Contributions of Department of Biotechnology to non-communicable disease biology research in India

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The last two decades have seen a shift of focus from communicable to non-communicable diseases (NCDs). NCDs, including cancer, diabetes, cardiovascular diseases, chronic lung disease, chronic kidney disease, neurological disorders, etc., pose devastating health consequences for individuals, families and communities, and threaten health systems. The socio-economic costs associated with these chronic diseases make their control a global priority. The Department of Biotechnology is working to provide leadership and evidence-based actions on surveillance, prevention and control of NCDs to reduce the disease burden.

The Department of Biotechnology (DBT) aims to develop and support competitive research and development (R&D) programmes and generate new programmes from basic to clinical and translational research under NCD conditions. Diseases addressed in the programme include but are not limited to cancer, diabetes, hypertension, cardiovascular diseases, lung diseases, kidney disorders, autoimmune disorders, eye diseases, osteoporosis and bone biology, diseases of the gastrointestinal system, neurological disorders, etc.

This article summarizes the contributions of DBT to NCD biology research in India through financial support.

Keywords: Bio-banks, cohort study, funding agency, non-communicable diseases, partnership centres.

CHRONIC non-communicable diseases (NCDs) are steadily increasing worldwide and are the major killers in the modern era. Globally, more than 70% of deaths are due to chronic diseases[1]. NCDs, including, cancer, diabetes, hypertension, stroke, heart disease, respiratory diseases, arthritis, obesity and oral diseases, are expected to cause three-quarters of the disease burden by 2030 (ref. 2). The increasing burden of NCDs has made their prevention and management a global priority[3].

India's burden on NCDs is escalating. Cardiovascular disease (CVD), ischaemic heart disease and stroke made the largest contribution (28.1%) to the total burden of mortality in the country in 2016; chronic obstructive pulmonary disease (COPD) and asthma made the second-largest contribution (10.9%) to the total mortality burden and diabetes contributed 3.1% (ref. 4).

The Department of Biotechnology (DBT), a funding agency under the Ministry of Science and Technology, Government of India (GoI), has made concerted efforts to strengthen NCD research and development through various endeavours. Major programmes are being implemented through review mechanisms of the Technical Expert Committee (TEC), Scientific and Technical Appraisal and Advisory Group (STAG) and Medical Biotechnology and Biotechnology APEX Board.

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Non-communicable diseases

Existing studies have concentrated on disease combinations or chronic disease incidence, prevalence and risk factors, leading to cohort studies and the establishment of disease-specific bio-banks. Joint cohort development addressing basic and clinical questions and monitoring structures with long-term funding has been implemented for chronic kidney disease (CKD) and systemic lupus erthematosus (SLE).

Indian chronic kidney disease study

The Indian Chronic Kidney Disease (ICKD) study is an ongoing nationwide, multicentre, prospective longitudinal cohort study of patients with mild to moderate CKD. Started in 2016, the ICKD study aims to ascertain the risk factors for the progression of CKD, development of CVD, develop predictive models to identify high-risk subgroups,

assess gender-related differences in the risk for progression of CKD and CVD, identify etiological factors and biomarkers, determine the consequences of CKD for general health, non-cardiovascular morbidity, quality of life, cognitive function, social status and cost of care, and develop and validate accurate, clinically useful multivariable equation for Glomerular Filtration Rate (GFR) estimation in the Indian subpopulation. Funding for the first phase of the study ended in March 2020, and the second phase was funded thereafter.

The notable achievements of the ICKD Study thus far include:

- Enrolment and deep phenotyping of over 4000 patients with early-stage CKD at 11 centres across India along with bio-banking.
- Setting up research infrastructure at these academic centres for cohort maintenance and additional studies.
- Capacity building through training more than 25 research staff at multiple levels at the 11 centres and contribution to other cohort studies in India by sharing methodology.
- Establishment of a distributed bio-bank, with the central facility at Post Graduate Institute for Medical Education and Research (PGIMER), Chandigarh and local facilities at various institutions, along with standard operating procedures, data dictionaries and tools.
- Development of an indigenous, low-cost laboratory management software that permits tracking individual bio-samples at the central as well as local facilities.
- Development of an electronic patient-friendly, COVID-proof clinical data collection and follow-up system to collect follow-up data and outcomes of interest.
- Successful joint funding applications by the study investigators (including two WT–DBT India Alliance fellowships) to explore additional research hypotheses.
- Creation of a registry of clinical trial-ready patients to provide a platform for clinical trials.
- Multiple publications and presentations.

The study has been recognized as unique in the developing world and has already become an important data resource for the global scientific community. The ICKD Study has been included in the International Society of Nephrology's (ISN) global network of cohort studies in CKD, i.e. iNET-CKD (International Network of Chronic Kidney Disease Cohort Studies), and the cohort has been invited to join other networks for harmonization of processes. Research findings of the ICKD study have been published[5–12].

Multi-institutional network programme on SLE

The cohort has accrued 1768 subjects since its inception in 2018. Most patients are young females from lower or middle socio-economic status. The clinical presentation is similar to that observed across the world. There are differences in phenotype in patients from different regions of India. Patients from South India have higher prevalence of discoid and subacute lupus and cytopenia. Patients from North India have higher alopecia and psychosis. Patients from eastern India have higher prevalence of oral ulcers and membranous nephropathy. Indian patients with SLE have higher prevalence of anti-Sm and anti-ribosomal P antibodies compared to data from the West. Due to late presentation and significant disease activity, there is a high rate of early mortality.

Samples (urine, blood, plasma) of 173 patients at baseline, 98 patients at 6 months, 61 at 12 months, 31 at 18 months, 36 at 24 months and 13 patients at 30 months have been stored. This is a rare resource of longitudinal samples from patients with SLE which can be used for biomarker analysis. Further, 1212 extracted DNA samples are available for genome studies. The project has helped other Project Investigators (PIs) make local biorepositories at each centre, and in total, baseline samples are available for 1700 subjects. This cohort study has two sub-studies – fever study and vitamin-D study, where the investigations are in progress.

Besides funding disease-specific cohort studies, DBT has supported establishing Centre of Excellence (CoE) programmes and projects related to cancer, diabetes, hypertension, CVD, lung diseases, eye diseases, osteoporosis and bone biology, diseases of the gastrointestinal system, neurological disorders, etc.

Centre of excellence in some disorders of the eye

Eight focal themes are being supported under this programme at the L V Prasad Eye Institute (LVPEI), Hyderabad, which covers: (i) public health studies and eye-care delivery across populations; (ii) innovation of devices; (iii) microbiology; (iv) genomics of eye diseases and associated proteins; (v) childhood eye care; (vi) neurophysics of vision; (vii) cancers of the eye, and (viii) application of stem cell-based treatment possibility of eye disorders. These eight focal themes have been studied under the following three broad objectives: the biology of eye diseases for biomarker identification and personalized medicine; stem cell-based ocular regeneration in eye diseases, and neurophysics of vision.

The notable achievements of this study thus far include:

- A binocular adaptive optics device for visual function assessment.
- Pediatric perimeter used to study visual fields in children with special needs.
- Battery of tests needed to assess visual status during high-performance sports identified.
- Predictive testing in age-related eye diseases and development of precision medicine towards disease management.

- Application of specific pre- and/or probiotic therapy may delay disease progression, if not reverse the disease process.
- Novel therapeutics for retinal dystrophies and retinoblastoma.
- Visio-motor performance in high-precision sports tasks.

Centre of excellence on low back pain and degenerative disc disease

Degenerative disc disease (DDD) occurs when the healthy state of the intervertebral disc deteriorates, and is a primary cause of low back discomfort (LBP). Poor understanding of etio-pathogenesis, lack of an early diagnostic modality that can identify the disease before point of no return and lack of treatment modalities to arrest/reverse disc degeneration have led to an increase in the number of spine surgeries performed worldwide for advanced disc degeneration and related disorders. The successful prevention and management of LBP lie in a thorough understanding of the etiology and pathomechanisms associated with it.

DBT has recently funded a Centre of Excellence on Low Back Pain and Degenerative Disc Disease at Ganga Orthopaedic Research Foundation, Coimbatore. The study will address delineation between normal ageing and inflammation-mediated degeneration for developing a targeted therapy, evaluate the role of sub-clinical infection in the initiation of DDD, identify early biomarkers and OMICS approaches to unveil the root cause of chronic LBP and find a cure.

Under the Glue Grant Scheme, a collaborative research programme between clinicians from the All India Institute of Medical Sciences (AIIMS), New Delhi and basic scientists from the Translational Health Science and Technology Institute (THSTI)/National Institute of Immunology (NII) has focused on improved understanding of the biological basis of kidney disease, asthma and blood cancer in children. This scheme has established completely functioning platforms in microscopy, flow cytometry, tissue culture/molecular biology laboratories at the St John's Medical College. The genomics platforms using the National Centre for Biological Sciences (NCBS) campus in Bengaluru have generated substantial progress in HLA multiplexing and pathogen discovery. Also, fully functioning 'crisper' platforms around the MIR-182-CML Notch project have been established.

National Alliance for Translational Research in Autoimmune Diseases (NATRAD)

A consortium programme encompassing 26 institutions involving basic and clinician scientists is under active consideration for financial support and implementation. The proposed alliance proposal will focus on three major autoimmune diseases in India; SLE, psoriasis and rheumatoid arthritis, and comprises a flagship programme on multiplex families with autoimmune diseases, clinical research projects on randomized control trials on low-cost biologics, basic research on disease mechanisms, preclinical validation of novel translatable technologies, new epidemiological investigation component, the NATRAD database for real-time acquisition and analysis of point-of-inception disease prevalence data and public awareness programmes.

Diabetes

Among NCDs, diabetes is one of the most common metabolic disorders. Existing studies focus on micro- and macrovascular complications of diabetes, toxicity of energy fuels; proteomics and metabolomics studies, biomarker identification, therapeutic potential of peptides, microbiome, etc. (Figure 1).

Recent advances in immunology, molecular biology and biotechnology provide exciting opportunities to delineate factors influencing disease initiation, progression and pathogenesis. New leads in these critical areas can help in early and accurate diagnosis, better prediction of disease course, complications and improved therapeutics. In order to address gaps in research associated with early detection, prevention and control, DBT will shortly launch a grant call specially directed towards pathogenesis of diabetes and its complications (retinopathy, nephropathy, vascular), therapeutics of diabetes and gestational diabetes.

Cancer biology

Shenoy and Dey[13] have recently summarized funding for cancer research by DBT. Since the publication of the above article, new initiatives in cancer research are discussed below.

New initiatives in cancer research

Virtual Network Centres in Cancer immunology and immunotherapy: As part of its commitment to address solutions in contemporary cancer research, DBT launched a grant call for the setting-up of Virtual Network Centres (VNCs) in Cancer Immunology and Immunotherapy. Through three rounds of evaluation, three VNCs have been recommended for support and implementation: (i) a phase-2 randomized controlled clinical trial to evaluate the role of metronomic chemotherapy and dendritic cell vaccine in recurrent hormone receptor-negative breast cancer at Adyar Cancer Institute, Chennai; (ii) development of genetically engineered 'Off-the-shelf' and inducible CAR-T cells for cancer therapeutics at IGIB, New Delhi, and (iii) Network Centre for Research on Glioblastoma Stem cell-targeted

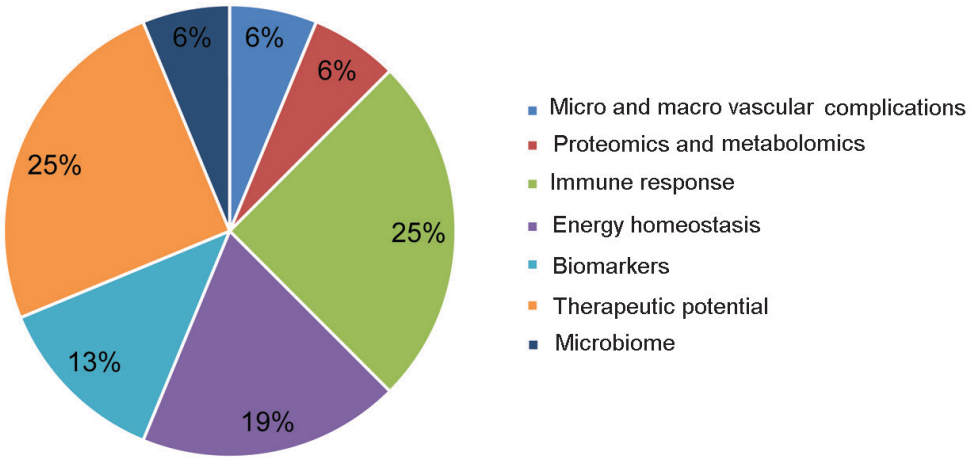

Figure 1. Fraction of funding to different areas of diabetes-related research.

T-Cell Immunotherapy using Non-Genetically Engineered Mesenchymal Stromal Cells at Siddaganga Institute of Technology, Karnataka.

DBT-AIIMS-NCI India Translational and Clinical Research Partnership Centre

DBT has recently recommended the establishment of DBT-AIIMS-NCI India Translational and Clinical Research Partnership Centre at the National Cancer Institute (NCI), Jhajjar as the 'National Cancer Centre for India' for five years in a phased manner; phase I – infrastructure development and phase II – translational and clinical research. The Partnership Centre envisages establishing: (1) a state-of-the-art cancer genomic research facility for personalized medicine; (2) Early Detection Research Network (EDRN) programme with international partnership; (3) a quality-enabled 'bio-bank' for 'India-centric cancers', enhancing the exploration and validation of novel diagnostic or therapeutic modalities, and (4) an advanced animal facility for gene-manipulated and immunocompromised small animals for preclinical cancer research and technology validation needed for clinical trials.

DBT–DAE–NCG partnership

DBT and the Department of Atomic Energy, GoI signed a Memorandum of Understanding (MoU) on 22 May 2019 support joint activities in the area of cancer. Under the aegis of the MoU, a partnership proposal entitled 'Proposal for DBT–NCG Collaboration for Support for Cancer Research in India' received from Tata Medical Hospital (TMH), Mumbai is under active consideration. The proposal envisages: (a) collaborative, metacentric, multidisciplinary research; (b) practice-changing studies on common/unique cancers; (c) commitment to data-sharing; (d) public and patient involvement; (e) focus on high-impact research areas, including comparative effectiveness, drug repurposing, translational research and epidemiology; (f) to foster multi-centric national and international collaborations; (g) creation of cooperative oncology groups; (h) interdisciplinary research with institutions like the IITs, IISc and NCBS and (i) develop novel and affordable solutions for prevention, diagnosis, treatment and rehabilitation. Capacity-building includes training – CReDo workshops, virtual research boards, mentoring and placement of Young Investigators funded by DBT, initiating zonal clinical trial units (modelled on DAE–CTC and MRC–CTU) and resources to promote cancer research.

Neuroscience

DBT has supported and funded projects and programmes that focus on understanding the basic biology and biotechnology of neurological disorders such as dementia, stroke, epilepsy, etc., neurological injuries such as brain and spinal cord injury as well as neuro-infections and neuromuscular and movement disorders, brain cancers, etc. Several Centres of Excellence (CoEs) in areas such as schizophrenia, stroke biology, epilepsy, neuroimmunopathy and neurological disorders have been established.

DBT has initiated programmes for identifying the functions of hypoxia-induced changes in blood-brain barrier, effect of hypoxia on different neuronal cell types, identification of the alterations of glutamatergic excitatory neurotransmission, role of notch signalling in abdominal neuronal stem cells and modulation of innate immune cells in neurocysticercosis. An impactful study funded by DBT has demonstrated that modulation of the insulin signalling pathway can be exploited as a novel approach to treating human neurodegenerative disorders[14].

A population-based cohort study titled 'Longitudinal Cognition and Aging Research on Population of the National Capital Region' (LoCARPoN) was supported under

Table 1. Overview of the non-communicable diseases programme since FY 2014

Year	Proposals received	Proposals sanctioned	Amount sanctioned (Rs in crore)	Manpower trained	Publications
2014–15	40	36	10.94	308	44
2015–16	20	15	6.34	260	24
2016–17	51	9	3.71	205	14
2017–18	53	50	32.78	156	47
2018–19	65	25	12.30	248	25
2019–20	28	15	10.83	276	31
2020–21	20	12	4.47	226	35

the Indo-Netherlands joint collaboration in 2014. The main aim of the project was to study the known as well as novel determinants (genetic, socio-economic, lifestyle and environmental factors) of stroke and cognitive function and to examine unique Indian determinants as well as their consistency and variation among the Indian population. A recent publication from this study indicates that the prevalence of stroke is 1.5%, and the causative factors are hypertension, diabetes, obesity, smoking and chewing tobacco.

A multi-centric programme on dementia involving eight centres across the country has been implemented with the National Brain Research Centre (NBRC), Manesar, as the nodal centre. The programme aims to arrive at reliable estimates of the prevalence and incidence of dementia, including Alzheimer's disease in the country. In addition, it involves basic scientific research, bio-banking of samples and data storage for long-term usage. All the participating institutions will use the standard operating procedure (SOP) developed for the programme. The pilot studies were conducted at Palwal (rural community site) and Bengaluru (urban community site). The standardization of neuropsychiatric assessment battery across seven sites in the country is in progress. Preliminary findings of the programme suggest that the *PICLAM* gene variant *rs3851179* might be associated with dementia.

A 'Collaborative Neuro-Engineering Platform for Excellence in Innovation and Translational Research' at AIIMS, New Delhi, has been supported to provide unsupervised, computerized evaluation of surgical skills and provide feedback to trainee neurosurgeons to improve their performance. Seven different technologies have been developed and validated in the project, including a virtual repository of neurological instruments, 3D animation modules and virtual 3D tracking and navigation simulators for neuro-endoscopy. The results have been summarized and published[15,16]. A YouTube link illustrates the development of 3D animation modules (https://youtu.be/b9NEl82IZX4), demonstrating the in-house development of hardware (https://youtu.be/kg5-bu0t2ag).

Funding from DBT has resulted in developing few products: KALPANA – Brain signal processing tool which is a comprehensive MATLAB-based toolbox for magnetic resonance spectroscopy data processing and metabolite quantitation; GAURI – An analytical and predictive diagnostic tool using metabolic pattern learning; Fluoro Doc – A comprehensive guide for *in vivo* 19F detection and quantification.

The projects supported in the area of neuroscience will help in the better management of diseases like stroke, cognitive decline and dementia in the Indian population and their clinical perspectives. In addition, the developed neurotools will be helpful to neurosurgeons both in the operation theatre and in skill development through training.

Funding and support

Table 1 depicts the number of projects sanctioned and grants released for new and ongoing projects for each financial year by DBT. The output and outcome indicators regarding workforce training and publication years have also been indicated. The data for proposals sanctioned and grants released have been extracted from ePromis (Electronic Proposal Submission Portal) of DBT. The data for workforce training have been extracted from the 'Manpower Due Drawn Statement' submitted by the PIs. This is large as some multicentric programmes employ staff in large numbers. Since these programmes continue for 5–7 years, the workforce gets reflected in each financial year. Further, the numbers due to attrition and re-employment have also been factored in. The number of publications appears modest against the number of projects sanctioned. This could be due to DBT's increasing emphasis on quality and high impact; translatability and benefits accrued to the society and clinics rather than quantity. The projects sanctioned fall into a broad spectrum of thematic areas within NCDs, ranging from basic to applied, translational, clinical trials and cohort studies.

The primary data presented in Table 1 were collated by the Programme Officer handling the Non-Communicable Disease Biology Programme in DBT.

Conclusion

DBT supports competitively submitted projects received through the ePromis window (electronic submission portal) as well as programmes depending on the disease burden and requirement in the area of NCDs. In consultation

with national experts, the Programme Division organizes brain-storming sessions, to identify thematic areas for funding and support. Top–down approaches are also adopted for developing proposals for multicentric programmes focusing on important chronic diseases and cohort studies, and for establishing disease-specific bio-banks. Being contemporary, DBT envisages initiating partnership centres in chronic and lifestyle diseases such as diabetes, CVDs, respiratory diseases, musculoskeletal disorders, neurological disorders, etc.

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