



## Funding for cancer research by an Indian funding agency, DBT

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Cancer is a group of diseases with major societal impact and accounts for approximately 55% of mortality in India. The Indian population is increasing in size and gradually ageing. As a result, the number of people diagnosed with and dying of cancer are increasing. Government funding agencies such as the Department of Biotechnology (DBT) has a clear definitive role in the management and control of cancer. Through Research & Development programs and multi-institutional networking programs, DBT has provided resources to individual investigators and to institutions, to carry out basic, applied, translational and clinical research and to develop new methods to prevent and treat disease and to conduct research especially in challenging areas pertaining to different types of cancer. This article summarizes the funding provided by DBT for different cancer research programs.

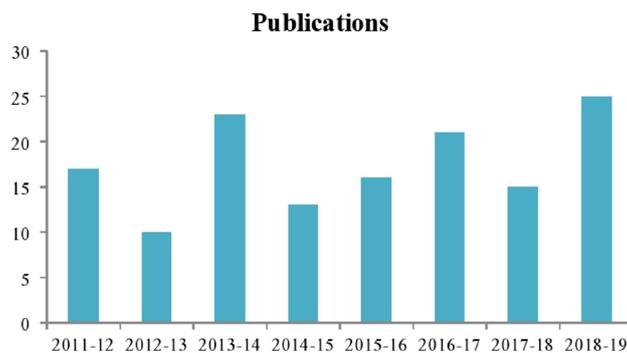
**Keywords.** Cancer research; funding agency

### 1. Introduction

Cancer is a group of diseases with major societal impact and is the leading cause of death in most countries (Brawley 2017). The projected ageing and increasing size of the world population in the next few decades portend an increase in the absolute number of cancers and cancer deaths (Thun *et al.* 2010). Cancer is a major public health concern in India as well. India sees an incidence of more than 1 million new cases of cancer every year, a number that is likely to increase given the increasing age of the Indian population and lifestyle changes (National Strategy Paper on Artificial Intelligence, Niti Ayog 2018). Cancer is enormously complex and highly adaptable; many subtypes of the disease have distinct clinical features and susceptibilities to therapy. Many cancers are still not diagnosed until they are at advanced stages, and some resist most attempts at treatment.

Cancer registries are key elements of the cancer control program for data collection, analysis, interpretation and health policy formulation. The changes in incidence rates also provide an opportunity for evaluation of the impact of intervention programs or changes in socio-cultural practices. Treatment practices and challenges posed due to several reasons get systematically documented (Report on National Cancer Registry Program, ICMR 2020). The two main types of cancer registries are Population Based Cancer Registry (PBCR), and Hospital Based Cancer Registry (HBCR). Recently a report published by ICMR (Report on National Cancer Registry Program, ICMR 2020) represents the work carried out by 28 population-based and 58 hospital-based cancer registries that provide insight into the data collected on incidence, mortality and clinical details of cancer, encouraging more research in cancer and in developing strategies for prevention, control and better patient care for cancer in India.





**Figure 2.** Number of publications in peer-reviewed journals financial-year-wise.

## 2. Centers of Excellence

Although traditional single-investigator-driven approaches consume a major chunk of DBT funding, coordinated teams of investigators with diverse complementary skill sets and knowledge have proven to be helpful in many areas of cancer research. As part of its commitment to address solutions in cancer research, DBT has supported a variety of team science approaches. One such is the Virtual National Cancer Institute (VNCI) Program. DBT identified Virtual National Cancer Institutes (VNCIs), one for Hormone Resistant Breast Cancer and the other for Oral Cancer, which are the centerpieces of the DBT's effort to create a centralized platform for sharing concepts and resources bringing in the complementary expertise of the individual PIs from different organizational settings, reflecting considerable diversity in the size and complexity of their research emphases and partnering scientific institutions to work together to develop and actualize a cancer research agenda. VNCIs are expected to capitalize on all institutional cancer research capabilities, integrating meritorious programs in laboratory, clinical, and population research into single transdisciplinary research across all institutional boundaries. DBT's support to VNCIs is focused on fostering excellence across two identified cancer research spectrum such as breast cancer and oral cancer. The Hormone Resistant Breast Cancer Program intends to identify key pathways and define therapies that target those pathways and will set the stage for clinical studies to test promising drugs in patients with hormone-refractory ER-positive breast cancer. The oral cancer program envisages understanding the genetic and epigenetic alterations influenced by 'geographical region and or population lineage' which would bring insight on the interaction of genetic and epigenetic components and also the role of environmental influence in the progression of precancerous lesions to cancer by genome sequencing, transcriptomics and epigenome analysis.

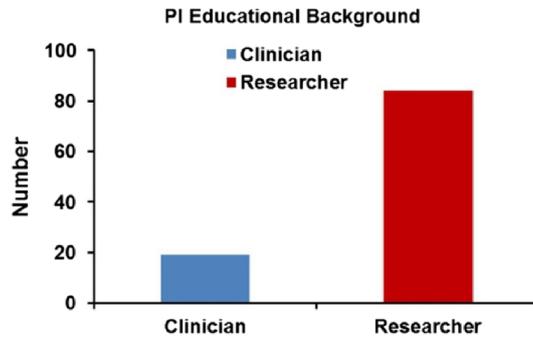
## 3. Building skilled workforce and leadership

In order to create Leaders in Cancer Biology, DBT has awarded the Unit of Excellence (UoEs) program to individual PIs who have demonstrated reasonable breadth and depth of research activities in their specialized domain of cancer research. The UoEs are in the areas of gastric cancer, chronic multiple myeloma, chronic myeloid leukemia, immunotherapy of cancer, etc.

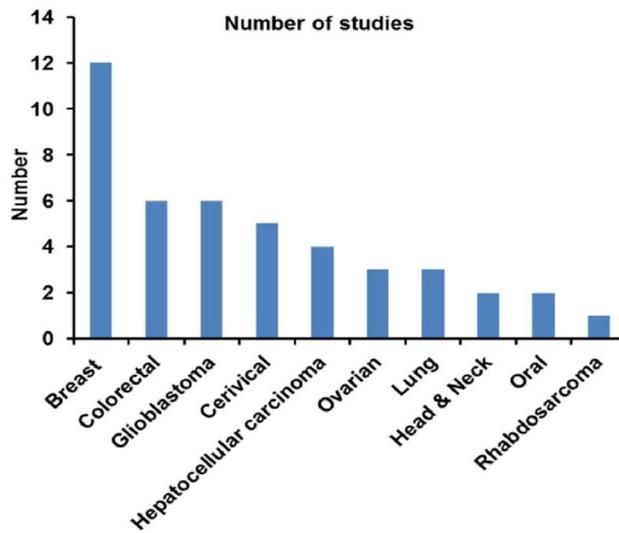
Attracting the best minds in cancer research is challenging today and retaining the talent is even more challenging. The uncertainty of a successful career in cancer research due to lack of funding opportunities is a significant barrier to embarking on, and remaining in this career path. DBT is committed to supporting the training and development of a strong workforce of cancer researchers. DBT has implemented a program entitled 'Pilot Projects for Young Investigators' to investigate a new hypothesis for establishing proof-of-concept in cancer research. 113 programs for young investigators have been awarded and the data below represents the outcome of funding. The program has been successful in enticing Indian researchers in Cancer Disease Biology, thus imbibing the overseas talent in the development process and some of the PIs in this program have relocated themselves back to their home country. This program has witnessed 166 publications published by the PIs with an average impact factor of 5.41; 73 conference presentations with 12 PhDs produced by the PIs and 94 JRFs and project staff trained. Most of the PIs who were beneficiaries of this grant have ventured into cancer research with Pilot Project as their first grant (figures 3, 4, 5).

**Table 1.** The fiscal funding for cancer research for different programs under Cancer Disease Biology

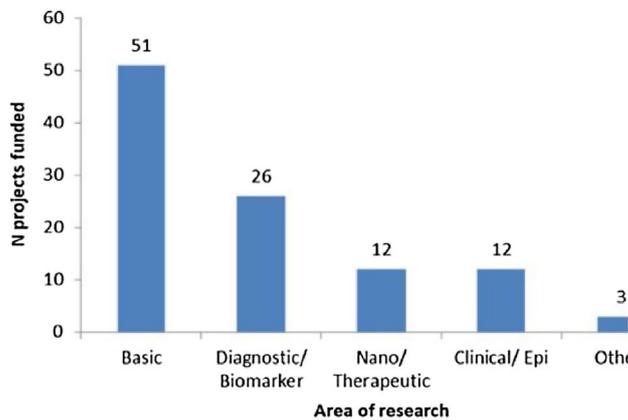
	FY	FY	FY	FY	Total								
Total Cancer Research Grant	2011–2012	2012–2013	2013–2014	2014–2015	2015–2016	2016–2017	2017–2018	2018–2019	2019–2020				
Research Project Grant	432.32	573.00	1054.12	942.43	875.24	943.67	1092.24	823.73	1798.86	8535.61			
Unit of Excellence (UoE), Center of Excellence (CoE)	0.00	94.75	147.96	142.45	1012.50	389.80	428.27	138.28	128.61	2482.62			
Virtual National Cancer Institutes	0.00	0.00	0.00	0.00	0.00	159.70	306.5	0.00	7.05	473.25			
Cancer Diagnostic Centers	0.00	312.53	0.00	600.14	0.00	35.12	15.06	86.4	0.00	1049.25			
Supporting Young Investigators	0	0	0	0	1438.11	0	714.06	499.9	0.00	2652.07			
Systems Medicine Cluster	0.00	0.00	0.00	0.00	0.00	0.00	3996.21	3601.177	1070.82	8668.21			
DBT-Cancer Research UK	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	182.00	182.00			
Total (Amount in Lakhs)	432.32	980.28	1202.08	1685	3325.85	1528.29	6552.34	5149.487	3187.34	24043.01			



**Figure 3.** Educational background of the PIs and beneficiaries of the Pilot Project.



**Figure 4.** Cancer types funded.



**Figure 5.** Areas of research: Basic, basic sciences; Diagnostic/Biomarker, diagnostic/biomarker discovery; Nano/Therapeutic, nanotechnology/therapeutic target identification; Clinical/Epi, clinical or epidemiological studies; Others, all other areas of cancer research.

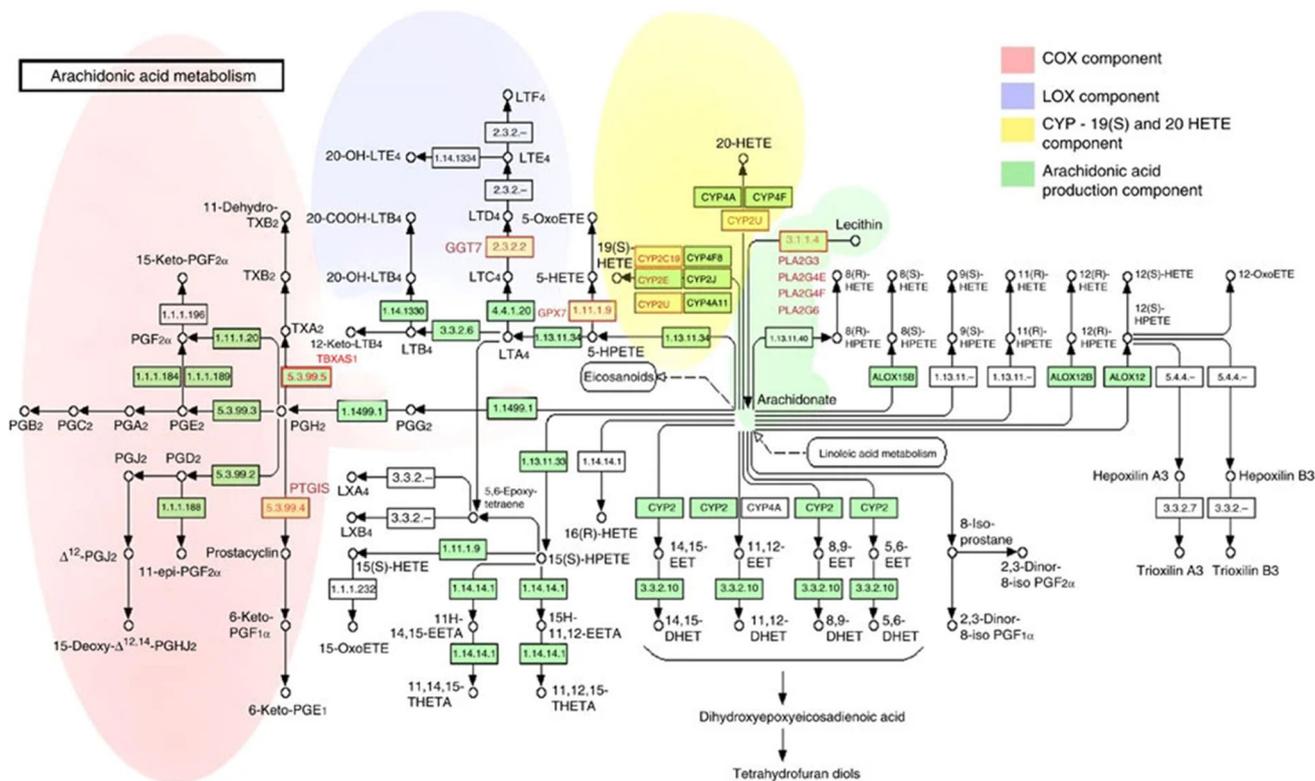


Figure 6. The arachidonic acid metabolism pathway promotes oral cancer progression.

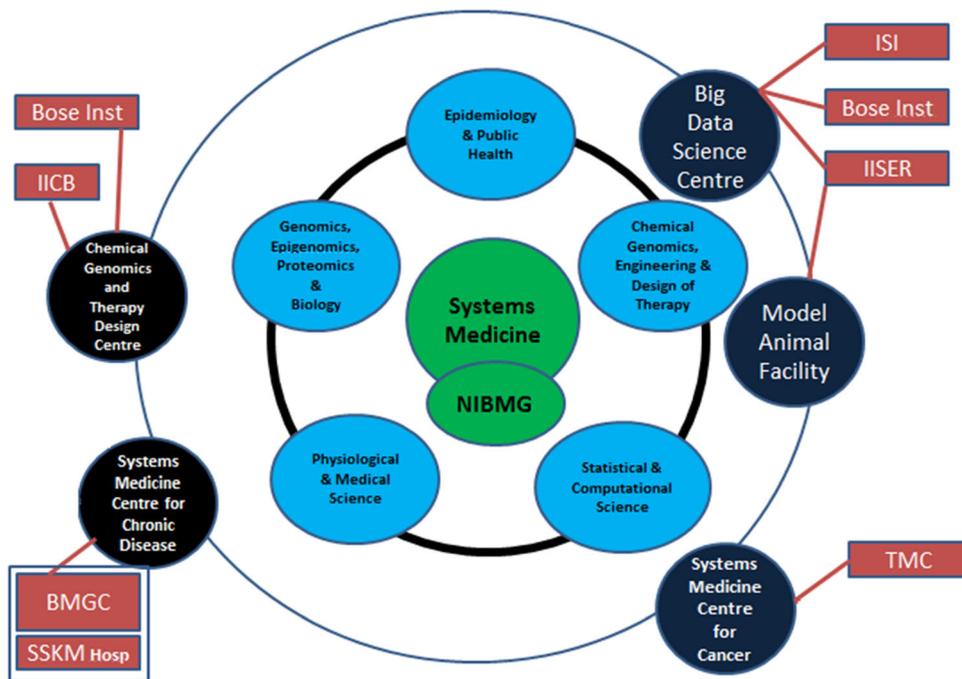


Figure 7. The trans-disciplinary systems medicine cluster that follows a federated structure to effect systems biology in medicine.

#### 4. Impact of funding

Cancer research publications, one of the major outputs of funding are an objective surrogate of overall cancer research activity. Research publications in peer-reviewed journals with reasonable impact factor have been a major outcome of funding under different theme based support, be it normal R & D funding for projects for three years or five years. These publications have largely been in the basic science arena.

DBT has also supported programs for the creation of state-of-the-art infrastructure for cancer diagnostics and research. Under this scheme, and as a special drive for the Kashmir state, DBT funded the Cancer Diagnostic Centre at Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Kashmir. During the past six years, this project has been providing high-end molecular-biology-based diagnostic investigations to the patients of J&K in general and the patients of Kashmir valley in particular.

Funding for cancer research in DBT has now become more applied i.e., movement from basic science to translational and clinical application. To exemplify:

DBT's support for Unit of Excellence Program at NII on 'Role of BLM Helicase as a Global Tumor Suppressor' have shown that BLM acts like a clamp or adaptor molecule, thereby enhancing the degradation of the oncogenic transcription factor, c-Jun; elucidated that absence of BLM increases a colon-cancer-specific microRNA signature which may be used as a biomarker to detect early stage of the disease; demonstrated that three FDA approved small molecules can revert chemotherapeutic drug-mediated resistance in cancer cell lines and mouse xenograft models; corrected the mutated BLM gene in patient fibroblasts, thereby generating an isogenic system which can be used for drug screening and mechanistic studies; discovered the mechanism by which patient-derived mutant proteins cannot enter mitochondria, thereby offering a therapeutic possibility for multiple mitochondrial defects. The work has been published in high impact factor journals, *Nature Communications* and *Cell Reports*. This is an example of DBT's support for a five-year program, transitioning from basic to translational.

DBT's support for the Centre of Excellence Program in Christian Medical College, Vellore on 'Mechanisms of Resistance in Leukaemia' has established low-cost effective care using arsenic trioxide in acute promyelocytic leukemia and moving this therapy to front line therapy in its management. A low-cost effective care clinical trial in the management of relapsed APL by re-purposing approved drugs to treat this cancer has also been developed. The research findings have been published in *Blood & Leukemia*.

DBT's support for Centre of Excellence Program in 'Triple Negative Breast Cancer' at Rajiv Gandhi Center for Biotechnology (RGCB), Trivandrum, and Hr. Resistant VNCI program on Breast Cancer with TMH Mumbai, ACTREC Mumbai, NIBMG Kalyani and NCCS Pune has successfully established the Patient Derived Xenograft Models for drug screening for the first time in India.

All five-year programs (CoEs, UoEs) have fared better in terms of impact evaluation, as outputs and outcomes are either towards publications with high impact factor or translational, moving towards drug screening and clinical trials. The gestation period of five years gives ample time for project maturity and evolution towards delivery science.

Over the years, the learning has been to support young investigators that will facilitate them to initially establish laboratories for cancer research; established scientists for interdisciplinary multi-centric programs towards translational outcomes across different portfolios of funding covering most domains of cancer science.

#### 5. International Cancer Genome Consortium – India project

With the objective of obtaining a comprehensive description of the genetic basis of human cancer, a multi-country project – called the "International Cancer Genome Consortium Project" – has been initiated. Specifically, the project aims to identify and characterize all the sites of genomic alteration associated with the significant frequency with all major types of cancers.

Comprehensive knowledge of the genetic basis of cancer provides a permanent foundation for all future cancer research and has far-reaching implications for basic, clinical and commercial efforts to understand, prevent and treat cancer. It has the capacity to reveal the subtypes of cancers and would systematically identify the cellular pathways that are deranged in each subtype. This would increase the effectiveness of research to understand tumor

initiation and progression, susceptibility to carcinogenesis, development of cancer therapeutics, approaches for early detection of tumors and the design of clinical trials.

India, after detailed national-level discussions and deliberations, is participating in this important international collaborative project with the goal of excavating and understanding the genomic basis of oral cancer, which is the most prevalent form of cancer in our country. The India project is being led by the National Institute of Biomedical Genomics (NIBMG), in collaboration with the Advanced Centre for Treatment, Research and Education (ACTREC) in Cancer. The India Project has made two important discoveries using next-generation sequencing technologies:

- (1) Alterations mainly in tumor suppressor genes are responsible for initiating oral cancer. Some genes are specific to oral cancer (*USP9X*, *MLL4*, *ARID2*, *UNC13C* and *TRPM3*), while some others are shared with general head and neck cancers (for example, *TP53*, *FAT1*, *CASP8*, *HRAS* and *NOTCH1*). Molecular subtypes of patients with distinctive mutational profiles have been identified. The mean duration of disease-free survival is significantly elevated in some molecular subgroups.
- (2) The arachidonic acid metabolism (AAM) pathway promotes tumor progression. It has been found that non-synonymous somatic mutations in genes of this pathway act as natural inhibitors and increase the post-treatment survival of oral cancer patients. Patients with mutations have a significantly longer median disease-free survival (24 months) than those without (13 months). Chemical inhibitors of the AAM pathway may therefore be used to prolong post-treatment survival of oral cancer patients.

The research findings of ICGC have been published in the following:

The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium (2020), Singh *et al.* (2020), Pansare *et al.* (2019), Chatterjee *et al.* (2016), Rajaraman *et al.* (2015), Biswas *et al.* (2014), India Project Team of the International Cancer Genome Consortium (2013) (figure 6).

## 6. Systems Medicine Cluster, SyMeC – accelerating systems medicine using a cluster approach

Today, medicine is largely reactive. A medical practitioner treats an illness, with varying levels of success. With the rise of genomics and the accumulation of large amounts of data on various diseases, a new systems-based approach to medicine is emerging. Clinical practitioners and researchers are increasingly realising that our bodies do not work as a set of independent components, but rather as an interacting *system*, with genes, proteins, cells and organs interacting with each other and the environment in complex ways. The understanding of this system will result in a transcendental change in medical practice; *from reactive medicine, based on disease, to a predictive and preventive one centered on health*. However, to effect this transition, complementary multi-domain expertise and experience are necessary.

In conformity with the national priority of stimulating investment in biotechnology, a Biocluster has been created. The Biocluster is a platform – both intellectual and logistical – for generating required biological and medical evidence to accelerate systems medicine. The Biocluster – spearheaded by the National Institute of Biomedical Genomics – comprises five other institutions: Bose Institute, CSIR-Indian Institute of Chemical Biology, Indian Institute of Science Education & Research, Indian Statistical Institute and Tata Medical Centre. The three main aims of SyMeC are: (a) To investigate and understand the dynamic systems of the human body as part of an integrated whole, incorporating biochemical, physiological, and environment interactions that sustain life, and identify perturbations that cause disease, in order to implement Systems Medicine; (b) to provide improved tools for prediction, prevention and treatment of diseases using a systems biology approach; and (c) to create a platform for multi-disciplinary training to build a cadre of scientific, clinical and technical personnel required to drive and to sustain systems medicine.

SyMeC's research has already resulted in the development of a powerful statistical and bioinformatics method to integrate genotype and gene-expression data for dissecting the genetic architecture of disease. Further, since lymph node (LN) metastasis is the most important prognostic factor in oral cancer with many (30–50%) oral cancer patients developing lymph node metastasis, the investigators have carried out systematic genome-scale investigations. They have identified that lymph node metastasis in oral cancer is driven by chromosomal instability and DNA repair defects. This finding has implications in the management of oral cancer.

The research findings of SyMeC have been published in the following:

Seal *et al.* (2020), Sinha *et al.* (2020), Ray *et al.* (2020), Das *et al.* (2019a, b), Palodhi *et al.* (2019), Biswas *et al.* (2019), Lall and Bandyopadhyay (2019), Lall *et al.* (2018), Sinha *et al.* (2018) (figure 7).

## **7. DBT DAE Partnership for Cancer Research**

The Department of Biotechnology and the Department of Atomic Energy signed an MoU on 22 May 2019 for supporting joint activities in the area of Cancer. Joint collaborative research and Clinical trials are envisaged under the already implemented Cancer Network Program. The MoU shall help in strengthening various initiatives specifically the development of new and affordable technologies, conducting clinical trials, and training of manpower and infrastructure development.

## **8. DBT-CRUK Bilateral Research Initiative for Affordable Approaches to Cancer**

The Government of India's Department of Biotechnology (DBT) and Cancer Research UK (CRUK) have signed a Memorandum of Understanding (MoU) for a Cancer Research Initiative, "Affordable Approaches to Cancer". This was signed during the Inaugural Researchers Summit that was held in New Delhi from 14 to 16 November 2018. DBT and CRUK have partnered to launch a £10 million, five-year research initiative focused on finding affordable approaches to cancer. This research initiative aims to stimulate a focused bilateral, multidisciplinary research effort to address important challenges in affordability in cancer prevention, diagnosis and treatment and drive collaboration between the two countries.

DBT, CRUK and DBT/Wellcome Trust India Alliance have signed a tripartite agreement that sets out the terms and conditions by which the India Alliance will undertake grant-funded activities for the second and the third phase of the India-UK Cancer Research Initiative.

DBT and CRUK Bilateral Research Initiative for Affordable Approaches to Cancer will be implemented in three phases; Phase I: Identifying Core Challenges; Phase II: Establishing New Research Partnerships, and Phase III: Program Awards. The Bilateral Initiative has successfully completed phase I with the identification of seven thematic areas/core challenges: (1) Prevention, (2) Early Detection, (3) Early Diagnosis, (4) Computational Approaches, (5) Small Molecule Treatment, (6) Affordable Treatment, and (7) Children's and Young People's Cancer.

Phase II: A joint call inviting seed grant applications for establishing new research partnerships between India and UK witnessed overwhelming response with 106 applications that were received against the grant call that subsequently went through eligibility checks and remits. Further triaging process was carried out to shortlist these applications. The second meeting of the Advisory Panel to evaluate the shortlisted applications was held during 20-21 January 2020 in Mumbai. Successful applicants have been awarded seed grant funding.

## **9. Conclusion**

DBT is committed to answering the most pressing questions about each type of cancer and to continuing the pursuit of fundamental knowledge about the inner working of cancer cells so that we can eventually prevent and control cancers of all types. Emphasis is also needed in areas of the cancer continuum beyond disease treatment including prevention and early detection research. Though some investments in such research have been made, when compared to biology and treatment research this area comprises a much smaller component of the cancer research portfolio of DBT's funding. A markedly greater emphasis on cancer prevention, early detection and early intervention is crucial to reduce the national cancer burden and DBT envisages initiating a program soon on 'Non-Invasive Cancer Diagnostics'.

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