inStem

Institute for Stem Cell Science and Regenerative Medicine

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ANNUAL REPORT

2021-2022


INSTITUTE FOR STEM CELL SCIENCE
AND REGENERATIVE MEDICINE

Content

1 Director's Note

Apurva Sarin

Director, inStem, 2019-2022

Despite the upheavals of the pandemic, which continue to reverberate even today, the research community at inStem has delivered excellent and exciting research, glimpses of which are provided in the pages of this Annual Report. A shout out to the excellent, high-level support offered by the advanced facilities on campus, as well as our committed and responsive administration and technical staff, who provide strong foundations for our efforts. As always, hats off to our newly minted PhDs *(page 68 of the Report)*, as they embark on the next phase of their lives, having defended their PhD thesis with enthusiasm and energy. Speaking of energy, it would be remiss on my part if the relentless efforts of the COVID19 sequencing and testing laboratory at inStem, were not acknowledged in the proudest terms. Our collective thanks to a group that not only contributes to the State and Nation-wide efforts but has been pivotal to the large-scale screening that underpins day-day safe functioning of the campus.

We welcomed two, much-awaited, new additions to the inStem faculty with **Drs. Diya Binoy Joseph** and **Sudarshan Gadadhar**, launching their careers as independent investigators in the Inflammation and Tissue Homeostasis theme at inStem. Congratulations to **Dhandapany Perundurai** who was promoted to Associate Professor with tenure. Our best wishes for the growth and success of all programmes!

Congratulations are also in order for **Drs. Sunil Laxman, Sudarshan Gadadhar, Diya Binoy Joseph** and **Kruttika Phalnikar**, *(postdoc in Bhavana Muralidharan's laboratory)*, for their successes with the DBT India- Wellcome Trust Alliance Fellowships! We look forward to a flow of exciting ideas emerging with this support.

The past year saw changes in leadership both at the Department of Biotechnology (DBT), inStem's nodal agency and at inStem itself. **Dr Rajesh S. Gokhale,** took charge as Secretary DBT in November 2021. We wish Dr Gokhale the very best and look forward to continuing our contributions to the growth in scope and scale of DBT's activities under his stewardship. Our thanks to **Dr. Renu Swarup**, former Secretary DBT, for her committed and thoughtful leadership and the support extended to inStem. Closer home, a warm welcome and the very best wishes for a fulfilling and exciting tenure to Professor **Maneesha Inamdar**, who joined as Director inStem in August this year.

We are extremely grateful to the outgoing members of the Scientific Advisory Board, **Azim Surani**, Chairperson of the SAB, **Marco Foiani** and **Mahendra Rao** for their support and the time they invested in inStem, especially in its formative years. Keeping up the momentum, the new Scientific Advisory Board, chaired by Professor **B Ravindran**, disregarded discordant time-zones and the travails of the online meeting format, to participate in more than two full days of talks and poster sessions at the Scientific Advisory Board meeting in February this year!

To **Kris Gopalakrishnan** *(Co-founder, Pratiksha Trust)* and **TT Jagannathan** *(Chairman, TTK Prestige)*, our deepest thanks for their generous support, which has enabled many opportunities, especially for our younger colleagues.

Finally, a personal note of thanks to all at inStem, the institutions of the Bangalore Life Science Cluster Campus and DBT. It was a privilege to have engaged with all of you.

DBT-inStem also congratulates Prof. Maneesha Inamdar, the new director of the institute.

We look forward to working under her leadership as we enter our 14th year. Prof. Inamdar joined as the new director on August 19th.

2 Year at a glance at inStem

2021-2022

- **3-year Catalysts program of EMBO Journal-2022:** Minhaj Sirajuddin
- **DBT-Wellcome Trust India Alliance Senior Research Fellowship-2022:** Sunil Laxman
- **SERB-OVDF (Overseas Visiting Doctoral Fellowship) 2022 fellowship from Purdue University for advanced research-2022:** Manisha Goyal
- **DST SERB-N-PDF (Dec 2021) BIRAC BIG-16 grant-2021:** Abrar Rizvi
- **Innovation Forum (Southeast Asia region)-2021:** Tanay Bhatt
- **Science Setu Programme, entitled "Discovering Possibilities" under the aegis of Azadi Ka Amrit Mahotsav.** Bi-monthly seminars since April 2021, accessible to undergraduate and postgraduate students from ten colleges in Bangalore, Mangalore, Ujire, Gadag, Kollam, and Chenna and apart from contemporary cutting-edge research, involves colleagues who have faced challenges and success in allied areas such as science journalism, publishing, communications, history of science etc.
- **Mechanisms to Medicine seminar series: supported by TTK Prestige's "Science without Boundaries" program:** translational impact of efforts at inStem and building collaborations nationally and internationally.
- **inStem-NCBS COVID-19 testing laboratory tested ~ 250,000 samples from throughout the state of Karnataka.** The inStem group has assisted 17 companies in the **development and optimization of 47 kits** that are based on multiple technologies. inStem and NCBS have received designation from the ICMR-NIV to serve as a validation centre for new testing kits.
- **inStem continued its outreach efforts for COVID-19 as one of the founding partners of COVID-Gyan,** a pan-institutional website and WebGyan webinar series which invited eminent researchers like Dr. Shahid Jameel, virologist and CEO of the Wellcome Trust DBT India Alliance.
- The **antimicrobial G99+ and A99+ fabric** developed by Praveen Vemula's laboratory, launched in 'Launch and Showcase of high impact C-CAMP innovation programs with Govt. of Karnataka'.
- Vigilance Awareness Week Oct 26-Nov 01, 2021, observing **"Independent India @75: Self-Reliance with Integrity".**
- **International Day for Women and Girls in Science-2022,** celebrated with a talk by Dr. Susmita Mohanty, a renowned spaceship designer, serial space entrepreneur and climate ambassador.
- **National Science Day 2022** and **Rare Disease Day** were observed with a talk from Prof. K. Vijay Raghavan, the then Principal Scientific Adviser to the Government of India.
- **Brain Awareness Week 2022:** A podcast series from DBT-inStem, curated by Dr. Bhavana Muralidharan on the theme "Brain functions: From Basic understanding to Translational Approaches"
- Minhaj Sirajuddin represented inStem at the **Indian Science Fest-2022** on a panel discussion, **"Exploring Science and Cinema".**
- **inStem Annual Meeting Feb 22-25, 2022 (virtual),** focused on the scientific activities and accomplishments of the past two years: talks on posters, online poster sessions, as well as investigator talks on the different themes, the heads of research facilities.
- DBT-inStem ranked in the **top 50 among Indian institutions in the Nature Index 2021**, ratings based on its research publications. inStem featured in the **5th position in the Nature Index 2021 Life Sciences** ranking from 7th place in the 2020 rankings.

Institutional Partnerships

3 Administration Report

The Institute has completed **thirteen years in its pursuit for excellence in stem cell research and allied areas.** The Centre for Stem Cell Research (CSCR) is a translational unit of inStem located at Christian Medical College Campus, Bagayam, Vellore. The accounts of CSCR are integrated into the accounts of the institute.

The table below indicates the status of grants received and personnel on rolls at the end of March 31, 2022.

Description	Details
Core grants received (Rs. in Crore)	39.64
EMG grants received (Rs. in Crore)	17.32
Number of Active grants (Nos)	50
Staff (including Contractual and Outsourced employees- Nos)	241

Funding has been affected due to Covid-19 pandemic during 2021-22.

Important administrative events that occurred during 2021- 2022 are as follows:

- **Hindi Week** and **Vigilance Awareness Week** were observed in September 2021.
- Planned Activities pertaining to **Swachh Bharat Abhiyan** was also observed during 2021-22. Purchase records pertaining to the years 2009-10 to 2015-16 were weeded out during the month of September 2021.
- **Oath to abide by the Constitution** was taken during November 2021.
- Online RTI replies **(RTIMIS)** and online Grievance redressal **(CPGRAMS)** were implemented during the year.
- **909** Orders for 969 indents valued at **Rs. 24.53 Crore** were issued.
- Status of vacancy positions (number) of various posts (as on March 31, 2022)

Cadre	Approved	Filled	Vacant	Advertised
Scientific	42	23	19	6
Admin	22	18	04	4
Technical	27	10	17	10
TOTAL	**91**	**51**	**40**	**20**

- Despite the lengthy lock down due to the pandemic in the State of Karnataka, essential support was extended by Administration to keep the Bangalore cluster and its research facilities operational.

- Vaccination was provided in co-ordination with MoHFW & DBT to all the frontline workers, Staff and Students.
- As part of Swachh Bharat Abhiyan, purchase records pertaining to the years 2009-10 to 2015-16 were weeded out during the month of September 2021.
- 84 RTI queries & 13 RTI Appeals have been answered through the RTI online portal. 10 RTI queries were answered after being transferred from DBT.
- 5 Grievances were resolved during this period.

The **following important meetings** were conducted during 2021-22 in the normal course of its activities:

S.No.	Meeting	Date
1	28th Finance Committee	12.10.2021
2	29th Finance Committee	08.04.2022
3	30th Governing Body	12.10.2021
4	31st Governing Body	12.04.2022
5	13th AGM inStem Society	12.11.2021

The following audits were conducted during 2021-22:

S.No.	Type of Audit	Date
1	Statutory audit FY 2020-21	June-July 2021

The following employees joined inStem during 2021-22:

S.No.	Name	Designation
Scientific Staff		
1	Arjun Guha	Associate Investigator/ Scientist-F
2	Sudharshan Gadadhar	Scientist E
3	Mahesh Sahare	Fellow-E/Scientist-D
4	Vineetha Raghavan	Fellow-E/Scientist-D
5	Diya Binoy Joseph	Fellow-E/Scientist-D
6	Sandya Rani	Fellow-E/Scientist-D
7	Ketan Vilas Thorat	Fellow-E/Scientist-D
8	Sabuj Bhattacharyya	Scientist-C

Technical Staff		
1	Avinash Kumar Kodical	Senior Technical Officer
2	Alok Kumar Baisare	Senior Technical Officer
Administrative Staff		
1	Madhu Chandan Roy	Administrative Officer (Finance & Accounts)
2	Thejaswini K	Section Officer
3	Sreeram V K	Section Officer
4	Shobha R	Section Officer
5	Gavernar M	Junior Management Assistant
6	Sarvesh Saini	Junior Management Assistant
7	Raghuram G	Clerk
8	Vinod Kulkarni	Clerk
9	Shravan Kumar Amancha	Junior Management Assistant

Note: Four personnel who joined on 01.04.2022 are also included.

Prof Apurva Sarin, Director, inStem retired on superannuation w.e.f 28.02.2022 and **Dr K Thangaraj, Director, CDFD** has taken over as Director *(Additional Charge)*, inStem w.e.f 01.03.2022.

Following faculties were promoted under Flexi Complementary Scheme after following due Administrative procedure from the post of Assistant Investigator to Associate Investigator/ Professor –

1. **Dr Minhajuddin Sirajuddin**
2. **Dr Sunil Laxman**
3. **Dr Dhandapany S**
4. **Dr Tina Mukherjee**

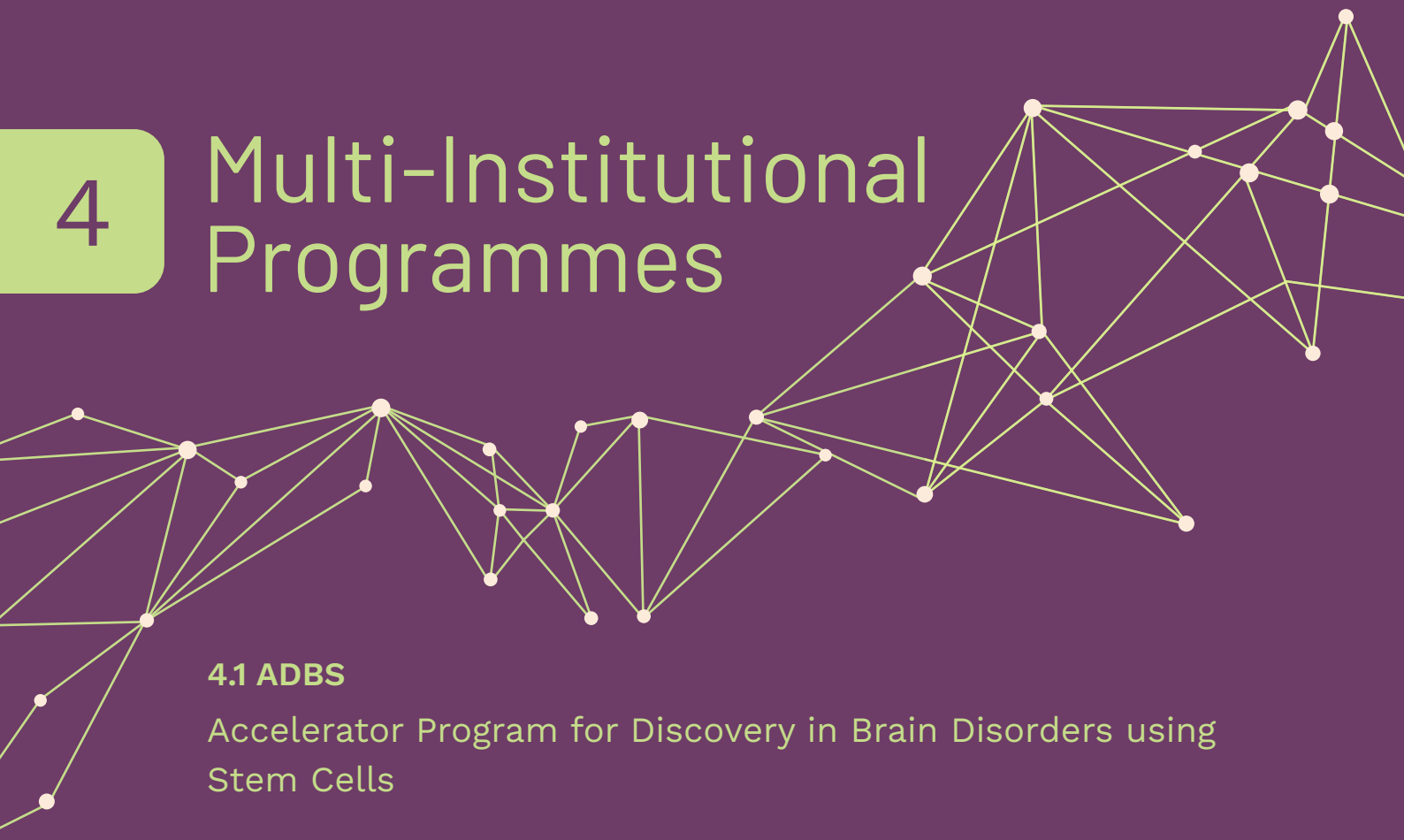
Following Administration Staff were promoted under vacancy-based promotion on recommendation of the duly constituted Departmental Promotion Committee –

1. **Sreenath B A** from AO (Purchase), L-10 to Senior AO (Purchase), L-11
2. **Valsala N** from Assistant (Admin), L-6 to Management Assistant, L-7

Mr Raju Verma, Junior Management Assistant (Accounts) was confirmed in his position after successful completion of probation period of two years.

Ramanathan K
Head-Administration, inStem

4 Multi-Institutional Programmes



4.1 ADBS

Accelerator Program for Discovery in Brain Disorders using Stem Cells

4.2 NAHD

Novel Approaches to Hematological Diseases Program

4.3 PCBT

Program for Chemical Biology and Therapeutics

4.1

Accelerator Program for Discovery in Brain Disorders using Stem Cells

The **Accelerator program for Discovery in Brain disorders using Stem cells (ADBS)** program, studies five major forms of **SMI: *schizophrenia, bipolar disorder, obsessive compulsive disorder, substance dependence and dementia***; they are thought to have a neurodevelopmental origin as well as an inherited basis. However, despite their high heritability, to date few genetic correlates that account for the high heritability have been identified. In order to study these disorders, in collaboration with the Department of Psychiatry, National Institute for Mental Health and Neurosciences **(NIMHANS)** and the National Centre for Biological Sciences **(NCBS)**, the Brain development and disease mechanisms theme at inStem has assembled a prospective cohort of patients with a strong family history of SMI.

The ADBS program is pursuing three distinct but complementary lines of analysis on these families: (i) The families are being clinically characterized in depth to understand changes in structure and function at multiple levels of brain organization; they are being followed over a period of twenty years at 3 year intervals in order to define the temporal development of disease through regular and detailed clinical phenotyping. (ii) We have established induced pluripotent stem cell lines (iPSC) and neural stem cell lines (Fig 2) from affected individuals in these families and unaffected controls. These lines are being used to generate cellular models to study cellular mechanisms that lead to brain disease. (iii) Next Generation Sequencing and family-based bioinformatics analysis is being used to uncover the genetic basis of SMI.

The multiple types of data generated by the ADBS program have been assembled into an integrated database to facilitate the application of sophisticated methods of data analysis to uncover new disease biology. The stem cell lines and other biomaterials are part of a biorepository that will allow the sharing and use of this resource to drive discovery biology in the area of SMI. The ADBS program has instituted mechanisms to facilitate the sharing of data and resources generated through its activities.

The theme is also studying the development of the human cerebral cortex, the seat for all higher-order functions in the brain namely learning, memory, language and consciousness. For a functional cerebral cortex in adulthood, a diverse number of neurons and glia are to be produced adequately and wired up accurately

during development. Chromatin level regulations play a very crucial role in building the neural network. Several neurodevelopmental disorders stem from mutations or perturbations to the process of chromatin regulation. Yet our molecular understanding of these mechanisms is very poor in the developing brain. We aim to understand chromatin-level control of brain development in health and in disease.

The LSD1 histone modifier plays differential role in regulating neurogenesis between mouse and humans. In mouse it promotes progenitor proliferation whereas in humans it promotes neuronal differentiation. We have uncovered downstream effectors of LSD1 in regulating human neurogenesis. These are genes belonging to the Notch pathway and several novel genes with human enriched expression in neural stem cells. Current work is focused on validating the role of these genes in regulating human neuronal differentiation. This work will shed light on mouse vs human differences in cortical development and provide deeper insights into the role of a neurodevelopmental disorder putative causative gene, LSD1.

The lab extends its work to understand cellular and molecular mechanisms of human neurodevelopmental disorders such as schizophrenia (SZ) and bipolar disorder (BPD). Mental illnesses are thought to be neurodevelopmental in origin but are poorly understood, in part due to the lack of appropriate mouse models that adequately recapitulate the human disease. To overcome this problem, the lab utilises the iPSC lines generated by the ADBS program from clinically dense families with SZ and BPD. Using 2D and 3D cerebral organoid cultures and combining CRISPR-Cas gene editing, the cellular and molecular origins of neuropsychiatric disorders are modelled in a dish.

4.2

Novel Approaches to Hematological Diseases (NAHD) Program

The program at CSCR/CMC - Novel Approaches to Hematological Disorders (NAHD) aims to enhance current methods/technologies including gene therapy for hereditary blood disorders such as haemophilia, thalassemia and sickle cell disease, all of which are causes of significant morbidity and mortality in India. To ensure maximum impact on hereditary hemoglobin diseases in the population at risk in India, this collaborative initiative blends these efforts with a community outreach program for the control of major haemoglobin disorders.

The NAHD has three components – **Gene Therapy, Applications of iPSC Technology (Haplobanking)** and **Control of Thalassemia and Sickle Cell Disease.** A brief summary of the different components is given below.

1. Gene Therapy

1.1 Clinical trials for gene therapy of Hemophilia A & B

Hemophilia B: As mentioned in the previous year's report, a unique transgene was designed for this clinical trial. The proof of preclinical animal model data was recently published *[Brown H et al Human Gene Therapy, Aug 17, 2020].* This data established the in-vivo functionality of this transgene and allowed us to proceed towards further development of a clinical product. After several attempts at obtaining this service from other academic GMP facilities in USA, as reported last year, we are now proceeding with establishing this technology for the first time in India with technical and knowhow support from our collaborators at the Emory University, who have now established their own facility for GMP vector production.

Towards this end over the last year:

(1) We have extended the existing GMP facility, compatible with the requirements for vector production *(both AAV and lentiviral vector).*

(2) The GMP grade HEK 293 cell line for the vector production was obtained from the NIH repository at the Indiana University *(courtesy Dr. Kenneth Cornetta)*. This has been expanded at CSCR to establish the necessary cell banks for process development work and vector production.

(3) For qualification of these cell banks, HEK293 cells have been sent to an appropriate agency overseas and report is expected in a few weeks.

(4) In parallel, for AAV3 manufacturing process development work, research-grade plasmids were obtained from a manufacturer in Europe.

(5) AAV packaging for manufacturing process optimization are in progress. Once this is standardized, three engineering runs will be

initiated to get the consistent yield and quality.

(6) Production of GMP like vector will be done to generate the material for completion of toxicity studies for an IND application.

(7) Once preclinical tox studies are completed then GMP vector production will be initiated for the clinical trial with this novel product after obtaining all necessary approvals.

While it is certainly unfortunate that the clinical trial could not proceed as planned originally, primarily because lack of AAV vector production technology in India and the failure of our initial collaboration for this purpose, the positive aspect is that we are able to bring this technology, which has wide applications in gene therapy for many diseases, into the country. The funds which were marked for payment of services overseas have been utilized for developing technology in India instead. We are working towards establishing an industry partnership for this AAV3 production in India. We are already in collaboration with another industrial group for developing another AAV serotype-based gene therapy for haemophilia outside of this program.

Hemophilia A: As mentioned previously, our long-term collaboration with Emory University has led to the development of a haematopoietic stem cell based lentiviral vector mediated gene therapy product for the treatment of haemophilia A. This is a novel first in human approach of gene therapy for haemophilia A *(factor VIII deficiency)* where the FVIII transgene is packaged in a lentiviral vector to transduce the haematopoietic stem cell (HSC) for stable integration and lifelong expression is similar to the principles being applied in the gene therapy for other haemoglobin disorders. The collaborative pre-clinical research has been published some time ago with all details of product development. *(Doering et al Human Gene Therapy. 2018; 29:1183).*

An investigational new drug (IND) proposal was reviewed in detail by CDSCO and RCGM over ~3 years *(Aug, 2018 to July, 2021)* and finally received the approvals to conduct the phase 1 clinical trial for patients suffering with Haemophilia A. The approval for Clinical trial was obtained in form CT-06 from CDSCO. We received the manufacturing license (CT-11) from CDSCO and in form 29 from state licensing authority.

Based on these approvals, sufficient-quantity of the vector was obtained to initiate the clinical trial. The first subject has been recruited and the requisite numbers of HSCs have been collected and transduced. Quality assessment of the product was carried out and release criteria were met. We are excited to conduct this first in human clinical trial of lentiviral vector-based gene therapy for haemophilia A in the world and are cautiously optimistic.

1.2 Standardization of anti-AAV Antibody assays

The goal is to standardize assessment of anti-AAV antibody through different assays to allow appropriate selection of patients for gene therapy. This work is coordinated by Asha M Abraham along with Hubert Daniel, and Rajesh Kannangai from Department of Clinical Virology, CMC, Vellore and Sanjay Kumar and Alok Srivastava from CSCR. It is being done in collaboration with the University of Florida, USA. Both binding and neutralizing antibodies are being assessed through the whole capsid and serotype-specific peptide ELISAs and transduction inhibitions assays (TIA), respectively. The whole capsid and peptide ELISAs have been standardized for AAV 3, 5 and 8. TIA by mCherry based flow-cytometry had been standardized for AAV 3 and 5. Screening for AAV 3, 5 and 8 total and AAV3 and 5 neutralizing antibodies was carried out in healthy individuals and individuals with hemophilia A or B.

1.3 Pre-clinical research - Lentiviral & Genome editing approach for Thalassemia and Sickle Cell Disease

This project aims to evaluate lentiviral vectors for developing gene therapy for the major haemoglobin disorders. This is coordinated by **R V Shaji** and **Alok Srivastava**. In collaboration with Emory University, lentiviral vectors have been generated for gene therapy of haemoglobinopathies.

Our lab is focused on the generation of novel lentiviral shRNA vectors for the knock down of BCL11A in human erythroid cells. We have generated two lentiviral vectors which contain hypersensitive sites of the locus control region of beta globin cluster and beta globin promoter for the erythroid specific expression of BCL11A shRNA. Further experiments are being carried out in mouse models and in the

cultured erythroid cells from patients with haemoglobinopathies.

Another important component of this program is the gene editing approach to reactivation of fetal haemoglobin production. This work is being carried out by **Saravanabhavan Thangavel** and **Mohankumar Murugesan** using the CRISPR-Cas9 technology in collaboration with the University of California.

Saravanabhavan Thangavel's lab aims to recapitulate the HPFH like deletions in the hematopoietic stem and progenitor cells (HSPCs) of SCD and thalassemia patients. Our target includes a region that is conserved among many HPFH deletions. We successfully introduced these deletions in the HSPCs with an efficiency of >70% and observed that when these edited HSPCs are differentiated into erythrocytes they express high fetal hemoglobin. We have also transplanted the gene edited cells into NSG mice and also in NBSG-W mice and observed that the gene edited cells engraft and re-populate in mouse bone marrow.

Research work in **Mohankumar Murugesan's lab** is focused on using different genome editing strategies for the treatment of beta hemoglobinopathies and hemophilia. The recent study by CRISPR Therapeutics and Vertex Pharmaceuticals (NEJM, 2020) emphasizes the promising effect of genome editing BCL11a enhancer in β-thalassemia and sickle cell disease patients and have reported showing therapeutic levels of fetal hemoglobin ameliorating their clinical symptoms. Towards this end, our study has identified a new target in the BCL11a enhancer region, which has shown robust induction of fetal hemoglobin comparable to the clinical trial target with better invitro erythroid differentiation potential *(comparable to that of control).*

2. Applications of Induced Pluripotent Stem Cell (iPSC)Technology

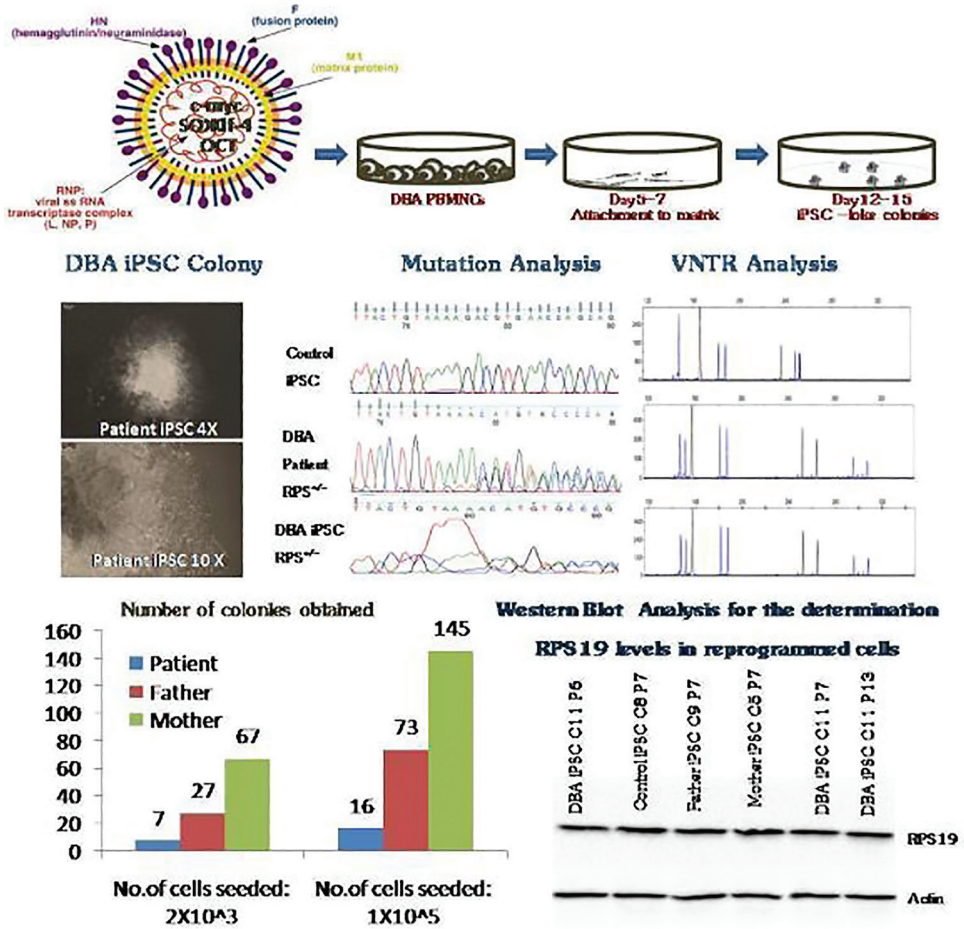


Figure: Reprogramming DBA PBMNCs. (a) Transduction of DBA PBMNCs with Sendai reprogramming kit (Cytotune 2.0). (b) DBA iPSC colonies on D12 of transduction. (c) iPSC colonies obtained. (d) Sanger sequencing for confirmation ofRPS19:NM_001022:exon2:c.22_23del mutation. (e) VNTR analysis for confirming iPSC clone identity with patient PBMNCs. (f) Determination of RPS19 levels in iPSC clones of the patient and his parents

2.1 Disease Modelling for Erythroid Disorders:

This work is coordinated by **RV Shaji**. The aim is to create disease models for two monogenic erythroid disorders, Diamond Blackfan Anemia (DBA) and Congenital Dyserythropoietic Anemia (CDA), by creating mutations in the associated genes by CRISPR/Cas9. The target genes have been successfully disrupted by CRISPR/Cas9.

Gene editing strategies CDN1, RPS19, RPL5 and SEC23B genes using lentiviral vectors to express Cas9 and gRNAs is being established. For creating biallelic mutations, we generated an iPSC line with tetracycline inducible Cas9 expression from the AAVS1 safe harbor site, which allows temporal control of editing of the genes of interest at a specific time window during haematopoietic differentiation.

2.2 Haplobanking - Bank of iPS cells from individuals with homozygous HLA haplotypes

This project is aimed at creating a bank of iPSCs derived from individuals homozygous for the most common HLA haplotypes in the Indian population. For future clinical applications using iPSCs there is a global initiative to generate iPSCs from individuals who have homozygous HLA haplotypes. Our center has joined Global Alliance of iPSC Therapies (GAiT) for haplobanking of iPSCs from normal donors of Indian origin. First, we generated a bank of blood cells from 235 donors with homozygous haplotypes from various regions of the country. We established a highly efficient feeder-free, xeno-free and integration-free protocol to generate GMP grade iPSCs. So far, we generated iPSCs from 20 donors with top 10 HLA haplotypes. The isolated clones were analyzed for pluripotency marker expression and in-vitro differentiation to three germ layers. In future, we will generate more iPSC lines from the donors with rarer haplotypes to have representation of all the top 20 HLA haplotypes. Further detailed molecular characterization for identity, sterility, differentiation and genomic stability is under progress.

3. Control of Sickle Cell Disease and Thalassemia Major in Odisha Program

Creating a model for India

The project aims to reduce the burden of these diseases in the affected populations in Odisha through the combined effort of **Ministry of Health, Odisha, NHM Odisha, Christian Medical**

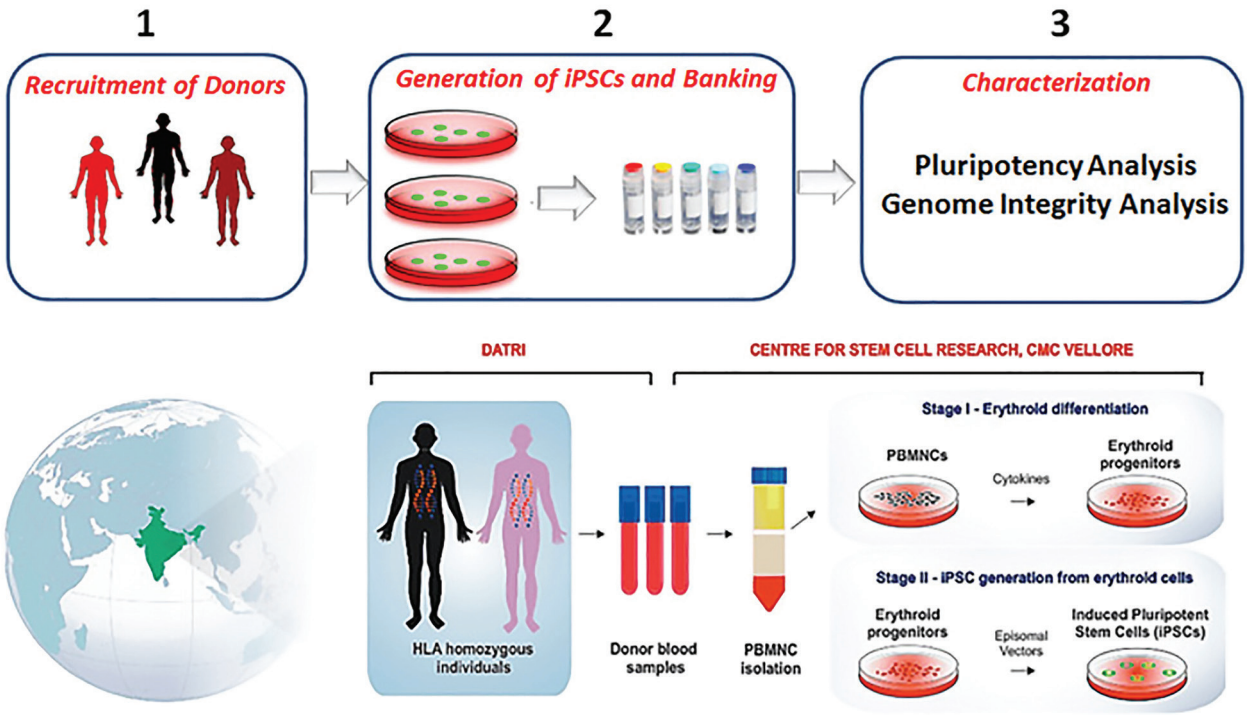


Figure: Schematic representation of Haplobanking from donors with homozygous HLA

College, Vellore and Centre for Stem Cell Research *(a unit of inStem, Bengaluru),* with the support of **Department of Biotechnology of the Ministry of Science and Technology, Government of India**. The project focuses on Major Hemoglobin Disorders (MHD) which is a significant public health issue in the country. In Odisha about 10% of the population are estimated to be either carriers or have disease. This is the first comprehensive program for the control of these major haemoglobin disorders in India to be carried out at this scale. Novel technologies have been developed for screening these haemoglobin disorder and genetic analysis of these diseases.

The ***Screening & Diagnosis*** component is being coordinated by **R.V. Shaji** and **Sukesh Nair**. Blood cell counters has been installed in 5 districts *(Koraput, Bargarh, Sambalpur, Balasore and Cuttack)*. HPLC instruments have been installed in SCB Medical college, Cuttack for confirmation of diagnosis.

Sentinel surveillance

Sentinel surveillance through cord blood sample collection and testing has been established in SCB Medical College Cuttack and VSS Medical College Burla. 7812 samples have been analyzed till May 2022. The results are mentioned in the table below: -

Haemoglobin disorders	Homozygous	Heterozygous	Compound Heterozygous
Sickle Cell Anemia	44	548	12
Thalassemia	6	256	

Genetic Lab:

A genetic lab has been established in SCB medical college Cuttack. 20 samples were collected for Chorionic Villus Sampling (CVS), of which 2 were homozygous for major haemoglobin disorders.

A novel technology called MALDI-TOF was introduced to the project and the validation is completed in CSCR. The field implementation of MALDI-TOF is expected to begin in few months.

The ***Behavioural change and communication*** component is being coordinated by **Shantidani Minz**. In the past year, the project had made a presence in 15 districts through BCC activities. Except for a few BCC materials installations, the BCC activities for the first phase districts (6) had almost been completed. The production of BCC materials for 15 districts is completed and the materials are being kept in the PMU office for distribution and installation. Folk shows and wall paintings have reached 15 districts. Several agencies such as Pabitra Pvt. Ltd, EmertechRnD Solution Pvt.Ltd, SamperkAdv. Pvt.Ltd and G-Mantra were hired to complete the BCC activities. The completed BCC activities include-51 Hoardings in 8 districts, 1865 Wall paintings in 14 districts, 782 Tin plates in 6 districts, 189000 Leaflets in 6 districts, 752 flex banners in 4 districts, 981 sun boards in 2 districts, 5306 stickers in 2 districts, and 500 posters in 4 districts.

The ***training*** component is coordinated by **Jiji Mathews** together with **Kuryan George** and **Alok Srivastava**.

Training is being offered to health care workers for both project implementation and to strengthen diagnosis and counselling. In the past one year, training of field functionaries (2648 ANMs) in sample collection and data management system was completed in 10 districts. ASHA orientation was completed in all first phase districts (8783 ASHAs). District workshops for district and block administrators in the health system & ToT for Lab Technicians and Counselors were completed in all 5 districts.

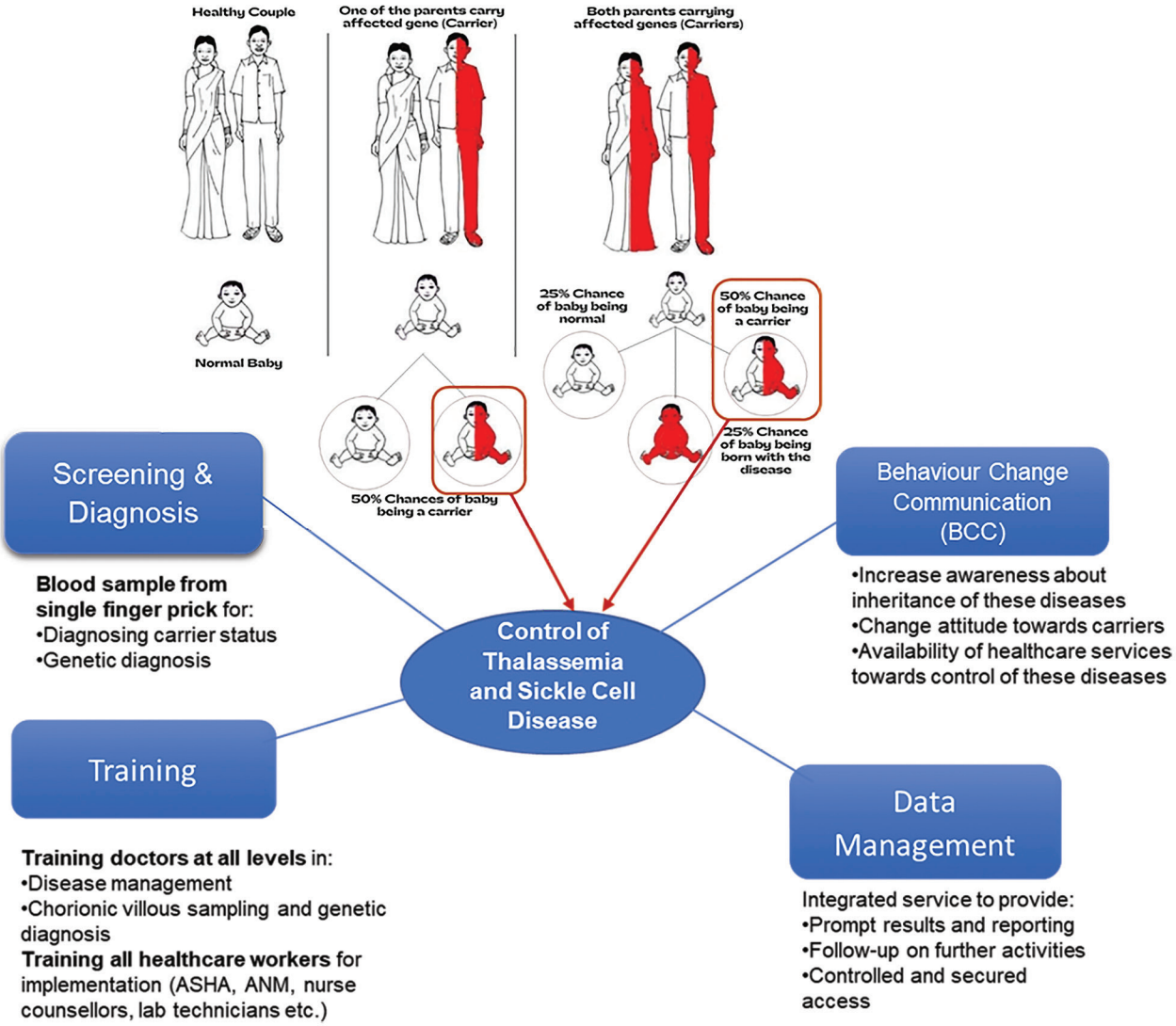
A district-level orientation for all Medical Officer in-charge (MO i/c) and administrators, as well as a separate training of trainers (ToT), were conducted for 5 districts. Data management training was provided to NHM staff under various categories in 11 districts. The training

activities will continue till the activities cover all 30 districts of Odisha.

Data management is coordinated by **Venkata Raghava.** Android app and web-based application to facilitate data management for each category of staff involved in the project were developed. A web application had also been developed for NHM officials to monitor the performance of the project in their corresponding blocks and districts. Android Application version 2.0 was developed and deployed to the play store and the updation of the application in ANM tablets is going on in all 11 districts. Training for the field staff to use the app and enter the data is completed in all 11 districts.

Monitoring and evaluation

To ensure the quality of services and effective program implementation, a contract has been signed with the Indian Institute of Public Health Gandhinagar (IIPHG) to carry out monitoring and external evaluation. They had submitted the baseline evaluation report and a proposal has been submitted for the midline evaluation.



Pictorial representation of the program (Control of Thalassemia and Sickle Cell Disease in Odisha)

4.3

Program for Chemical Biology and Therapeutics (PCBT)

The **Program for Chemical Biology & Therapeutics (PCBT)** was established to explore innovative approaches to modulate intracellular signalling pathways disrupted in disease through a unique, integrated and multidisciplinary programme. Our first goal was to target domains that recognize phosphorylated proteins - a key class of protein modification vital for signalling to create a unique palette of chemical probes which will not only provide novel insights into disease mechanisms, but also help to translate this new knowledge into the discovery of novel approaches for therapy. Our work provides a framework for chemical biology and translational research across the campus.

Since its inception, the PCBT has made headway in expanding the druggable proteome with its unique multidisciplinary format. We have made strong progress towards our first focus, BRCT domains, which represent an important class of domains that recognize pSer/pThr motifs using structurally distinct mechanisms. We have reported (Cell Chemical Biology, 2018; ChemMedChem, 2019, US2018/0346461 A1) the development of Bractoppin, a first drug-like inhibitor of phosphopeptide recognition by the human BRCA1 tBRCT domain, which selectively inhibits substrate binding in vitro, and in cells, selectively blocks BRCA1-dependent signals triggered by DNA damage. To further develop Bractoppin lead series towards commercialization, several challenges need to be addressed. First, although Bractoppin had good (~75nM) potency in vitro, cellular activity is evident at >1-10μM only. Second, high Plasma protein binding (PPB) is unfavorable as shown in Table 1. Third, solubility of Bractoppin (~70μM) hindered co-crystallization.

Table 1: Results of Human Plasma Protein Binding Assay

Compound ID	Species / Plasma	% Unbound in Plasma (n = 2) *	% Bound in Plasma	% Recovery (n = 2)	Classification
Ketoconazole	Human	1.23	98.77	94.54	High
Metoprolol	Human	93.94	6.06	108.69	Low
Bractoppin	Human	0.16	99.84	92.97	High
2171	Human	1.88	98.12	118.82	High

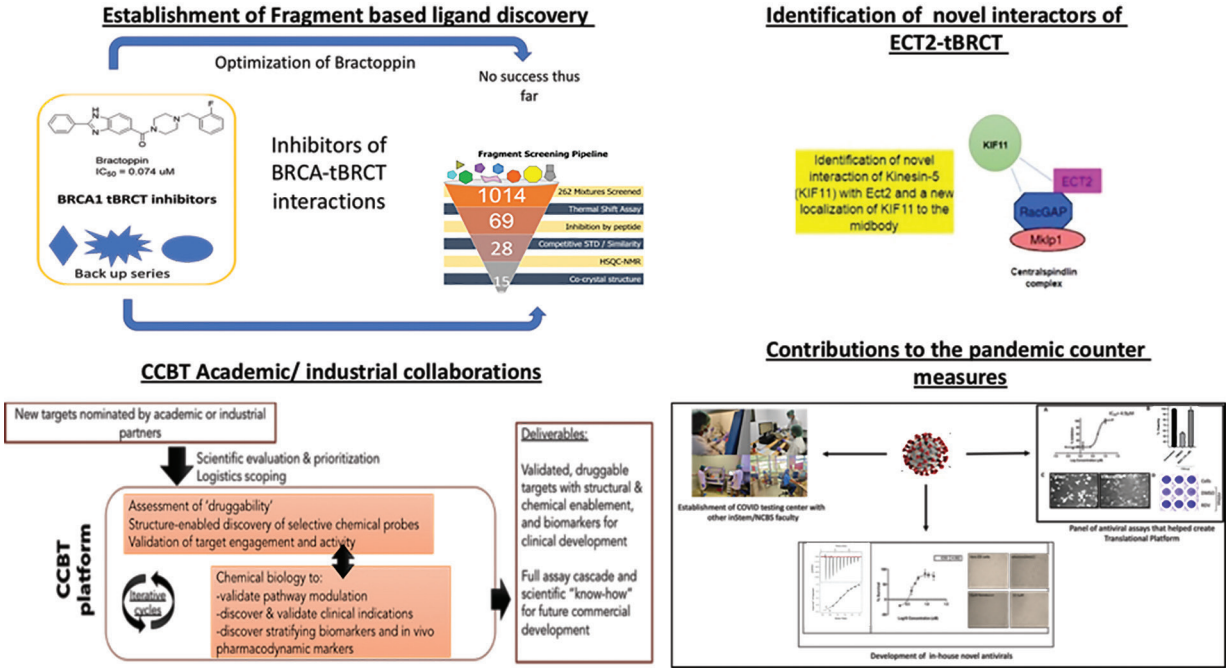
** % Unbound is the percent of free fraction of test compound in total plasma following 4 hrs dialysis.*

Excitingly, structure-guided coupling of Bractoppin to an E3 ligase ligand for developing PROTACs (Proteolysis targeting chimera) that induce BRCA1 degradation was explored. Linkers of different lengths, attachment chemistry, composition and two well studied E3 ligase ligands (Thalidomide and VHL ligand) were explored and the PROTACS were tested for in vitro binding to BRCA1 tBRCT. Our data strongly support the premise for the proposed work, and offer promise for the future utility of the PROTAC approach.

In addition, as a back-up to the Bractoppin series, strategies for identifying new scaffolds including the Fragment-based ligand discovery (FBLD). FBLD provides an alternative opportunity for discovering modulators of protein-protein interactions (PPIs), which represent an untapped target class. FBLD aims to identify small organic molecules typically within MW ~150 Da that binds target proteins. We screened 1014 fragments for their binding to BRCA1 t-BRCT domain by NMR spectroscopy using the Saturation Transfer Difference (STD) method. Using competitive STD-NMR we further shortlisted active hits that potentially bind to the phosphopeptide pocket of BRCA1 t-BRCT domain. The shortlisted hit molecules were evaluated by Heteronuclear Single Quantum Coherence (HSQC) Spectroscopy to identify their binding sites by chemical shift mapping. The binding mode of one of the best hit was revealed by the co-crystal structure. Optimization of potency by structure-guided hit expansion and medicinal chemistry efforts are in progress. In summary, applying a combination of approaches, we have successfully identified novel small molecule inhibitors for BRCA1 tBRCT domain that could be optimized and applied for biological dissection.

We have also Identified and characterized leads against ECT2, a distinct member of the tBRCT family. An optimal peptide that binds to ECT2 was identified. We also uncovered new binding partners of the ECT2 tBRCT domain. We have identified 210 high-confidence *(previously unknown)* interactions with the ECT2 tBRCT domain which unravel novel functions of ECT2 tBRCT in mitosis, ribosome biogenesis and other pathways. One of the validated novel interactors includes the Kinesin protein Kif-11. Studies for the biological significance of this interaction is underway.

Thus, our success in these strategies in interrupting intracellular signalling by not only tBRCT domain family, but as well as other phosphopeptide-recognizing domains like 14-3-3 *(in collaboration with the Venkitaraman laboratory)* that were previously considered "undruggable", against which we expect to create a palette of selective small-molecule leads, exemplifies an attractive new approach for enlarging the druggable proteome. Our niche expertise has been utilized in several forums. We have contributed in various capacities for pandemic mitigation measures which is highlighted in the schematic below.



5 Theme Reports

5.1 BDDM

Brain Development and Disease Mechanisms

Bhavana Muralidharan

5.2 CITH

Centre for Inflammation and Tissue Homeostasis

Colin Jamora | Arjun Guha | Diya Binoy Joseph

5.3 CDDM

Cardiovascular Development and Disease Mechanisms

Dhandapany Perundurai | Minhaj Sirajuddin | Sivaraj Sivaramakrishnan

5.4 ICB

Integrative Chemical Biology

Dasaradhi Palakodeti | Praveen Kumar Vemula | Ashok Venkatiraman

5.5 RCF

Regulation of Cell Fate

Arvind Ramanathan | Sunil Laxman | Tina Mukherjee | Apurva Sarin

5.6 CSCR

Centre for Stem Cell Research, CMC Vellore

Alok Srivastava(Head) | Vrisha Madhuri | Shaji R Velayudhan
Mohankumar Murugesan | Srujan Marepally | Sarvanabhavan Thangavel
Dr. Aloukick Singh | Sanjay Kumar

5.1

BDDM

Brain Development and Disease Mechanisms

FACULTY

Bhavana Muralidharan

Brain Development and Disease Mechanisms

Brain disorders are a global health challenge with the vast majority having no effective treatments. Despite obvious differences in their clinical presentation, many of these disorders appear to share molecular, cellular and circuit mechanisms. Our vision is to accelerate the discovery of these mechanisms and thus facilitate the delivery of effective therapeutics for these disorders

The **Brain Development and Disease Mechanisms** theme at inStem seeks to understand the development of the mammalian brain at multiple scales of organization *from molecules to brain circuits and behaviour.* In particular, we are interested in exploring cell-cell interactions and sub-cellular processes that underpin normal brain development and physiology that may result, when altered, in brain diseases (Fig 1). Such processes include but are not limited to membrane organization, translational control, chromatin regulation, RNA mediated mechanisms and related processes. The work within this theme seeks to link these basic biological mechanisms to aspects of human brain diseases including disease susceptibility, disease progression and pharmacogenomics to inform on the development of novel diagnostic and therapeutic options.

The theme adopts a multi-disciplinary approach to understanding brain function through discovery biology and disease modelling using modern stem cell technology including organoids, human genomics and gene editing technology, imaging and sophisticated physiological analysis. The scientific strategy of the theme links these technologies to clinical cohorts of relevant human brain diseases with associated biorepository resources as well as suitable animal models for in vivo analysis. A number of such resources have been attached including genomic data set, iPSC collections and clinical data sets *(https://ncbs.res.in/adbs/home)* and facilities for genetic and physiological analysis in rodent models *(https://ncbs.res.in/research-facilities/acrc* and h*ttps://www.instem.res.in/bddm/cns).*

Ongoing work in the theme incorporates studies addressing multiple aspects of brain development and function.

Severe mental Illness (SMI) are a major source of disability in young adults with about 2– 3% of the population at risk for developing these disorders both in India and across the world. These disorders are recognized as one of the major non-communicable diseases (NCD) and a significant contributor to morbidity as articulated by the World Health organization's New Delhi call for action on combating NCDs in India. Given this huge disease burden, the development of novel ways to diagnose and treat mental illness will have important positive social and economic benefits. To achieve this goal, there is a pressing need to

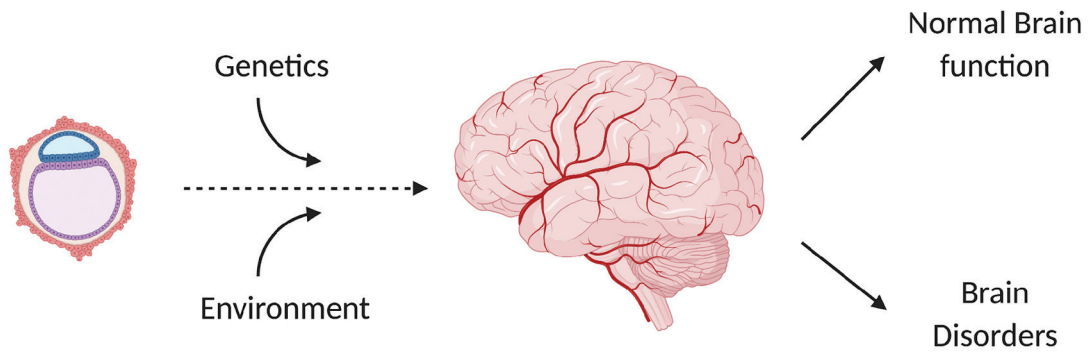


Fig 1: *During development specific cells in the human embryo divide and differentiate to give rise to the adult human brain. These developmental events are influenced by both genetic and environmental factors and these can lead to either normal brain (Image created with BioRender.com)*

understand the mechanistic basis of these disorders; such discovery could form the basis for the development of novel diagnostic and therapeutic approaches.

The **Accelerator program for Discovery in Brain disorders using Stem cells (ADBS)** program, studies five major forms of SMI: schizophrenia, bipolar disorder, obsessive compulsive disorder, substance dependence and dementia; they are thought to have a neurodevelopmental origin as well as an inherited basis. However, despite their high heritability, to date few genetic correlates that account for the high heritability have been identified. In order to study these disorders, in collaboration with the Department of Psychiatry, National Institute for Mental Health and Neurosciences (NIMHANS) and the National Centre for Biological Sciences (NCBS), the Brain development and disease mechanisms theme at inStem has assembled a prospective cohort of patients with a strong family history of SMI. The ADBS program is pursuing three distinct but complementary lines of analysis on these families: (i) The families are being clinically characterized in depth to understand changes in structure and function at multiple levels of brain organization; they are being followed over a period of twenty years at 3 year intervals in order to define the temporal development of disease through regular and detailed clinical phenotyping. (ii) We have established induced pluripotent stem cell lines (iPSC) and neural stem cell lines (Fig 2) from affected individuals in these families and unaffected controls. These lines are being used to generate cellular models to study cellular mechanisms that lead to brain disease. (iii) Next Generation Sequencing and family-based bioinformatics analysis is being used to uncover the genetic basis of SMI.

The multiple types of data generated by the ADBS program have been assembled into an integrated database to facilitate the application of sophisticated methods of data analysis to uncover new disease biology. The stem cell lines and other biomaterials are part of a biorepository that will allow the sharing and use of this resource to drive discovery biology in the area of SMI. The ADBS program has instituted mechanisms to facilitate the sharing of data and resources generated through its activities.

The theme is also studying the development of the human cerebral cortex, the seat for all higher-order functions in the brain namely learning, memory, language and consciousness. For a functional cerebral cortex in adulthood, a diverse number of neurons and glia are to be produced adequately and wired up accurately during development. Chromatin level regulations play a very crucial role in building the neural network. Several neurodevelopmental disorders stem from mutations or perturbations to the process of chromatin regulation. Yet our molecular understanding of these mechanisms is very poor in the developing brain. We aim to understand chromatin-level control of brain development in health and in disease.

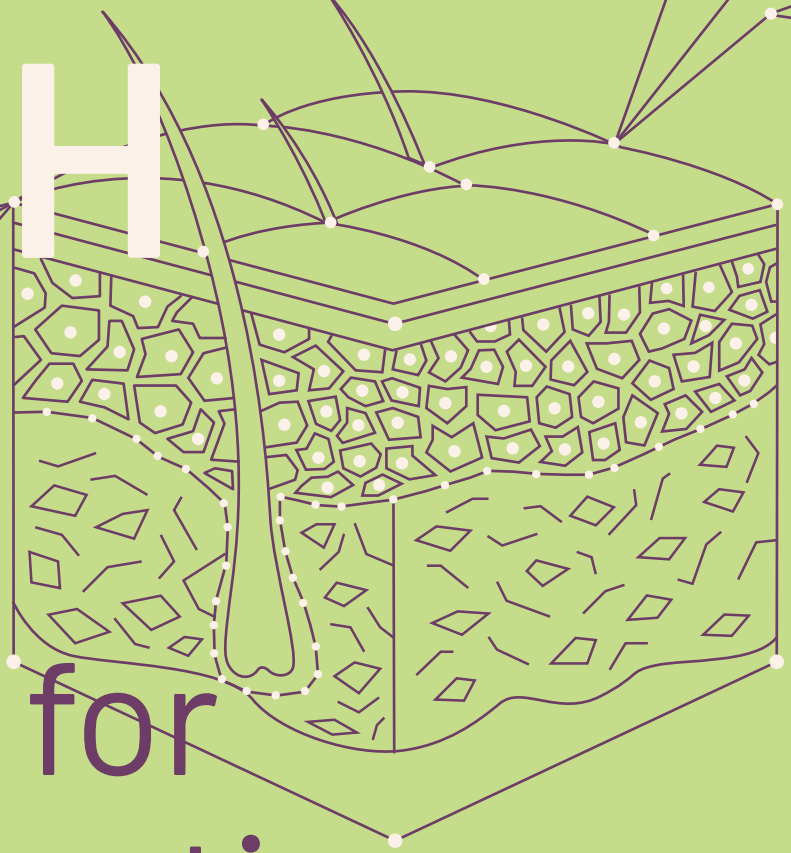
The LSD1 histone modifier plays differential role in regulating neurogenesis between mouse and humans. In mouse it promotes progenitor proliferation whereas in humans it promotes neuronal differentiation. We have uncovered downstream effectors of LSD1 in regulating human neurogenesis. These are genes belonging

to the Notch pathway and several novel genes with human enriched expression in neural stem cells. Current work is focused on validating the role of these genes in regulating human neuronal differentiation. This work will shed light on mouse vs human differences in cortical development and provide deeper insights into the role of a neurodevelopmental disorder putative causative gene, LSD1.

The lab extends its work to understand cellular and molecular mechanisms of human neuro-developmental disorders such as schizophrenia (SZ) and bipolar disorder (BPD). Mental illnesses are thought to be neurodevelopmental in origin but are poorly understood, in part due to the lack of appropriate mouse models that adequately recapitulate the human disease. To overcome this problem, the lab utilises the iPSC lines generated by the ADBS program from clinically dense families with SZ and BPD. Using 2D and 3D cerebral organoid cultures and combining CRISPR-Cas gene editing, the cellular and molecular origins of neuropsychiatric disorders are modelled in a dish.

5.2

CITH



Centre for Inflammation and Tissue Homeostasis

FACULTY

Colin Jamora

Arjun Guha

Diya Binoy Joseph

Centre for Inflammation and Tissue Homeostasis

The **Centre for Inflammation and Tissue Homeostasis (CITH)** seeks to uncover the mechanisms regulating the processes of regeneration and repair and utilizing these insights for biomedical applications. A common platform that unifies the laboratories of CITH are epithelial barrier tissues, which include the lungs, skin, and urethra. Using these experimental systems, our research endeavors is to understand the regulation of epithelial stem/progenitor cells that replenish these tissues that constantly regenerate over the lifetime of the animal and to uncover the mechanisms that stimulate their activation and behaviors during wound repair.

An important aspect of the process of regeneration and repair is the growing realization of the unconventional contributions of immune cells and signals that regulate the cells within a tissue. Not only is inflammation involved in the defense of the host from pathogenic invasion but is increasingly being implicated in regulating the overall program of tissue homeostasis. Understanding the regulation of the inflammatory response in epithelial tissues also holds the promise of identifying novel therapeutic interventions for the treatment of chronic inflammatory diseases. In close collaboration with clinicians and the biotechnology industry, we seek to utilize the knowledge gained from our basic science studies to replace/repair tissues lost to disease, trauma, or aging.

The theme itself has undergone a regeneration over the last fiscal year that has brought an infusion of new ideas and energy. Joining Professor **Colin Jamora** and **Dr. Srikala Raghavan** *(visiting scientist from Singapore)* in CITH in January 2022 was **Dr. Diya Binoy Joseph** as an Assistant Professor/Assistant Investigator from her postdoctoral position at the University of Texas Southwestern Medical Centre. She is establishing her independent laboratory focused on an exciting program of epithelial homeostasis and barrier defenses against infection using the urethra as a model system. At the same time, **Dr. Arjun Guha** transferred to CITH from the Regulation of Cell Fate (RCF) theme at inStem as an Associate Professor/Associate Investigator and continues his groundbreaking work on lung repair and regeneration. Further, we look forward to the arrival of **Dr. Sudarshan Gadadhar** in FY 2022-2023 from his postdoctoral position at the Institut Curie in France, who will bring a new perspective on the regulation of tissue homeostasis at the cellular level through structures called cilia.

IFOM-inStem Joint Research Laboratory

PI: Colin Jamora, PhD, Professor

The IFOM-inStem Joint Research Laboratory is broadly interested in understanding the molecular mechanisms that govern tissue homeostasis and the wound healing response in the skin. Our ultimate aim is to use these fundamental insights to develop therapies for diseases where the wound healing process

perturbed, such as in diabetes or in cases where there is a “chronic wound” phenotype such as fibrosis. We are continuing our studies of deciphering the extensive crosstalk between multiple cell types in the skin including epidermal keratinocytes, dermal fibroblasts, dermal fat cells/adipocytes, cells of the blood vessels, and immune cells. The exchange of signals between this constellation of cells play a major role in coordinating skin regeneration and repair.

Over the past year we have made important advances in understanding wound healing therapies with our clinical and industry collaborators. In collaboration with clinicians from the Rajiv Ganghi University of Health Sciences, we have shown that the grafting of hair follicle units, with its cocktail of different stem cells, is able to heal chronic non-healing wounds in diabetic patients that we resistant to standard wound care procedures. Importantly, not only did the non-healing wound close, but there were new blood vessels, nerve cells, and sweat glands that formed, which are important for the full functioning of the skin *(Saha et al., 2021; Figure 1)*. This is a critical advance in treating conditions such as diabetic wounds that are increasingly common in India and often lead to the amputation of limbs. In addition, with our collaborators at L’Oreal, we have discovered an unexpected role for nerve cells in regulating the wound healing response *(Zaarour et al., 2022)*. Together we found nerve cells in the wounded skin releases a peptide called “Substance P” that can dampen inflammation and promote processes required to rebuild the skin such as new blood vessel formation and the production of collagen to provide structural support for the repaired skin.

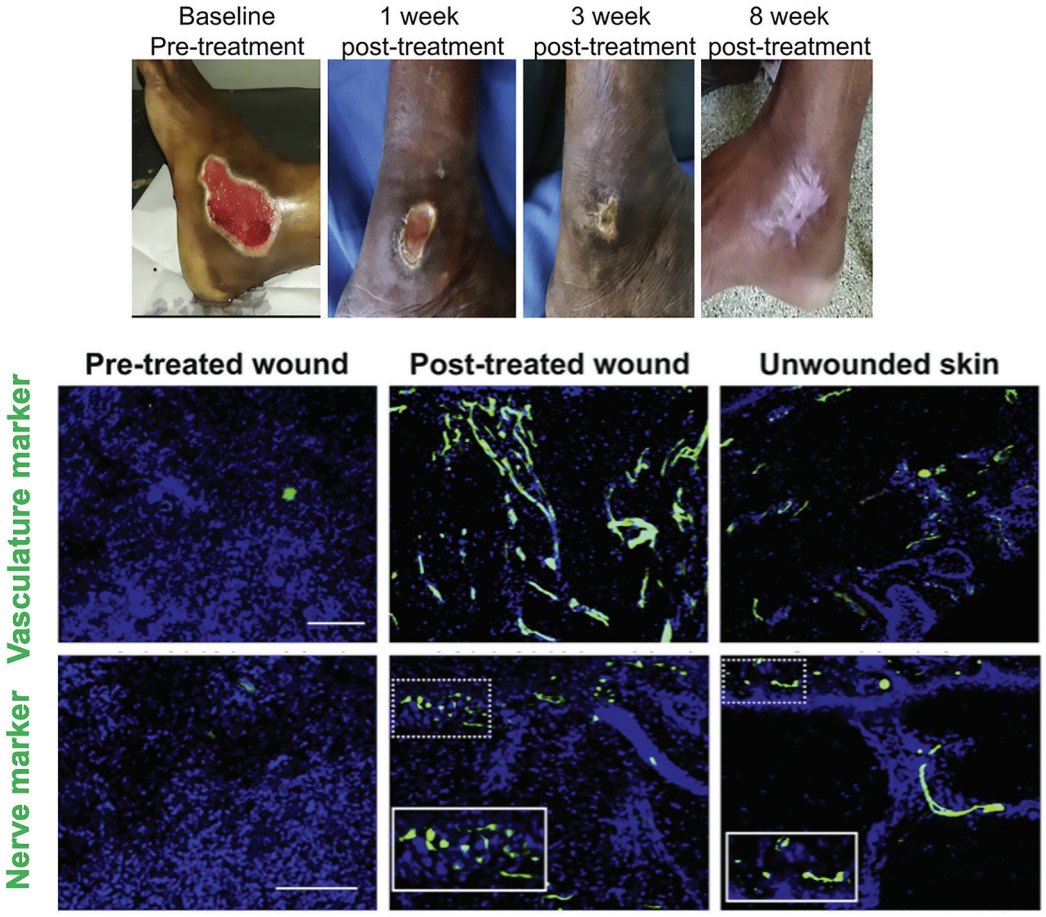


Figure 1. *Promotion of wound healing by hair follicle stem cell therapy. Top row: Pictures of wound healing before (pretreatment) and after treatment with hair follicle stem cell grafting. Regeneration of blood vessels (middle row) and nerve cells (bottom row) in diabetic wounds post hair follicle stem cell treatment, which are nearly absent in the pre-treated diabetic wound. The amount of regenerated vessels and nerve cells is equivalent to the unwounded skin. (From Saha et al., JID Innovations 2021)*

Urogenital Tract Homeostasis and Repair Laboratory

PI: Diya Binoy Joseph, PhD (Fellow E/Scientist D)

Dr. Diya Binoy Joseph joined the CITH theme in mid-January 2022. Diya trained at the University of Wisconsin-Madison for her PhD where she worked on novel mechanisms of bladder regeneration and prostate organogenesis. She went on to do her postdoctoral training at UT Southwestern Medical Center in Dallas, Texas where she worked on resolving cellular heterogeneity in the normal and diseased prostate using single cell RNA-sequencing and spatial transcriptomics. The discovery of novel immuno-secretory club and hillock cells in the human urethral lining from her postdoctoral training led her to start her independent research program at inStem looking at the innate defenses of the urethral epithelium against urinary tract infections. The constitutive expression of genes related to antimicrobial defense, barrier function and immunomodulation in the urethral lining suggests that this barrier is primed to respond to urinary tract infections. Diya will look at factors regulating the priming of this barrier including exposure to the urethral microbiota and sex hormones. Diya will also establish new transgenic mouse models to study the role of the NF-KB pathway in the urethral lining, where the pathway has a constitutive basal level activity even in the absence of infection. Further, she will use uropathogenic E. coli strains to model urinary tract infections in mice and study the response of the urethral lining to infection. Diya's research program on the urethral epithelial lining adds to the repertoire of barrier structures being investigated in the CITH theme which also includes the skin barrier and the lung lining. Diya plans to collaborate with **Dr. Arjun Guha**, a CITH theme member, on common mechanisms underlying the specification of club cells in the lung and the urinary tract. Additionally, she is planning to investigate the similarities between the immuno-secretory profiles of sweat gland cells in the skin and club cells in the urethra in collaboration with Dr. Colin Jamora to decipher the underlying mechanisms that maintain the commonalities in gene expression profiles in these cells from distinct barrier sites.

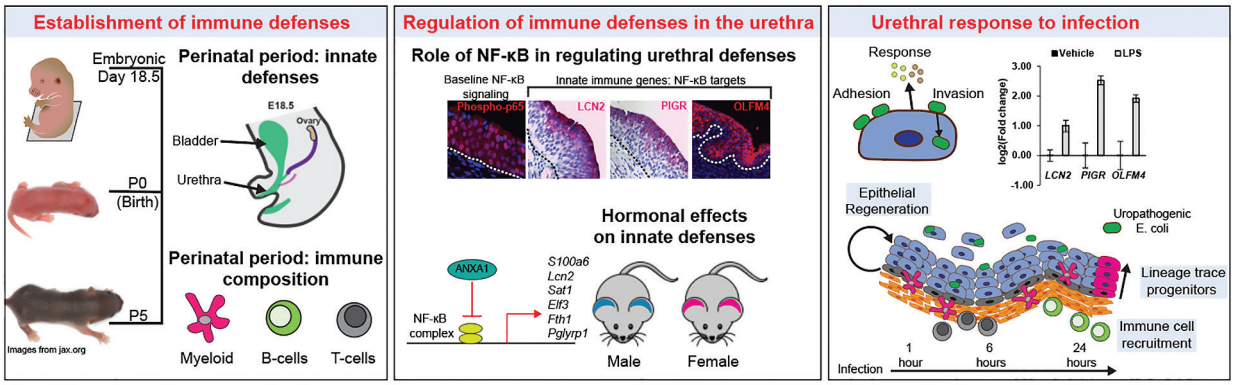


Figure Summary of proposed work. (1) Establishment of immune defenses: The change in innate defenses and immune composition in the perinatal period from exposure to microbiota will be assessed in mouse pups across late fetal and early postnatal stages. (2) Regulation of immune defenses in the urethra: The role of the NF-KB pathway and hormones on innate immune defenses in the urethra will be studied. (3) Urethral response to infection: Using in vivo and in vitro models of uropathogenic bacterial infection, the response of the urethral epithelium to infection will be studied.

Lung Injury and Repair Group

PI: Arjun Guha, PhD (Scientist F)

Our group is broadly interested in the mechanisms that enable the lung to cope with exposure to chemical and biological agents and to deal with the aftermath.

During repair and regeneration, tissues like the skin typically employ undifferentiated tissue-resident stem cells to replace the differentiated cells that are lost. Yet, with the lung emerging as a paradigmatic model, it is clear that the tissue's own differentiated cells also contribute toward replacement of lost cells. A major part

of the lab's research effort is devoted toward delineating the mechanisms underlying cellular plasticity during lung repair using the insect (Drosophila) respiratory system and the mouse lung as model systems.

Our studies on cellular plasticity are motivated by the central idea that the differentiated state is an actively maintained state contingent on certain conditions. We have found that developmental signals like Wnt in the larval respiratory (tracheal) system in fruit flies, and Notch in Club cells in the airways of the adult lung in mice, maintain cells that are differentiated in particular fates. The downregulation of these signals in the respective systems lead to changes in the fates of cells. We are trying to work out how these signals control gene regulatory networks in cells and in turn their and fates.

We have recently discovered that an oxidative innate immune defense mechanism in the respiratory tract plays an active role in regulating cell fate and plasticity. These studies have alerted to the role of ***immune signals***, both innate and acquired. Our future research at CITH will probe the role of immune signals in the regulation of cellular plasticity during lung regeneration.

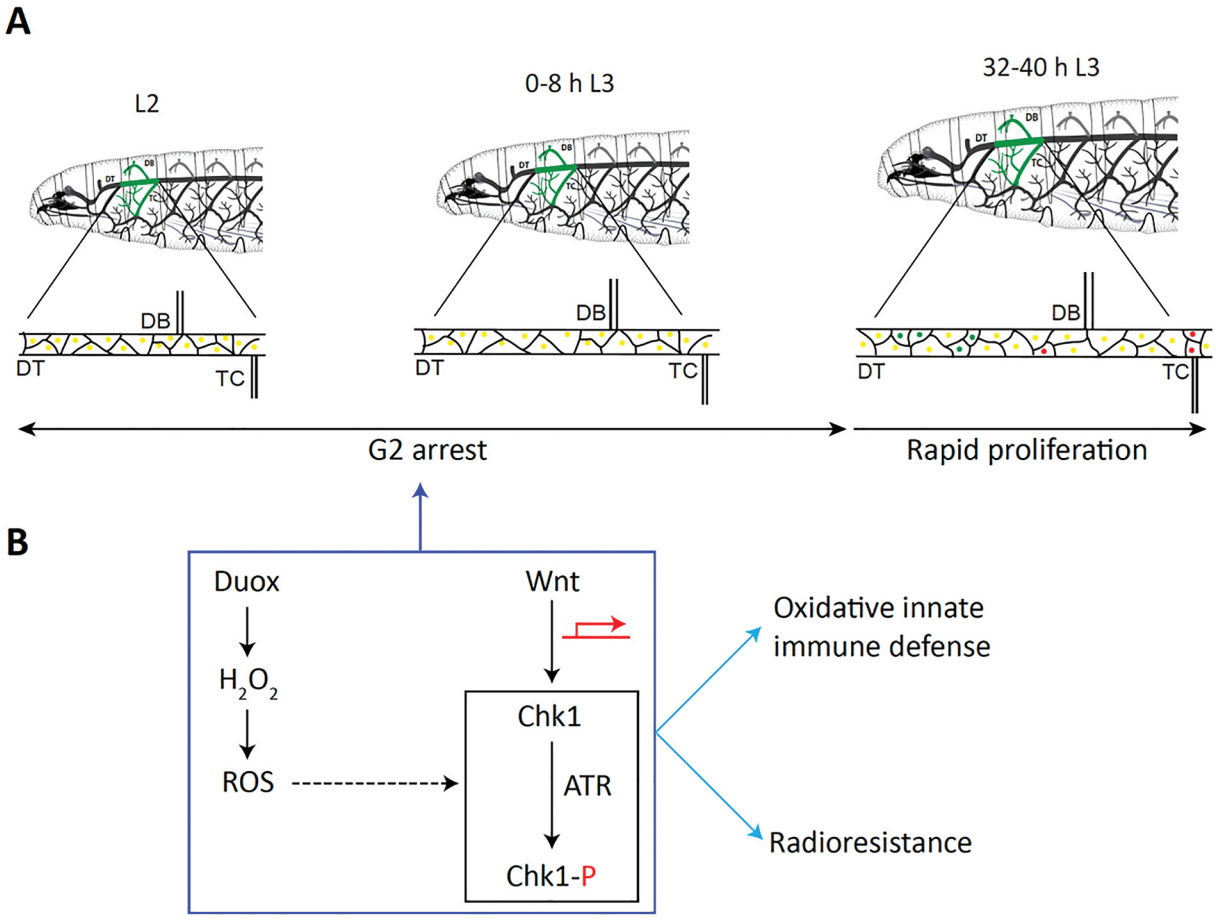


Figure. Duox-generated reactive oxygen species activate ATR/Chk1 to induce G2 arrest in Drosophila tracheoblasts

(A) Cartoon showing the cell cycle program of a group of differentiated adult progenitors in larval respiratory epithelium (Tr2 DT) at different larval stages. Cells of Tr2 DT remain arrested in G2 from the second larval instar (L2) till 32-40 h L3 (~56 h), grow dramatically in size during this period and proliferate rapidly thereafter. (B) Mechanism for G2 arrest in Tr2 DT. We propose that Duox-dependent production of H2O2 can directly activate ATR and lead to the phosphorylation and activation of its substrate Chk1. Activated Chk1 in turn phosphorylates specific substrates leading to G2 arrest. Our studies have also revealed that this network is also active in other tissues like the lymph gland and the gut. However, the activation of the pathway in these tissues does not directly induce G2 in these tissues. We hypothesize that the active network broadly facilitates oxidative immune defense and radioresistance in all cells and G2 arrest in a specialized set of these cells with the requisite machinery.

5.3

CDDM

Cardiovascular Development and Disease Mechanisms

FACULTY

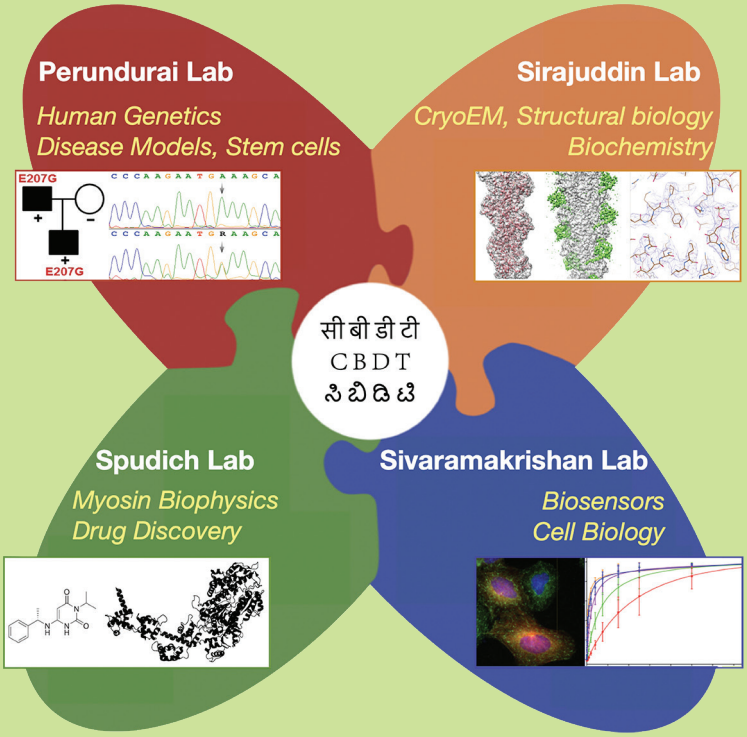
Dhandapany Perundurai

Minhaj Sirajuddin

Sivaraj Sivaramakrishnan

Cardiovascular Development and Disease Mechanisms

Functional genomics of hypertrophic cardiomyopathy



Theme organization with specialized expertise and overlapping interests to tackle cardiomyopathies.

Sivaraj Sivaramakrishnan

Genetic basis of PKCα dysfunction in disease

PKCα is a multi-functional kinase that exhibits contradictory (both tumor suppressive and oncogenic) roles in cancer. Over 540 somatic mutations in PKCα have been catalogued in the cancer genome atlas. PKCα is a multi-domain protein with four regulatory domains *(pseudo-substrate, C1a, C1b and C2)* and a catalytic domain that phosphorylates multiple substrate proteins. These cancer-associated mutations are spread across both the kinase and regulatory domains. Cell biological studies reveal that the cancer-associated PKC mutants exhibit loss-of-function phenotypes. However, the precise structural basis of this aberrant PKC function remains unclear. Using SPASM sensors, the Sivaramakrishnan lab has characterized disparate structural mechanisms of across the PKC molecule triggered by HCM mutations.

Dhandapany Perundurai

Functional genomics of cardiomyopathies

Cardiomyopathies are a group of heart muscle diseases that often lead to progressive heart failure with significant mortality. The cause of a significant percentage of cardiomyopathies (~40%) remains unknown with poorly defined mechanisms and no curative therapies. To address these questions, our group encompasses a multi-disciplinary approach involving Next Generation Sequencing (NGS) in identifying new genes and various models to understand the mechanistic basis and therapeutic targets for the new cardiomyopathy genes.

1. Whole exome sequencing to identify novel genes for cardiomyopathies:

We have organized fifty unrelated Indian cardiomyopathy patients *(who are negative for reported genes)* and their family members (*a total of 150 individuals)*. We performed whole-exome sequencing in selected index patients with their respective family members as controls. In unrelated patients, we identified novel mutations in Adiponectin Receptor R1 and RPS6KB1. We are exploring the critical mechanisms of these genes using cellular models. For the remaining patient samples, the exome analysis is in progress.

2. Patient-specific induced pluripotent stem cells (iPSC)-derived cardiomyocytes:

Our research work on the molecular genetics of cardiomyopathies led to crucial discoveries, including an ancient common variant (25bp deletion) associated with cardiomyopathies in cardiac myosin-binding protein c3 (MYBPC3) gene in South Asians. This variant, in its homozygous nature, causes severe childhood cardiomyopathies We generated the hiPSCs with VSV-pseudotyped Maloney-based retroviral vectors encoding OCT4, MYC, SOX2, and KLF4 from patient fibroblasts harboring the MYBPC3 mutations with a 25bp deletion respectively. These are differentiated into cardiomyocytes and subsequently purified by cell sorting using the cardiomyocyte-specific cell surface marker SIRPα. We next examined the signaling pathways modulated by various gene variants by assessing their effects on lysates obtained from cardiomyocytes overexpressing WT and mutants using immunoblotting for various downstream targets. Our plans also include screening for new candidate therapeutics for cardiomyopathies from FDA-approved drugs using cardiomyocytes derived from patient-specific iPSCs

3. Humanized transgenic mice models of cardiomyopathies:

We have generated a humanized cardiac-specific transgenic mouse models for 25bp variant using standard Cre-loxP recombination methods. We obtained five viable founder lines and are in the process of characterizing the physiological, functional, and molecular aspects of this mouse model.

Also, we generated a transgenic mouse model with a novel PRKCA mutation observed in children cardiomyopathies. The mice develop cardiomyopathy for around four weeks. The histological analyses in these mouse hearts revealed massive cardiomyopathy with the hallmarks of hypertrophy, including increased cells sizes and myocardial fibrosis. We are studying the mechanisms related to PRKCA mutant mice.

Minhaj Sirajuddin

Structure and function of contractile systems across scale dimension

Eukaryotic biological motions across orders of magnitude scale involve cytoskeleton elements, and mutations in them are frequently associated with human pathology. My research program is geared towards delineating physiological and pathological mechanisms related to biological motility from molecular, cellular to organ scale. At molecular scale, our lab employs cryoEM and in vitro reconstitution, our goal here is to understand the molecular basis of cardiomyopathy disease causing mutations. In this regard, we have determined cryoEM structures of F-actin bound to toxin, peptide and proteins widely used in visualizing actin structures in cell biology. Currently we are resolving structures of F-actin bound to nexilin a Z-disc protein and mutations in nexilin are known to cause cardiomyopathies. Similar molecular approaches are being employed to study PKC-alpha and cardiac myosins, implicated in cardiomyopathies, the central focus of our theme. Our research at cellular scale is to understand the spatial and temporal

organization of microtubule post-translation modifications. Detyrosinated microtubules, a well-known microtubule modification is known to bear the load during contraction in cardiomyocytes. Elevated levels of detyrosinated microtubules have been shown to occur in cardiomyopathies. In our lab, we have developed a live cell sensor against tyrosinated microtubules (unmodified microtubules). This live cell sensor will serve as a marker and enable us to study differentially modified microtubules in cells e.g., cardiomyocytes. Our methodology also provides a platform to obtain live cell sensors against the remaining microtubule modifications. Which will become invaluable tools towards understanding the spatial-temporal organization of microtubule modifications. Lastly, in our quest towards understanding the cardiomyopathies and heart remodeling during pathological conditions, we have developed microscopy methods to image whole mouse hearts at micron scale resolution. This tour de force imaging work has provided unique insights into the myofiber organization of normal hearts. In the near future, we aim to extend the imaging work to compare and contrast the normal versus cardiomyopathy hearts. The high-resolution comparison of normal and pathological heart organization will inform our understanding of dysfunction caused by cardiomyopathies and will aid in designing potential therapeutic interventions. Thus, our lab has established a robust research program to study cytoskeleton and contractile systems at various organization scales. In addition, the pipelines setup in our lab can be leveraged to study heart related diseases under the collaborative thematic approach envisioned at inStem.

5.4

ICB

Integrative Chemical Biology

FACULTY

Dasaradhi Palakodeti

Praveen Kumar Vemula

Ashok Venkatiraman

Integrative Chemical Biology

The broad vision of ICB theme is to develop systems and chemical biology based approaches to study complex cellular processes, which could provide mechanistic insights into disease progression under altered physiological conditions. Further, the focus of the theme is to establish integrated platforms and model systems to identify novel drug molecules and delivery methods for therapeutic interventions in altered disease states. ICB theme has investigators with diverse expertise in the field of chemical, physical, molecular and cellular biology. This combination of expertise within the theme provides a unique ecosystem to address challenging fundamental questions in biology with strong translational and clinical implication in disease biology. In the last two years, based on our core expertise and multidisciplinary approach, two major research programs have emerged within the theme.

1. Use of chemical probes to dissect biological processes, for example systems and chemical based approaches to study RNA biology.

2. Identify new targets of potential relevance to disease, generate chemical probes, delivery systems against such targets to interrogate biology thereby developing potential therapeutics.

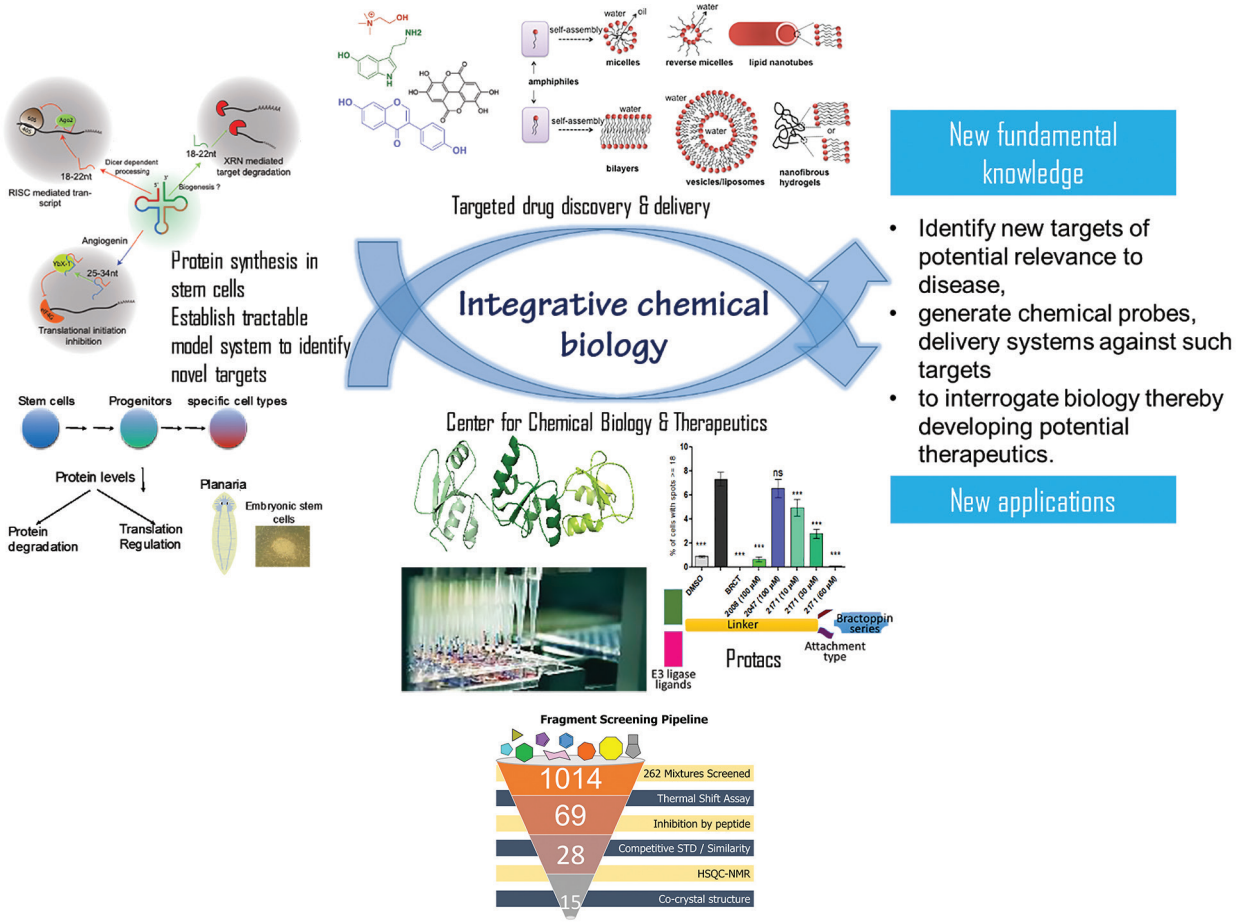
Program 1: We have used the chemical-based approach to dissect the biology of an emerging field, namely RNA biology. The last decade witnessed the emergence of RNA as a key regulator of gene expression. The core expertise within the theme to study RNA mediated regulation of gene expression in combination with biophysical and biochemical characterization led to the discovery of novel RNA molecules and their functions critical for stem cell and regenerative biology. For instance, the theme has discovered novel class of small RNAs known as tRNA derived small RNA (tsRNAs) in the pluripotent stem cell populations. Molecular and biochemical studies show that these tsRNAs and their associated proteins repress translation of specific transcripts critical for maintenance of stemness, thereby, facilitating the differentiation. Further, their work also showed maternally and paternally deposited tsRNAs in the fertilized egg of the mouse embryo, whose functions are not yet characterized. Using confocal studies, the group has shown that an endoribonuclease, Angiogenin is spatially localized both in the nucleus and cytoplasm in the one and two cell embryos, and subsequently localize only to the cytoplasm in the later stages of the embryogenesis. Using chemical biology approaches, a specific inhibitor was synthesized to block the function of Angiogenin, the group has shown that the inhibitin of Angiogenin led to the block in the progression of the embryo from two cell to four cell stage. This result suggests that Angiogenin and tsRNA might be important for the zygotic genome activation, which is critical for the progression of two cell embryo to four cell embryo. Currently, research is underway to characterize the regulatory factors including post-transcriptional modification of

tRNAs and its associated proteins in tsRNAs biogenesis and function. In summary, the work identified novel mechanism mediated by tsRNA to regulate mammalian ealry embryogenesis.

Program 2: The investigators in this program aim to develop genetically tractable models and chemical probes to identify new targets and study structure-function relationships in the context of a specific biological pathway under normal and diseased condition. The **two major focus areas** under this program include:

1. Establish tractable model system to identify novel targets for disease intervention

Previous work from the theme and many other laboratories across the world showed planaria, as a tractable model to study regeneration and stem cell biology. The group found that the planarian pluripotent stem cells (PSCs) have low mitochondrial mass compared to their lineage-primed progenitors. A change in mitochondrial state has a deterministic role in PSC differentiation. Using mitochondrial states as a readout, the group has developed innovative flow cytometry methods for the purification of live, functionally active, PSCs from different cell cycle stages (G0/G1 and S, G2/M). An active line of research is underway to dissect the molecular mechanism of mitochondrial regulation of stem cell function which has implications for stem cell therapy and cancer. Even though being an excellent model system, planarian research has been crippled due to a lack of genome editing techniques and transgenic lines. To address this long-lasting problem, our group is developing novel membrane penetrating liposomes as potential gene delivery agents for planarian PSCs. Further, high-throughput screening of optimal cell adhesion substrates is being carried out to optimize in vitro PSC culture. This will allow us to perform genome editing and biochemical assays to understand PSC maintenance and differentiation. In summary, the work has advanced the understanding of the role of mitochondria in stem cell function and developed cutting-edge techniques in planarian research making it a powerful model to carry genome-wide RNAi screens to identify novel targets for drug discovery with strong implications in regenerative medicine.



2. Expanding the druggable proteome using Chemical Biology tools

Our group adapts innovative approaches to modulate intracellular signalling pathways disrupted in disease through a unique, integrated and multidisciplinary programme. We have focused on the conceptually novel approach of inhibiting phosphopeptide recognition to modulate kinase-initiated intracellular signalling pathways. We reported the development of Bractoppin, a first drug-like inhibitor of phosphopeptide recognition by the human BReast CAncer gene 1 (BRCA1) tBRCT domain, which selectively blocks BRCA1-dependent signals triggered by DNA damage that bind to BRCA1 tBRCT with good in vitro potency, opening a new therapeutic concept for cancer via the interruption of intracellular signaling. To this end, we have applied multiple new strategies including Bractoppin optimization, PROTAC design, Backup series optimization, and Fragment-based ligand discovery. Second, we have identified and characterized leads against Epithelial Cell Transforming-2 (ECT2), a distinct member of the tBRCT domain family involved in mitosis. We have identified optimized peptide partners for the human ECT2 tBRCT domain using protein engineering approaches as well as validated the binding pocket of ECT2 tBRCT peptides compound by mutational and biophysical studies. We have also identified and validated high-confidence interactors of the human ECT2 tBRCT domain. In response to the pandemic, the CCBT has also helped set up assays to evaluate /develop antiviral modalities including chemical inhibitors, therapeutics, vaccines and other modalities. Our success in discovering selective/ enabling discovery of small-molecule inhibitors has attracted various academic and industrial partners.

5.5

RCF

Regulation of Cell Fate

FACULTY

Arvind Ramanathan

Sunil Laxman

Tina Mukherjee

Apurva Sarin

Regulation of Cell Fate

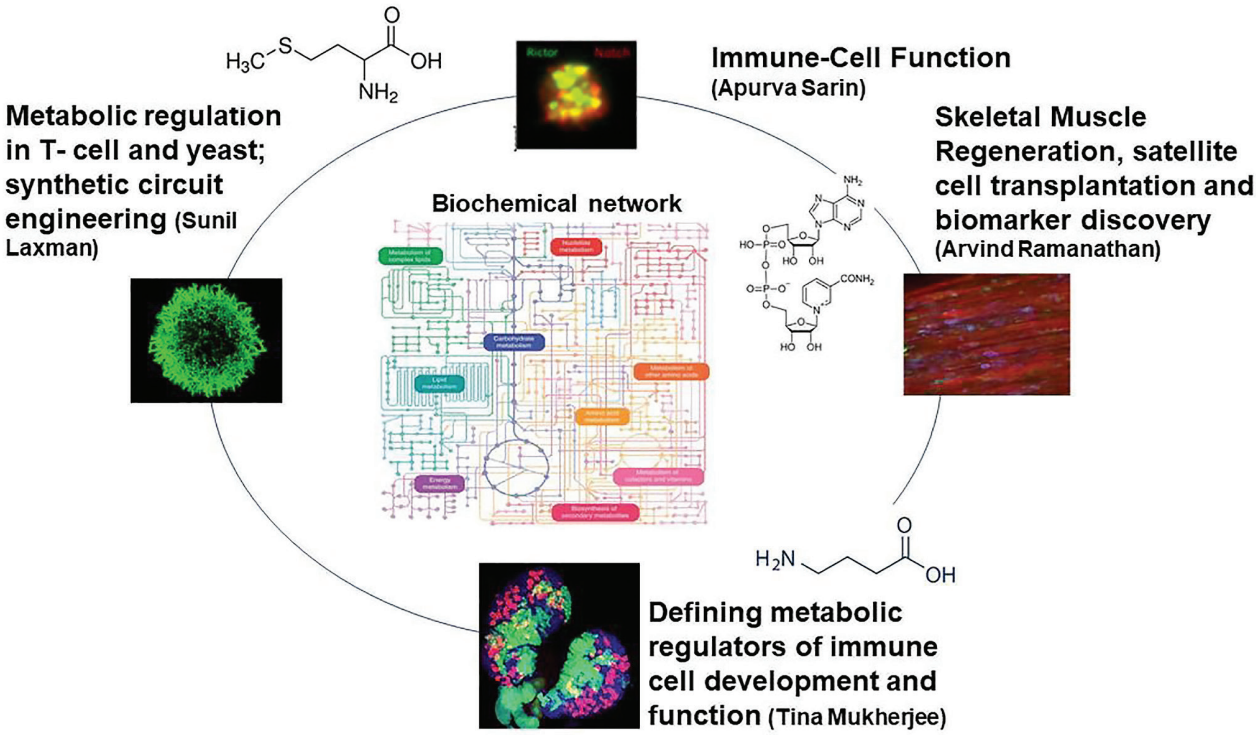
The overarching connection within the theme is based on how metabolic networks and in some case specific metabolites control cellular behavior and fate both in vitro and in vivo. imaging and mass spectrometry based analytical measurements of metabolic pathways and fluxes forms the underlying connection within the theme. The theme works on various cell states including, **satellite cell based skeletal muscle regeneration *(Arvind Ramanathan Lab)*; Metabolic regulation of T-Cell differentiation *(Apurva Sarin and Sunil Laxman Laboratories)*** and **immune cell development *(Tina Mukherjee)*.**

The **Ramanathan laboratory** has been modeling skeletal muscle diseases *(fatty acid oxidation disorders)* using iPSCs *(in collaboration with Prof. Vasanth Damodaran at TIGS)*, Clinical biomarker discovery of aging related sarcopenia (in collaboration with Baptist Hospital and Vayah Vikas) and metabolic enhancement of satellite cell transplantation using mouse models. His laboratory in conjunction with Baptist Hospital and **Prof. VijayRaghavan** has initiated the country's first Sarcopenia and Frailty group in 2022. Dr. Ramanathan has published a chapter in a book for training clinicians in new technologies such as bioengineering as a part of this collaboration. Bridging clinical collaborations with mechanistic studies is expected to lead to new metabolic insights and nutritional interventions against skeletal muscle loss in aging and disease.

Work from the **Mukherjee laboratory** has revealed that ***Drosophila*** have distinct metabolic states of immune cells and their importance in immune development, immunity and implications in non-immune contexts such as coordinators of organismal physiology and stress tolerance. In this regard, the direct utilization of neurotransmitters as metabolites in blood development has emerged as a key finding. The use of dopamine as a proliferative cue by the immune progenitor cells *(Kapoor et.al., 2022)* and GABA *(Goyal et.al. 2022)* in moderating blood progenitor ROS homeostasis and immunity strengthens this notion. As part of an ongoing collaborative initiatives with **Prof. Giangrande's** laboratory, her work has revealed distinct metabolic and functional states of embryonic and larval immune cells. Overall the investigations are leading to the paradigm that "immune cells are mobile sensors of animal physiology". The lab aims to develop a comprehensive framework that will define novel non-immune functions of innate immune cells. The role of innate immune cells as key sensors of the animal's internal state and its relevance in organismal development, metabolism, behavior and predisposition to metabolic disorders will be some of the key findings that are expected to emerge from this program.

The goal of the **Laxman lab** is to holistically understand the biochemical logic for how cell fates are regulated by metabolic states, and translate this basic understanding to address key problems in human health. From studying metabolic signaling mechanisms, our lab now addresses questions on metabolic organization from molecules to systems and networks. In the past year, the discovery that during nutrient limited conditions, two major signaling pathways thought to be antagonistic, the AMPK and TORC1 pathways, actually converge to function together in regulating carbon allocations

between anabolic and catabolic processes was published *(Rashida et al, Sci Adv 2021)*. In addition, in the culmination of collaboration with **Prof. Apurva Sarin** of the RCF theme, they have identified metabolic regulation of T cell fate, culminating in the finding that Tregs cells have a critical requirement for methionine in their survival, via a novel function of an amino acid transporter in a Notch1 signaling pathway dependent manner *(Saini et al, under revision)*. The laboratory anticipates exciting collaborations within the RCF theme and beyond to converge synergistically in this emerging area of cell fate research. Overall the program is using the growing systems-level understanding of collective cell state control to develop synthetic circuits for optimized metabolic cellular engineering in cells.



5.6

CSCR

Centre for Stem Cell Research

FACULTY

Alok Srivastava (Head)

Vrisha Madhuri

Shaji R Velayudhan

Mohankumar Murugesan

Srujan Marepally

Sarvanabhavan Thangavel

Dr Aloukick Singh

Sanjay Kumar

Centre for Stem Cell Research (CSCR)

The **Centre for Stem Cell Research (https://www.cscr.res.in/)** continues to focus on translational research in cell and gene therapy towards regenerative medicine to bring stem cell science and other novel therapies to the management of patients with unmet needs. It is the goal of scientist at CSCR to work in teams directed at particular themes to find solutions for current medical needs in the country. Three thematic research programs in multi-individual, multi-disciplinary and multi-institutional programs are described below.

1. Musculoskeletal Regeneration

This program is coordinated by **Vrisha Madhuri**. The other investigators in this group include, **Srujan Marepally, Mohan Kumar, Nihal Thomas, Vikram Mathews, Dolly Daniel, Lilly Verghese, Alok Srivastava**. The major focus is on clinical and preclinical translation related to physis, articular cartilage, bone, and muscle regeneration. Towards this we have two major areas of focus. The first is a cell-based therapy for bone, cartilage and muscle regeneration. In collaboration with Karolinska Institute, Sweden, we have an ongoing phase I/II clinical trial for the treatment of osteogenesis imperfecta using fetal liver derived mesenchymal stem cells. In parallel we are exploring the paracrine and immunogenic effects of multiple infusions of MSCs via intraosseous and intravenous routes. Another phase I/II trial where the culture expanded muscle derived stem cells is used for the treatment of urinary sphincter incontinence. The second is the cell-free therapy for cartilage and bone regeneration using biomolecules. In collaboration with multidisciplinary groups from SCTIMST, Trivandrum, Kerala and CSCR we have identified suitable biomaterials with kinetics for sustained release of therapeutic biomolecules. The newer initiative includes the use of extracellular vesicles for the treatment of osteoporosis in genetic defect animal and cellular models. We are also generating in vitro data to convert autologous chondrocyte therapy for physis or articular repair to a single step procedure bypassing the cell expansion step.

Under the same theme, **Elizabeth Vinod** coordinates another research program. The other co-investigators in this group include **Solomon Sathishkumar, Alfred Job Daniel, Abel Livingston, Soosai Manickam Amirtham** and **Viju Daniel Varghese.** The primary focus is on the characterization of cartilage-derived progenitors and studying their potential implications for cartilage regeneration using in-vitro and in-vivo conditions. Their work also involves characterizing soluble factors derived from these progenitors and assessing their potential for cultivating injectable therapeutic molecules. They also work towards the creation and validation of osteoarthritic models in animals and the development of novel histological processing techniques for the assessment of chondrogenesis.

2. Gene Therapy

A major focus of research at CSCR is on gene therapy. The goal to capitalize on the recent advances in the world towards gene therapy of

monogenic haematological disorders. and make them possible for patients in India. Several scientists and physicians are involved with this work which is coordinated by **Alok Srivastava** and includes **R V Shaji, Saravanabhavan Thangavel, Mohankumar Murugesan, Srujan Marepally, Aloukick Singh** and **Gurbind Singh** at CSCR and several other faculties from CMC, Vellore as well as many external collaborators.

Haemophilia: This involves two major areas at present – The first is directed towards haemophilia where two programs are being pursued. First, a clinical trial for AAV vector-based gene therapy for haemophilia B in collaboration with Emory University, Atlanta, USA and the University of Florida, Gainesville, USA. Given the success of AAV based gene therapy reported in recent years, we have developed a novel transgene and vector combination for gene therapy of haemophilia B. The challenge with manufacturing the GMP grade vector is now being met through academic collaborations for transfer of technology from our collaborators. We are able to bring this technology to our country, which has wide applications in gene therapy for many diseases. We are working towards establishing an industry partnership for this AAV3-hFIX vector production in India. The second component is a clinical trial of a lentiviral vector mediated haematopoietic stem cell based first in human gene therapy for haemophilia A. After submitting the data from above transduction experiments with haemophilia A patient CD 34 HSC, we received the approvals to conduct the phase 1 clinical trial. The approval for clinical trial was obtained in form CT-06 from CDSCO. We received the manufacturing license (form CT-11) from CDSCO and in form 29 from state licensing authority (SLA). Based on these approvals, sufficient-quantity of the vector was obtained to initiate the clinical trial. The first subject has been recruited and the requisite numbers of HSCs have been collected and transduced. Quality assessment of the product was carried out and release criteria were met. We are excited to conduct this first in human clinical trial of lentiviral vector-based gene therapy for haemophilia A in the world and are cautiously optimistic.

The second part of the gene therapy program involves gene therapy for the major haemoglobin disorders. Here there are two approaches being developed – a lentiviral vector-based gene addition as well as gene modulation technologies as well gene editing approaches using CRISPR-Cas9 (Mohankumar Murugesan) and base editing technologies which have all been tested in cellular and animal models and are now getting close to clinical translation. This program also involves close collaboration with the Emory University, USA as well as other collaborators at University of Florida College of Medicine, USA. Other non-vector mediated gene transfer technologies are also being explored for nucleic acid transfers for gene therapy including the development of a mRNA-based vaccine against for SARS-CoV2 virus infection (Srujan Marepally).

An industry collaboration has been established with Intas Pharmaceuticals for the development of rAAV8-hFIX-Padua based gene therapy for Hemophilia B. This work is coordinated at CSCR by Sanjay Kumar. *In-vivo* efficiency of expression in being evaluated in the transgenic haemophilia mouse models at CSCR. To improve the current approaches of gene therapy for Hemophilia A, Mohankumar Murugesan is working on a novel ex vivo gene therapy approach for targeted integration of FVIII in hematopoietic stem cells for the treatment Hemophilia A. A protocol has been developed for effective transfection of Cas9-RNP complex for the targeted integration of transgene in to lineage specific promoter.

Towards developing a novel lipid mediated gene therapy strategy for hemophilia, galactosylated lipid nanocarriers have been developed by Srujan Marepally that can specifically deliver nucleic acids including pDNA, siRNA, mRNA effectively into the liver. Further, safety profiles and therapeutic efficacy are being assessed in Hemophilia B mouse model.

Haemoglobin disorders: Another major thrust of the gene therapy is on the major haemoglobin disorders such as thalassemia and sickle cell disease which are major public health problems in India. Two approaches are currently under development – lentiviral vector-based gene transfer approach which is already being evaluated in animal models (RVS/AS - details under the NAHD section) and a novel gene-editing approach using the CRISPR-Cas9 technology for correction of the phenotype of β-thalassemia major and sickle cell disease by altering the expression γ-globin

chains through transcriptional modifications (Saravanabhavan Thangavel and Mohankumar Murugesan) in collaboration with two groups at the University of California, USA.

COVID-19: Srujan Marepally's lab has developed a novel Shikimoylated Mannose Receptor Targeting (SMART) nanoparticle system for delivering mRNAs into dendritic cells for vaccine development, synthesized chemically modified mRNA and validated functionally. The group has also developed tools for COVID-19 research as pseudovirion and human ACE-2 receptor stably expressing HEK-293 cells for in vitro neutralization efficiency of the vaccine. We have successfully demonstrated that the vaccinated animal could produce strong immune responses against spike protein and could neutralize SARS-CoV2 pseudovirus.

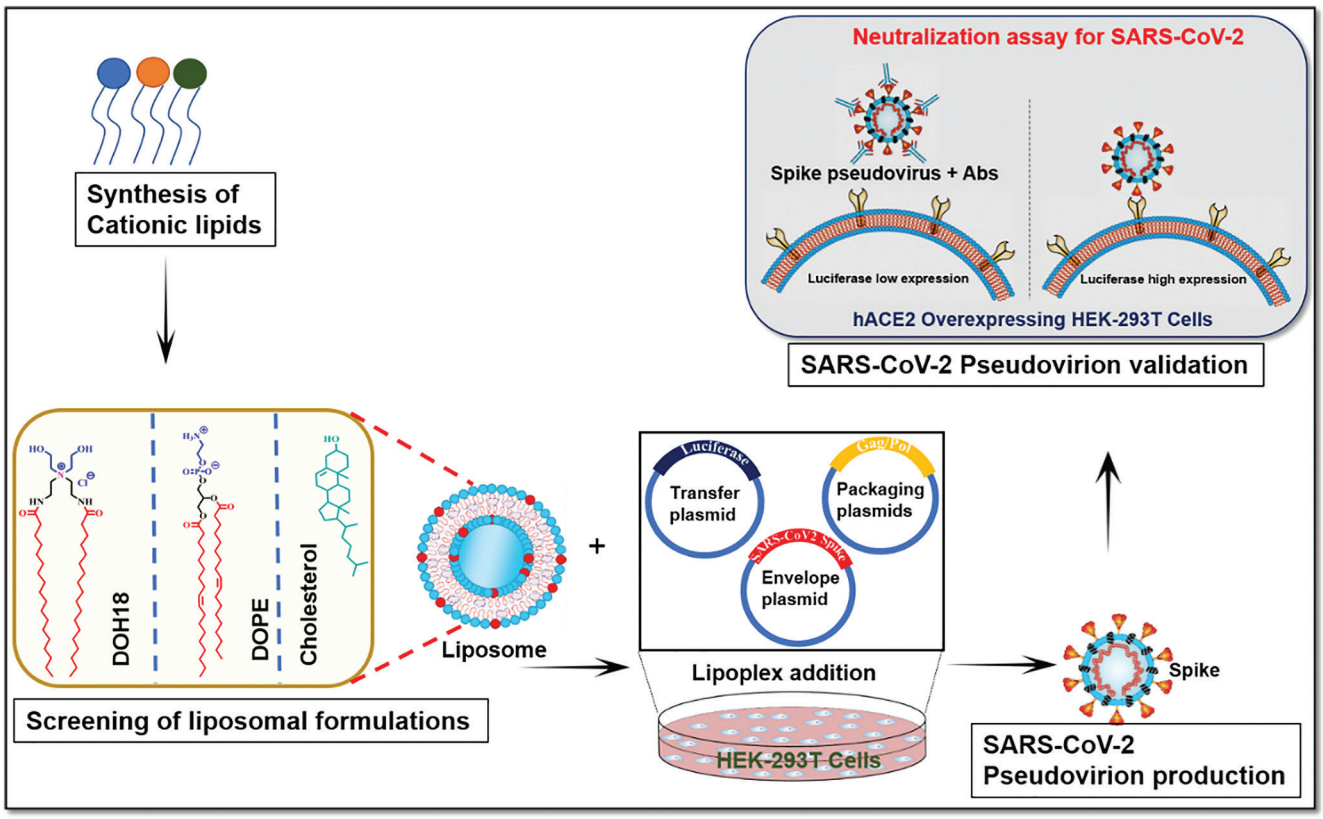


Figure: Schematic presentation of SARS-CoV2 pseudovirus production

Other diseases: Using CRISPR/Cas9 gene editing tools preclinical studies are also ongoing to develop gene correction in Wiskott-Aldrich syndrome (WAS). Gene editing tools and strategies are being tested for the targeted integration of the WAS transgene in the hematopoietic stem cells. Saravanabhavan Thangavel's lab now has now achieved targeted replacement of WAS gene with WAS transgene in HEL cell lines. In addition to the generation of plasmid-based WAS transgene HDR donor, we are also in the process of developing the AAV6 based donor.

Chimeric antigen receptors (CARs) against a cancer antigen are used frequently to engineer patients' T cells to treat cancer; especially the anti-CD19 CAR against B-cell malignancies. With this approach, most of the clinical success was observed among patients with ALL. To generate anti-viral T cells and engineer them with an anti-CD19 CAR construct. The area of immune cell therapy is being coordinated by **Aloukick Singh**.

3. Cellular Reprogramming and its Applications - Disease Modeling and Haplobanking

The area of cellular reprogramming technology is coordinated by **R. V. Shaji** at CSCR along with **Dolly Daniel**. This is now being applied to two areas: ***disease modeling*** and ***haplobanking***. Towards the former, reprogramming technology

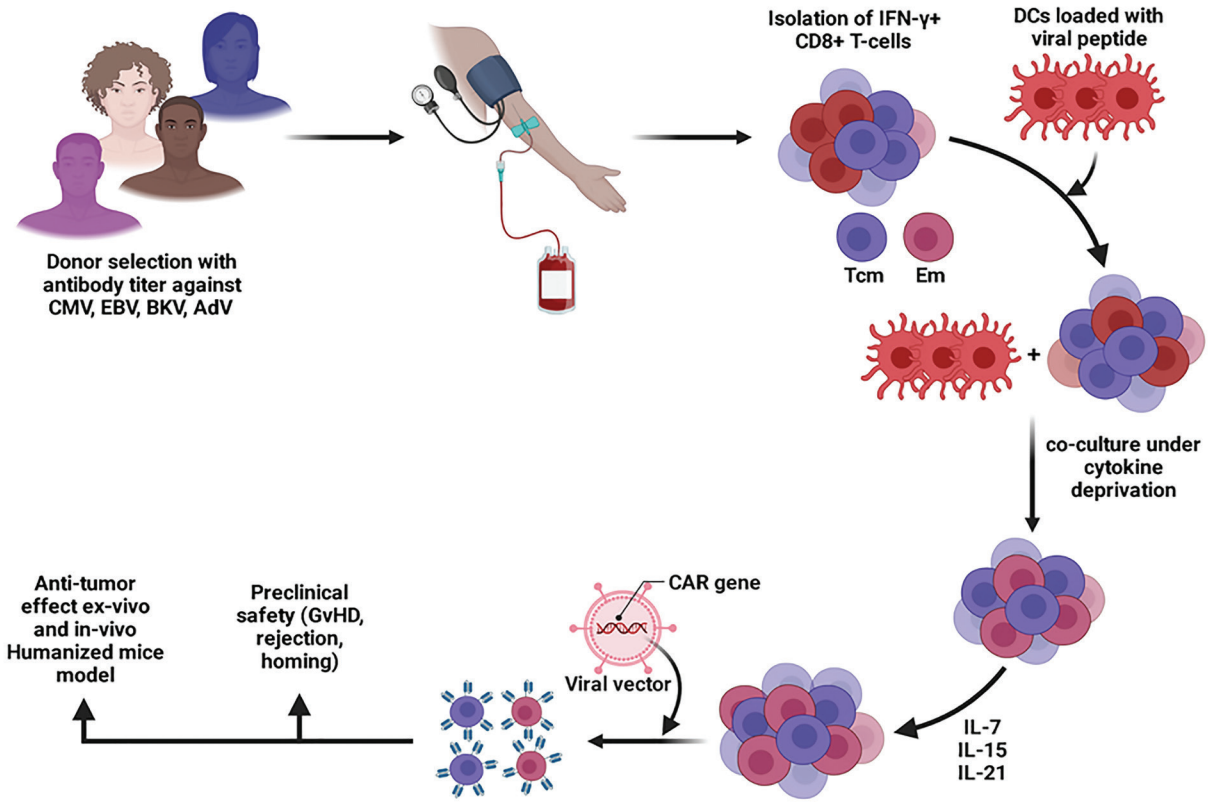


Figure: Protocol for the clinical-grade rapid generation of allo-CAR-T cells from antigen-specific CD8+T(Em+Tcm)

has been applied to the develop disease models of various bone marrow failure syndromes – Fanconi anemia, Diamond Blackfananemia and congenital dyserythropoieticanemia. The models are being used to evaluate disease phenotypes and mechanisms as well as evaluation of gene correction strategies.

A major translational application has been the development of a "haplobank" – cells from HLA haplotype homozygous individuals whose mononuclear cells are being converted into iPSC lines for potential use in regenerative medicine. The field and clinical aspects of procuring these peripheral blood samples through our collaborators, the DATRI unrelated donor registry, represented by Nezih Cereb, is being coordinated by Dolly Daniel. So far 15 GMP cell lines have been produced – one of the largest such collections in the world. This is also being done in collaboration with the international consortium for this effort – Global Alliance for iPSC Therapies (GAiT). More details on the haplobanking project are provided in the NAHD section.

6 Publications and Awards

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Integrative Chemical Biology

Praveen Vemula

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Regulation of Cell Fate

Sunil Laxman

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Minhaj Sirajuddin

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Colin Jamora

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INSTEM AWARDS/HONOURS (APRIL 2021-MARCH 2022)

1. Gaurav Kansagara, a PhD student at inStem won first place - BWF Virtual Poster Award at 25th Annual Woods Hole Immunoparasitology Meeting (WHIP 2022) held at Marine Biological Laboratory (MBL), USA (Participated virtually)-2022

2. Edries Yousaf, a PhD student at inStem, awarded the Scholarship Keystone eSymposium: Innate Immunity - Mechanism and Modulation-2022

3. Edries Yousaf, won third place - BWF Virtual Poster Award at 25th Annual Woods Hole Immunoparasitology Meeting (WHIP 2022) held at Marine Biological Laboratory (MBL), USA (Participated virtually)-2022

4. Edries Yousaf won the Rapid-Fire Talk prize at the Singapore International Skin Conference, organised by the Skin Research Society & the Skin Research Institute of Singapore-2022.

5. Dr. Minhaj Sirajuddin is selected in the 3-year Catalysts program of EMBO Journal-2022

6. Dr. Sunil Laxman, awarded the DBT-Wellcome Trust India Alliance Senior Reseach Fellowship-2022

7. Manisha Goyal, is a recipient of SERB-OVDF (Overseas Visiting Doctoral Fellowship) 2022 fellowship, to conduct research work at Purdue University, USA-2022.

8. Dyuti Saha, a PhD student at inStem won Runner up Award - Professor Obaid Siddiqi Prize 2021 issued by CIFF, BLiSc-2022.

9. Gaurav Kansagara won Best Poster Award at International Conference on Emerging Trends in Biological Sciences (ICETBS), CHARUSAT, India (Participated virtually)-2022.

10. Subhanshini Pandey, a PhD student at inStem won 3 minutes-Thesis Competition in Life Sciences category at “SARANSH”, a National Level Science Communication organized by the Indian Young Academy of Sciencea (INYAS)-2021.

11. Dr. Abrar Rizvi, a postdoctoral fellow, awarded DST SERB-N-PDF (Dec 2021) BIRAC BIG-16 grant-2021.

12. Dr. Tanay Bhatt, a postdoctoral fellow won Innovation Forum (Southeast Asia region)-2021.

13. Edries Yousaf won iBiology Share Your Research Competition-2021.

14. Dyuti Saha received Society of Investigative Dermatology Annual Meeting Registration Grant Award-2021.

7 Patents and Technologies

S.No.	Appln. No.	Filed on	Country	Title	Inventors
1	PCT/ IB2021 /053780IB2 021/053780 IB2021/053780	05.05.2021	PCT	Disease modifying agents, drug delivery system and method thereof for the management of osteoarthritis	Akrit Pran Jaswal, Amitabha Bandyopadhyay, Praveen Kumar Vemula, Manohar Mahato, Bhupendra Kumar
2	202141029243	29.06.2021	India	Molecular markers for infection-induced lung damage	Neha Vyas (St. John's Research Institute) and Apurva Sarin (inStem)
3	202141033290	23.07.2021	India	Formulation, Lipid Compounds And Methods Thereof	Srujan Marepally, Alok Srivastava
4	202241006792	08.02.2022	India	Single-step molding process for fabrication of hollow microneedle array	Ghate V, Renijith A, Badnikar KA, Nataraja Jayadevi S, Pahal S, Vemula PK, Nayak MM, Narasimhaiah Subramanyam D.
5	202241014827	17.03.2022	India	Compositions and methods to enhance the quality and shelf-life of biological materials	Praveen Kumar Vemula, Manohar Mahato, Subhashini Pandey, Preethem Srinath, Utkarsh Bhutani

6	63/251,229		USA	Compositions and methods for treating a b-Thalassemia Disease	David I.K. Martin, Mark DeWitt, Mark C. Walters, Wendy J. Magis, Saravanabhavan Thangavel and Dario Boffelli.
7	202241030885	30-05-2022	India	A method for modification of ß-globin gene	Mohankumar K. Murugesan, Alok Srivastava, Kirti Prasad.
8	202241030465	27-05-2022	India	A method for reactivation of fetal hemoglobin and a composition thereof	Saravanabhavan Thangavel, Alok Srivastava

8 COVID-19 Response Report

inStem's Efforts to Combat COVID-19

The COVID-19 pandemic is having a devastating impact on global public health and crippling socioeconomic consequences. The goal of containing the spread of SARS-CoV-2, the virus causing COVID-19, relies on a comprehensive strategy of rapid testing of the virus in the population, effective treatments, and development of therapeutics to prevent viral infection. As the pandemic was taking hold in India, the Institute for Stem Cell Science and Regenerative Medicine (inStem) recognized the need to rapidly contribute on all these fronts. The swift deployment of the institute's world class research infrastructure and highly skilled personnel has resulted in a broad spectrum of efforts ranging from testing and diagnostics, generating enabling resources to facilitate the understanding of viral infection and progression, and interdisciplinary research programs to find new anti-viral treatments. Altogether, the large breadth of programs contribute significantly in the national efforts to combat SARS-CoV-2 and reduce its detrimental impact on society.

TESTING & DIAGNOSTICS & TRACKING

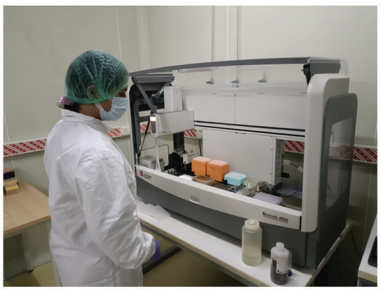
COVID-19 Testing Laboratory

Recognizing the need for aggressive testing in India's battle against COVID-19 inStem and NCBS brought their resources, community and facilities together to set up a testing laboratory. The testing laboratory not only meets the highest standards for safety and ethical management of information, but also emphasizes the overall well-being of the COVID-19 testing team who undergo routine medical checkups and have access to support programs for their mental health. The testing facility has since tested ~ 250,000 samples from throughout the state of Karnataka. These efforts have been buoyed by a combination of central and state funds along with generous philanthropic support to enable free-of-cost testing for COVID-19 to a large number of people from disadvantaged and marginalised communities.

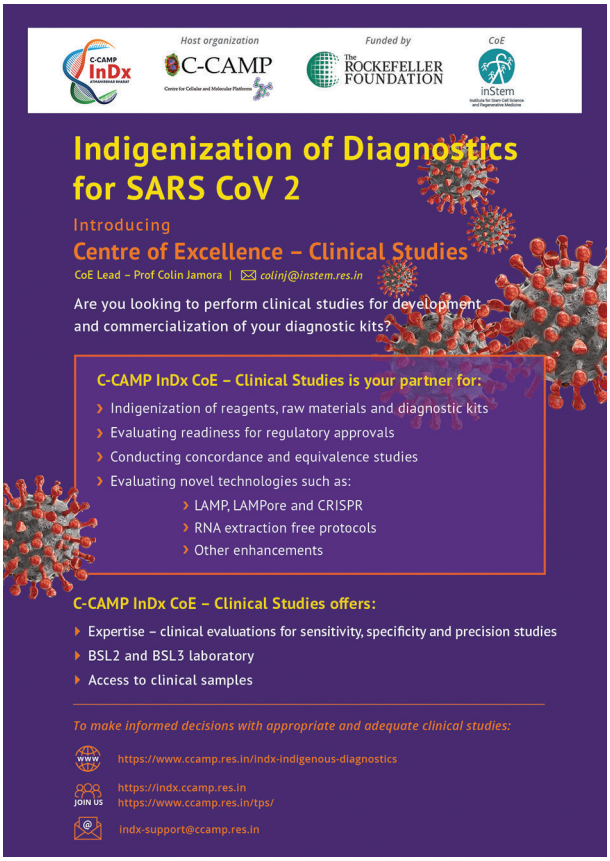
Diagnostic kit evaluation and optimization

As a natural extension of the infrastructure and trained personnel to handle patient samples and to conduct covid testing efficiently, inStem and NCBS have received designation from the ICMR-NIV to serve as a validation centre for new testing kits developed by academic and biotechnology laboratories. The inStem validation centre will use patient samples received through the testing facility to gauge their performance in providing results with the same sensitivity and accuracy as the currently approved testing kits.

Additionally, inStem manages the Centre of Excellence for Clinical Studies of the Indigenisation of Diagnostics (InDx) program, which aims to locally build a large capacity of COVID-19 molecular diagnostic kits and reagents. Thus far, the inStem group has assisted 17 companies in the development


and optimization of 47 kits that are based on multiple technologies including RT-PCR, LAMP, and CRISPR on nasopharyngeal swab and saliva samples. These efforts have significantly contributed to the InDx goal of producing kits to conduct 1,000,000 tests per day at an affordable cost, thereby playing an important role in managing and containing the spread of COVID-19 in India.



INSACOG (Indian SARS-CoV-2 Genomics Consortium)

inStem is a partner in the Indian SARS-CoV-2 Genomics Consortium. This activity builds upon the previous nationwide effort called PAN-INDIA 1000 SARS-CoV-2 RNA Genome Sequencing Consortium, and has completed the sequencing of ~9000 SARS-CoV-2 genomes. INSACOG is locally spearheaded by Dr. Dasaradhi Palakodeti at inStem and is providing important real-time sequence analysis to track the evolution and spread of the virus in the nation that will help guide the public health response to the waves of viral infections. The INSACOG program at inStem and NCBS was the first to identify the Omicron variant in India.

INSACOG
INDIAN SARS-COV-2 GENOMICS CONSORTIUM

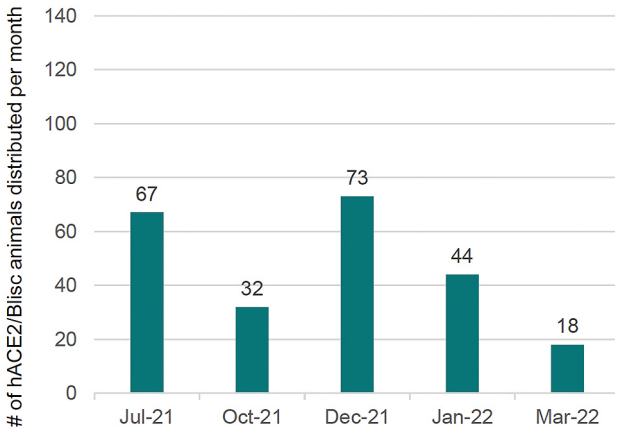
RESEARCH

In addition to the activities to address the immediate public health need to test individuals and control the spread of the virus causing COVID-19, ultimately the cure for the disease will lie in scientific advances to understand how SARS-CoV-2 infects humans and affects different organs of the body.

Generating Mouse Models to Study COVID-19

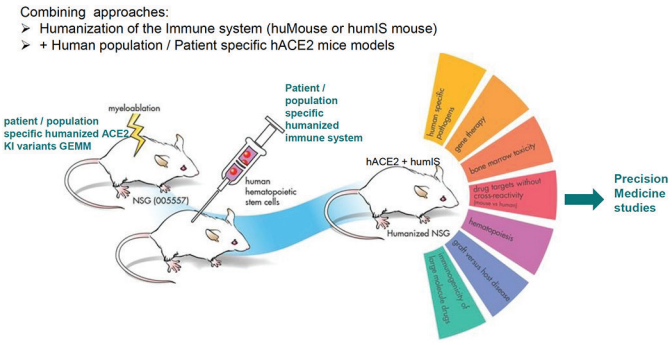
There are no cell culture systems that can reproduce the complex interactions that take place during the pathogenesis of the SARS-CoV-2 virus . These processes affect multiple tissues and has a systemic effect, and inflammation has been shown to be a major contributor to tissue damage. To date there is no in vitro system capable of reproducing these interactions that recapitulate what happens in the human disease. With major support from the National Mouse Resource grant from the DBT, the campus Mouse Genome Engineering Facility and Animal Care and Resource Centre were able to use the state-of-the-art infrastructure and highly skilled personnel to rapidly deploy these resources to generate mouse models of COVID-19 infection. In general, we have generated three so-called “humanized” mice wherein the mice express the human version of

ACE2, thereby rendering the animal susceptible to infection by the SARS-CoV-2 virus. The vector carrying the human ACE2-coding sequence into wild-type mice was developed in the laboratory of Paul McCray at the University of Iowa and obtained through Professor Sudhanshu Vrati from the Regional Centre for Biotechnology. These animals are available to academic and biotech researchers nationwide to facilitate their projects to identify new modes of treating infected patients *(or blocking infection in the first place)* and information can be found at *https://www.ncbs.res.in/research-facilities/acrc*. In collaboration with the Institute of Life Sciences, Bhubaneswar the initial characterization of the locally engineered K18-hACE2 transgenic mice recapitulates the same pathophysiology of the human ACE2 transgenic mouse generated at the Jackson Laboratory in Bar Harbor, Maine. Thus far these mice have been utilized by ILS scientists to develop new therapeutics against COVID and by scientists at the Indian Institute of Science (IISc), Bangalore for the testing of a novel vaccine.



Animal BSL-3 (ABSL-3 Facility)

In partnership with NCBS, inStem are in the process of building animal BSL-3 facility in which challenge studies using the mouse models generated on campus can be performed to test new vaccines and therapies. This project is supported by grants from the DBT and BIRAC and is being designed to meet the strict national and international regulatory requirements of a high end biosafety laboratory. Ongoing plans includes the establishment of the capability to humanize the inflammatory response in the animals to more faithfully recapitulate the pathophysiology of SARS-CoV-2 symptoms in infected patients.



COVID19 Biorepository

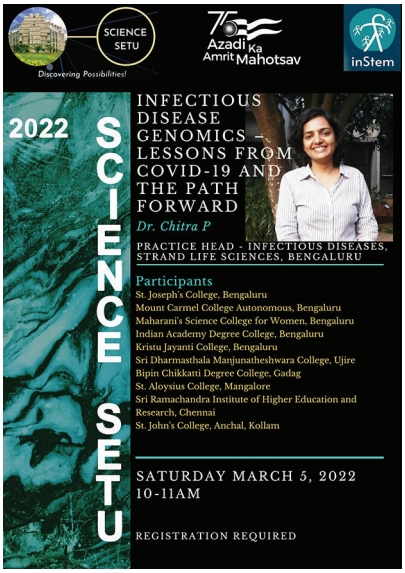
inStem is one of the five dedicated bio-repositories established by the Department of Biotechnology for clinical and viral samples linked to the coronavirus disease (Covid-19). The purpose of this biorepository is to share biological materials from infected patients with clinicians and researchers from the academia and industry to speed up innovations to combat the pandemic. Starting off with the storage of nasopharyngeal and oropharyngeal swab samples, the biorepository has teamed up with Hospitals in Bangalore to grow the collection to include serum (blood), saliva, PBMCs, bronchioaveolar lavages. Though initially projected to collect up to 2000 samples, the biorepository now contains ~9300 samples. These samples are shared with researchers to increase our understanding of the virus, the variability in the severity of symptoms caused by this infection in different individuals, and potential new routes of therapeutic intervention.

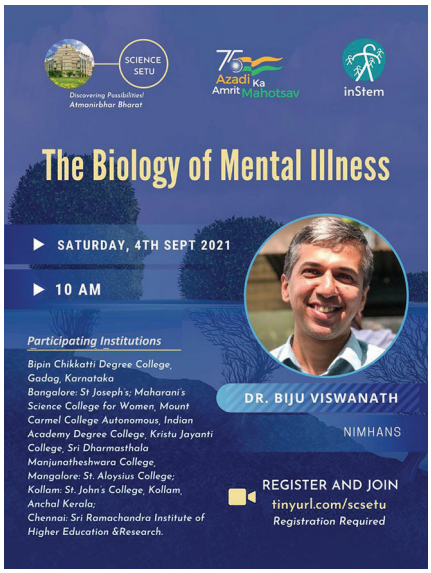
9 Science Outreach and Communication: Report and Activities

Science outreach and communication forms a critical component of DBT-inStem's social engagement with the larger community. The primary goal of our efforts is ***to instill curiosity driven science in the young minds while promoting the value of collaborative research to address real world problems***. Through engagement with schools and colleges and diverse programmes in the form of online webinars, Open Days and regular visits, DBT-inStem's mission is to promote an opportunistic participation that facilitates interactions with the lay public. We provide hands-on interaction in the labs and using 3D models, easy illustrations and student-scientists interactions we aspire to inspire our next generation of young scientists. Owing to the COVID-19 pandemic, digital modes of communication had become a key mode of our engagement in the previous years as this allowed us a wider reach even during the pandemic. We continued to leverage this platform in the past year and as conditions improved we were able to conduct hybrid meetings. Albeit at a much smaller scale, keeping the Covid guidelines in mind, these hybrid meetings reinstated opportunities for personal interactions and engagement with the wider community that was lost in the past years. In the sections that follow, a few events from our repertoire of outreach and communication activities are highlighted.

Engagement with Schools, Undergraduate Colleges and our Communities

The **Science Setu programme**, called ***Discovering Possibilities*** is a celebration of India@75, Azadi Ka Amrit Mahotsav, under the aegis of the Atmanirbhar Bharat campaign. This is an online interactive series, which includes lectures on current, contemporary areas of research being undertaken in laboratories in India, and is presented in a format accessible to college students. Attracting an enthusiastic audience of 150-175 participants, the sessions began in April 2021 and touched on areas ranging from genomes and organ function to the study of populations. Quizzes and virtual lab visits are also planned to keep the offerings diverse and interesting. The sessions are clustered in areas such as "Big lessons from small organisms", "Breaking down complexity", "Communicating Science", "Researching Disease", as well as a "Special Talk Series" by thought leaders in Science, Science Policy, Industry and Heads of Technical Hubs, and these are interspersed with regular sessions on "Careers in Science". This programme has speakers and events planned

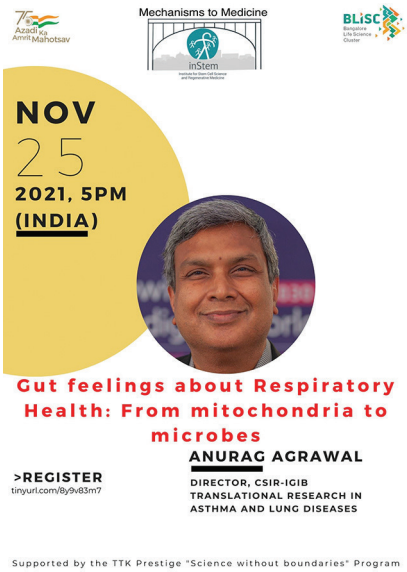


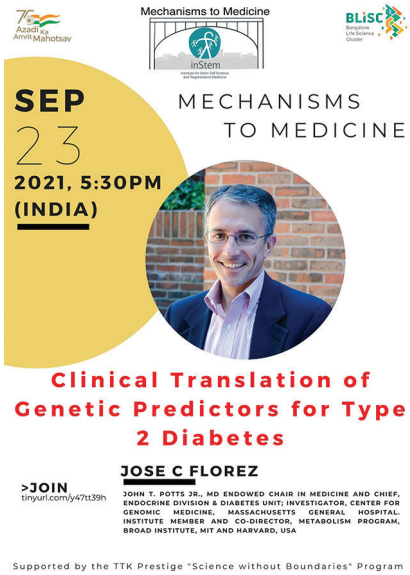


for the next 18 months! The participants are students from colleges in Bangalore, Mangalore, Ujire and Gadag in Karnataka, Chennai (Tamil Nadu) and Anchal (Kerala). Sessions are posted on social media handles, and talks can be accessed on the inStem website *https://www.instem.res.in/dbt-instem-science-setu*

- St. Aloysius College, Mangalore
- St. Joseph's College, Bengaluru
- Mount Carmel College Autonomous, Bengaluru
- Maharani's Science College for Women, Bengaluru
- Indian Academy Degree College, Bengaluru
- Kristu Jayanti College Bengaluru
- Sri Dharmasthala Manjunatheshwara College, Ujire
- Bipin Chikkatti Degree College, Gadag
- Sri Ramachandra Institute of Higher Education & Research, Chenna
- St. John's College, Anchal, Kollam

Supported by TTK Prestige under the "Science without Boundaries" program, the **Mechanisms to Medicine (M2M)**, a monthly seminar series at DBT-inStem was initiated. Coordinated by Dr. Arvind Ramanathan, this series aim at featuring talks on outstanding questions in disease pathogenesis and clinical practices of interest to academics, clinicians and industry. The primary objective was to accelerate the translational impact of efforts at inStem and build collaborations both nationally and internationally.





DBT-inStem, as one of the founding partners of **COVID-Gyan**, a pan-institutional website, continued its COVID-19 outreach efforts through the webinar series **WebGyan**. The series hosted eminent researchers and science communicators as Dr. Shahid Jameel, Prof. Gagandeep Kang, Prof. Sandhya Kaushika and Prof. Vikram Patel. WebGyan focused on the spectrum of topics ranging from immune response to SARS-CoV-2, how it links to protection from disease, exacerbation of the disease, diagnostics in India, implications for therapy, and the future of COVID-19 vaccines.

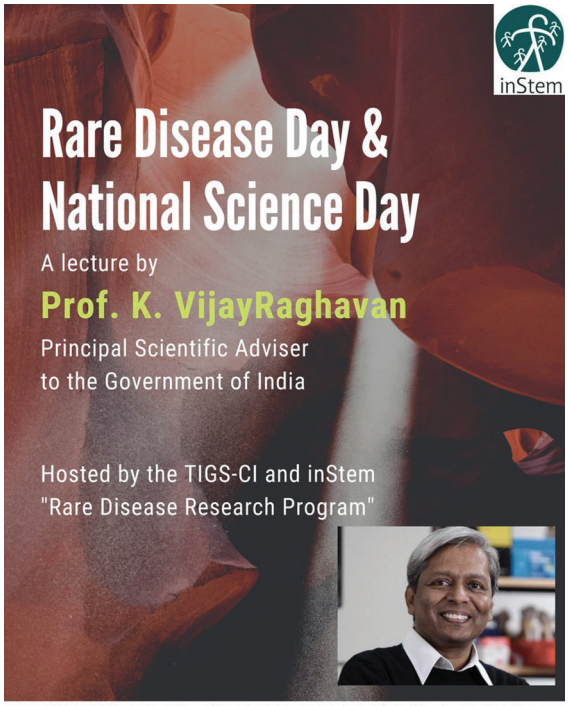
As part of our goals to showcase campus initiative and opportunities that support start up initiatives and propel innovative ideas in the areas of drug discovery and product design, inStem on July 23, 2021, hosted an event 'Launch and Showcase of high impact C-CAMP innovation programs with Govt. of Karnataka'. This took place on BLiSC campus and was inaugurated by Dr. Ashwathnarayan C.N., the Deputy Chief Minister of Karnataka. Attended by a small number of attendees bearing in mind covid-19 restrictions, the event saw entrepreneurs talk about their leading innovations. The unique, scientifically-tested, G-99 and A-99 germicidal fabric developed and designed by the research team led by Dr. Vemula, of DBT-inStem propagated by Color Threads – a C-CAMP incubated start-up was a noteworthy example of #MakeInIndia and #AtmaNirbharBharat campaigns, not the least the inter-institutional collaboration on campus. Allied to a similar initiative, in the month of February, 2022, DBT-inStem with C-CAMP hosted a online mini-symposium showcasing "Innovations and Opportunities at C-CAMP". The symposium saw participation by Pandorum Technologies Pvt Ltd, Boyce Synthetics, Peptris, String Bio and Eyestem.

Image: A researcher from Dr. Vemula's lab showcasing the products made from G-fab technology at the C-CAMP event

National and International Initiatives

As part of inStem and TIGS initiative to lead the "Rare Disease Research Program", on **National Science Day** and **Rare Disease day**, inStem with TIGS-CI hosted a lecture by Prof. K. VijayRaghavan, who was then the preceding Principal Scientific Adviser to the Government of India. This was a webinar and saw attendance by a large number of researchers from institutions across India. His talk focused on the

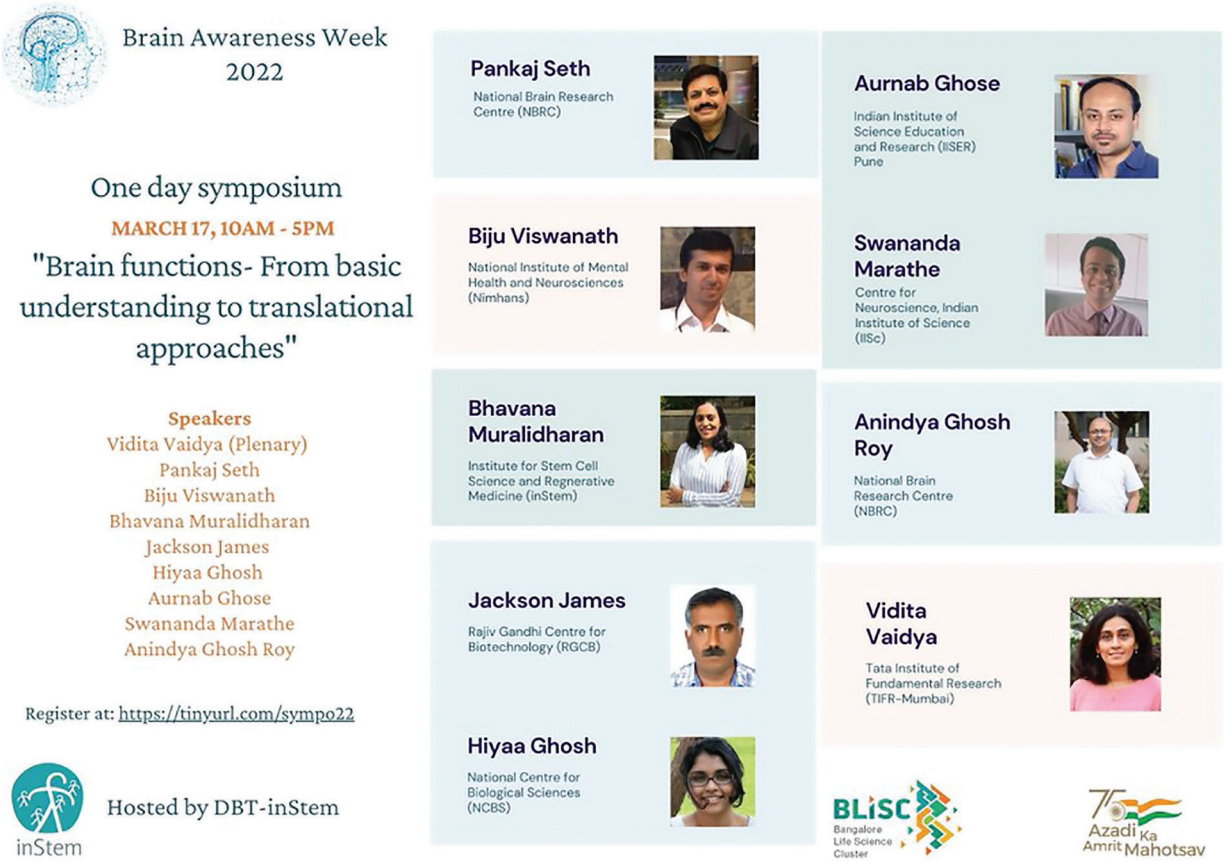
challenges in the rare disease areas, identifying rare diseases, the complexity of treating rare diseases and how institutes can collaborate to accelerate research in this area.



Brain Awareness Week 2022

DBT-inStem hosted a one-day online symposium on March 17, 2022, and **a series of podcasts** with experts in Neuroscience and brain diseases to commemorate Brain Awareness Week 2022. The Symposium was put together to build interactions and new collaborations across institutional boundaries in the country. The Symposium entitled "Brain functions: From Basic understanding to Translational Approaches" organised by Dr. Bhavana Muralidharan, Brain Development and Disease Mechanisms theme, inStem was initiated by Prof. Vidita Vaidya, DBS, TIFR, Mumbai. The speakers in the Symposium included Prof. Pankaj Seth, DBT-NBRC, Dr. Biju Viswanath, NIMHANS, Dr. Bhavana Muralidharan, DBT-inStem, Dr. Jackson James, DBT-RGCB, Dr. Hiyaa Ghosh, NCBS-TIFR, Dr, Swananda Marathe, IISc, and Dr. Anindya Ghosh Roy, DBT-NBRC. Link: *https://soundcloud.com/dbt_instem*

To strengthen our collaborations and correspondence in Indo-French relations, the communications office hosted the French delegation composed of researchers from the University of Bordeaux, Perfume School ISIPCA and members of the cosmetic corporation



"Cosmetic Valley" on March 21, 2022. It was an introductory visit to learn more about their projects and inform them about research at DBT-inStem concerning natural products and health.

Outreach: Celebrating Days, Promoting Exhibits And Social Media Events

Apart from our scientific outreach endeavors, inStem's vision is also to promote a general sense of awareness within the society and of this a key mission is to promote women empowerment. To this end, DBT-inStem commemorated **International Day for Women and Girls in Science** (February 11, 2022), where we hosted Dr. Susmita Mohanty, a spaceship designer, a serial space entrepreneur and a climate ambassador. She delivered the talk "Born to Explore" where she spoke about her life's journey to where she stands today and plays a vital role in India's space mission. We also hosted Priyanka Mohite and Munmun Dhalaria in a webinar entitled, "Expanding boundaries" to celebrate International Women's day, 8th March 2022,. Priyanka Mohite, the first Indian woman to climb Mount Annapurna and a recipient of 'Tenzing Norgay National Adventure 2021' award along with Munmun Dhalaria, a NatGeo Explorer and the director of Moon Peak Films in India talked about their personal journeys and their motivations to pursue careers in their respective fields. These events were attended by the much larger scientific and non-scientific communities nationally and saw students, scientists and staff from IISERs, universities, IISC, JNCSAR and other institutes. The webinars saw active participation from both scientific and non-scientific staff and the sessions brought together a platform that discussed opportunities to drive women empowerment and safe practices in our working environment.

The use of art as the language to communicate science is a key goal of our outreach activities

and showcase this aspect of our scientific community, DBT-inStem organized an art display event on 15th August 2021, as we part of our Independence Day celebrations. Partnering with NCBS, CCAMP, other institutions of the Bangalore Life Science Cluster the campus celebrated the 75th Independence Day. The art event saw contributions by scientists, students, and researchers, which showcased local talent and also bringing a splash of colour to the day. DBT-inStem, also commemorated Hindi Diwas, by organizing a virtual event. An essay competition on the topic **'Covid-19 pandemic and Science'** was organized in collaboration with Bangalore Life Science Cluster (BLiSC) via e-submission. This was followed by a talk on September 15, 2021, where the chief guest - Dr. Rakesh Sharma, Senior Hindi Officer at CSIR-NIO (National Institute of Oceanography) Goa, spoke on an intriguing topic titled **'Hindi ki Dasha and Disha'.**

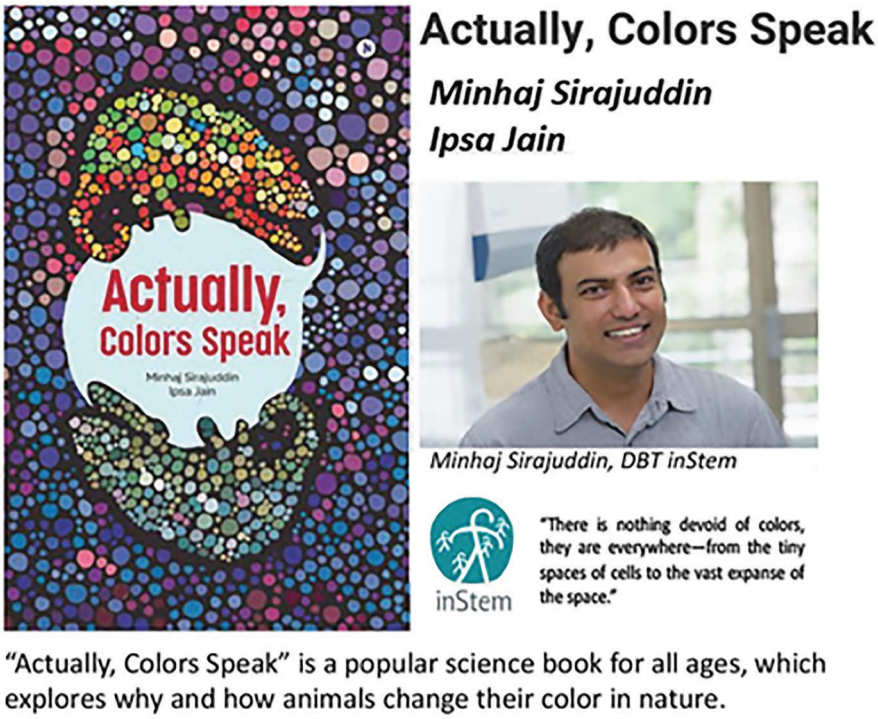
Media and Public engagement

An initiative led by Dr. Sirhajudin of inStem, where the medium of documentary film making was opted to educate and excite the lay audiences with key scientific discoveries made by Indian researchers. He was the driver of the documentary film **"Written Out Of History- Forgotten Indian Scientists"** which was produced by DBT inStem, in collaboration with DBT-WT India Alliance and Moon Park Films.

The movie was screened on March 25, 2022 by DBT-inStem. The documentary 'Written Out of History- Forgotten Indian Scientists' celebrates eminent figures, Sipra Guha, Sambhu Nath De and Obaid Siddiqui, who are from the Indian Scientific community and have shaped our future in elemental ways. Following the movie screening, the event saw a panel discussion with the crew members that included producers of the movie, Dr. Minhaj Sirajuddin, DBT-inStem, Munmun Dhalaria, director of Moon PeakFilms, Ruth Lobo, film editor, cinematographer Ram Alluri, scriptwriter Meghna Nandy, a biomedical illustrator and animator Shraddha Nayak and the manager of science Communications and public engagement for DBT/Wellcome Trust India Alliance Nicolette Jadhav.

Dr. Minhaj Sirajuddin collaborative efforts with freelance illustrator Dr. Ipsa Jain to create a book **'Actually Colors Speak'** saw its launch at the India Science Fest 2022 (#ISF2022). This fully illustrated book explains through conversations between a camera, a binocular, and a microscope - that try to understand the wonderful world of colors in animals.

These initiatives at inStem have led to establishment of many interactive sessions and social media engagement platforms. The use of media in particular has been effective in communicating the wealth of scientific research and its impact on the general public and overall has bolstered our outreach to the much larger audiences nationally and internationally.



"Actually, Colors Speak" is a popular science book for all ages, which explores why and how animals change their color in nature.

10 Graduate Thesis Awarded

1. 

Name: Sudhriti Dastidar
Registered University: MAHE
Thesis Guide: Ravi Muddashetty
Thesis Title: Bioenergetics of glutamate receptor-mediated protein synthesis
Date of thesis awarded: 11/02/2021

2. 

Name: Bhakti Vyas
Registered University: MAHE
Thesis Guide: Ramkumar S
Thesis Title: Genetic program regulating vertebrate mesoderm development along anterior-posterior axis
Date of thesis awarded: 17/02/2021

3. 

Name: Aritra Misra
Registered University: MAHE
Thesis Guide: Ramkumar S
Thesis Title: Function of T-box transcription factor Tbx6 in vertebrate development: Regulation of left-right asymmetry patterning and mesoderm formation during axial elongation
Date of thesis awarded: 25/02/2021

4. 

Name: Shubham Kesarwani
Registered University: MAHE
Thesis Guide: Minhaj Sirajuddin
Thesis Title: Spatial and temporal organization of microtubule posttranslational modifications
Date of thesis awarded: 24/05/2021

5. 

Name: Sukanya Madhwal
Registered University: MAHE
Thesis Guide: Tina Mukherjee
Thesis Title: Metabolic control of immune cells in Drosophila
Date of thesis awarded: 30/08/2021

6. 

Name: Zeenat Rashida
Registered University: MAHE
Thesis Guide: Sunil Laxman
Thesis Title: Roles of Kog1/Raptor in maintaining metabolic homeostasis under fluctuating nutrient environments
Date of thesis awarded: 23/11/2021

7. 

Name: Neetu
Registered University: MAHE
Thesis Guide: Apurva Sarin
Thesis Title: Spatial regulation of Notch family proteins underpins anti-apoptotic activity
Date of thesis awarded: 22/03/2022

8. 

Name: A. Radhika Rao
Registered University: SASTRA University
Thesis Guide: Shravanti Rampalli
Thesis Title: Understanding the Role of Histone Methyl Transferases in Development and Aging
Date of thesis defended: 15/4/2021

9. 

Name: Ananya Mukherjee
Registered University: SASTRA University
Thesis Guide: Akash G
Thesis Title: Visualizing Spatio Temporal protein Activation and dynamic signal integration with engineered fluorescent Biosensors
Date of thesis defended: 16/07/2021

10. 

Name: Bharti Nawalpuri
Registered University: SASTRA University
Thesis Guide: Ravi Muddashetty
Thesis Title: The role of miRISC protein GW182 in dendritic development
Date of thesis defended: 21/02/2022

11. 

Name: Mohamed M
Registered University: SASTRA University
Thesis Guide: Praveen Vemula
Thesis Title: Advanced methods for isolation and characterization of pluripotent stem cells from planariaSchmidtea mediterranea
Date of thesis defended: 10/03/2022

12. 

Name: Ritusree Biswas
Registered University: SASTRA University
Thesis Guide: Srikala Raghavan
Thesis Title: Role Of Adhesion Molecules in Regulating the Quiescence of Hair Follicle Stem Cells
Date of thesis defended: 26/04/2022

13. 

Name: Oindrila Bhattacharjee
Registered University: SASTRA University
Thesis Guide: Srikala Raghavan
Thesis Title: Elucidating the Functions of Embryonic Macrophages during Sterile Inflammation and Skin Development
Date of thesis defended: 15/06/2022

14. 

Name: Sarayu R
Registered University: TDU
Thesis Guide: Ravi Muddashetty
Thesis Title: APOE4 affects basal and NMDAR mediated protein synthesis in neurons by perturbing calcium homeostasis
Date of thesis awarded: 13/05/2021

15. 

Name: Shreya Sharma
Registered University: TDU
Thesis Guide: Sumantra Chattarji
Thesis Title: Characterization of the electrophysiological properties of human pluripotent stem cell derived neurons (hPSC) from Fragile X Syndrome patients
Date of thesis awarded: 11/08/2021

11 inStem Leadership Committees 2021-2022

DIRECTOR

- **Prof. Apurva Sarin,** Director, inStem, Bengaluru (upto February 2022)
- **Dr. K. Thangaraj,** Director (Additional Charge, inStem) (from 1st March 2022 to 19th August 2022)

SOCIETY

- **Dr Jitendra Singh,** Union Minister for Science and Technology, New Delhi - President
- **Dr. C. N. Ashwath Naraya**n, Minister in-charge of the Department handling Biotechnology in Karnataka
- **Dr Rajesh S Gokhale,** Secretary to the Government of India, Department of Biotechnology, Ministry of Science & Technology
- **Prof. Ravichandran,** Secretary DST, New Delhi
- **Dr. Shekhar C. Mande,** Director General, CSCR and Secretary DSIR, New Delhi
- **Dr. E. V. Ramana Reddy,** Principal Secretary-in-charge of the of the Department handling Biotechnology in Karnataka
- **Shri Sunil Kumar,** Joint Secretary Administration, DBT, New Delhi (till 27th Mar 2022)
- **Mr. Chaitanya Murti,** Joint Secretary (Admin), DBT, New Delhi (from 28th Mar 2022)
- **Shri Vishvajit Sahay,** Financial Advisor, DBT, New Delhi
- **Prof. Sharath Chandra,** Hon. Director, Centre for Human Genetics, Bengaluru
- **Dr. Kiran Mazumdar-Shaw,** Chairperson & Managing Director, Biocon India Ltd., Bengaluru
- **Prof. Goverdhan Mehta,** Former Director, IISc & CSIR Bhatnagar Fellow, Hyderabad
- **Prof. P. Balaram,** Former Director, IISc, Bengaluru
- **Dr. Jyotsna Dhawan,** Chief Scientist, CCMB, Hyderabad
- **Prof. Satyajit Mayor,** Centre Director, NCBS, Bengaluru
- **Prof. Apurva Sarin,** Director, inStem, Bengaluru (till Feb 2022)– Member Secretary
- **Dr. Thangaraj K,** Director (Addl. Charge), inStem & Director, CDFD, Hyderabad

GOVERNING COUNCIL

- **Dr. Renu Swarup,** Secretary to the Government of India, DBT, New Delhi (till Oct 2021)
- **Dr. Rajesh S Gokhale,** Secretary to the Government of India, DBT, New Delhi-Chairperson (from Nov 2021)
- **Prof. Apurva Sarin,** Director, inStem, Bengaluru (till Feb 2022)
- **Dr. Thangaraj K,** Director (Addl. Charge), inStem & Director, CDFD, Hyderabad (from Mar 2022)
- **Mr. Vishvajit Sahay,** Additional Secretary & Financial Advisor, DBT, New Delhi
- **Dr. Alka Sharma,** Senior Adviser/Scientist H, DBT, New Delhi
- **Shri Sunil Kumar,** Joint Secretary Administration, DBT, New Delhi (till 27th Mar 2022)
- **Mr. Chaitanya Murti,** Joint Secretary (Admin), DBT, New Delhi (from 28th Mar 2022)
- **Dr. Kalaivani Ganesan,** Scientist 'E', DBT, New Delhi (till 12th Jan 2022)

- **Dr. Sangita M Kasture,** Scientist 'F', DBT, New Delhi (from 13th Jan 2022)
- **Dr. Arvind Ramanathan,** Head-Research, inStem, Bengaluru
- **Dr. Dasaradhi Palakodeti,** Scientist-F, inStem, Bengaluru
- **Prof. Satyajit Mayor,** Centre Director, NCBS-TIFR, Bengaluru
- **Dr. J. V. Peter,** Director, CMC, Vellore
- **Dr Ramakrishnan,** Director, TIFR, Mumbai
- **Dr Vidita A. Vaidya,** Professor, TIFR, Mumbai
- **Dr. Gagandeep Kang,** Dept. of Gastroenterology, CMC, Vellore
- **Dr. Soniya Nityanand,** Director, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow
- **Dr. Dinakar M Salunke,** Director, ICGEB, New Delhi
- **Mr. Ramanathan K,** Head-Admin & Finance, inStem, Bengaluru (Non-member Secretary)

SCIENTIFIC ADVISORY COMMITTEE

- **Prof. B Ravindran,** Professor Emeritus and Former Director, Institute of Life Science (DBT-ILS), Bhubaneswar – Chairperson
- **Prof. Alejandro Sánchez Alvarado,** Howard Hughes Medical Institute, Stowers Institute for Medical Research, USA
- **Prof. Gagandeep Kang,** Dept. of Gastroenterology, CMC, Vellore and Former Executive Director, DBT-THSTI, Faridabad
- **Dr. Satyajit Rath,** Indian Institute of Science Education and Research (IISER), Pune
- **Dr Dinakar Salunke,** International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi
- **Prof. Helen Skaer,** Emeritus Professor of Developmental Biology, University of Cambridge, UK
- **Prof. Mriganka Sur,** Newton Professor, Simons Centre for the Social Brian, MIT, Harvard, USA
- **Dr. K Thangaraj,** Centre for DNA Fingerprinting and Diagnostics (DBT-CDFD), Hyderabad
- **Prof. Vidita Vaidya,** Department of Biological Science, Tata Institute of Fundamental Research (TIFR), Mumbai
- **Prof. Umesh Varshney,** J. N. Tata Chair Professor, Dean, Faculty of Science, Indian Institute of Science (IISc), Bangalore

FINANCE COMMITTEE

- **Mr. Vishvajit Sahay,** Additional Secretary & Financial Advisor – Chairperson
- **Dr Alka Sharma,** Senior Adviser/Scientist'H', New Delhi
- **Prof. Apurva Sarin,** Director, inStem, Bengaluru (till Feb 2022)
- **Dr. Thangaraj K,** Director (Addl. Charge), inStem & Director, CDFD, Hyderabad (from Mar 2022)
- **Dr. M. Krishna Murthy,** Joint Registrar (Finance), IISc, Bengaluru
- **Mr R. Shivakumar,** Sr. Head, IAW, Dept. of Space, Bengaluru
- **Prof. Alok Srivastava,** Head-CSCR, CMC, Vellore
- **Dr. Thangaraj K,** Director, CDFD, Hyderabad
- **Mr. Ramanathan K,** Head-Admin & Finance, inStem, Bengaluru (Member Secretary- from March 2021)

12 In Memoriam

P Ranganath
Security Guard
Years of Service: 2
Date of Death: 01.04.2021

M N Muniraju
Supervisor (Housekeeping Services)
Years of Service: 20
Date of Death: 22.10.2021

Manjunatha A
Outsourced Contract (HVAC)
Years of Service: 3+
Date of Death: 24.02.2022

Madhu L
Housekeeping Staff
Years of Service: 3
Date of Death: 02.07.2022

13 New Appointments

Sudarshan Gadadhar

Sudarshan Gadadhar received his MSc in Biochemistry from the Dayananda Sagar College of Arts, Science and Commerce, Bangalore University. In 2007, he joined the Department of Biochemistry, Indian Institute of Science, Bangalore for his PhD, working on developing immunotoxins for targeted cancer therapy. In 2014, he moved to Institut Curie, Paris, France for his postdoctoral research, where he studied the role of tubulin posttranslational modifications in regulating the structure and function of mammalian cilia and flagella.

His study focussed on a specific tubulin modification, glycylation, that is exclusive to cilia and flagella. He established that primary cilia are also glycylated, an enigma till that time. In an interdisciplinary study, he also established the first molecular role for glycylation in mammalian sperm, which has important implications in male fertility. His work at inStem will focus on the study of how tubulin posttranslational modifications impact functions of primary cilia and their signalling pathways, thus controlling organ function and tissue homeostasis.

Diya Binoy Joseph

Diya Binoy Joseph is a faculty member (Fellow E/Scientist D) at the Centre of Inflammation and Tissue Homeostasis, inStem. She completed her B.Tech in Biotechnology from the National Insitute of Technology, Calicut in 2013. Following this, she obtained a PhD in Cellular and Molecular Biology in 2018 from the University of Wisconsin-Madison training with Dr. Chad Vezina. During her PhD, she worked on prostate development and novel mechanisms of bladder regeneration. She did her postdoctoral training with Dr. Douglas Strand at UT Southwestern Medical Center in Dallas working on single cell and spatial transcriptomics approaches to understand cellular heterogeneity in the healthy and diseased prostate. Diya joined inStem in January 2022. Her lab investigates the role of novel cell types in the urethral lining during urinary tract infections.

Mahesh Sahare

Dr. Mahesh Sahare joined as Fellow-E/Scientist-D at inStem, Banglore. He is a veterinary science professional specialized in Animal Genetics and Breeding from Nagpur Veterinary college, MAFSU university, Nagpur, Maharashtra.

He was awarded the MEXT Fellowship to pursue Ph.D in JAPAN. Mahesh completed his PhD in Reproductive Biology from Kyoto University, JAPAN. His work was focussed on the establishment of spermatogonial stem cells line in bulls for generation of male mediated transgenesis in livestock.

In 2016, Mahesh joined the Indian Institute of Science Education & Research IISER Pune to established and lead the transgenic facility with support from Department of Biotechnology, Ministry of Science and Technology, (grant number BT/INF/22/SP17358/2016). During this time Mahesh had the opportunity to go for training in genome editing technologies and model generation in rodents at the Transgenic Core, University of Alabama, USA.

Currently, He will be responsible for the management and coordinating operations of the Mouse Genome Engineering Facility.

Vineetha Raghavan

Dr. Vineetha Raghavan is a trained scientist with more than 10 years of experience in research management and administration. Dr. Raghavan obtained her PhD in Life Sciences from ICGEB/JNU, New Delhi in 2004 with specialization in plant virology. After completing 6 years of postdoctoral training in Memorial Sloane Kettering Cancer Centre, New York, and Yale University, School of Medicine, respectively she returned to India in 2010 and joined the Research Development Office (RDO) - a single office for scientific administration for the combined campus of the Bangalore Life Science Cluster, as a Grants Adviser.

She currently heads the Grants Management and Research Collaborations Team of the Research Development Office. Her responsibilities include strategic grants advise, bid development, operations management, strategy formulation, global engagement, management of GoI clearances for international funding or collaboration, managing grant contracts and collaborative research agreements and developing institutional policies impacting grants and development of the Team RDO. She is also actively involved in outreach to different funding agencies and in organising and participation in grant writing/ funding/science career workshops.

Sandya Rani B

Dr. Sandya Rani is currently working as Scientist-D at CSCR, managing the Flow cytometry and Molecular imaging core facilities involving the following responsibilities:

Applications support: Offer assistance in initial experiment planning, panel design and optimization of flow cytometry and imaging experiments. Assist with data analysis, interpretation, and data management. Provide technical advice on experimental methods related to flow cytometry and imaging.

Training: Providing training to the students and faculty on various flow cytometry and imaging instruments and related software. Conducting training and education programs on microscopy and flow cytometry applications. Conducting extensive training module on FlowJo and Kaluza flow cytometry offline data analysis software and on image processing software to the users.

Facility Management Tasks: Scheduling and prioritizing instruments bookings to ensure adequate coverage. Coordinate with the Infrastructure

team and other members of the facility to ensure smooth running of the facility and support users.

System Maintenance and Support: Overseeing all technical aspects and day-to-day management of Microscopy and Flow cytometry facility. Troubleshoot problems with instruments especially microscopes and flow cytometers. Communicating with the company personnel and service engineers for instrument servicing and maintenance. She worked as Scientific Officer CSCR managing core flow cytometry and imaging facilities for 4 years prior to joining as Scientist-D.

Educational Background: Dr. Sandya Rani obtained her B.Sc., in Microbiology, Biochemistry and Chemistry from Sri Lakshmi Narasimha College, Palluru and M.Sc., in Applied Microbiology from VIT, Vellore. She obtained PhD in Microbiology from Christian Medical College, Vellore, did Post-Doctoral Fellowship at CMC and TUFTS university in the Tufts University and Tufts Medical Center (Tufts)- Christian Medical College (CMC) Framework Program for Global Health Innovation.

Ketan Vilas Thorat

Ketan obtained his Masters (M.Sc. Biotechnology) from the Indian Institute for Technology (IIT), Bombay, and his Ph.D. in Biological Sciences from the Institute for Stem Cell Sciences and Regenerative Medicine (inStem), Bangalore. During Ph.D., he developed platform technologies to alleviate pesticide-induced neurotoxicity in farmers. His Ph.D. work was awarded the Gandhian Young Technological Innovation Award-2019 conferred by the Hon'ble Vice President of India. He has served as Scientist 'C' at the Department of Biotechnology (DBT), Ministry of Science and Technology, Govt. of India between June 2019 to March 2022. During his tenure at DBT, he was the nodal officer for International Cooperation where he managed partnerships with various countries in Asia, Europe, North America, and South America.

He was trained as a Climate Reality Leader by Nobel Laurette Mr. Al Gore at Brisbane in 2019 under the Climate Reality Project.

Ketan joined inStem as Scientist D- Regulatory Compliance Officer in April 2022. His office advises the researchers on the Bangalore Life Sciences Cluster (BLiSC) about the regulatory requirements and facilitates the process of obtaining due approvals from institutional and national statutory committees.

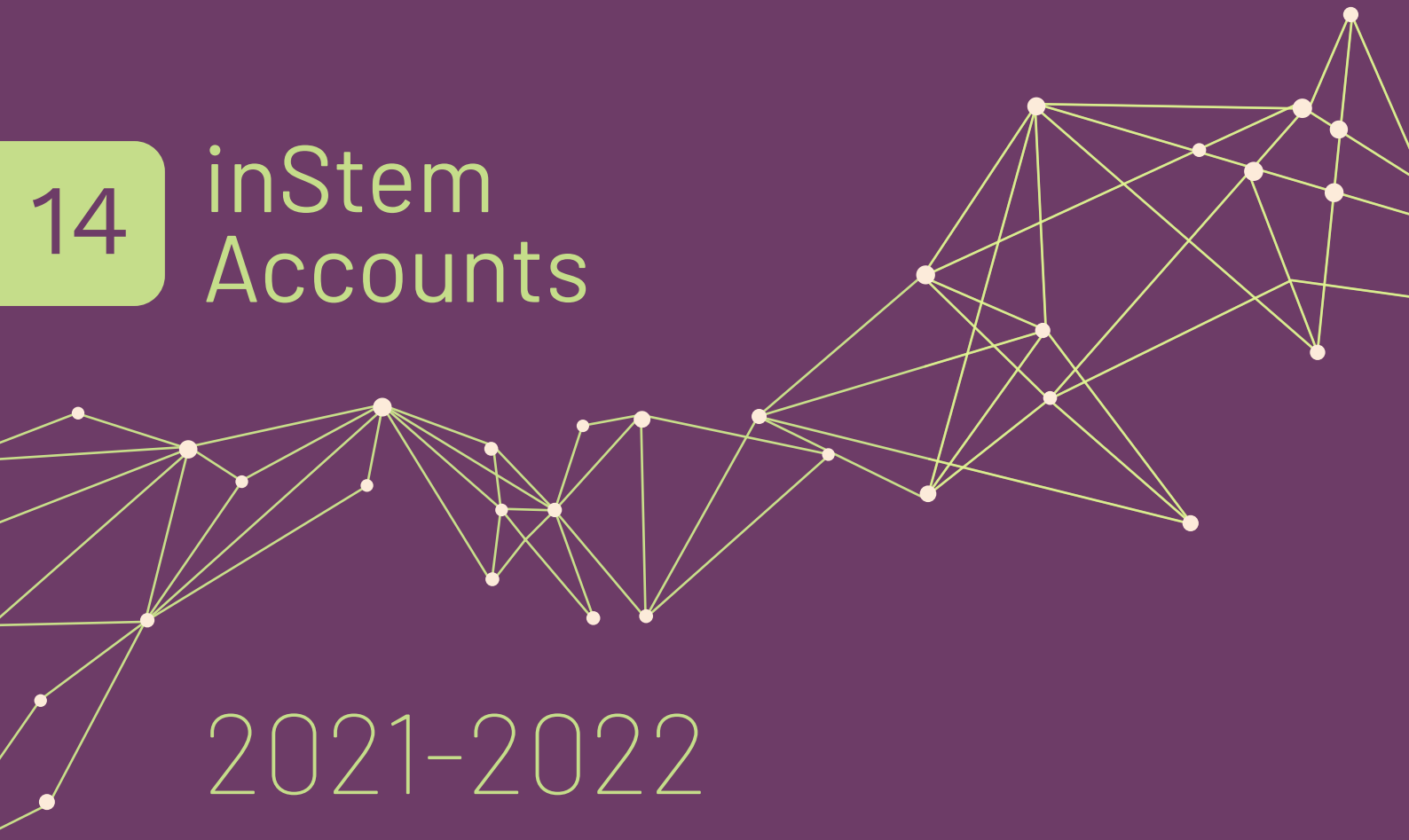
Sabuj Bhattacharyya

Sabuj Bhattacharyya recently joined inStem as Scientist and Research Ethics and Integrity Officer at inStem, Bangalore. He is leading the The Research Ethics, Integrity and Documentation office (RIO) at inStem, Bangalore and Bangalore Life Science Cluster (BLiSc) campus to provide support to various stakeholders for ensuring ethical and responsible conduct of research across various fields of life science research.

He has received training in field ecology during his doctoral degree tenure at Wildlife Institute of India, Dehradun, and the University of Colorado, Boulder (through CSIR and Nehru Fulbright Doctoral Fellowship) as well as during postdoctoral tenure at Indian Institute of Science, Bangalore, and the University of Sheffield, UK (through DBT RA and British Commonwealth Fellowship). Sabuj has also received training in policy evaluation, systematic review and meta-analysis from Bangor University, Wales, UK (through RaviSankaran Inlaks fellowship). Prior to joining inStem, he worked as a grant adviser at leading Indo-UK funding agency, DBT-Wellcome Trust India Alliance. He is currently serving as a member of Commonwealth Scholarship Commission Advisory Panel (2021-2023), UK and member of Species Survival Commission at International Union for Conservation of Nature (IUCN), Switzerland.

14

inStem Accounts



2021-2022

B.P.RAO & CO.
CHARTERED ACCOUNTANTS

No.5, POORNA PRASAD ROAD,
HIGH GROUNDS, BANGALORE –560 001.
PH : 22200200, 22200201,29903200
E-MAIL: bpraoco@gmail.com
Website: bpraoco.com

INDEPENDENT AUDITOR'S REPORT

To,
The Members
Governing Council of
M/s. Institute for Stem Cell Science and Regenerative Medicine
Bangalore-560065

Report on the Audit of the standalone Financial Statements

Opinion

We have audited the financial statements of "Institute for stem Cell Science and Regenerative Medicine", which comprises the Balance Sheet as at 31st March 2022, the Income and Expenditure Account and Receipts and Payment account for the year then ended, and notes to the financial statements, including a summary of significant accounting policies.

In our opinion and to the best of our information and according to the explanations given to us, the accompanying financial statements give a true and fair view of the financial position of the Institute as at 31st March 2022, of its financial performance and Receipts and Payments for the year ended in accordance with the Accounting Standards issued by the Institute of Chartered Accountants of India (ICAI).

Basis forOpinion

We conducted our audit in accordance with the Standards on Auditing (SAs) issued by ICAI. Our responsibilities under those Standards are further described in the Auditor's Responsibilities for the Audit of the Financial Statements section of our report. We are independent of the entity in accordance with the Code ofEthics issued by ICAI and we have fulfilled our other ethical responsibilities inaccordance with the Code of Ethics. We believe that the audit evidence we haveobtained is sufficient and appropriate to provide a basis for our opinion.

Emphasis of Matter

We draw attention to Note no 1.4 under Schedule 25, where the contingent liability to the extent of Rs.3.48 crores and Rs.80 lakhs in the form of claims from contractors on the executing agency (NCBS-TIFR) in respect of construction of Instem Building is reported.

Our opinion is not modified in respect of this matter

Other Matter

We have not audited the financial statements of CSCR at Vellore, whose financial statements reflect total assets of Rs.14.19 crore, total revenue of Rs.6.48 crore and excess of expenditure over income of Rs.1.51 crorefor the year ended as on 31-03-2022. These financial statements have been audited by other auditor whose reports have been furnished to us by the Management.

Responsibilities of Management and Those Charged with Governance for the Financial Statements

Management is responsible for the preparation of the financial statements in accordance withgenerally accepted accounting principles in India. This responsibility includes the design, implementation and maintenance of internal control relevant to the preparation and presentation of the financial statements that give a true and fair view and are free from material misstatement, whether due to fraud or error.

In preparing the financial statements, management is responsible for assessing the entity's ability to continue as a going concern, disclosing, as applicable, matters related to going concern and using the going concern basis of accounting unless management either intends to liquidate the entity or to cease operations, or has no realistic alternative but to do so.

Those charged with governance are responsible for overseeing the entity's financial reporting process.

Auditor's Responsibilities for the Audit of the Financial Statements

Our objectives are to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement, whether due to fraud or error, and to issue an auditor's report that includes our opinion. Reasonable assurance is a high level of assurance, but is not a guarantee that an audit conducted in accordance with SAs will always detect a material misstatement when it exists. Misstatements can arise from fraud or error and are considered material if, individually or in the aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of these financial statements.

As part of an audit in accordance with SAs, we exercise professional judgment and maintain professional skepticism throughout the audit. We also:

• Identify and assess the risks of material misstatement of the financial statements, whether due to fraud or error, design and perform audit procedures responsive to those risks, and obtain audit evidence that is sufficient and appropriate to provide a basis for our opinion. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the override of internal control.

• Obtain an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control.

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• Evaluate the appropriateness of accounting policies used and the reasonableness of accounting estimates and related disclosures made by management.

• Conclude on the appropriateness of management's use of the going concern basis of accounting and, based on the audit evidence obtained, whether a material uncertainty exists related to events or conditions that may cast significant doubt on the entity's ability to continue as a going concern. If we conclude that a material uncertainty exists, we are required to draw attention in our auditor's report to the related disclosures in the financial statements or, if such disclosures are inadequate, to modify our opinion. Our conclusions are based on the audit evidence obtained up to the date of our auditor's report. However, future events or conditions may cause the entity to cease to continue as a going concern.

We communicate with those charged with governance regarding, among other matters, the planned scope and timing of the audit and significant audit findings, including any significant deficiencies in internal control that we identify during our audit.

We also provide those charged with governance with a statement that we have complied with relevant ethical requirements regarding independence, and to communicate with them all relationships and other matters that may reasonably be thought to bear on our independence, and where applicable, related safeguards.

For B.P. Rao and Co.
Chartered Accountants
FRN: 003116S

Prashanth. C
Partner
M No:214431
UDIN **22214431ATCOQW4861**

Place: Bangalore
Date: 19-09-2022

B.P. RAO & CO. Bangalore 560 001. Chartered Accountants

स्टेम कोशिका विज्ञान एवं पुनर्योजी औषधि संस्थान (डीबीटी-ईनस्टेम)
जैव प्रौद्योगिकी विभाग,भारत सरकार के अधीन स्वायत्त संस्थान
Institute for Stem Cell Science and Regenerative Medicine (DBT- inStem)
AI under Department of Biotechnology, Govt. of India

inStem

Management response to "Emphasis of Matter" in Auditor's report for the year 2021-22

Details	Management Response
Emphasis of Matter We draw attention to Note no 1.4 under Schedule 25, where the contingent liability to the extent of Rs.3.48 crores and Rs.80 lakhs in the form of claims from contractors on the executing agency (NCBS-TIFR) in respect of construction of Instem Building is reported.	This is related to a disputed claim for GST between the executing agency (NCBS-TIFR) and two contractors. The first claim is for the difference in GST rate claimed by the Contractor and admitted by the executing agency. The issue is under arbitration and a single arbitrator has been appointed by the Honourable High Court of Karnataka vide its order dated 30.06.2022. The second claim is related to additional work stated to be performed by the contractor but yet to be certified by the Project Team and engineer's in charge. Since the validity of the claim in both cases is not clear, they have been depicted as Contingent Liability in notes to accounts.

(Ramanathan. K)
Head A&F

(Madhu Chandan Roy)
Admin Officer (Accounts & Finance)

जीकेवीके पोस्ट, बेल्लारी रोड, बैंगलोर -560065
GKVK Post, Bellary Road, Bangalore, 560065, India
Phone +91 80 6717/2366-6319 Office: +91 80 6717/2366-6371
email: headadm@instem.res.in

File No.InStem/G/110/21-22/

inStem

UTILISATION CERTIFICATE

(Towards establishment of Institute for Stem Cell Science and Regenerative Medicine for the financial year: 2021-22 (01-04-2021 to 31-03-2022)

1. Title of the Project/Scheme : Institute for Stem Cell Science and Regenerative Medicine

2. Name of the Organization: : Institute for Stem Cell Science and Regenerative Medicine

3. Department of Biotechnology Sanction Order No anddate of sanctioning the project: : No. BT/PR7972/MED/14/1208/2006 dated 25.08.2008

4. Amount brought forward from the previous financialyear 2020-21 quoting DBT letter No. & date in which the authority to carry forward the said amount was given: : Rs. 7,91,90,125/-

5. Amount received from DBT during the financial year 2021-22 (Please give No. & date of sanction orders showing the amount paid):

1	No. BT/PR7972/MED/14/1208/2006	30.07.2021	Rs. 61,00,000/-
2	No. BT/PR7972/MED/14/1208/2006	30.07.2021	Rs 7,34,00,000/-
3	No. BT/PR7972/MED/14/1208/2006	30.07.2021	Rs. 4,30,00,000/-
4.	No. BT/PR7972/MED/14/1208/2006	13.12.2021	Rs. 3,70,00,000/-
5.	No. BT/PR7972/MED/14/1208/2006	13.12.2021	Rs. 7,29,00,000/-
6.	No. BT/PR7972/MED/14/1208/2006	16.03.2022	Rs. 7,14,00,000/-
7.	No. BT/PR7972/MED/14/1208/2006	16.03.2022	Rs. 7,76,00,000/-
8.	No. BT/PR7972/MED/14/1208/2006	16.03.2022	Rs. 1,50,00,000/-
			Rs.39,64,00,000/-

6. Other receipts/interest earned, if any on the DBT grants: : Rs. 33,08,342/-

7. Total amount that was available for expenditure incurred during the financial year (Sl.No. 4, 5, and 6): : Rs.47,88,98,467/-

8. Actual expenditure incurred during the financial year (Statement of expenditure is enclosed) : Rs.39,40,47,664/-

9. Unspent balance refunded, if any (Please give details)
: Rs.1,08,53,579/- refunded vide Bharatkosh (T. No. 0904220002038)
: Rs.4,47,30,580/- refunded vide Bharatkosh (T. No. 1104220009319)
: Rs.15,35,484/- refunded vide Bharatkosh (T. No. 1909220004172)

Amount lapsed and returned back from TSA : Rs.42,66,005/- lapsed and returned back from TSA on 31.03.2022

9A. Interest refunded, if any (Please give details)
: Rs.44,81,020/- refunded vide Bharatkosh (T.No.0408210015287)
: Rs.24,41,998/- refunded vide Bharatkosh (T.No.2610210019694)
: Rs.26,75,742/- refunded vide Bharatkosh (T.No.0708210002365)
: Rs.19,67,783/- refunded vide Bharatkosh (T.No.1703220010810)
: Rs. 5,17,150/- refunded vide Bharatkosh (T. No.3103220006537)
: Rs. 3,11,844/- refunded vide Bharatkosh (T.No. 1204220008897)
: Rs. 5,11,565/- refunded vide Bharatkosh (T No. 1909220003399)

B. P. RAO & CO. Chartered Accountants Bangalore 560 008

10. Balance amount available at the end of the financial year:(as on 31.03.2022) : Rs. 1,29,16,946/-

Note:
(1) As on 31.03.2022, balance is TSA pertaining to inStem GIA General amounting to Rs.42,66,005/- lapsed and returned back to GoI.
(2) Out of Instem Capital Expenditure of Rs.5,43,51,566, an amount of Rs.3,53,38,680/- was trasferred from TSA to Commercial Bank for meeting LC Commitment which was settled in April-22.
(3)(a) For CSCR, under GIA General an amount of Rs. 1,44,41,801/- pertaining to March -22 was paid to CMC in 2022-23, excluded in above expenditure.
(3)(b) For CSCR, under GIA Manpower an amount of Rs. 35,37,304/- pertaining to March-22 was paid to CMC in 2022-23, excluded in above expenditure.
(4) Refund of Rs.1,08,53,579 & Rs.4,47,30,580 (GIA Capital) were processed in April-22 after FC recommendation. Rs.15,35,484/- (GIA General) was processed after Accounts Finalization in September -22.
(5) Refund of interest of Rs.1,20,83,693/- was processed in 2021-22 & Rs.8,23,409/- was processed 2022-23, BharatKosh details for all refunds are provided in UC.

11. Amount allowed to be carried forward to the financial year 2022-23 vide letter no. & date : **Rs. 1,29,16,946/-**

CERTIFICATE

Certified that the amount of **Rs.39,40,47,664/-** mentioned against col.8 has been utilized on the project/scheme for the purpose for which it was sanctioned and that the balance as on 31.03.2022 is **Rs. 1,29,16,946/-.**

Certified that I have satisfied myself that the conditions on which the grants in aid was sanctioned have been duly fulfilled /are being fulfilled and that I have exercised the following checks to see that money was actually utilized for the purpose for which it was sanctioned.

1. Verification of audited books of accounts

2. Checking of vouchers and bank balances

For B. P. RAO & CO.
Chartered Accountants
FRN 003116S
Partner
M.No. 214431
(Prashanth C)
Partner
(M No. 214431)
UDIN: 22214431ATCRFD6447

19-09-2022

(Madhu Chandan Roy)
Admin Officer (F& A)

(Ramanathan K)
Head Admin. & Finance

(Prof. Maneesha S Inamdar)
Director
प्रो. मनीषा एस इनामदार / Prof. Maneesha S Inamdar
निदेशक / Director
स्टेम कोशिका विज्ञान एवं पुनर्योजी औषधी संस्थान (डीबीटी-इंस
Institute for Stem Cell Science and Regenerative Medicine (DBT - inSte
जैव प्रौद्योगिकी विभाग, विज्ञान एवं प्रौद्योगिकी मंत्रालय,
भारत सरकार के अधीन एक स्वायत्त संस्थान
(An Autonomous Institute under Department of Biotechnology, MoST, Govt. of

inStem
Institute for Stem Cell Science and Regenerative Medicine

INSTITUTE FOR STEM CELL SCIENCE & REGENERATIVE MEDICINE, BANGALORE

STATEMENT OF EXPENDITURE FOR THE PERIOD FROM 01.04.2021 TO 31.03.2022

(Amount in Rs.)

Sl.No.	Particulars	Unspent balance as on 01.04.2021 as per Audited SOE & UC	Grants received from DBT during the period 01.04.2021 to 31.03.2022	Other receipts/interest earned on the DBT Grants	Total	Expenditure incurred (excluding commitments) from 01.4.2021 to 31.3.2022	Interest or Unspent amount Refunded/Amount Lapsed in TSA	Balance as on 31.03.2022
1	2	3	4	5	6=3+4+5	7	8	9=6-7-8
	INSTEM :							
A	**GIA - Capital**							
(i)	**Equipments & Accessories**	31,708,972	32,600,000		64,308,972	54,351,566	10,853,579	-896,173
	Total (A)	**31,708,972**	**32,600,000**	-	**64,308,972**	**54,351,566**	**10,853,579**	**-896,173**
B	**GIA - Salary**							-
(ii)	**Manpower**	8,269,863	73,500,000		81,769,863	82,227,583	-	-457,720
	Total (B)	**8,269,863**	**73,500,000**	-	**81,769,863**	**82,227,583**	-	**-457,720**
C	**GIA - General**							
(iii)	**Recurring Expenses**	20,085,018	174,700,000		194,785,018	188,983,529	4,266,005	1,535,484
	Total (C)	**20,085,018**	**174,700,000**	-	**194,785,018**	**188,983,529**	**4,266,005**	**1,535,484**
D	**Other receipts**	-	-		-			-
E	**Interest Earned**	6,923,018	-	2,996,498	9,919,516	-		9,919,516
F	**Interest Refunded**	-	-		-	-	9,407,951	-9,407,951
	GRAND TOTAL (A+B+C+D+E+F) - INSTEM	**66,986,871**	**280,800,000**	**2,996,498**	**350,783,369**	**325,562,678**	**24,527,535**	**693,156**
	CSCR Vellore :							
G	**GIA - Capital**	2,829,453	51,100,000		53,929,453	9,198,873	44,730,580	-
H	**GIA - Salary**	5,401,095	21,500,000		26,901,095	27,217,050		-315,955
I	**GIA - General**	1,313,990	43,000,000		44,313,990	32,069,064	17,026	12,227,900
J	**Interest Earned**	2,658,716	-	311,844	2,970,560	-		2,970,560
K	**Interest Refunded**			-	-	-	2,658,716	-2,658,716
	GRAND TOTAL (G+H+I+J+K) - CSCR	**12,203,254**	**115,600,000**	**311,844**	**128,115,098**	**68,484,987**	**47,406,322**	**12,223,789**
	GRAND TOTAL - INSTEM + CSCR	**79,190,125**	**396,400,000**	**3,308,342**	**478,898,467**	**394,047,664**	**71,933,857**	**12,916,946**

Note: (1) As on 31.03.2022, balance is TSA pertaining to inStem GIA General amounting to Rs.42,66,005/- lapsed and returned back to GoI.
(2) Out of Instem Capital Expenditure of Rs.5,43,51,566, an amount of Rs.3,53,38,680/- was trasferred from TSA to Commecial Bank for meeting LC Commitment which was settled in April-22.
(3)(a) For CSCR, under GIA General an amount of Rs. 1,44,41,801/- pertaining to March -22 was paid to CMC in 2022-23, excluded in above expenditure.
(3)(b) For CSCR, under GIA Manpower an amount of Rs. 35,37,304/- pertaining to March-22 was paid to CMC in 2022-23, excluded in above expenditure.
(4) Refund of Rs.1,08,53,579 & Rs.4,47,30,580 (GIA Capital) were processed in April-22 after FC recommendation. Rs.15,35,484/- (GIA General) was processed after Accounts Finalization in September -22.
(5) Refund of interest of Rs.1,20,83,693/- was processed in 2021-22 & Rs.8,23,409/- was processed 2022-23, BharatKosh details for all refunds are provided in UC.

(Prashanth. C)
Partner (M.No.214431)
Place: Bangalore
Date : 19.09.2022

B. P. RAO & CO. Chartered Accountants Bangalore 560 001

UDIN: 22214431ATCRFD6447

Madhu Chandan Roy
Accounts Officer

(Ramanathan K)
Head Admin. & Finance

(Prof. Maneesha S. Inamdar)
Director
प्रो. मनीषा एस इनामदार / Prof. Maneesha S Inamdar
निदेशक / Director
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Institute for Stem Cell Science and Regenerative Medicine (DBT - inStem)

INSTITUTE FOR STEM CELL SCIENCE & REGENERATIVE MEDICINE, BANGALORE
(Registered under the Karnataka Societies' Registration Act)
GKVK, BELLARY ROAD, BANGALORE - 560 065
RECEIPTS AND PAYMENTS STATEMENT FOR THE YEAR ENDED MARCH 31, 2022

(Amount -Rs)

RECEIPTS	CURRENT YEAR	PREVIOUS YEAR	PAYMENTS	CURRENT YEAR	PREVIOUS YEAR
I. Opening Balances			I. Expenses		
a) Cash in hand	1,224	21,943	a) Establishment Expenses	12,22,74,961	9,75,87,618
b) Bank Balances			b) Administrative Expenses	23,48,85,104	24,00,35,431
i) in current accounts	6,34,81,240	4,07,52,806		**35,71,60,065**	**33,76,23,049**
ii) in deposit accounts	30,60,03,848	39,38,15,116	II. Payments made against projects	**20,84,83,315**	**20,50,44,932**
iii) in savings accounts	5,21,06,464	13,75,12,740	III. Investments made		
	42,15,92,776	**57,21,02,604**	a) Out of Earmarked/End. Funds	-	-
II. Grants Received			b) Out of own funds	-	-
a) From Govt. of India	39,64,00,000	38,71,79,000	IV. Increase in Current Assets	-	-
b) From State Govt.	-	-	V. Capital Expenditure		
	39,64,00,000	**38,71,79,000**	a) Purchase of fixed assets-Projects	1,12,22,521	1,25,70,172
III. Project Receipts-Projects	**18,19,53,848**	**24,02,55,533**	b) Exp. On Building	2,84,87,598	10,87,569
			c) Exp on Equipments & Furnitures	5,66,62,841	10,16,48,053
IV. Decrease in Current Assets	**2,32,87,604**	**-3,44,69,790**		**9,63,72,960**	**11,53,05,794**
V. Interest Received			VI. Refund of surplus money/Loans	-	-
a) On Bank deposits	1,10,99,832	1,97,10,847	a) To the Govt. of India	1,63,49,698	2,02,58,139
b) on Loans, Advances etc.		-	a) To the Govt. of India-EMG	3,94,49,957	1,77,03,787
	1,10,99,832	**1,97,10,847**		**5,57,99,655**	**3,79,61,926**
VI. Other Income (Specify)	**81,06,378**	**1,26,88,726**	VII. Finance Charges (Interest)	-	-
VII. Amount Borrowed	-	-	VIII. Decrease in Current Liabilities	**-2,69,12,437**	**7,99,38,445**
VIII. Any other receipts	-	-	IX. Closing Balances:		
			a) Cash in hand	24	1,224
			b) Bank Balances		
			i) in current accounts	59,00,638	6,34,81,240
			ii) in deposit accounts	16,30,11,390	30,60,03,848
			iii) in savings accounts	18,26,24,829	5,21,06,464
				35,15,36,880	**42,15,92,776**
TOTAL	**1,04,24,40,438**	**1,19,74,66,921**	TOTAL	**1,04,24,40,438**	**1,19,74,66,921**

Vide our report of even date
For B. P. RAO & CO.
Chartered Accountants
FRN 003116S

(Prashanth. C)
Partner (M.No.214431)
UDIN: 22214431ATCDQW4861
Place: Bangalore
Date : 19-09-2022

(Madhu Chandan Roy)
Admin Officer (F&A)

(Ramanathan K)
Head Admin & Finance

(Prof. Maneesha Inamdar)
Director

प्रो. मनीषा एस इनामदार / Prof. Maneesha S Inamdar
निदेशक / Director
स्टेम कोशिका विज्ञान एवं पुनर्योजी औषधी संस्थान (डीबीटी-इंस्टेम)
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भारत सरकार के अधीन एक स्वायत्त संस्थान

INSTITUTE FOR STEM CELL SCIENCE AND REGENERATIVE MEDICINE BANGALORE

(Registered under the Karnataka Societies' Registration Act.)

GKVK, BELLARY ROAD, BANGALORE - 560 065

INCOME AND EXPENDITURE ACCOUNT FOR THE YEAR ENDED MARCH 31, 2022

(Amount- Rs.)

Particulars	Schedule	Current Year	Previous Year
INCOME			
Income from Projects - to the extent of expenditure included	3	20,84,83,315	20,50,44,932
Income from Sales and Services	12	20,87,056	69,43,703
Grants/Subsidies	13	31,27,00,000	32,71,79,000
Fees/Subscriptions	14	-	-
Income from Investments	15	-	-
Income from Royalty, Publications etc.	16	-	-
Interest earned	17	34,37,598	1,02,46,635
Other Income	18	58,77,112	57,45,023
Increase/(decrease)in stock of Finished goods and works-in-progress	19	-	-
TOTAL (A)		**53,25,85,081**	**55,51,59,293**
EXPENDITURE			
Establishment Expenses	20	12,22,74,961	9,75,87,618
Other Administrative Expenses	21	23,48,85,104	24,00,35,431
Expenditure on Grants/Subsidies etc.	3	20,84,83,315	20,50,44,932
Interest	23	1,20,83,693	2,02,58,139
Depreciation (Net Total at the year -end -corresponding to Sch.8)		32,26,85,016	35,82,81,599
TOTAL (B)		**90,04,12,089**	**92,12,07,719**
Balance being excess of Expenditure over Income (A-B)		**-36,78,27,007**	**-36,60,48,426**
Less- Transfer to Capital Reserve - equivalent to depreciation charges	2(1)	32,26,85,016	35,82,81,599
Less- Transfer to/from General Reserve - Recurring Grant Account	1(B)	-4,51,41,991	-77,66,827
Balance being surplus/deficit carried to Corpus/Capital Fund		-	-

Vide our report of even date

For B. P. RAO & CO.

Chartered Accountants

FRN 003116S

(Prashanth. C)
Partner (M.No.214431)
UDIN: 22214431ATCOQW4861
Place: Bangalore
Date : 19-09-2022

(Madhu Chandan Roy)
Admin Officer (F&A)

(Ramanathan K)
Head Administration & Finance

(Prof. Maneesha Inamdar)
Director

प्रो. मनीषा एस इनामदार / Prof. Maneesha S Inamdar
निदेशक / Director
स्टेम कोशिका विज्ञान एवं पुनर्योजी औषधी संस्थान (डीबीटी-इंस्टेम)
Institute for Stem Cell Science and Regenerative Medicine (DBT - inStem)
जैव प्रौद्योगिकी विभाग, विज्ञान एवं प्रौद्योगिकी मंत्रालय,
भारत सरकार के अधीन एक स्वायत्त संस्थान
(An Autonomous Institute under Department of Biotechnology, MoST, Govt. of India)

INSTITUTE FOR STEM CELL SCIENCE AND REGENERATIVE MEDICINE BANGALORE

(Registered under the Karnataka Societies' Registration Act.)

GKVK, BELLARY ROAD, BANGALORE - 560 065

BALANCE SHEET AS AT MARCH 31, 2022

(Amount- Rs.)

Particulars	Schedule	Current Year	Previous Year
CORPUS/CAPITAL FUND AND LIABILITIES			
CORPUS/CAPITAL FUND	1	14,40,54,767	19,49,13,202
RESERVES AND SURPLUS	2	2,48,66,66,494	2,71,29,78,550
EARMARKED/ ENDOWMENT FUNDS	3	21,19,64,501	28,15,04,212
SECURED LOANS AND BORROWINGS	4	-	-
UNSECURED LOANS AND BORROWINGS	5	-	-
DEFERRED CREDIT LIABILITIES	6	-	-
CURRENT LIABILITIES AND PROVISIONS	7	8,43,73,331	5,74,60,894
TOTAL		**2,92,70,59,094**	**3,24,68,56,858**
ASSETS			
FIXED ASSETS	8	2,53,37,90,410	2,76,02,44,676
INVESTMENTS - FROM EARMARKED /ENDOWMENT FUNDS	9	-	-
INVESTMENTS - OTHERS	10	600	600
CURRENT ASSETS, LOANS, ADVANCES ETC.	11	39,32,68,083	48,66,11,582
MISCELLANEOUS EXPENDITURE		-	-
TOTAL		**2,92,70,59,094**	**3,24,68,56,858**
SIGNIFICANT ACCOUNTING POLICIES	24		
CONTINGENT LIABILITIES AND NOTES ON ACCOUNTS	25		

Vide our report of even date

For B. P. RAO & CO.

Chartered Accountants

FRN 003165

(Prashanth. C)
Partner (M.No.214431)

(Madhu Chandan Roy)
Admin Officer (F&A)

(Ramanathan K)
Head Admin & Finance

(Prof. Maneesha Inamdar)
Director

UDIN: 22214431ATCOQW4861

Place: Bangalore

Date : 19-09-2022

B. P. RAO & CO. Chartered Accountants Bangalore 560 001.

प्रो. मनीषा एस इनामदार / Prof. Maneesha S Inamdar
निदेशक / Director
स्टेम कोशिका विज्ञान एंव पुनर्योजी औषधी संस्थान (डीबीटी-इंस्टेम)
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भारत सरकार के अधीन एक स्वायत्त संस्थान
(An Autonomous Institute under Department of Biotechnology, MoST, Govt. of India)

- **Editorial Team:**
  Tina Mukherjee, *inStem Communication Coordinator*
  Arvind Ramanathan, *Head of Research*
  inStem Communications Office
- **Hindi Translation:**
  Awantika Tripathi, *Chief Executive Ananya Edu-Tech Consultancy Services G-45, HUDCO Place*
- **Design:**
  www.superpixel.in

inStem
Institute for Stem Cell Science and Regenerative Medicine

Institute for Stem Cell Science and Regenerative Medicine
Bangalore Life Science Cluster, Bellary road, Bangalore -560005 (IN)

Website: www. instem.res.in
Social Media: /DBT_inStem /DBTinStem