

## Mani Awarded CPRIT Grant



For his project “Characterization of 3D Genome Organization and Transcriptional Regulation in Prostate Cancer”, Ram Mani, Ph.D., was given an Individual Investigator grant of \$1.049M. This is Dr. Mani’s second CPRIT award.

Enhancers are DNA switches that regulate the expression of genes in cells. Alterations in enhancer activity is increasingly linked to cancer development. Prostate cancer (PCa) is the prototypical enhancer-driven cancer. It harbors recurrent genomic rearrangements and structural variations that promote the mis-regulation of transcription factor genes by enhancer hijacking. Enhancers can be located within or outside genes and can regulate multiple genes simultaneously. However, pairing enhancers with their target genes is extremely challenging. This is because enhancers can regulate genes that are located hundreds of kilobase pairs away and can often skip the nearest genes. Our group has created the first-in-field atlas of enhancer-target gene interactions in PCa models. Analysis of this atlas has helped us understand how mutations influence enhancer activity to drive malignancy. The enhancer connectome is regulated by transcription factors and structural proteins like cohesins.

The first goal of this proposal is to create a conceptual framework to unravel the functional link between cohesins, enhancers, transcription and genome folding. The proposed experiments will be conducted in human prostate specimens by using cutting-edge genomic methods and machine learning models. PCa is also one of the most heritable human cancers. Genome-wide association studies (GWAS) have identified at least 185 PCa germline risk alleles. We have shown that PCa germline risk alleles are enriched in enhancers.

The second goal of this proposal is to unravel the mechanisms by which these risk alleles modulate enhancer activity to promote PCa development. The knowledge emanating from our study will usher the development of intervention strategies to prevent or delay PCa. The enhancer-target connectome data stemming from our proposed studies can in principle be used to interpret PCa GWAS signals across all ancestries and will have tremendous value in addressing PCa health disparities.

Dr. Mani, an Assistant Professor of Pathology, holds a secondary appointment in Urology. He is also a member of the Simmons Cancer Center. He has been a UTSW faculty member since 2014.