Preface

Tackling diabetes with a trans-disciplinary integrated scientific approach

In a world characterized by rapid change, uncertainty and increasing interconnectedness, there is a growing need for science to contribute to the solution of persistent, complex systems. As the disease pathogenesis of diabetes is heterogeneous and highly complex, both its prevention as well as management require solutions from trans-disciplinary fields. Thus, cross-institutional multi-disciplinary collaboration has become a trend today as researchers move towards building more productive and innovative teams for scientific research. Trans-disciplinary collaboration is essential in addressing the translation gap between scientific discovery and delivery of evidence-based interventions to prevent and treat diabetes. Today ever than before, there is a need for collaboration among professionals from clinical science, basic biology, developmental physiology, nutrition, dietetics, biostatistics, cognitive science and psychology, exercise physiology, social and community sciences, information technology and bioinformatics, educational fronts, health promotion boards and public health consortia, family and consumer sciences and Government policy implementation. Keeping the above in mind and the multidisciplinary nature of *Current Science*, this special section on diabetes is devoted to articles encompassing different fields of research specialization with the core objective of addressing the recent trends in our understanding of diabetes pathogenesis, prevention and management. We discuss the importance and significance of each of these contributions aimed to expand our understanding on the recent and contemporary trends in diabetes research.

Both the general public and diabetic patients often ask this question: is there a cure for diabetes? Type-1 diabetes mellitus (T1D) is an autoimmune disease that results from the destruction of insulin-producing pancreatic β-cells in the islets of Langerhans, and hence patients solely rely on the exogenous administration of insulin. As immunotherapy approaches have remained unsuccessful, the only cure for T1D is transplantation of donor-derived pancreas or islets. However, donor scarcity, graft loss and immune response to the foreign tissue are issues challenging this approach and limiting the number of patients who can benefit from such treatments. The increased understanding of the pathophysiology of type-2 diabetes (T2D) has led to the development of a number of drug classes with novel mechanisms of action. Despite these advancements in medical therapy, T2D is a progressive disease as most patients will require treatment intensification to achieve recommended glycaemic (HbA1c) levels. This typically involves combination therapy of two or more oral medications or escalation to injectable therapies (insulin or GLP-1). Tracking the first report of T1D reversal in seven consecutive patients by the Edmonton protocol in 2000, Balamurugan *et al.* (**page 1267**) summarize the state-of-the-art developments in this field. This review elaborately covers the history of pancreatic islet transplantation for T1D, Edmondon protocol and results of the recent Clinical Islet Transplant Consortium, hurdles faced by pancreatic islet transplantation, portal vein and other alternative sites for transplantation, advancements in the immunosuppressive protocols, the emerging biomarkers to monitor islet graft rejection and alternative β-cell replacement approaches/stem cell therapies. Recent developments in β-cell differentiation and genome engineering modifications are now propelling investigations into the mechanisms behind β-cell failure and autoimmunity, and are expected to offer new strategies for reducing the propensity for immunogenicity. Much hope and hype is also expected from the latest genome engineering research that can transcend many of the remaining challenges of stem-cell technologies, leading to superior transplantation and diabetes drug discovery platforms.

In the last couple of decades, tremendous progress has been made in understanding the genetic etiology of T1D and T2D, with hundreds of susceptibility gene loci identified, but the use of molecular testing to customize treatment is unfortunately not yet a reality. In particular, T2D is highly heterogeneous and has a range of risk factors, etiologies and clinical presentations, and arises due to a multitude of genetic variants that may interact with lifestyle and environmental factors. Recent genetic studies, especially genome-wide association studies, have identified a multitude of variants associated with T2D. However, available data to date do not provide robust evidence to support the utility of genetic screens (composed of recently identified genetic variants) for T2D predictions. Nevertheless, there is tremendous progress in genetic testing for monogenic forms of diabetes – the prominent one being the identification of deleterious mutations in genes that cause an early-onset, non-obese and non-auto-immune form of diabetes, known as maturity-onset diabetes of the young (MODY). That is, a personalized medicine 'remedy' for MODY is now clinically available. This is what is elegantly summarized by Radha and Mohan (**page 1277**), who discuss in detail the clinical and genetic investigations on MODY and neonatal diabetes mellitus (NDM). The fact that genetic testing for MODY and NDM has now become feasible and can offer personalized medicine-based diagnosis and treatment for the affected individuals is an encouraging development in the field of diabetes. Patients with NDM were originally believed to require lifelong insulin treatment; however, identification of K^{ATP} channel mutations via genetic testing has now revolutionized the treatment of NDM with sulphonylurea-based oral medication. As several monogenic

diabetes gene-panel tests are under development, there is more hope for genetic screening to enter into precision medicine-focused diabetes clinics.

Diabetic retinopathy (DR) is the leading cause of visual impairment and preventable blindness; it represents a significant socio-economic expenditure for healthcare systems worldwide. In the early stages of DR, the only therapeutic strategy that physicians can offer is a tight control of the risk factors, mainly blood glucose and blood pressure. The currently available treatments for DR are applicable only at advanced stages of the disease and are associated with significant adverse effects. Therefore, new treatments for the early stages of DR and therapeutic strategies targeting the main pathogenic mechanisms involved in the development of DR are the need of the day. DR is the progressive degeneration of retinal blood vessels and neurons and inflammation is known to play an important role in the pathogenesis of DR. Das *et al.* (**page 1287**) discuss the recent advancements focusing on the limitations of anti-VEGF (vascular endothelial growth factor) medications and newer biologic agents that are currently under investigation to improve the treatment of DR. Their review addresses the role of inflammation and the breakdown of the blood–retinal barrier, cellular alterations in different tissues of retinal vasculature, inflammatory mediators, targeting inflammation as a novel strategy to treat DR, the results so far obtained with steroids, non-steroidal anti-inflammatory drugs, cytokine inhibitors and other novel inhibitors currently under different phases of clinical trials. Recognition of non-VEGF contributions to the pathogenesis of DR may lead to novel therapeutics to enhance existing treatments for patients who do not respond to anti-VEGF therapies. Continuous research is needed to exploit the potential treatment strategies involving fibrates, connexins, neuroprotectants, photobiomodulation and anti-inflammatory agents against the development and progression of DR.

There is no doubt that non-communicable diseases like diabetes are causing a huge health burden globally. However, developing countries are still dealing with the double burden of both communicable as well as non-communicable diseases. Despite the success of vaccination programmes for polio and some childhood diseases, other communicable diseases like tuberculosis (TB) are still highly prevalent in many regions of the globe, and this is especially a major problem in developing countries like India. The association between diabetes mellitus (DM) and TB and their synergistic role in causing a huge health burden have been recognized for centuries. The effect of diabetes on the development and severity of TB, and the complex interrelations among nutrition, obesity, diabetes and TB remain provocative issues in public health and clinical medicine. With special reference to the situation in India, Kumpatla and Viswanathan (**page 1296**) present an excellent review on the epidemiology of diabetes and tuberculosis, tuberculosis and its clinical manifestations, effects of diabetes on TB treatment outcomes, screening methods and diagnosis, economic impact on the health sector, and the need for integrated national-level TB and DM programmes for prevention and control. With the increasing overlap of populations at risk (like India) for both diseases, the co-epidemic of TB and DM represents a greater health threat. More research and consensus guidelines are needed to better understand the impact of diabetes on multi-drug-resistant TB and on the clinical manifestation of TB and treatment outcome, the yields of bi-directional screening, and economic evaluation for TB screening among diabetes patients.

Non-alcoholic fatty liver disease (NAFLD) is on the rise worldwide and has become a major etiology for chronic liver disease. It is frequently associated with obesity, insulin resistance, hyperglycaemia, hypertension, and dyslipidaemia, and is considered the hepatic manifestation of metabolic syndrome. While the prevalence of NAFLD is high worldwide, it seems that epidemic of the disease is under-recognized and under-appreciated. The prevalence of NAFLD ranges between 10% and 35% based on the study population and method of diagnosis. It also varies between various races and ethnic groups and this may be attributed to several factors, including insulin resistance, lifestyle and diet, distribution of adiposity, and genetic factors. Surveying the literature on NAFLD in Asian Indians. Misra *et al.* (**page 1303**) provide a masterly overview of the epidemiology of the disease, the rising concern of NAFLD in children, several clinical correlates of disease, including body composition, insulin resistance, metabolic syndrome, T2D, atherosclerosis and subclinical inflammation along with other determinants of NAFLD, including vitamin-D deficiency, autonomic dysfunction, genetics and dietary factors. Predictive equation for NAFLD by Indian Fatty Liver Index and prediction of diabetes using liver span measurement are emerging as appropriate tools for both researchers and clinicians.

The global epidemic of T2D is often causally linked to marked changes in diet and lifestyle. However, less attention has been paid to the role of developmental plasticity and alterations in phenotypic outcomes resulting from altered environmental conditions during the early life period. Extensive experimental animal studies and epidemiological observations have shown that environmental influences during early development affect the risk of later pathophysiological processes associated with several non-communicable diseases, including T2D. The concept of the developmental origins of health and disease suggests that adverse influences early in development, particularly during intrauterine life, may results in permanent changes in the physiology and metabolism of the infant, which in turn results in an increased risk of non-communicable diseases in adulthood. Prabhakaran and Tandon (**page 1311**) provide an interesting snapshot on how early life factors encompassing maternal (own birth weight, nutrition, growth, socio-economic conditions,

toxic stress, intrauterine influences), foetal (nutrition, growth trajectory, placental stress) and post-natal (birth weight, nutrition, growth trajectory, socio-economic status) characteristics could programme and mediate disease risk in adulthood. Genetic and epigenetic factors also comprise important early life influence, and the study of gene–environment interactions is a challenging and thrust area for future research. It is now widely accepted that the intrauterine environment influences key developmental processes and has long-lasting effects on health and disease. This is endorsed by Krishnaveni and Yajnik (**page 1321**) in their review that summarizes how maternal diabetes and foetal growth are linked to fuel mediated teratogenesis, long-term effects of maternal diabetes to the offspring of diabetic mothers and non-glucose centric mechanisms of foetal programming. Foetal overnutrition and undernutrition have similar long-lasting effects on the setting of the neuroendocrine control systems, energy homeostasis and metabolism, leading to life-long increased morbidity. There are sensitive time windows during early development, where environmental cues can programme persistent epigenetic modifications which are generally assumed to mediate these gene–environment interactions. Understanding the role of early life nutrition and mechanisms of transgenerational epigenetic inheritance is essential for the development of future intervention strategies to modulate not only the immediate adult phenotype but also that of offspring and even subsequent generations.

Physical inactivity is a global pandemic responsible for over five million deaths annually through its effects on multiple non-communicable diseases. Physical activity is likely to be determined as a complex interplay between personal, interpersonal and environmental factors. According to the International Physical activity and Environment Network adult study, appropriate design of urban environments has the potential to contribute substantially to physical activity. Exploring the ways in which the built environment influences physical activity and dietary behaviours might provide fertile ground for research into the epidemic of non-communicable diseases, including diabetes. In this context, Anjana and Pradeepa (**page 1327**) present an excellent overview with a focus on the global burden of diabetes epidemic, the emerging issue of physical inactivity as a major risk factor for diabetes and the recent attention on the built environment science to encourage greater physical activity to prevent non-communicable diseases as well as to improve the overall health. Coalitions Linking Action and Science for Prevention initiative from Canada also emphasizes that enhanced multisectoral collaborations are needed to accelerate the development and implementation of physical activity and built environment policy in new jurisdictions across the globe, and it is significantly important for the developing countries like India.

International Day of Yoga is celebrated annually on 21 June. In contrast to the older view of yoga as a domain of spirituality or alternative health, we are now beginning to recognize a deeper understanding on its health benefits with the expanding science of yoga. Extensive research directed to the better understanding of the pathogenesis of diabetes by molecular medicine techniques now indicates that several chronic cellular stress mediators appear to be the common denominators in both the genesis of diabetes and its complications. In this context, yoga is conceived as a stress buster (both exogenous as well as endogenous stressors) and metabolic regulator. While diabetes is a multifactorial disorder that definitely requires lifestyle interventions, Nagarathna *et al.* (**page 1337**) present a systematic review of 46 controlled yoga trials which demonstrates significant improvement due to yoga practices not only in the primary outcome measures such as blood glucose levels, but also on the secondary outcome variables such as cardiac autonomic variables, lipid profiles, liver enzymes, respiratory variables, cognitive function and overall betterment in the quality of life, anxiety and depression. Such gold standard randomized controlled trials are warranted with more specific set of yoga practices and universal guidelines so as to prescribe yoga in the medical mainstream for the prevention and management of diabetes.

Although we could not cover every aspect of the specialized area in this special section, we hope that the in-depth articles will motivate readers to delve deeper into various issues linked to the prevention and management of diabetes. We also hope that this special section will introduce students and other young researchers to the fascinating world of diabetes research and expose them to the widening opportunities for working in trans-disciplinary settings with the ultimate aim of preventing or curing diabetes.

M. Balasubramanyam
V. Mohan
– Guest Editors

Madras Diabetes Research Foundation,
Chennai, India
e-mail: baluglobaldiab@gmail.com;
drmohans@diabetes.ind.in