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GUEST EDITORIAL

100 Years of Biochemistry at the Indian Institute of Science

A department that is 100 not out! This is the best way to describe the Department of Biochemistry at IISc which is reminiscing into the past and looking into the future. Established on 16 February 1921, the department celebrated its Golden Jubilee and Platinum Jubilee in 1971 and 1996 respectively in the iconic building located in Tala Marg (see cover page). The centenary will be celebrated in the newly constructed Biological Sciences building in which the department occupies the first floor. I consider it a privilege to be the Chairperson of this department in its centennial year and write this article that provides a glimpse of various research activities of the department for the past 100 years.

In the early years, research of societal relevance resulted in development of methods for conversion of municipal wastes into organic manures, commercial production of acetone from mahua flowers, control of spike disease of sandal wood, fluoride removal from drinking water, identification of β-N-oxalyl-L-α,β-diaminopropionic acid as the toxic principle of kesari dhal (*Lathyrus sativus*), study of nutritive value of milk and milk products as well as vitamin A assay of ghee and preservation of fruits and vegetables. In the area of basic research, key contributions were made which include: unravelling the mechanism of intestinal absorption and transport of vitamin A, identification of yeast chromosomes and nuclear membrane, identification of Allohydroxy-L-proline, as a new non-protein amino acid in sandal leaves, introduction of circular paper chromatography as an analytical tool and demonstration of use of dilatometry and calorimetry for the quantitative measurement of volume and heat changes in biochemical reactions, demonstration of the role of ubiquinone in regulation of cholesterol biogenesis, study of structure and function of pancreatic ribonuclease and sorghum acid protease, structural studies on DNA using antibodies raised against nucleosides, identification and separation of unusual bases in tRNA, isolation of a galactolipid and sulphur-containing sphingolipid from plants; characterization of retinyl ester hydrolase, cholesteryl ester hydrolase, acyl-CoA-GPC acyltransferase and phospholipases of rat intestine and demonstration of the presence of lysolecithin transacylase in pancreas.

In the area of reproductive biology and endocrinology, studies on follicle-stimulating hormone and leutinizing hormone led to the development of a new immunocontraceptive technology. Role of steroids in the regulation of placental proteins and gonadotropins in the differentiation of Leydig cells was investigated. Specific carrier proteins were shown to mediate trans-placental delivery of vitamins such as riboflavin, thiamine and biotin during gestation in female mammals and antibodies against these carrier proteins were shown to cause termination of pregnancy.

Studies were carried out on cellular thermogenesis, oxidative modifications of enzymes by H_2O_2, oxidative properties of metal-oxy radicals and peroxovanadium radicals. A novel mechanism involving lipid peroxidation for cellular thermogenesis was discovered. The parasitic plant Cuscuta was used as a model system to study a variety of biochemical processes such as trehalose toxicity, regulation of shoot and haustoria formation. A model for measuring the specificity using free energy of association of amino acids of proteins with nucleic acid bases was proposed. Supernumerary nuclei in filamentous fungi were shown to serve as store house for nitrogen and phosphorus in the form of DNA to be degraded by regulated autophagy. Mechanistic studies were carried out on enzymes such as aspartate transcarbamylase, serine hydroxymethyl transferase (SHMT), pyridoxal phosphate-dependent enzymes, xylanase as well as enzymes involved in microbial biodegradation of aromatic compounds. Restriction-modification (R-M) enzymes were used as model systems to understand how proteins recognize, cleave and modify DNA. Phase variable DNA methyltransferases of *Helicobacter pylori* as well as DNA mismatch repair proteins of *Haemophilus influenzae* and *Neisseria gonorrhoeae* were studied. Studies on molecular characterization of plant viruses led to the determination of complete genomic sequences and characterization of a viral non-structural protein as an RNA helicase. Extensive studies were carried out on malnutrition and brain development, biosynthesis of myelin lipids, the process of myelination, synaptogenesis, receptor ontogeny in the developing human brain and signal transduction mechanisms in brain. A novel, soluble pathway of synthesis of triacyl glycerol was identified. Oleosin, a structural protein was shown to have catalytic activities. Screening of 12,000 newborn children from Bangalore and Mysore showed that consanguinity had no significant effect on the incidence of inborn errors of amino acid metabolism.

Transcriptional regulation of genes involved in hepatic drug metabolism was investigated and heme was shown to play a key role in transcriptional activation of these genes. Several transcriptional and post-transcriptional regulators such as Mxr1p, Rop1p, Trm1p and Rtg1p were

identified and characterized in the methylotrophic yeast, *Pichia pastoris*. In the area of chromatin biology, histones and histone variants were studied. A meiotic recombination hot-spot locus in the mouse genome was shown to encode a novel non-protein coding RNA. Cohesin was shown to have a key role in subtelomeric silencing. Sumoylation defective variants of cohesin and condensin were found to be defective in gene silencing. A *tRNA*(*Gln*) gene and the Ty1 long terminal repeat was shown to have barrier activity.

In the area of translational regulation, arginine methylation was shown to promote translation repression activity of repressors Scd6 and Sbp1 by promoting interaction with conserved translation initiation factor eIF4G and self-association of RGG-motif proteins was found to regulate their repression activity by competing with eIF4G binding. Translational readthrough in AGO1 (encoding Argonaute 1) resulting in a longer isoform was shown to act as a global inhibitor of miRNA pathway. MTCH2, a mitochondrial carrier protein was shown to undergo double translational readthrough resulting in a novel isoform that affects the membrane potential and ATP synthesis.

In the area of recombination and DNA repair, a negative regulatory mechanism of homologous recombination that prevents deleterious effects of genomic rearrangements and induction of genotoxicity by inappropriate recombinational DNA repair was discovered. DNA damage response proteins were shown to be directly involved in telomere length homeostasis, cell senescence and cell cycle checkpoint control. A homing endonuclease encoded by RecA inteins of pathogenic mycobacteria was characterized. The mammalian RAD51 paralog, RAD51C was demonstrated to have distinct roles in DNA repair and DNA damage signalling. XRCC3 was shown to be a novel phosphorylation target of ATM and ATR kinases. RAD51 paralogs were shown to be involved in mitochondrial DNA replication and maintenance of mitochondrial genome stability. Studies on non-homologous end joining (NHEJ) and non-B DNA structures led to the discovery of non-canonical role of recombination activating genes (RAGs) in these processes. A novel miRNA was shown to mediate regulation of RAG expression. A specific inhibitor of NHEJ (SCR7) was discovered and its potential use in cancer therapy was demonstrated. Another small molecule inhibitor, Disarib, that can specifically target BCL2, an anti-apoptotic protein was demonstrated.

Certain carbohydrate-containing IgE-binding epitopes of extensins were identified as the major allergens among specific pollens and foods while tropomyosin was found to be the major shrimp allergen. The role of Cytotoxic T Lymphocytes in mediating protection against Japanese encephalitis virus was demonstrated. Glycodelin A (GdA) was shown to induce apoptosis in T helper cells and natural killer cells while Abrin, a ribosome inactivating protein was shown to induce apoptosis in cells. Peptidase N (PepN), a major aminopeptidase in *Escherichia coli* and *Salmonella enterica serovar Typhimurium* was characterized. Further studies uncovered the roles of Lon protease, MarA transcription factor and the AcrAB–TolC efflux pump during phenotypic antibiotic resistance in *E. coli*. The mechanism of anti-tumour action by heat killed *Mycobacterium indicus pranii*, was studied. The efficacy of DNA vaccines for JEV and rabies was investigated. A novel virus-inducible, nuclear noncoding RNA (VINC/NEAT1) was discovered and Apolipoprotein L9 was identified as a phosphatidylethanolamine-binding protein.

The malaria parasite was shown to synthesize its own heme and enzymes of this pathway were found to be essential for parasite survival in mosquito. Curcumin was shown to prevent parasite recrudescence and cerebral malaria in the mouse model paving the way for the initiation of human clinical trial. A novel, trans-splicing based expression of Hsp90 gene was discovered in *Giardia lamblia*. The heat shock response pathway of malaria parasite was studied in detail. Nuclear organization of uniquely trans-spliced genes in *Giardia* and analysis of flagellar motilities of pathogens such as *Trichomonas*, *Giardia* and *Trypanosoma* are being examined.

Studies on protein folding and protein translocation across mitochondrial membranes led to the identification of three different mitochondrial translocase machineries for protein import across the mitochondrial inner membrane. One of the components of the pre-sequence machinery was found to be involved in regulating apoptotic pathways, thus imparting chemoresistance in cancer cells. Two novel classes of ubiquitous redox-sensitive proteins (P16 and DJ-1) were identified.

A novel drug combination for MDR and XDR TB as well as new blood-based biomarker signatures of host genes for diagnosis of tuberculosis and for detecting response to antitubercular therapy are being developed. An RNA-based biomarker for discriminating metastatic from primary melanoma has been identified and a strategy for enhancing the efficacy of sorafenib in hepatocellular carcinoma has been demonstrated. Studies on secondary metabolites of plant and microbial origin paved the way for the possibility of enhanced production of drugs of clinical importance such as tropane alkaloids, vinca alkaloids, vinblastine, vincristine, and taxol from plant cell cultures, fermentation of their endophytic fungi or marine algal resources.

Over the years, the faculty of the department played a key role in the establishment of several institutions and industries in the country. Alumni of the department have occupied high administrative and leadership positions in academic institutions and industry. A yeast-based recombinant Hepatitis B vaccine was successfully commercialized. With 100 years of glorious history behind, the department is forging ahead, constantly adapting to the changing research environment, never deviating from its original objective of carrying out high quality basic and applied research.

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