DEPARTMENT OF BIOLOGICAL SCIENCES

PH.D. VIVA VOCE

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Date/Time: **Monday, May 15, 2017 at 5:00 pm** Venue: **L-2, LHC**

Implication of Budding Yeast as a Model Organism for Understanding the Chemical-Genetics and Functional Toxicogenomics

Eukaryotes have their genome in the compacted form of chromatin. The dynamics in chromatin structure is facilitated by epigenetic modifications on both the DNA and histone proteins. These modifications are reversibly influenced by one's lifestyle and in response to a variety of environmental cues and stress, for modulating the gene expression at innumerable locations throughout the genome and thus to achieve cellular adaptation and survival. The modern genome-wide approaches such as transcriptomics, proteomics and chemogenomics have implied budding yeast *Saccharomyces cerevisiae* as a privileged model organism for exploring the biological targets and mechanisms of action of pollutants and various bioactive molecules (**1**). In my graduate study, I have utilized *S. cerevisiae* as a model organism for investigating the molecular targets and mode of action of Acrolein (using its precursor Allyl Alcohol-AA), a very common environmental pollutant; Valproic acid (VA), a histone deacetylase inhibitor as well as an anticancer molecule; and KP1019, a ruthenium-based anticancer drug undergoing clinical trials.

Genome-wide microarray analysis upon treatment with a sublethal dose of AA, KP1019, and VA has evidenced transcriptional regulation of 30% of the yeast genome significantly. Subsequent functional enrichment analysis of transcriptome revealed that the genes belonging to diverse cellular processes were regulated differentially. Furthermore, I have identified several new molecular targets that were required for AA/Acrolein, KP1019, and VA tolerance through genetic screening approach. In particular, the detailed biochemical and genetic analysis of different pathways including redox homeostasis, DNA repair, cell wall integrity, metal homeostasis, lipid homeostasis, and TOR Signaling that were targeted by AA/Acrolein, KP1019, and VA have revealed their comprehensive mode of action. Notably, my findings also have established the role of histone tails, chromatin modifiers in mediating the AA/Acrolein toxicity and suggested the use of both pyrazole and ethanol as probable antidotes for AA intoxication. Also, I have established the reproductive toxicity of AA/Acr on spermatogenesis using yeast meiosis model (**2**).

Furthermore, I have found that VA exhibits its effect by modulating the MAP kinase signaling, both mitochondrial and ER architecture and functions. Also, I have found that the effects of VA were neutralized in cells lacking lipid droplets (**3**). Besides, KP1019 was found to increase the accumulation of neutral lipids in both yeast and HeLa cells. Strikingly, the activity of KP1019 was increased by several folds in the presence of various metal ions, whereas neutralized by Fe^{2+}, osmotic stabilizer, ethanolamine, and reducing agents. Moreover, I have found that the mutations and loss/gain of post-translational modifications on histone H3/H4 modulates the effectiveness of KP1019, a clinically important anticancer drug (**4**). Collectively, these findings in budding yeast strengthened our current knowledge and facilitated the prediction of biomarkers for toxicity assessment, therapeutic targets along with their detoxification approaches. In summary, these studies favor the use of toxicogenomics and chemical genetics approaches in yeast for investigating the mode of action of bioactive molecules, pollutants, and toxicants.

References:

1. Dos Santos, S. C., Teixeira, M. C., Cabrito, T. R., and Sa-Correia, I. (2012) ***Frontiers in genetics*** 3, 63.
2. Golla, U., Bandi, G., and Tomar, R. S. (2015) ***Chemical research in toxicology*** 28, 1246-1264.
3. Golla, U., Joseph, D., and Tomar, R. S. (2016) ***Scientific Reports*** 6, 35322.
4. Golla, U., Swagatika, S., Chauhan, S., and Tomar, R. S. (2017) ***Manuscript under review***.