

Dr.M.Balasubramanyam is Senior Scientist & Head, Cell and Molecular Biology at the MDRF. He is a member of the Asia-Pacific International Molecular Biology Network (A-IMBN) and had an extensive post-doctoral training (1991-95) at the Hypertension Research Centre, New Jersey Medical School, USA, in the areas of signal transduction in health and metabolic diseases with special reference to molecular pathogenesis of Type 2 diabetes and vascular biology. Having worked as a faculty at the Center for Biotechnology, Anna University, Chennai for 3 years (1996-99) he has joined MDRF in 1999. He is instrumental in setting up the basic infrastructural facilities at MDRF and coordinates various research programmes and educational activities from time-to-time.

Mission & Vision: Dr.Balu's laboratory is involved in studying cell and molecular signatures with special reference to insulin secretion, insulin action and vascular function. Our research integrates physiological and pharmacological approaches with biochemical, molecular biological and proteomics techniques to study mechanisms underlying development and progression of diabetes, its complications and cardiovascular diseases. This challenging multi-disciplinary research specialization dwells around the following themes:

Insights into biochemistry and molecular biology of diabetes and its vascular complications by studying nutrient-sensing pathways, redox signaling, advanced glycation end products, calcium signaling and epigenetic mechanisms.

Investigating the role of organellar dysfunction (Endoplasmic reticulum (ER) stress and mitochondrial mess) in insulin resistance and Type 2 diabetes utilizing the target tissue specific (skeletal muscle, adipose, β -cell) microarray, proteomics, siRNA and epigenetics studies.

Bio-prospecting biomarker(s) potential in body fluids and tissue biopsies (human skeletal muscle and adipocytes) adapting to proteomic tools and identification of prediabetes/diabetes/diabetic complications-specific molecular fingerprints and protein post-translational modifications.

Studying telomere biology and test whether shortening of telomeres are related to inter-individual differences in biological ageing that predisposes one to 'lifestyle diseases' and serve as a long-term biomarker.

Demonstration of oxidative stress as a therapeutic target, testing natural products (herbals, marine resources) from the Indian biodiversity for their molecular actions beyond antioxidant property and validation of their utility as novel insulin secretagogues/insulin sensitizers/vascular protectants.

The department now serves as an excellent 'interface' for biomedical/biotechnology/biopharmaceutical work with translational applications. The goal of the department is set to evolve as a '**Centre for Cellular and Molecular Medicine**' (CCMM) with state-of-the-art facilities for preclinical research, biomarker(s)

identification, high-throughput cell-based assay systems, and to offer world-class contract research and consultancy work in the areas of specialization.

Research Highlights

One of the thrust areas of research at the Madras Diabetes Research Foundation (MDRF) is to use the biochemical and proteomic technologies for identifying novel biomarkers and drug targets in the development and progression of diabetes and its associated complications. In the sub-set of subjects from CURES, we have shown elevated oxidative reactions (Sampathkumar et al 2005) and increased advanced glycation end products (AGEs) (Sampathkumar et al 2004) in patients with Type 2 diabetes and its vascular complications. Related to oxidative damage, our pilot observations indicated that there was increased lipid and protein oxidation as early in the stage of impaired glucose tolerance (prediabetes). In addition, we have seen telomere shortening in prediabetes subjects and patients with Type 2 diabetes (Adaikalakoteswari et al 2005; Adaikalakoteswari et al 2007), arising either from a cumulative burden of oxidative stress and/or other phosphorylation or epigenetic post-translational mechanisms. Another study (Adaikalakoteswari et al 2007) has demonstrated an association of oxidative DNA damage with PARP and NFkB activation, indicating a role for poly (ADP)-ribosylation in the pathogenesis of Type 2 diabetes. Moreover, a role for oxidative stress in diabetes patients was also substantiated with differential expression of NADPH oxidase and hemoxygenase gene (Adaikalakoteswari et al 2006). While these effects have been studied by classic biochemical and molecular biology methods, the recent onset of proteomics methods are expected to allow studying oxidative stress responses on a much wider scale with more emphasis and focus on identification of biomarkers. In this direction, in collaboration with Indian Institute of Science, Bangalore, we have recently identified increased positivity for glutathionylated hemoglobin (HbSSG) as a specific biomarker in diabetic patients with microangiopathy (Sampathkumar et al 2005b). As a prerequisite to study the proteomics & genomics of Type 2 diabetes, we have standardized in-house, the culturing of human skeletal muscle cells (HSMCs). Since insulin resistance of skeletal muscle primarily results from impaired glucose uptake and glycogen synthesis, these two metabolic read-out assays were first standardized in HSMCs (Balasubramanyam, 2006). The fact that defects in these metabolic read-outs are persisted in culture conditions of HSMCs obtained from patients with Type 2 diabetes, indicates that these cells are an excellent model system to study the proteomics & genomics of Type 2 diabetes. From the clinical proteomics view, our pilot studies also indicated protein spots with region-specific differences in plasma samples of subjects exhibiting varying degrees glucose tolerance. Other interesting studies which yielded preliminary data include: convergence of ER stress and insulin resistance in L6 skeletal muscle cells, palmitate-induced impairment of multimerization of adiponectin in 3T3 adipocytes, characterization of a novel PTP inhibiting activity in prodigiosin, etc. As a part of the NMITLI diabetes project on herbal medicine, both curcumin and gallic acid have been extensively studied and scientifically documented for their specific molecular actions. Gallic acid has been shown to possess novel (hitherto unknown) actions at the interface of transcription factors, membrane transport, down regulation of oxidants and upregulation of antioxidant enzymes etc.

Specialized training: Dr.M.Balasubramanyam is a member of the Asia-Pacific International Molecular Biology Network (A-IMBN) and had an extensive post-doctoral training (1991-95) at the Hypertension Research Centre, New Jersey Medical School, USA, in the areas of signal transduction in health and metabolic diseases with special reference to molecular pathogenesis of Type 2 diabetes and vascular biology. Under the Scientific Investigator training programme at AIIMS, New delhi, he has learned both basic and advanced applications of Electron Microscopy techniques. He is well-versed with transport assays, fluorescence imaging techniques and flowcytometry applications. In the year 2003, he has visited the University of San Diego and learned techniques related to human skeletal muscle and adipose tissue culturing, differentiation protocols, and he is well-versed with the insulin signaling assays such as, glucose uptake, lipolysis, tyrosine phosphorylation, PTP inhibition, glycogen synthase activity, lipid accumulation, palmitate oxidation etc. He has participated in several training programmes of frontier technologies including microarray, siRNA, 2-Dgel electrophoresis and mass spectrometry and his team is actively collaborating with Indian Institute of Science (Prof.P.Balaram & Dr.Utpal Tatu) on body fluid and tissue proteomics profiling. He is instrumental in setting up the basic science infrastructure in MDRF and with his efforts the tissue culture facility at MDRF is now fully tuned to conduct research on target-specific cells such as human skeletal muscle cells, human retinal endothelial cells, 3T3-L1 adipocytes, L6 muscle cells, THP-1 monocytes and RINm5F. The training offered at this department is considered unique in that it is tailor-made for the students of biotechnology and pharmaceutical research.