March 9, 2023
- **Savardekar L:** EC Structure and Responsibilities, Bioethics Training Program to IEC Members of the SMART Project Collaborating Institutes Organised by National Ayurveda Research Institute for Panchakarma - Online, March 11, 13, 16 and 18, 2024

- **Mehta N:** Osteoporosis and Depression: Is There a Link? International Women's Day 2024, Padmashali Yuvak Sangh Hall, Naigaon, March 13, 2024
- **Savardekar L:** Sailing through Menopause: The symptoms: International Women's Day 2024, Padmashali Yuvak Sangh Hall, Naigaon, March 13, 2024
- **Thomas S:** Expanding the Therapeutic Options for Candidiasis Through in Silico Approaches, Bioinformatics for Health and Food Security (ICB-HFS 2024), School of Life Science, Pondicherry University, March 15, 2024
- **Mukherjee N:** Toll Like Receptors as Therapeutic Candidates in Triple Negative Breast Cancer, 8th World Cancer Congress 2024, JNU, New Delhi, March 18-20, 2024
- **Mukherjee S:** Multiomics Approaches to Delineate Pathophysiology of Polycystic Ovary Syndrome, National Symposium on 'Recent Trends in Biology', Department of Zoology, Savitribai Phule Pune University, Pune, March 22-23, 2024

12. CAPACITY BUILDING

12.1 Workshops / Training Programs Organized

- **Pande S:** Orientation Program for Nursing Students from SNDT Women's University at ICMR-NIRRH, April 18, 2023
- **Kulkarni R:** One-week workshop on 'Randomized Clinical Trials' by MRHRU, Dahanu at ICMR-NIRRH, May 8-12, 2023
- **Patel V, Bhor V:** DHR 2023 sponsored Training Course on Harnessing the Power of Immunology in Medicine: Tools, Translation and Therapy at ICMR-NIRRH, May 15 – June 9, 2023
- **Pande S:** DHR Sponsored Training Course on Medical Genetics at ICMR-NIRRH, June 19 - July 14, 2023
- **Patil A, Tandon D:** XXXII Prof. P. K. Devi Memorial Oration at ICMR-NIRRH by Prof. (Dr.) Gagandeep Kang Director-Enterics, Diagnostics, Genomics and Epidemiology, Global Health, Bill and Melinda Gates Foundation, November 17, 2023
- **Joshi B:** HTA Sensitization and Project Dissemination Meeting of State Family Welfare Bureau, Pune, December 28, 2023
- **Joshi B:** Regional Consultative Workshop on Health Technology Assessment for Evidence-Based Informed Decision Making in India for Maharashtra State Program officials and Consultants including staff from State Health Resource Centers, January 16, 2024
- **Thomas S:** Omics in Biomedical Research held at ICMR-NIRRH, February 17, 2024
- **Pande S:** Scientific Program on Rare Genetic Disorders, February 29, 2024
- **Itta KC:** National Science Day Celebrations on "Indigenous Technologies for Viksit Bharat", ICMR-NIRRH Mumbai, March 2, 2024
- **Mukherjee S:** "Indigenous Technologies for Viksit Bharat" Seminar for National Science Day Celebrations, March 2, 2024
- **Pande S:** Orientation Program for Nursing Students (Genetics in Nursing Practice), March 7, 2024

12.2 Community Outreach Activities

- **Savardekar L:** Awareness about Traditional Folk Paintings/ Art (Gond art, Kalamkari, Madhubani, Warli, Aipan etc) by Involving the Community Youth, May 11, 2023
- **Savardekar L:** Community Involvement for Old 18A BDD Chawl residents towards cleanliness drive through the Safalya Yuvak Mandal, May 15, 2023
- **Savardekar L:** Sensitization of Local Community on Cleanliness through Street Play by Pranam Pratishthan (NGO) Team in Collaboration with the Maharashtra Labour Welfare Board (MLWB), Mumbai, May 29, 2023
- **Savardekar L:** Cleanliness Drive and Induction of Behavior Change by Self-involvement of the Clinic Staff for the Swachh Bharat Abhiyan, May 2023
- **Bhavya MK:** Session on Swachh Bharat, 'Swasthya Bharat- Monsoon Edition', Abhyudaya Nagar Municipal Public School, June 23, 2023

- **Pande S:** Community Awareness on Pediatric Rare Genetic Disorders, August 29, 2023, September 30, 2023; October 9, 2023; February 22-23, 2024
- **Bhavya MK:** Awareness Session on Cleanliness as Part of Swachh Bharat Activity in Antop hill, Mumbai, October 12, 2023
- **Savardekar L:** Awareness and Screening Camp for Diabetic Retinopathy and Peripheral Neuropathy at Reproductive and Bone Health Clinic in Collaboration with Prof Saroj Sahdev, Vitreo Retinal Surgeon, Maharashtra Ophthalmological Society, ZEST Diabetes Car, November 24, 2023
- **Joshi B:** Adolescent Health Awareness Program for School Girls, December 15, 2023
- **Bhavya MK:** Awareness Session about TB in PVV Gyanapith Kudacha, Dadra Nagar Haveli, January 31, 2024
- **Kulkarni R, Munne K:** Demonstration of New Diagnostic Device Gazelle Hb Variant at MRHRU, February 2, 2024
- **Bhanothu V:** Visit of School Students from K.M.S. Dr. Shirodkar High School (English Medium), Parel, Mumbai, February 14, 2024.
- **Bhavya MK:** Awareness Session on TB in TCPL Industry, Masat, Dadra Nagar Haveli, February 23, 2024
- **Savardekar L:** IWD2024 Celebrations at Reproductive and Bone Health Unit by Guiding Women to Self-screen for Depression and Anxiety and Estimating Nutrition Intakes with 24 Hour Dietary Recall and Counselling, March 11, 2024
- **Savardekar L:** Lecture Series on 'Mindful Menopause: The Journey begins' on Woman`s Day, March 13, 2024
- **Bhavya MK:** Awareness Session about TB in Dayat Faliya Silvassa, March 21, 2024

12.3 Meetings / Conferences / Seminars / Workshops Attended

- **Shukla P:** Digital PCR by Qiagen, Vashi, Mumbai, April 5, 2023
- **Patil A, Tandon D:** Planning and Development Department, Government of Sikkim, Online, May 2, 2023
- **Gajbhiye RK:** 15th World Congress on Endometriosis, Edinburgh, UK, May 3-6, 2023
- **Bhavya MK:** Workshop on Randomized Clinical Trials, Mumbai, May 8-12, 2023
- **Bhise M:** Indian Association for the Study of Population (IASP) 2023, Kokrajhar, Assam, May 18-19, 2023
- **Shukla P:** Digital Pathology and Artificial Intelligence, TMC, Mumbai, May 20, 2023
- **Joshi B, Kulkarni R:** SANGAM 2023 Conference on Health Systems Research & Innovation, IIT Mumbai, June 2-3, 2023
- **Joshi B:** Regional Meeting to Strengthen RMNCAH Program Management Capacity to Achieve the Universal Health Coverage Within Primary Health Care Framework Towards SDG 3, Bangkok, June 19-23, 2023
- **Kuppusamy P, Prusty RK:** Two-day Online Workshop on Epicollect5: A Data Management System, Online by Med Analytics India, June 22-23, 2023
- **Bhise M:** eWorkshop MED Analytics India, Mumbai, June 22-23, 2023

- **Joshi B:** Third Guidelines Development Group Meeting on Updating WHO's Guidelines on Preventing Early Pregnancy and Poor Reproductive Outcomes in Adolescents in Developing Countries, WHO Geneva, June 26-28, 2023
- **Kulkarni R, Munne K:** Video Conference from DHR-Regarding Redcap Data Portal Monitoring of MRU/MRHRU Units, June 30, 2023.
- **Sachdeva G, Patil A, Tandon D:** Identifying Research Priority and Roadmap for Understanding the Declining Fertility Rates, Sikkim, Gangtok, July 10, 2023
- **Joshi B:** National Expert Consultation on WHO's Guidelines on Self-Care Interventions for Health and Well-Being, MOHFW, WHO India Office New Delhi, July 23, 2023
- **Kulkarni R:** Serosurveys for Public Health Decisions, Virtual, July 26, 2023
- **Surve S:** Training Meeting on Qualitative Component Related to Newborn Sickle Cell Screening Project, ICMR-NIIH, August 1-3, 2023
- **Pande S:** Principal Investigator Training at Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad, August 16-19, 2023
- **Itta KC:** Randomized Controlled Trials, St. John's Medical College & Research Institute, Bangalore, September 4-8, 2023
- **Bhavya MK:** National Conference of Indian Association of Women's Studies, Trivandrum, Kerala, September 6-10, 2023
- **Das DK:** National Symposium on Crosstalk between Animal Research and Alternative, CSIR-North East Institute of Science and Technology, Jorhat, Assam (CSIR-NEIST), September 7-9, 2023
- **Bhavya MK:** MOOC on Implementation Research, Online, September 8-15, 2023
- **Bhavya MK:** CME on Community Based Birth Defects Surveillance: Current Scenario and Way Forward, Palghar Maharashtra, September 12, 2023
- **Kulkarni R, Surve S:** Dissemination Meeting for Project 'Population Based Birth Defects Surveillance in Tribal Blocks of Palghar District in Maharashtra' and CME-Community Based Birth Defects Surveillance: Current Scenario and Way Forward, Govardhan Ecovillage, Wada, District Palghar, September 12, 2023
- **Chaudhari U:** 9th Asian Federation for Laboratory Animal Science (AFLAS) Association Congress, Jeju, South Korea, September 12-15, 2023
- **Shukla P:** International Conference on Molecular Medicine, Reproduction and Endocrinology 2023, Navrachana University, Vadodara, September 14-16, 2023
- **Tandon D:** Protocol Development Workshop on Chemicals in Sanitary Pads, ICMR, September 18-19, 2023
- **Bhanothu V:** SAIF-CRNTS IITB-National R&D Meet 2023 Organized by SAIF-CRNTS, IIT Bombay, Mumbai, September 22, 2023
- **Bhor V:** Launch of WHO Benchmarking Tool for Research Ethics Oversight, Virtual Meeting, September 25, 2023
- **Gajbhiye RK:** 11th Asian Congress on Endometriosis, Manila, Philippines, September 25-26, 2023
- **Kulkarni R, Munne K:** Health Mela under Ayushman Bhav Campaign in SDH Dahanu, September 30, 2023.
- **Gajbhiye RK:** Massive Open Online Course (MOCC) on Implementation Research (IR) with A Focus on Infectious Diseases of Poverty (IDP), Online, October 2, 2023- November 27, 2023

- **Pande S:** Quarterly Training Meeting Q2 for Mission Program on Pediatric Rare Genetic Disorders, CDFD, Hyderabad, October 4, 2023
- **Gajbhiye RK:** National Conclave on Endorsement of National Action Plan for Prevention and Control of Snakebite Envenoming (NAPSE) by Stakeholders, New Delhi India, October 18-19, 2023
- **Bhanothu V:** Hands-on Workshop on Human/Cancer Cell Culture Techniques & MTT Assay, Programs in Stem Cell Biology and Molecular Medicine Conducted by International Center for Stem Cells, Cancer and Biotechnology (ICSCCB), New Delhi, India, October 20-26, 2023
- **Bhor V:** 15th Annual Conference & Workshops of The Cytometry Society (I) (TCS, India), AIIMS, New Delhi, October 27-29, 2023
- **Savardekar L:** Course Advisory Group (CAG) Constituted for the Program of Online Training on Ethical Considerations – PROTECT at the Translational Health Science and Technology Institute an Autonomous Institute of the Department of Biotechnology, Online, November 03, 2023
- **Joshi B:** Brainstorming Meeting on Anemia, New Delhi, November 16, 2023
- **Pande S, Bhanothu V:** Mission Program on Pediatric Rare Genetic Disorders, CDFD, Hyderabad, November 21, 2023
- **Patil A, Kokate P, Akula A:** Investigators Meeting-Cum-Training Workshop for ICMR-PCOS Cohort Study Phase II, SKIMS Srinagar, November 26-27, 2023
- **Savardekar L:** FERCAP Update Surveyor Training, Online, November 29, 2023
- **Kulkarni R:** Task Force Meeting on Malnutrition in Maharashtra, Virtual, November 30, 2023
- **Mukherjee N:** The National Academy of Sciences Meeting, BARC, Mumbai, December 2-5, 2023
- **Banerjee A:** 93rd annual session of National Academy of Sciences, India (NASI), BARC, Mumbai, December 3-5, 2023
- **Kulkarni R:** First Technical Meeting of the Reproductive Health in India Study (RHIS), IIPS, Mumbai, December 5, 2023
- **Joshi B:** National Consultative Workshop on HTA, New Delhi, December 7, 2023
- **Miya V, Panchal D:** 19th National Research Scholars Meet – NRSN, ACTREC, Navi Mumbai, December 7-8, 2023
- **Savardekar L:** FERCICON 2023, International Conference of the Forum for Ethics Review Committees in India, Online, December 7-9, 2023
- **Gajbhiye RK:** 3rd International Congress on Endometriosis, Kolkata, India, December 9-10, 2023
- **Pande S:** Quarterly Update Meeting and Training Q3 for 'Mission Program on Pediatric Rare Genetic Disorders', CDFD, Hyderabad, January 3, 2024
- **Surve S:** Preconference Workshop on Health Economics, Department of Community Medicine, Mahatma Gandhi Mission Medical College, Kamothe, Navi Mumbai, January 4, 2024
- **Surve S:** MHIAPSMIPHACON 2024, Department of Community Medicine, Mahatma Gandhi Mission Medical College, Kamothe, Navi Mumbai, January 5-6, 2024
- **Bhor V:** A Scientific Framework for Epidemic and Pandemic Research Preparedness, Virtual Meeting, January 9, 2024
- **Joshi B:** Regional Consultative Workshop on Health Technology Assessment for Evidence Based Informed Decision Making in India, Arogya Bhavan Mumbai, January 16, 2024

- **Kuppusamy P:** Developing a Common Study Protocol for ICMR Task Force Study on 'Establishment of Reference Intervals in Indian Population [TERIIP], ICMR, New Delhi, January 23-24, 2024
- **Banerjee A, Jagtap D:** TNQ Distinguished Lecture in Life Sciences- Series II, 2nd edition by Nobel Laureate Prof. David Julius Titled 'How We Sense Pain', TIFR, Mumbai, January 24, 2024
- **Kuppusamy P:** Genomics and Proteomics Data Analysis, Online by Division of Biomedical Informatics, ICMR, New Delhi, January 30-31, 2024
- **Bhise M, Prusty RK:** The Indian Association of Social Sciences and Health (IASSH) 2024, Pondicherry University, Puducherry, January 31, 2024 - February 2, 2024
- **Joshi B:** Health System Costing Workshop, NIV Pune, February 6-7, 2024
- **Surve S:** Clairvoyance Conference, Tata Institute of Social Sciences, February 7, 2024
- **Tandon D:** 1st Model Rural Health Research Unit (MRHRU) Local Advisory committee, Vani, Taluka Dindori, District Nasik, Maharashtra, February 14, 2024
- **Banerjee A, Jagtap D:** TNQ Distinguished Lecture in Life Sciences- Series II, 3rd Edition by Nobel Laureate Dr. John Jumper Titled 'Highly Accurate Protein Structure Predictions: Using AI to Solve Biology Problems in Minutes Instead of Years', TIFR, Mumbai, February 23, 2024
- **Kuppusamy P:** Introduction to Systematic Reviews of Diagnostic Test Accuracy (DTA), Online, ICMR-Cochrane Affiliate Center, February 27, 2024
- **Tandon D:** Principles & Practice of Cancer Prevention and Control, Preventive Oncology Department of Tata Memorial Hospital, Parel, Mumbai, March 11-12, 2024
- **Chaudhari U:** 15th Annual International One Week Course on 'Health Research Methodology and Evidence Based Medicine' E-week Course, Bengaluru, March 11-15, 2024
- **Kulkarni R:** Workshop to Develop Costing Component of ICMR National Health Research Priority Projects-Online, March 14-15, 2024
- **Bhise M:** Chief Information Security Officers (CISO) Deep Dive Training on Cyber Security for ICMR, Delhi, March 18-22, 2024

12.4 Inter-Institutional Collaborations

12.4.1 National Collaborations

- Amrita Institute of Medical Sciences, Kochi
- ART Fertility Clinic, Mumbai
- Apollo Hospitals, Navi Mumbai
- Bai Jerbai Wadia Hospital for Children, Mumbai
- District Health Office, Palghar District, Maharashtra
- District Health Office, Thane District, Maharashtra
- Fertility Clinic & IVF Center, Mumbai
- ICMR - National Institute of Immunohaematology, Mumbai
- Indian Institute of Technology Bombay, Mumbai
- Indian Institute of Technology, Madras
- Institute of Chemical Technology, Mumbai

- Maharashtra University of Health Sciences Regional Centre, Mumbai
- Mumbai Oncocare Hospital, Mumbai
- Municipal Corporation of Greater Mumbai, Mumbai
- National Institute of Mental Health and Neuro Sciences, Bengaluru
- Nowrosjee Wadia Maternity Hospital, Mumbai
- Pimpri Chinchwad Municipal Corporation Medical Department, Pune
- Saifee Hospital, Mumbai
- Seth GS Medical College & KEM Hospital, Mumbai
- Speciality Surgical Oncology Hospital, Mumbai
- SRL Avinash Phadke Labs, Mumbai
- Tata Institute of Fundamental Research, Mumbai
- Tata Memorial Hospital, Mumbai
- Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital, Mumbai
- Translational Health Science and Technology Institute, Faridabad

12.4.2 International Collaborations

- Texas Biomedical Research Centre, USA

12.5 Trainees

Forty nine summer and winter trainees were inducted in various departments namely Molecular Endocrinology, Gamete Immunobiology, Genetic Research Centre, Cell Physiology and Pathology, Molecular and Cellular Biology, Infectious Diseases Biology, Cellular and Structural Biology, Bioinformatics, Neuroendocrinology, Molecular Immunology and Microbiology, Innate Immunity, National Center for Preclinical Reproductive and Genetic Toxicology, Biochemistry, Infectious Diseases Biology, Clinical Research Laboratory. These trainees were introduced to technological innovations in different fields and were trained in various scientific processes in ongoing projects.

13. HONORS AND AWARDS

13.1 Awards

1. **Bhanothu V.** ISSRF Best Scientist Award - 2024 by Indian Society for the Study of Reproduction and Fertility (ISSRF), CSIR-IICT, Hyderabad, February 23-25, 2024
2. **Bhide A.** Best poster award at International Conference on Molecular Medicine, Reproduction and Endocrinology 2023 and The 40 Annual Meeting of The Society For Reproductive Biology and Comparative Endocrinology (SRBCE 2023), September 14-16, 2023
3. **Bhide A.** Best poster award at Joint Annual Meeting of the SBC (I) Mumbai Chapter and GATC-Lite, West, October 2, 2024
4. **Bhide A.** Best poster award at 93rd Annual Session of NASI and Symposium on 'India Secure @75' December 3-5, 2023.
5. **Bhowmick S.** Best Poster Award, 50th Annual Meeting of the Indian Immunology Society, Immunocon-50, held at AIIMS, New Delhi, October 5-8, 2023
6. **Chaudhari U.** Travel Award to attend 9th Asian Federation for Laboratory Animal Sciences meeting, Jeju Island, South Korea, September 12-15, 2023
7. **Ganguly K.** Best Poster Award, 50th Annual Meeting of the Indian Immunology Society, Immunocon-50, held at AIIMS, New Delhi, October 5-8, 2023
8. **Ganguly K.** Prof. G. P. Talwar Young Scientist Award by Indian Society for the Study of Reproduction and Fertility (ISSRF), CSIR-IICT, Hyderabad, February 23-25, 2024
9. **Gurav P.** Won travel award at TCS 15th Annual Conference & Workshops, October 26-29, 2023, AIIMS, New Delhi.
10. **Itta KC.** Long-term ICMR-DHR International Fellowship Award for Young Indian Biomedical Scientists 2023-2024.
11. **Karandikar K.** Best Poster Award, 50th Annual Meeting of the Indian Immunology Society, Immunocon-50, held at AIIMS, New Delhi, October 5-8, 2023
12. **Kuppusamy P.** Second prize for oral presentation for the study on "Serum HE4 levels in Indian women with endometriosis: A preliminary study" at International Congress on Endometriosis organized by Endometriosis Society India, Kolkata, December 9-10, 2023
13. **Mukherjee S.** Elected as a fellow of NASI for immense contribution in understanding the molecular mechanism involved in the pathophysiology of PCOS at 93rd Annual Session of NASI, BARC, Mumbai, December 3, 2023
14. **Mukherjee N.** Long-term ICMR-DHR International Fellowship Award for Young Indian Biomedical Scientists 2023-2024
15. **Munne K.** Second prize for oral presentation entitled, "Trichomonas vaginalis infection and its association with other RTI/STIs among women screened for cervical precancers and cancers in Maharashtra", 1st Conference of Indian Academy of Tropical Parasitology (Maharashtra Chapter) - "MAHATROPACON 2024", AIIMS Nagpur, January 13-14, 2024
16. **Munshi I.** Best poster award at International Congress on Endometriosis organized by Endometriosis Society India, Kolkata, December 9-10, 2023
17. **Pandey T.** Won travel award at TCS 15th Annual Conference & Workshops, October 26-29, 2023, AIIMS, New Delhi

18. **Patankar A.** Prof. N. R. Moudgal young scientist award, ISSRF conference, CSIR-IICT, Hyderabad, February 23-25, 2024
19. **Patel V.** Travel award to attend the Annual American Society for Virology (ASV) 2023 Meeting in Athens, Georgia, USA, June 24 - 28, 2023
20. **Pranya N.** Best poster award at International Conference on Molecular Medicine, Reproduction and Endocrinology 2023 and The 40 Annual Meeting of The Society For Reproductive Biology and Comparative Endocrinology (SRBCE 2023), September 14-16, 2023
21. **Sachdeva G.** Dr TC Anand Kumar Memorial Oration by Indian Society for the Study of Reproduction and Fertility (ISSRF), CSIR-IICT, Hyderabad, February 23-25, 2024
22. **Tiwari A.** Second prize in oral presentation at South Asian College of Clinical Pharmacology (SAC-ACCP), January 6-8, 2023
23. **Yadav S.** Won third prize award for oral presentation at TCS 15th Annual Conference & Workshops, October 26-29, 2023, AIIMS, New Delhi.

13.2 Patents Filed/ Granted:

1. **Modi D, Sengupta A.** Fertility predictor: web application for prediction of the likelihood of successful sperm retrieval, fertilization, clinical pregnancy and live birth in males with “Y” chromosome microdeletions. Copyright granted. Technology transferred to APS Lifetech Pune.
2. **Thomas S.** An intravenous pharmaceutical medicament for candidiasis infection. Provisional patent (No. 202411019977) filed on March 18, 2024.

13.3 Ph.D. Degrees Awarded

1. **Mr Amit Kumar Singh**
Thesis title: Delineation of Immune Signatures Influencing HIV Disease Progression
Research Guide: Dr Vainav Patel
2. **Ms Ankita Kaushik**
Thesis title: Investigating the Effects of Neonatal Exposure to Estrogen on Mouse Testicular Stem Cells
Research Guide: Dr Deepa Bhartiya
3. **Ms Anuradha Mishra**
Thesis title: Functional Significance of Homeobox Gene HOXA10 in Endometriosis
Research Guide: Dr Deepak Modi
4. **Ms Diksha Sharma**
Thesis title: Studies on Stem Cells and their Niche in Mouse Ovary
Research Guide: Dr Deepa Bhartiya
5. **Ms Nandini Kasarpalkar**

Thesis title: Studies on the Expression of Integrin $\alpha 4\beta 7$ on Immune Cells and its Association with Reproductive Tract Infections

Research Guide: Dr Vikrant Bhor

6. **Ms Parul Shishpal**

Thesis title: *Gardnerella vaginalis* Membrane Vesicles: Isolation, Characterization and Potential Role in Biofilm Formation and Cellular Pathogenesis

Research Guide: Dr Vikrant Bhor

7. **Mr Pawan Kumar**

Thesis title: Expression of Natural Killer and Natural Killer T Cell Receptors and their Association with Ovarian Cancer

Research Guide: Dr Jayanti Mania-Pramanik

8. **Ms Pushpa Singh**

Thesis title: Investigating the Effects of Follicle-Stimulating and Steroid Hormones on Uterine Stem Cells

Research Guide: Dr Deepa Bhartiya

14. ADVISORY COMMITTEES

14.1 Scientific Advisory Committee

Dr Neerja Bhatla (*Chairperson*)

Professor, Obstetrics and Gynaecology
All India Institute of Medical Sciences
Ansari Nagar, New Delhi 110 029

Dr Ashutosh Halder

Professor & Head, Reproductive Genetics
All India Institute of Medical Sciences
Ansari Nagar, New Delhi - 110029

Dr Sanjay Mehendale

Director Research
PD Hinduja Hospital and Medical Research Center
8-12, SVS Rd, Mahim West, Mahim, Mumbai - 400016

Dr Smita Mahale

ICMR Emeritus Scientist
A-503, Devdeveshwar CHS, Telly Galli Cross Lane
Andheri (East), Mumbai - 400069

Dr Vishwajeet Kumar

Founder, Community Empowerment Lab, Shivgarh Main Rd
Shivgarh, Uttar Pradesh - 229308

Dr Rajinder Singh

Central Drug Research Institute,
Sitapur Rd, Sector 10, Jankipuram Extension
Lucknow, Uttar Pradesh - 226031

Dr Sanjeev Galande

Dean, School of Natural Sciences, Shiv Nadar University
Gautam Buddha Nagar, Uttar Pradesh - 201314

Dr Kumaraswamy Thangaraj

JC Bose Fellow, Centre for Cellular and Molecular Biology
Hyderabad - 500 039

Dr Bharati Kulkarni (*ICMR representative*)

Scientist-G and Head, Division of RBMCH & Nutrition

Indian Council of Medical Research, V Ramalingaswami Bhawan
Ansari Nagar, New Delhi - 110029

Dr BK Thelma (*Special Invitee*)
Department of Genetics, Delhi University
Benito Juarez Marg, New Delhi - 100021

Dr Manisha Madkaikar (*Special Invitee*)
Director, ICMR - National Institute of Immunohaematology
13th floor, New Multistoreyed Building
KEM Hospital Campus, Parel, Mumbai - 400012

Dr Sunita Taneja
Deputy Director, Centre for Health Research and Development
Society for Applied Studies
45, Kalu Sarai, New Delhi - 110016

Dr Pawan Kumar (*Special Invitee*)
Advisor, (Family Planning/Maternal Health & Immunization)
Ministry of Health and Family Welfare
Nirman Bhawan (Room No. 522 A), New Delhi-110011

Dr Geetanjali Sachdeva (*Member Secretary*)
Director, ICMR-NIRRH, Parel, Mumbai

Representative from Ministry of Health and Family Welfare, Govt. of India

Dr Zoya Ali Rizvi (*Special Invitee*)
Deputy Commissioner (Child Health Nutrition)
Room No. 207-D
Ministry of Health and Family Welfare, Government of India
Nirman Bhawan, New Delhi - 110011

Representative from Local Municipal Corporation

Dr Daksha Y Shah
Executive Health Officer
Municipal Corporation of Greater Mumbai (MCGM)
F/S Ward Office Building
Dr B Ambedkar Marg
3rd Floor, Parel, Mumbai - 400012

14.2 Members of ICMR-NIRRH Ethics Committee for Human Studies

Prof Shubhada Chiplunkar (*Chairperson*)

Former Director ACTREC
Tata Memorial Centre, Kharghar
Navi Mumbai

Dr Yogeshwar S. Nandanwar

Professor, Obstetrics and Gynaecology
DY Patil Medical College, Nerul, Navi Mumbai

Dr Sandeep Bavdekar

Ex-Professor & Head, Paediatrics Department
BYL Nair Charitable Hospital & TN Medical College, Mumbai

Dr Sivakami Muthusamy

Professor, Tata Institute of Social Sciences
Deonar, Mumbai

Dr Rakhi Tripathi

Department of Pharmacology
Acharya Donde Marg, Parel, Mumbai

Dr Ketki Kulkarni

Assistant Professor
Nowrosjee Wadia Maternity Hospital, Parel, Mumbai

Dr Bipin Kulkarni

Scientist E, ICMR-NIIH, Parel, Mumbai

Adv Ajay Shinde

Gulisatan, 3rd floor, CAT Bar Association
Ghanshyam Talwatkar Road, Fort, Mumbai

Dr K. V. Ganapathy

30, Shantinath Bhavan, Sion Road, King Circle, Mumbai

Mrs Sudha Sathaye

C/9/8 Sukumar society, Dayaldas Road, Vileparle (East), Mumbai

Dr Shailesh Pande

Scientist-D, ICMR-NIRRH, Parel, Mumbai

Dr Sadhana Gupta

Scientist-D, ICMR-NIRRH, Parel, Mumbai

Dr Smita Nair

Assistant Professor

Tata Institute for Social Sciences, VN Purav Marg, Deonar, Mumbai

Adv Mrs. Meghana Shirke (*Alternate Member - Legal Expert*)

Room No. 81, 3rd floor, Mahavir Sukh Building

Dr Ambedkar Road, Dadar (East), Mumbai

Dr Ashwini Karve (*Alternate Member – Pharmacologist*)

Associate Professor

Topiwalla National Medical College, RTO Colony, Mumbai Central, Mumbai

Dr Bhakti Pathak (*Joint Member Secretary*)

Scientist-F, ICMR-NIRRH, Parel, Mumbai

Dr Vikrant Bhor (*Member Secretary*)

Scientist-E, ICMR-NIRRH, Parel, Mumbai

14.3 Members of Institutional Animal Ethics Committee

Dr Geetanjali Sachdeva

Director, ICMR-NIRRH, Parel, Mumbai

Dr K Pani Prasad

Principal Scientist, ICAR-Central Institute of Fisheries Education

Yari Road, Panch Marg, Varsova, Mumbai

Dr Prabhakar Ukale

Veterinarian, Animal House facility, Institute of Chemical Technology

Nathalal Parekh Marg, Matunga (E), Mumbai

Dr Eshita Kishor Waghela

Veterinarian, Mumbai Veterinary College

Parel Village, Sindhu Nagar, Parel, Mumbai

Dr Sangram Shankarrao Chavan

Central Laboratory Animal House, Department of Pharmacology & Toxicology

Bombay Veterinary College, Parel, Mumbai

Dr Padma Devrajan

Dean Research & Innovation, Professor in Pharmacy
Former Head, Department of Pharmaceutical Sciences and Technology
Institute of Chemical Technology, NP Marg, Matunga, Mumbai 400019

Dr Vikas Dighe

Scientist-F, ICMR-NIRRH, Parel, Mumbai

Dr Dhanjit Das

Scientist-E, ICMR-NIRRH, Parel, Mumbai

Dr SM Metkari

Principal Technical Officer, ICMR-NIRRH, Parel, Mumbai

14.4 Members of the Local Research Advisory Committee of MRHRU, Dahanu

Dr Sanghamitra Pati (*Chairperson*)

Director & Scientist-G, ICMR-RMRC Bhubaneswar, Odisha

Dr Vishwajeet Kumar (*Co-chair*)

Founder & Principal Scientist,
Community Empowerment Lab, Gomti Nagar, Lucknow

Dr Krishnamurthy Jayanna

Professor and Dean,
M. S. Ramaiah University of Applied Sciences, Bangalore

Dr Rajesh Karyakarte

Professor and Head, Department of Microbiology,
BJ Government Medical College & Sassoon Hospitals, Pune

Dr Manisha Madkaikar

Scientist 'G' & Director, ICMR-NIIH, Parel, Mumbai

Dr Mamta Manglani,

Director, Comprehensive Thalassemia Care & BMT Centre, Mumbai

Dr Anuradha Khadilkar

Deputy Director, Hirabai Cowasji Jehangir Medical Research Institute (HCJMRI)

Dr Reena Wani

Prof & Head of Dept. Obstetrics & Gynecology
HBTMC) and Dr Rustom Narsi Cooper Municipal General Hospital, Mumbai

Dr Pallavi Saple

Dean, JJ Group of Hospitals, Mumbai

Dr Dilip Mhaisekar

Director, Directorate of Medical Education and Research (DMER), Mumbai

Dr Nitin Ambadekar

Additional Director of Health Services

Executive Director, SHSRC, Maharashtra

Dr Geeta Pardeshi (*Nodal Officer, Linked Medical College*)

Prof. and Head, Dept of Community Medicine

Grant Medical College and Sir JJ group of Hospitals, Mumbai

Dr Aparna Mukherjee (*DHR Representative*)

Scientist F, Development Research Division

Indian Council of Medical Research, V Ramalingaswami Bhawan

Ansari Nagar, New Delhi - 110029

Dr Tanu Anand (*DHR Representative*)

Scientist E, Development Research Division

Indian Council of Medical Research, V Ramalingaswami Bhawan

Ansari Nagar, New Delhi - 110029

Dr Geetanjali Sachdeva

Scientist G & Director, ICMR-NIRRH, Parel, Mumbai

Dr Ragini Kulkarni (*Nodal Officer, ICMR Mentor Institute*)

Scientist F, ICMR-NIRRH, Parel, Mumbai

Dr Kiran Munne (*Member Secretary*)

Scientist C, ICMR-NIRRH, Parel, Mumbai

14.5 Members of the Local Research Advisory Committee of MRHRU, Vani

Dr Manisha Madkaikar (*Chairperson*)

Director, ICMR-NIIH, Parel, Mumbai

Dr Yogesh Kalkonde (*Co-chair*)

Public Health Researcher, Sangwari, Chhattisgarh

Dr Himmatrao Bawaskar

Director, Bawaskar Hospital and Research Center
Mahad, District Raigad, Maharashtra

Dr Satish Pawar

Former Director of Health Services, Maharashtra

Dr Archana Patil

Former Director of Health Services, Maharashtra

Dr Sadanand Raut

Director, Vighanhar Nursing Home
Narayangaon, District Pune, Maharashtra

Dr Rajesh Dikshit

Director, Centre for Cancer Epidemiology
Tata Memorial Centre, Mumbai

Dr Shubhra Sengupta

Associate Professor, Microbiology
SMBT Institute of Medical Sciences and Research Centre
Ghoti, District Nashik, Maharashtra

Dr Niraj Mahajan

Associate Professor, Department of Obstetrics and Gynaecology
Topiwala National Medical College and BYL Nair Hospital, Mumbai

Dr Sanjay Prabhu

Senior Consultant Paediatrics and
In-charge of Nutritional Rehabilitation Centre (State CoE)
BJ Wadia Hospital for Children, Parel, Mumbai

Dr Geetanjali Sachdeva

Director, ICMR- NIRRH, Parel, Mumbai

Dr Rahul Gajbhiye (*Nodal Officer, ICMR Mentor Institute*)

Nodal Officer, MRHRU Vani - ICMR Mentor Institute)
Scientist E, ICMR-NIRRH, Mumbai

Dr Kapil Aher (*Nodal Officer, State Health Department*)

Deputy Director Health Services, Nashik Division
Public Health Department, Government of Maharashtra

Dr Sarika Patil (*Nodal Officer, Linked Medical College*)
Associate Professor, Department of Community Medicine
Shri Bhausaheb Hire Govt. Medical College, Dhule

Dr S V Bhamre
Dean, Shri Bhausaheb Hire
Government Medical College, Dhule

Dr Charudatta Shinde
Civil Surgeon, Nashik

Dr Sudhkar More
District Health Officer, Nashik

Dr B N More
Medical Superintendent, Rural Hospital Vani, Nashik

Dr Subhash Mandge
Taluka Health Officer, Dindori, Nashik

Dr Tanu Anand (*DHR representative*)
Scientist E, Department of Health Research, New Delhi

15. EXTRAMURALLY FUNDED PROJECTS

S.No	Name of PI	Title	Start year	End year	Funded by
1	Antara Banerjee	Role of kisspeptin mediated signaling in the onset of puberty	2021	2024	SERB
2	Antara Banerjee	Delineation of the role of isoforms of kisspeptin in mammalian reproduction	2022	2024	SERB
3	Antara Banerjee	Study of kisspeptin receptor oligomerization and its functional significance	2022	2025	BRNS
4	Anushree Patil	ICMR-Center for Product Development Development of Recommendations for Multidisciplinary management of PCOS for the Indian Health care system	2019	2024	ICMR
5	Beena Joshi	Understanding availability of Essential Diagnostics in Health care system identifying barriers and facilitators	2023	2024	ICMR
6	Beena Joshi	Feasibility acceptability and costs of providing comprehensive preconception care services to young couples in maharashtra	2024	2027	ICMR
7	Beena Joshi	Equitable Quality universal health coverage implementation research project for optimizing comprehensive primary health care through Health and wellness Centres in Pimpri Chinchwad Municipal Corporation Pune district of Maharashtra EQUIP HWC	2024	2027	ICMR
8	Beena Joshi	Implementation research to explore operational feasibility acceptability and cost effectiveness of using IV Ferric Carboxy Maltose FCM in Management of iron deficiency anemia IDA among pregnant women through district health system of india	2021	2024	DHR
9	Beena Joshi	To estimate cost of diagnosis of infertility and its management including IVF and quality of life among infertile couples	2023	2024	DHR
10	Beena Joshi	Assessment of RMNCAH N services delivery costs work patterns and efficiency healthcare teams at Ayushman Bharat Health and Wellness Centers	2024	2024	UNICEF
11	Beena Joshi	Regional Resource Hub at NIRRH for Health Technology Assessment	2018	2024	DHR
12	Bhakti Pathak	Evaluating the role and proteolytic processing of Trop1 and trop2 in normal placentation and placental pathologies	2021	2024	DBT
13	Bhavya M K	Acceleration efforts to END TB in India (Multi centric study)	2023	2025	ICMR

14	Deepak Modi	Deciphering the immunomodulatory role of homeobox10 in the endometrium during embryo implantation	2021	2024	DBT
15	Deepti Tandon	Evaluating the inflammatory, microbiome profile and co-infections in women diagnosed with treatment failure, relapse or recurrent Bacterial vaginosis -A Prospective analytic study	2023	2026	ICMR
16	Deepti Tandon	Assessing usage and disposal pattern of menstrual hygiene products among women in rural and urban India	2024	2024	ICMR
17	Deepti Tandon	Longitudinal cohort study to evaluate the effect of various contraception methods on the composition and diversity of the vaginal microbiota	2019	2024	ICMR
18	Dhanjit K Das	Omics of serum exosomes in endometriosis: an attempt to identify a possible biomarker	2022	2025	ICMR-Adhoc
19	Dhanjit K Das	Human endometrial stem cells and their possible role in the etiology of endometriosis	2023	2026	DBT
20	Dhanshree Jagtap	Utility of estimating serum PSP94 levels in management of patients with raised PSA in clinical setting: A multicentric study	2024	2027	ICMR
21	Dhanshree Jagtap	Delineating the role of human β -microseminoprotein in male reproduction	2023	2025	ICMR
22	Dipty Singh	Clinical relevance of differentially methylated sperm lncRNA genes in male partners of couples experiencing idiopathic recurrent pregnancy loss	2024	2027	SERB
23	Dipty Singh	Validation of sperm DNA epimutations as diagnostic biomarker for idiopathic recurrent pregnancy loss	2024	2027	DHR
24	Dipty Singh	Therapeutic potential of Epigallocatechin-3-gallate (EGCG) for improving sperm quality, fertility and pregnancy outcomes in a murine model of endocrine disruption	2023	2026	ICMR
25	Geetanjali Sachdeva	Eutopic endometrial cell repertoire in women presenting different subtypes of endometriosis and its association with endometrial receptivity	2023	2025	ICMR
26	Geetanjali Sachdeva	Investigating the contribution of DNA damage, repair and demethylation in the pathogenesis of endometriosis	2019	2023	DBT
27	Krishna Chaaithanya Itta	Molecular analysis of HLA-G in pregnant tribal women and its role in infectious etiologies modulating intrauterine inflammation - A prospective cohort study	2023	2026	ICMR
28	Kumari Nishi	Investigating the role of endocannabinoid system in chorionic villi of women experiencing recurrent spontaneous abortions (ongoing)	2023	2026	SERB

29	Lalita Savardekar / Kuldeep Chaudhary (CARI-CCRAS)	Impact of Mukta Shukti Bhasma and Saubhagya Shunti in reversal of bone mineral density among lactating women consuming traditional diet foods in Maharashtra: A randomized controlled preliminary clinical study	2023	2026	CCRAS
30	PI: Nirmalya Moulik, TMH Co-PI: Vikrant Bhor	Gut microbiome in children with Acute Lymphoblastic Leukaemia (ALL) – Association with leukemogenesis, serial surveillance and effect on toxicity, disease outcome and immunological recovery	2023	2026	Lady Tata Memorial Trust, Mumbai
31	Nupur Mukherjee	Role of Wnt/ β -catenin signalling pathways in placenta mediated breast carcinogenesis during pregnancy	2023	2026	DST
32	Pallavi Shukla	Study of maternally inherited mitochondrial DNA variants in women with Polycystic Ovarian Syndrome	2021	2024	ICMR
33	Pallavi Shukla	Delineating pathogenesis of obese and lean PCOS phenotype using integrated transcriptomics and proteomics approach	2023	2026	DHR
34	Periyasamy Kuppusamy	ICMR-Taskforce on Establishment of Reference Intervals in Indian Population (TERIIP) for southern region – Andaman and Nicobar Islands	2024	2027	ICMR
35	Priyanka Parte	Design and development of a microfluidic chip for sperm selection/sorting based on chemotaxis	2021	2024	DBT
36	Priyanka Parte	Functional significance of testis specific histone H2B variant (TH2B) in spermatozoa and early embryonic development	2021	2024	DBT
37	Rahul K Gajbhiye	Utilizing the Model Rural Health Research Units to improve snakebite management through rationalized antivenom distribution models in India: An implementation research project	2024	2026	DHR
38	Rahul K Gajbhiye	Clinical phenotypes and genetic regulation of endometriosis in Indian women	2019	2024	DBT Wellcome Trust India Alliance
39	Rahul K Gajbhiye	ICMR National Snakebite Project (INSP) on capacity building of health system on prevention and management of snakebite envenomation including its complications	2022	2024	ICMR
40	Rahul K Gajbhiye	Nationwide study to estimate incidence, mortality, morbidity, and economic burden due to snakebites in India	2021	2024	ICMR
41	Ragini Kulkarni	Integrated Palliative, Elderly and Mental Health Care (I-PEM) under for establishment of	2023	2025	DHR

		MRHRU under the umbrella scheme of development of infrastructure			
42	Ragini Kulkarni	Validation of novel serum biomarkers in prediction of early onset preeclampsia among pregnant women and correlation with maternal and neonatal outcomes in a tribal district of Palghar, Maharashtra	2024	2026	ICMR
43	Ragini Kulkarni	Assessing the feasibility of point of care device in community-based screening of sickle cell disease and thalassemia in tribal district of Palghar, Maharashtra	2024	2026	ICMR
44	Ragini Kulkarni	Improving Infant and Young Child Feeding (IYCF) practices in tribal block of Palghar District, Maharashtra through involvement of frontline workers	2024	2026	ICMR
45	Ragini Kulkarni	Strengthening Maternal and Perinatal Death Surveillance and Response (MPDSR) Action in tribal blocks of Palghar district in Maharashtra	2024	2026	ICMR
46	Sadhana Gupta	Identification of circulating microRNA signatures as diagnostic markers for early stage and metastatic breast cancer	2021	2024	ICMR
47	Shahina Begum	Pragmatic stepped wedge cluster randomization trial to evaluate the screening of clinical breast examination through health education interventions in rural Maharashtra	2023	2025	DHR
48	Shailesh Pande	Support to conduct training programme "Operations research in public health" support to Indian Institutes for imparting training	2021	2025	DHR
49	Shailesh Pande	Comprehensive genetic evaluation of fetus in antenatally detected abnormal pregnancies with fetal malformations: Outcomes, benefits, and limitations- a pilot study	2021	2024	DHR-GIA
50	Shailesh Pande	Mission program on pediatric rare genetic disorders	2023	2028	DBT
51	Shailesh Pande	Establishment of Centre for Maternal & Child Genetics at ICMR-NIRRH, Mumbai under UMMID initiative	2024	2029	DBT
52	Srabani Mukherjee	Exploring 5-hydroxymethylcytosine (5hmC) marks as epigenetic drivers in PCOS pathophysiology	2021	2024	DHR
53	Srabani Mukherjee	Unravelling the metabolic nexus in the granulosa cells	2023	2026	DHR
54	Srabani Mukherjee (Co-PI)	Unravelling the influence of genetic variants on follicular micro environment, ovarian response and pregnancy outcome in the young women undergoing ART treatment	2023	2026	SERB

55	Srabani Mukherjee	Analysis of gut microbiome and metabolome in women with PCOS	2023	2026	DBT
56	Suchitra Surve / Ragini Kulkarni	Assessment of neonatal screening approaches for sickle cell disease and the effect of early intervention in management of the disease in tribal population	2019	2024	ICMR
57	Suchitra Surve	Exploring clinical and therapeutic relevance of novel biomarkers among children presenting with idiopathic and incomplete precocious puberty at tertiary hospital in Mumbai	2021	2024	ICMR
58	Susan Thomas	Machine learning algorithms trained on voice to predict psychological distress and postpartum depression	2023	2025	ICMR-AI cell
59	Susan Thomas	Integrated analyses of genomic scale metabolic models and omics profiles to capture the host-pathogen-environment interplay of Candida sp.	2021	2024	SERB
60	Susan Thomas	Establishment of Bioinformatics and Computational Biology centre (Centre for advanced research in bioinformatics and computational biology for woman and child health)	2021	2026	DBT
61	Susan Thomas	National Network Project of ICMR-National Institute for Research in Reproductive and Child Health, Mumbai	2023	2028	DBT-NNP
62	Uddhav Chaudhari	To investigate role of HMGB1-RAGE axis in regulation of immune cells repertoire during endometrial breakdown and repair	2024	2027	SERB
63	Vainav Patel (Site PI)	Immune response to precautionary third dose of COVISHIELD/COVAXIN among healthy adult population: an ICMR Cohort study, India	2022	2024	ICMR
64	Vainav Patel	An integrated approach towards characterizing the Treg reservoir in HIV-1 infection	2023	2026	DST
65	Vikas Dighe	Evaluation of synergistic impact of oral Nano-curcumin and Alpha-Linolenic Acid on maternal and fetal health in rat model of preeclampsia	2021	2024	ICMR
66	Vikas Dighe	Evaluation of immunomodulatory and anti-cancer properties of Hydroxychavicol, a major constituent of Piper betel	2024	2027	DHR
67	Vikas Dighe	Sertoli and leydig cell homing peptides as molecular steering for testicular targeted drug delivery	2021	2024	DHR
68	Vikas Dighe	Evaluation of drugs-cytochrome P450 enzyme interaction through fluorometric high throughput screening assays	2021	2024	CCRAS

69	Vikas Dighe	Preclinical study on efficacy, safety, and toxicity of Swarna Prashan regimen as adjunct therapy in paediatric acute lymphoblastic leukemia	2023	2026	CCRAS
70	Vikas Dighe	Exploring the therapeutic potential of peptides targeting Lysophosphatidic Acid (LPA) receptors in ovarian cancer	2022	2025	DBT
71	Vikrant Bhor	Longitudinal cohort study of lactating women to assess the impact of SARS-CoV- 2 exposure and vaccination on systemic and vertically transferred SARS-CoV-2 specific immunity in the mother-infant dyad	2023	2025	ICMR
72	Vikrant Bhor	Development of a sustainable network of laboratories in India for identification, monitoring and research on virus and bacteria causing acute encephalitis syndrome and other novel pathogens through capacity building in advanced biomedical technologies	2023	2025	ICMR (PM-ABHIM)
73	Vikrant Bhor	Evaluation of the immunogenic potential of membrane vesicles from clinical isolates of <i>Gardnerella vaginalis</i> in a murine model of bacterial vaginosis	2024	2027	DST-SERB
74	Vikrant Bhor	Intranasal mucosal vaccine for COVID-19	2020	2023	DBT-BIRAC

AYUSH	<i>Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopathy</i>
BioCARE	<i>Biotechnology Career Advancement and Re-orientation Programme</i>
BIRAC	<i>Biotechnology Industry Research Assistance Council</i>
BRNS	<i>Board of Research in Nuclear Sciences</i>
CCRAS	<i>Central Council for Research in Ayurvedic Sciences</i>
DAE	<i>Department of Atomic Energy</i>
DBT	<i>Department of Biotechnology</i>
DHR	<i>Department of Health Research</i>
DST	<i>Department of Science and Technology</i>
HMSC	<i>Health Ministry Screening Committee</i>
HTAI	<i>Health Technology Assessment in India</i>
IAVI	<i>International AIDS Vaccine Initiative</i>
ICMR	<i>Indian Council of Medical Research</i>
NACO	<i>National AIDS Control Organization</i>
SERB	<i>Science and Engineering Research Board</i>
STAR	<i>Science and Technology Award for Research</i>
UNICEF	<i>United Nations International Children's Emergency Fund</i>
WHO	<i>World Health Organization</i>

16. INTRAMURALLY FUNDED PROJECTS

S.No	Name of PI	Title	Start year	End year
1.	Anushree Patil	Implementation of Multidisciplinary Intervention Model (MDIM) to improve reproductive and health outcomes in women with Polycystic Ovary Syndrome (PCOS)	2023	2024
2.	Antara Banerjee	Developing indigenous diagnostics for evaluating the levels of kisspeptin	2023	2026
3.	Bhakti Pathak	Deciphering the role of PSP94 and CRISP family proteins in ion channel modulation	2019	2024
4.	Bhakti Pathak	Analyzing urinary PLGF and its association with preterm birth and SGA infants	2021	2024
5.	Bhakti Pathak	Assessing Trop2 expression and its correlation with the anti-Trop2 immune status in ovarian cancer patient	2017	2024
6.	Bhakti Pathak	Analysis of molecular cargo and paracrine effects of extracellular vesicles secreted by ovarian cancer cells	2021	2026
7.	Deepak Modi	Deciphering the immunomodulatory roles of Homeobox A10 in the endometrium during embryo implantation	2021	2024
8.	Deepak Modi	Development of a microfluidic-based tool for assessing placental functions and evaluating its potential application in pregnancy-related disorders	2023	2027
9.	Deepak Modi	Determining the role of HOXA10 in the pathogenesis of endometriosis	2023	2025
10.	Deepak Modi	Investigating the role of epithelial to mesenchymal transition in the process of embryo implantation	2023	2026
11.	Deepak Modi	Study on placenta of women with coronavirus disease 2019 (COVID-19) and its correlation with pregnancy and neonatal outcomes	2023	2025
12.	Deepti Tandon	Three dimensions of <i>Mycoplasma genitalium</i> infection- Detection, cure rate and co-infections in women attending STI Clinics	2019	2023
13.	Dhanjit K Das	Genetic aberrations and their functional analysis in patients with intellectual disability: Implications of genetic defect in iPSCs derived neurons	2024	2029
14.	Dipty Singh	Effect of maternal gestational micronutrient deficiency on offspring's fertility and its underlying epigenetic mechanisms in germline	2019	2024

15.	Dipty Singh	In vitro studies to investigate the permeability and effects of phthalates and VOCs on vaginal epithelium	2024	2026
16.	Dipty Singh	Blood and urine levels of phthalates and VOCs and their association with the use of menstrual hygiene products	2024	2026
17.	Dipty Singh	Idiopathic recurrent pregnancy loss: Possible association with paternal exposure to endocrine disruptors and epigenetic modifications in sperm	2021	2026
18.	Dipty Singh	Unravelling the sperm epigenetic landscape in infertile men with clinical varicocele	2020	2025
19.	DVS Sudhakar	Identification and characterization of genetic factors associated with multiple morphological abnormalities of sperm flagella (MMAF)	2022	2025
20.	Geetanjali Sachdeva	Investigating the contribution of DNA damage, repair and demethylation in the pathogenesis of endometriosis	2023	2026
21.	Geetanjali Sachdeva	Uterine alarmins and their relevance in implantation	2019	2025
22.	Geetanjali Sachdeva	Investigating the key elements in estrogen signalling in the context of prostate cancer	2021	2027
23.	Kiran Munne	Exploring the association of cervicovaginal microbiome with transient and persistent high-risk HPV infection and cervical precancerous lesions	2023	ongoing
24.	Kiran Munne	Evaluating utility of molecular workflow for establishing microbial profile and antimicrobial resistance for neonatal sepsis in a tertiary care NICU, Mumbai	2023	ongoing
25.	Kumari Nishi	Transgenerational effects of paternal hypertension on fertility and pregnancy outcome: An epigenetic approach	2021	2025
26.	Kumari Nishi	Development of a point of care electrochemical biosensor for the estimation of autoantibodies for obstetric antiphospholipid syndrome - A proof of concept study	2024	2029
27.	Kushaan Khambata	Unravelling sperm epigenetic landscape regulated by estrogen receptors in adult male rats	2021	ongoing
28.	Kushaan Khambata	Investigating sperm 5hmC landscape in male infertility and recurrent pregnancy loss	2023	ongoing
29.	Mahadev Bhise	Trends, patterns and determinants of sex-selective abortions in India using nationally representative survey data	2023	ongoing

30.	Nupur Mukherjee	Role of Toll-like receptors and TLR agonists in modulating response to chemotherapy in TNBC patients	2019	2024
31.	Nupur Mukherjee	Deciphering the trophoblast-breast epithelial cell cross talk in pregnancy associated breast cancer (PABC)	2021	2024
32.	Pallavi Shukla	Investigating the clinical relevance of environmental chemicals and exosomal miRNA biomarkers in the pathophysiology of polycystic ovary syndrome	2023	2026
33.	Pallavi Shukla	Analysis of mitochondrial DNA sequence variants in polycystic ovarian syndrome women with insulin resistance	2018	2024
34.	Pallavi Shukla	Study of epigenetic factors involved in mitochondrial dysfunction in PCOS women	2019	2026
35.	Periyasamy Kuppusamy	Implications of gonadotropin and their receptor gene variants in male infertility	2022	2026
36.	Periyasamy Kuppusamy	Identification of steroid metabolites as prognostic markers for spontaneous preterm delivery: A prospective cohort study	2024	2027
37.	Priyanka Parte	Investigation of potential chemotactic metabolites in the follicular fluid	2020	ongoing
38.	Ranjan Kumar Prusty	Trends, pattern, and determinants of pregnancy and birth outcomes in India: Evidence from 5 rounds of National Family Health Surveys (1991-2021)	2022	2023
39.	Sadhana Gupta	Deciphering gut microbial signatures in breast cancer and impact of their modulation on immune response following therapy	2023	2026
40.	Shahina Begam	Factors associated with intimate partner violence: Insights from National Family Health Survey-5	2023	2024
41.	Shailesh Pande	Understanding the genetics of sudden intrauterine fetal death (IUFD)/ still birth (SB): A comprehensive, reflex and targeted approach along with genetic counseling-a pilot study	2020	2025
42.	Shaini Joseph	Deciphering the functional significance of candidate genes associated with polycystic ovary syndrome identified from network analysis	2021	2024
43.	Shaini Joseph	Establishing a predictive algorithm for fetal growth restriction in Indian population: a prospective cohort and a nested case-control study	2024	ongoing
44.	Srabani Mukherjee	DNA methylation and histone modifications in dehydroepiandrosterone induced cystic ovarian murine model	2023	ongoing

45.	Srabani Mukherjee	Investigation of epigenetic alterations in estradiol-treated cystic ovarian murine model	2022	ongoing
46.	Srabani Mukherjee	Assessment of coagulation and fibrinolytic factors as contributors of thrombotic state in PCOS	2021	ongoing
47.	Srabani Mukherjee	Epigenetic alterations regulating miRNA expression in women with PCOS	2021	ongoing
48.	Srabani Mukherjee	PON1 expression, activity and its relationship with oocyte and embryo quality in women with PCOS undergoing assisted reproductive technique	2014	2023
49.	Susan Thomas	Establishment of Bioinformatics and Computational Biology Centre	2021	2026
50.	Uddhav Chaudhari	Role of HMGB1 and RAGE in endometrial repair	2023	2026
51.	Uddhav Chaudhari	Heterogeneity of gestational diabetes mellitus based on insulin resistance	2022	2025
52.	Vainav Patel	Studies on HIV latency and reactivation in cellular reservoirs	2020	2025
53.	Vainav Patel	Host pathogen signatures associated with congenital transmission and pathogenesis of human cytomegalovirus Part A: Immune correlates and viral signatures associated with congenital transmission and pathogenesis of human cytomegalovirus	2020	2025
54.	Vikas Dighe	Deciphering the molecular mechanism of effects of triclosan on hypothalamus pituitary gonadal axis	2018	2025
55.	Vikas Dighe	MicroRNA regulation in prostate and ovary upon exposure to endocrine disruptors	2019	2025

17. STAFF AND STUDENTS

DIRECTOR'S OFFICE

Dr. Geetanjali Sachdeva, *Director*
Mr. M. P. Chabukswar, *Personal Assistant*
Mr. K. N. Kadam, *Attendant Services*

BIOMEDICAL INFORMATICS CENTRE

Dr. Susan Thomas, *Scientist 'E'*
Mr. R. S. Barai, *Technical Officer* * Resigned on 16.10.2023
Ms. Sailee D. Shahane, *Technical Assistant (Bioinformatics)* * Appointed on 23.02.2024
Mr. S. Bhajeekhaye, *Technician - 1 (Computer Science)* * Appointed on 12.02.2024
Mr. Saravanan P, *Technician - 1 (Laboratory)* * Appointed on 21.02.2024
Mr. S. D. Shinde, *Technician - 1 (Information Technology)* * Appointed on 19.02.2024
Mr. N. B. Shelar, *Laboratory Assistant*
Ms. Shuvechha Mukherjee, *Ph.D. Scholar*
Ms. Indra Kundu, *Ph.D. Scholar*
Ms. Kshitija S. Rahate, *Ph.D. Scholar*
Ms. Karishma Desai, *Ph.D. Scholar*
Ms. Ulka Gawde, *Ph.D. Scholar*

BIOSTATISTICS DEPARTMENT

Dr. Shahina Begum, *Scientist 'E'*
Dr. R. K. Prusty, *Scientist 'C'*
Mr. M. Bhise, *Scientist 'C'*
Ms. Madhuri Kumre, *Laboratory Assistant*

CELL PHYSIOLOGY AND PATHOLOGY LABORATORY

Dr. Geetanjali Sachdeva, *Scientist 'G'*
Dr. U. K. Chaudhari, *Scientist 'E'*
Dr. R. R. Katkam, *Principal Technical Officer* * Retired on 31.12.2023
Ms. Sushma Gadkar, *Sr. Technical Officer-2 & Ph.D. Scholar*
Mr. B. G. Jamdare, *Technical Assistant (Life Sciences)* * Appointed on 14.02.2024
Mr. B. P. Mayekar, *Laboratory Assistant*
Ms. Kashmira V. Bhusane, *Ph.D. Scholar*
Ms. Rithika Rajendran, *Ph.D. Scholar*
Ms. Junita Desouza, *Ph.D. Scholar*
Ms. Itti Munshi, *Ph.D. Scholar*
Mr. M. I. F. J. Shaikh, *Ph.D. Scholar*
Mr. A. Khandvilkar, *Ph.D. Scholar*
Mr. G. R. Paswan, *Ph.D. Scholar*
Ms. Nikita Sharma, *Ph.D. Scholar*
Ms. Nisha Bilkhiwal, *Ph.D. Scholar*

Ms. Padmaja Deore, *Ph.D. Scholar*
Ms. Rishigandha Salunkhe, *Ph.D. Scholar*

CELLULAR AND STRUCTURAL BIOLOGY LABORATORY

Dr. Bhakti Pathak, *Scientist 'F'*
Dr. Dhanashree Jagtap, *Scientist 'D'*
Dr. Antara Banerjee, *Scientist 'C'*
Ms. Ananya Breed, *Sr. Technical Officer - 1*
Mr. B. J. Kulkarni, *Technical Assistant*
Mr. R. G. Rane, *Laboratory Assistant*
Mr. J. M. Rabhadiya, *Laboratory Assistant*
Ms. Vaidehi Miya, *Ph.D. Scholar*
Ms. Apoorva Pawar, *Ph.D. Scholar*
Ms. Meghali Borkotoky, *Ph.D. Scholar*
Ms. Amruta Naik, *Ph.D. Scholar*

CHILD HEALTH RESEARCH DEPARTMENT

Dr. Suchitra Surve, *Scientist 'D'*
Dr. Kiran Munne, *Scientist 'C'*
Ms. Leena V. Tendulkar, *Sr. Technical Officer - 2*
Ms. Varsha H. Tryambake, *Sr. Technical Officer - 2*
Ms. Rachana R. Dalvi, *Sr. Technical Officer - 2*
Ms. Shilpa C. Kerkar, *Technical Officer -C*
Ms. Sharmila S. Kamat, *Technician A*
Ms. Sarita Bhanghe, *Attendant (Services)*
Ms. Guguloth Saritha, *Lab. Attendant - 1*
Ms. Sonali Kamble, *Technician - 1*

** Appointed on 19.02.2024*

** Appointed on 05.03.2024*

CLINICAL RESEARCH LABORATORY

Dr. R. Gajbhiye, *Scientist 'E'*
Dr. P. Kuppusamy, *Scientist 'C'*
Ms. Shagufta A. Khan, *Sr. Technical Officer-2*
Ms. Vaishali Chalke, *Laboratory Assistant*

GAMETE IMMUNOBIOLOGY LABORATORY

Dr. Priyanka Parte, *Scientist 'F'*
Dr. Kushaan Khambata, *Scientist 'C'*
Ms. Smita Yevate, *Technical Officer*
Mr. M. T. More, *Laboratory Assistant*
Mr. D. G. Gaikwad, *Laboratory Assistant*
Ms. Veena Dalvi, *Ph.D. Scholar*
Mr. A. Patankar, *Ph.D. Scholar*
Ms. Isha Singh, *Ph.D. Scholar*
Ms. Durva Panchal, *Ph.D. Scholar*

GENETIC RESEARCH CENTER

Dr. S. Pande, *Scientist 'D'*
Dr. Shaini Marina Joseph, *Scientist 'D'*
Dr. D. V. S. Sudhakar, *Scientist 'D'*
Dr. V. Bhanothu, *Scientist 'C'*
Mr. H. M. Gawde, *Sr. Technical Officer-2*
Ms. Neha Minde, *Sr. Technical Officer-2*
Ms. Shiny Babu, *Sr. Technical Officer-2*
Mr. D. C. Naik, *Technical Assistant (Life Sciences)*
Ms. Rushali Jadhav, *Technician – 1*
Mr. K. Mali, *Laboratory Assistant*

** Appointed on 19.02.2024*

** Appointed on 11.03.2024*

INFECTIOUS DISEASES BIOLOGY LABORATORY

Dr. Sadhana Gupta, *Scientist 'D'*
Ms. Mohini Barku Vishve, *Technician - 1 (Laboratory)*
Mr. A. S. Hatle, *Laboratory Assistant*
Mr. A. K. Tembhurne, *Ph.D. Scholar*
Ms. Samruddhi Ranmale, *Ph.D. Scholar*
Ms. Puja Kumari, *Ph.D. Scholar*

** Appointed on 29.02.2024*

INNATE IMMUNITY LABORATORY

Dr. Taruna M. Gupta, *Scientist 'F'*
Dr. Susan Thomas, *Scientist E*
Mr. M. Ghosalkar, *Sr. Technical Officer-2*
Mr. R. D. Shinde, *Laboratory Assistant*
Ms. Aishwarya Rao, *Ph.D. Scholar*
Ms. Kasturi Ganguly, *Ph.D. Scholar*
Ms. Hajra Gupta, *Ph.D. Scholar*
Ms. Rutwija Athalye, *Ph.D. Scholar*

** Transferred to ICMR on 24.07.2023*

MOLECULAR AND CELLULAR BIOLOGY LABORATORY

Dr. D. N. Modi, *Scientist 'F'*
Dr. Nupur Mukherjee, *Scientist 'C'*
Ms. Sarika Ahire, *Technical Officer*
Mr. S. G. Sakpal, *Laboratory Assistant*
Ms. Nancy S. Achary, *Ph.D. Scholar*
Ms. Richa R. Sharma, *Ph.D. Scholar*
Mr. A. Bhide, *Ph.D. Scholar*
Ms. Babita Negi, *Ph.D. Scholar*
Ms. Pranya N, *Ph.D. Scholar*
Mr. P. Rasal, *Ph.D. Scholar*

MOLECULAR ENDOCRINOLOGY LABORATORY

Dr. Srabani Mukherjee, *Scientist 'G'*
Dr. Pallavi Shukla, *Scientist 'D'*
Ms. Sushma Khavle, *Technical Officer-C*
Ms. Gayatri Shinde, *Sr. Technical Officer-1*
Ms. Nanda Joshi, *Technical Officer*
Mr. P. P. More, *Technician 'C'*
Mr. V. M. Khedekar, *Laboratory Assistant*
Mr. A. Naigaonkar, *Ph.D. Scholar*
Ms. Snehal Bhingardev, *Ph.D. Scholar*
Ms. Komal Khade, *Ph.D. Scholar*
Ms. Medini Samant, *Ph.D. Scholar*
Ms. Manisha Kumari, *Ph.D. Scholar*
Ms. Jyotsna Khitani, *Ph.D. Scholar*
Ms. Chandra Biswas, *Ph.D. Scholar*

MOLECULAR IMMUNOLOGY AND MICROBIOLOGY

Dr. V. Bhor, *Scientist 'E'*
Dr. K. C. Itta, *Scientist 'C'*
Dr. Clara Aranha, *Principal Technical Officer* * Retired on 31.10.2023
Ms. Gauri Bhonde, *Sr. Technical Officer-1*
Mr. S. D'Souza, *Laboratory Assistant*
Ms. Kalyani A. Karandikar, *Ph.D. Scholar*
Mr. P. Devadiga, *Ph.D. Scholar*
Ms. Jyoti S. Batgire, *Ph.D. Scholar*
Mr. R. Pawar, *Ph.D. Scholar*
Ms. Niteeka Chandel, *Ph.D. Scholar*

NEUROENDOCRINOLOGY LABORATORY

Dr. Dipty Singh, *Scientist 'D'*
Dr. Kumari Nishi, *Scientist 'C'*
Ms. Vaishali H. Nakhawa, *Sr. Technical Officer- 2*
Ms. Shobha Sonawane, *Sr. Technical Officer- 1*
Ms. Reshma Gaonkar, *Technical Officer*
Mr. M. G. Pawar, *Technician 'C'*
Mr. S. Mandavkar, *Technician 'C'*
Mr. D. B. Shelar, *Technician 'C'*
Mr. P. G. Tawade, *Lab Assistant*
Mr. P. K. Varma, *Technician-1* * Appointed on 19.02.2024
Ms. Sweta Mohan, *Ph.D. Scholar*
Ms. Mamata V. Datar, *Ph.D. Scholar*
Ms. Sandhya G. Nair, *Ph.D. Scholar*
Ms. Sanketa Raut, *Ph.D. Scholar*

Ms. Delna Irani, *Ph.D. Scholar*
Ms. Deepashika Arya, *Ph. D. Scholar*
Ms. Anushruti Singh, *Ph. D. Scholar*
Ms. Nayanika Roy, *Ph. D. Scholar*

OPERATIONAL AND IMPLEMENTATION RESEARCH DEPARTMENT

Dr. Beena Joshi, *Scientist 'F'*
Dr. Ragini Kulkarni, *Scientist 'F'*
Ms. Bhavya M K, *Scientist 'B'*
Ms. Kimthianhoih, *Technical Assistant (Social Worker)* * Appointed on 19.02.2024
Mr. I. S. Mashal, *Technician A*
Mr. P. S. Sanap, *Technician A*
Ms. Devyani Dhiraj Rathod, *Nursing Orderly*
Mr. J. Jayanth, *Lab. Attendant – 1* * Appointed on 15.02.2024

PRECLINICAL REPRODUCTIVE AND GENETIC TOXICOLOGY CENTRE

Dr. V. D. Dighe, *Scientist 'F'*
Mr. S. V. Jadhav, *Sr. Technical Officer-2*
Ms. Shilpa C. Kerkar, *Technical Officer-C*
Mr. Y. N. Kamble, *Technical Assistant (Life Sciences)* * Appointed on 21.02.2024
Mr. P. S. Salunkhe, *Sr. Technician-1*
Mr. N. B. Shelar, *Laboratory Assistant*
Ms. Yugandhara Jirwankar, *Ph.D. Scholar*
Ms. Bhavana Bhat, *Ph.D. Scholar*
Mr. A. Tiwari, *Ph.D. Scholar*
Mr. B. Saha, *Ph.D. Scholar*
Ms. Akanksha Nair, *Ph.D. Scholar*
Ms. Shilpa Kerkar, *Ph.D. Scholar*

REPRODUCTIVE AND BONE HEALTH DEPARTMENT

Dr. Lalita Savardekar, *Scientist 'F'*
Ms. Neera Mehta, *Technical Officer 'B'*
Mr. K. Y. Chavan, *Laboratory Attendant-2*
Ms. Swarupa Ravindra Khedekar, *Technician - 1 (Laboratory)* * Appointed on 26.02.2024
Mr. V. Prashanth, *Lab. Attendant – 1* * Appointed on 15.02.2024

REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY DEPARTMENT

Dr. Anushree Patil, *Scientist 'E'*
Dr. Deepti Tandon, *Scientist 'C'*
Ms. Pratibha Kokate, *Sr. Technical Officer-2*
Ms. Shobha Banage, *Sr. Technical Officer-2*
Ms. Sunita Kale, *Sr. Technical Officer-2*
Ms. Anamika Akula, *Sr. Technician -1*

Ms. Sunita Kharat, *Sr. Technician-1*
Ms. Sunita Kendre, *Laboratory Assistant*
Ms. Akshaya A. Rathod, *Attendant (Services)*
Ms. Shalini S. Lambade, *Attendant (Services)*
Mr. A. Hussain, *Technician - 1 (Laboratory)*

STEM CELL BIOLOGY LABORATORY

Dr. D. K. Das, *Scientist 'E'*
Dr. Shyla Ravindran, *Technical Officer -C*
Dr. Sandhya Anand, *Technical Officer – B*
Ms. Jidnyasa Rajendra Kore, *Technical Assistant (Life Sciences)*
Mr. S. Gondhali, *Laboratory Assistant*
Mr. S. Ghadigaokar, *Laboratory Assistant*
Mr. B. R. Shekhar, *Ph.D. Scholar*
Ms. Debolina Saha, *Ph.D. Scholar*
Ms. Mousumi Bal, *Ph.D. Scholar*

VIRAL IMMUNOPATHOGENESIS LABORATORY

Dr. V. Patel, *Scientist F*
Ms. Varsha Padwal, *Sr. Technical Officer-3*
Ms. Shilpa M. Velhal, *Sr. Technical Officer-2*
Mr. S. T. Bhagat, *Technical Officer -B*
Mr. G. A. Shinde, *Laboratory Assistant*
Mr. S. S. Musale, *Laboratory Attendant-1*
Ms. Snehal Kaginkar, *Ph.D. Scholar*
Ms. Harsha Palav, *Ph.D. Scholar*
Ms. Shilpa Bhowmick, *Ph.D. Scholar*
Mr. N. Mohite, *Ph.D. Scholar*
Ms. Sapna Yadav, *Ph.D. Scholar*

* Appointed on 07.02.2024

EXPERIMENTAL ANIMAL FACILITY

Dr. D. K. Das, *Scientist 'E'*
Dr. S. M. Metkari, *Principal Technical Officer*
Mr. S. C. Gondhalekar, *Sr. Technician-1*
Mr. S. Petkar, *UDC*
Mr. K. R. Naik, *Laboratory Assistant*
Mr. Y. C. Joshi, *Laboratory Attendant- 2*
Mr. P. R. Chavan, *Laboratory Attendant- 2*
Mr. G. C. Patil, *Laboratory Attendant- 2*
Mr. R. S. Sandis, *Laboratory Attendant- 2*
Mr. S. B. Bavdane, *Laboratory Attendant- 2*
Mr. V. V. Pawar, *Laboratory Attendant- 2*
Mr. M. V. Mali, *Attendant (Services)*

Mr. S. S. Chavan, *Attendant (Services)*
 Mr. K.V. Kadam, *Attendant (Services)*
 Mr. S. S. Kadam, *Attendant (Services)*
 Mr. P. K. Shingare, *Attendant (Services)*
 Mr. M. S. M. S. Qureshi, *Attendant (Services)*
 Mr. R. S. Marchande, *Attendant (Services)*
 Mr. B. K. Koli, *Attendant (Services)*
 Mr. Y. B. Shinde, *Attendant (Services)*
 Mr. S. Ram, *Lab. Attendant - 1 (Welder)*
 Mr. R. Kumar, *Lab. Attendant - 1*
 Mr. A. Musale, *Lab. Attendant - 1*
 Mr. P. Adepu, *Lab. Attendant - 1*
 Mr. Sujendra, *Lab. Attendant - 1*
 Mr. A. Kumar, *Lab. Attendant - 1*
 Mr. S. S. Mane, *Lab. Attendant - 1*
 Mr. A. Kumar, *Lab. Attendant - 1*

** Appointed on 19.02.2024*
** Appointed on 19.02.2024*
** Appointed on 08.02.2024*
** Appointed on 19.02.2024*
** Appointed on 22.02.2024*
** Appointed on 07.02.2024*
** Appointed on 16.02.2024*
** Appointed on 27.02.2024*

CONFOCAL FACILITY

Dr. Dipty Singh, *Scientist 'D'*
 Ms. Shobha Sonawane, *Sr. Technical Officer- 1*
 Ms. Reshma Gaonkar, *Technical Officer*

DNA SEQUENCING FACILITY

Dr. Srabani Mukherjee, *Scientist 'G'*
 Ms. Nanda Joshi, *Technical Officer*

ELECTRON MICROSCOPY FACILITY

Dr. Dipty Singh, *Scientist 'D'*
 Dr. Kumari Nishi, *Scientist 'C'*
 Ms. Vaishali Nakhwa, *Sr. Technical Officer-2*
 Mr. M. G. Pawar, *Technician 'C'*

FLOW CYTOMETRY FACILITY

Dr. Srabani Mukherjee, *Scientist 'F'*
 Ms. Sushma Khavale, *Technical Officer-C*
 Ms. Gayatri Shinde, *Sr. Technical Officer-1*

ETHICS SECRETARIAT

Dr. V.M. Bhor, *Scientist 'E'*
 Dr. Suchitra Surve, *Scientist 'D'*
 Ms. Vaishali Bhogate, *Sr. Technical Officer-1*
 Ms. Zakiya Ansari, *Technical Assistant*
 Mr. A. H. Hankare, *Laboratory Assistant*

ACCOUNTS

Mr. W. Narkar, *Accounts Officer (Additional Charge)*

Ms. Supriya Lad, *Section Officer*

Mr. M.K. Kanukuntala, *Assistant*

** Transferred to NIRF on 13.04.2023*

Mr. S. S. Gaikwad, *UDC*

Mr. M. D. Gavit, *UDC*

Mr. M. M. Shinde, *UDC*

Ms. Swara M. Zagde, *UDC*

ADMINISTRATION

Ms. Swati Gaikwad, *Sr. Administrative Officer*

** Transferred from NARI on 20.11.2023*

Mr. A. S. Gaikwad, *Sr. Administrative Officer*

** Retired on 31.08.2023*

Ms. Sunayna L. Barde, *Sr Private Secretary*

** Voluntary retirement on 01.11.2023*

Mr. A. Sarnaik, *Assistant*

Mr. A. Ghodake, *Assistant*

** Appointed on 29.09.2023*

Mr. K. Pawar, *UDC*

Mr. K. Keni, *Laboratory Assistant*

Mr. O. Shiraskar, *Technical Assistant*

** Appointed on 07.03.2024*

GENERAL ADMINISTRATION

Ms. Akanksha A. Dalvi, *Section Officer*

Mr. S. A. Sangelkar, *Office Assistant*

PROJECT CELL

Mr. V. M. Guram, *Sr. Technician – 1*

Ms. Ruchita Veerkar, *UDC*

Mr. H. Raut, *UDC*

PAY BILL SECTION

Ms. Akanksha A. Dalvi, *Section Officer*

Mr. V. M. Satav, *Office Assistant*

Mr. H. V. Jadhav, *Office Assistant*

Mr. S. T. Chorage, *UDC*

STORES

Mr. P.K. Chavan, *Section Officer*

Mr. G. M. Darpe, *Office Assistant*

Mr. K. Rama Rao, *Office Assistant*

Mr. A. Ghodake, *Office Assistant*

Mr. K.R. Sukumar, *Technical Assistant*

Mr. C. G. Nakade, *Technical Assistant (Mechanical)*

** Appointed on 08.02.2024*

Ms. Mamta Jadhav, *UDC*

Mr. S. S. Sawant, UDC
Mr. N. P. Bavdane, Laboratory Assistant

ESTABLISHMENT

Mr. K. T. Solanki, Section Officer
Ms. Kranti S. Patankar, Personal Assistant
Ms. Harsha Kurup, UDC
Mr. R. K. Parab, Laboratory Attendant – 1 * Appointed on 15.02.2024

ICMR INTERNATIONAL HOSTEL AND STAFF QUARTERS

Dr. Shahina Begum, Scientist 'E'
Mr. G. R. Devadiga, Sr. Technician – 3 * Retired on 31.12.2023

INSTRUMENTATION RESEARCH & MAINTENANCE/WORKSHOP

Mr. V. D. Koli, Sr. Technical Officer-2
Mr. J. Patharwat, Technical Officer-C
Mr. K. R. Sukumar, Technical Assistant
Mr. J.D. Lobo, Sr. Technician - 3
Mr. V. G. Rane, Sr. Technician – 2
Mr. A. Anglekar, Attendant (Services)
Mr. G. Shivakrushna, Technical Assistant (Civil) * Appointed on 16.02.2024
Mr. P. Meena, Technical Assistant (Civil) * Appointed on 16.02.2024
Mr. D. Prajapati, Technical Assistant (Mechanical) * Appointed on 08.02.2024
Mr. S. M. Mahadik, Technician - 1 (Electrical) * Appointed on 12.02.2024
Mr. V. S. Jadhav, Technician - 1 (Mechanical) * Appointed on 08.02.2024
Mr. A. Kumar, Technician - 1 (Mechanical) * Appointed on 15.02.2024
Mr. S. S. Kamble, Technician -1 (Electronics/ Instrumentation) * Appointed on 19.02.2024
Mr. A.D. Bhandwalkar, Laboratory Attendant- 2
Mr. M. Singh, Lab. Attendant - 1 (Refrigeration & AC) * Appointed on 19.02.2024
Mr. D. Ram, Lab. Attendant - 1 (Carpenter) * Appointed on 20.02.2024
Mr. Indraj, Lab. Attendant - 1 (Plumber) * Appointed on 01.03.2024
Mr. R. K. Meena, Lab. Attendant - 1 (Electrician) * Appointed on 07.02.2024
Mr. S. Meena, Lab. Attendant - 1 (Electrician) * Appointed on 13.02.2024
Mr. V. K. Nayak, Lab. Attendant - 1 (Mason) * Appointed on 26.02.2024

LIBRARY AND INFORMATION CENTER

Dr. Prabhjeet Kaur, Library and Information Officer
Ms. Simmy Saji, Sr. Technical Officer-C
Ms. Priya Menon, Technical Officer-B
Mr. V. L. Shinde, Technician A
Mr. A. Gode, Laboratory Assistant * Transferred from NIIH on 19.03.2024

SECURITY AND MAINTENANCE

Mr. J. D. Lobo, *Sr. Technician - 3*

Ms. Swaruparani Karunakaran, *Office Assistant*

Mr. N. S. Bhilare, *Sr. Technician - 2*

Mr. G. P. Narayan, *Sr. Technician - 2*

Mr. S. L. Shिवतarkar, *Sr. Technician - 1*

Mr. S. S. Subramnian, *Technician- 2*

Mr. S. K. Jadhav, *Technician- 2*

Mr. A. Y. Lokhande, *Laboratory Assistant*

Mr. S. F. Cardoza, *Laboratory Assistant*

Mr. M. Palande, *Laboratory Assistant*

Mr. R. Naik, *Laboratory Assistant*

Mr. A. D. Bhandwalkar, *Laboratory Attendant-2*

Mr. S. Y. Urankar, *Laboratory Attendant-2*

18. ACITIVITIES DURING THE YEAR 2023-2024



On National Sports Day, various sport competitions were organized on August 29, 2023



Visit by MRHRU pioneers Dr VM Katoch, former DG, ICMR and Former Secretary, DHR, GoI, and Dr Mrs Kiran Katoch, Former Director, ICMR-NJILOMD to the newly established MRHRU, Vani, to address MOs and HCWs in the area on September 11, 2023



Hindi Pakhwada was celebrated from September 14-29, 2023 during which various activities and competitions were organized to promote Hindi language.



Awareness session on 'Mission Program on Pediatric Rare Genetic Disorders' at Kindergarten School Ghansoli for parents and teachers on genetic conditions and tests available on October, 9 2023



Scientific Advisory Committee was held during December 7-8, 2023



Awareness session for Mumbai Public School girls on all aspects of 'Growing Up' was held on December 16, 2023



A Knee Camp was organized at our Reproductive and Bone Health Clinic on January 7, 2024



HTA Resource Hub at ICMR with Department of Health Research HTAIn jointly organized a Regional Consultative Workshop on Health Technology on January 16, 2024



Exposure visit of students and teachers from Turtuk Valley School and Leh School, Ladakh, organized by AFAC Trust, January 19, 2024



Dr Geetanjali Sachdeva unfurled the National Flag during the celebration of Republic Day on January 26, 2024



Local Research Advisory Committee meeting was held at MRHRU, Vani on February 14, 2024



A cultural programme was organized to celebrate the 54th Foundation Day of the institute on February 21, 2024



Community awareness session was conducted by our Genetic Research Centre at Society for the Education of the Challenged SEC Day School Agripada on February 22, 2024



Local Research Advisory Committee meeting was held at MRHRU, Dahanu on February 27, 2024



National Science Day was celebrated by awarding winners of competitions on the theme “Indigenous Technologies for Viksit Bharat” were held for the students of KMS Dr Shirodkar High School on March 2, 2024



Union Health Minister of State, Dr Bharati P Pawar ji, virtually laid the Foundation Stone of Model Rural Health Research Unit at Vani on March 13, 2024



Safai Karamcharis were felicitated during the celebration of Swachhata Pakhwada held during September 15, 2023 to October 2, 2023



DHR sponsored course on 'Harnessing the Power of Immunology in Medicine: Tools, Translation & Therapy' was organized during May 15, 2023 to June 9, 2023