inStem

INSTITUTE FOR STEM CELL SCIENCE
AND REGENERATIVE MEDICINE

Annual Report

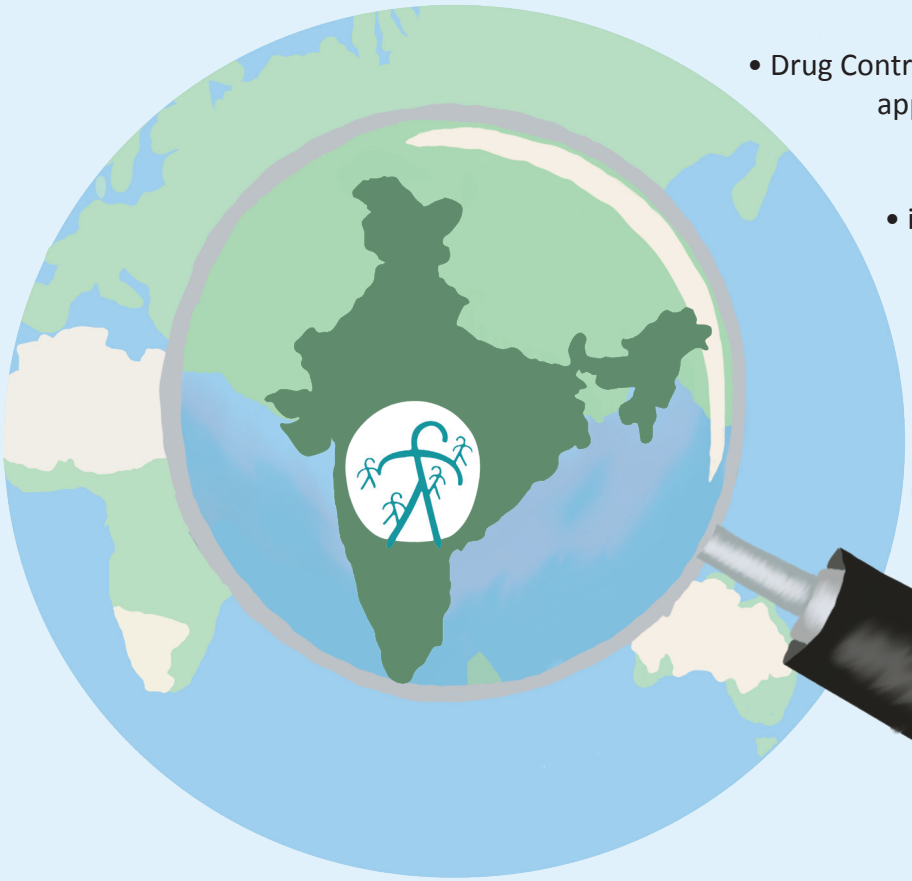
2020 - 2021

inStem

An Autonomous Institute of
the Dept. of Biotechnology, Govt. of India

DBT-inStem, Year at a Glance 2020-2021

- European Molecular Biology Organisation Global Investigator 2020: Sunil Laxman
- Har Gobind Khurana DBT IYBA Fellowship 2020: Bhavana Muralidharan
- DBT Biotech Product, Process Development & Commercialization Award 2020: Praveen Vemula
- Fellowship from the University of Strasbourg for Advanced Study, 2021: Tina Mukherjee
- MK Bhan Young Researcher Fellowship 2021: Kavitha Govarthanan & Rajalakshmi Srinivasan



- inStem - NCBS COVID19 testing laboratory conducted > 175000 RT-PCR tests since April, 2020
- Drug Controller General of India (DCGI) approval for the commercial use of tapestry pooling test for COVID19
- inStem-NCBS INSACOG Regional Laboratory sequenced >3000 viral genomes since January 2021
- COVID19 Bioresource, to facilitate efforts for academia, clinic and industry: 1429 samples till date
- InDx Centre of Excellence for Clinical Studies at inStem evaluated 45 indigenously developed kits from 15 different companies.

- Cell & Gene Therapy Symposium organised by CSCR CMC Vellore, September 2020
- International Women's Day, 2021 celebrated with an engagement of inStem postdocs and students with girl students in rural Tamil Nadu (in partnership with CARE).
- Brain Awareness Week March 15-21, 2021: Daily podcasts from DBT-inStem, NCBS-TIFR, NIMHANS, DBT-NBRC, coordinated by Bhavana Muralidharan.
- National Science Day 2021: Talks on "Future of Science, Technology, and Innovation: Impact on Education, Skills, and Work" for students from colleges in Bangalore, Mysore, Kerala and Chennai
- Science Setu Programme, entitled, "Discovering Possibilities" under the aegis of Azadi Ka Amrit Mahotsav. Bi-monthly seminars since April 2021, for undergraduate and postgraduate students from ten colleges in Bangalore, Mangalore, Ujire, Gadag, Kollam, and Chennai.
- inStem participated in the India International Science Festival 2020
- inStem participated in the Global Bio-India Conference 2021, organised by DBT

Institutional Partnerships

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Director's Note

2020-21 challenged us in ways none could imagine or be fully prepared for. Professionally, we rapidly pivoted our capabilities and resources to contribute to both the national response and work towards the safety and well-being of our communities. With others, we too grappled with personal losses on a scale unimaginable. However, the lessons that endure should be of the importance of investing in communities, both neighhouring and global, and a commitment to inclusive, equitable growth, building partnership with all stakeholders. It is in that spirit that we look forward with some measure of optimism, and through this report share positive highlights of the past year and the accomplishments of our staff and researchers.

I'd like to congratulate our doctoral students, the bedrock of our research community, who despite the disruptions at a very crucial stage in their careers, have submitted their PhD thesis and in many cases enthusiastically defended these, *sans* the celebrations and the gatherings that are typical of these occasions. Congratulations to all! Our gratitude to the campus Academic Office, and their counterparts at Manipal University, SASTRA, Thanjavur and TDU Bengaluru for their commitment to staying with the process. The newly minted doctorates are listed on page 48 of this report. Congratulations are also due to our faculty colleagues, Sunil Laxman, Minhaj Sirajuddin and Tina Mukherjee who achieved an important milestone in their careers and were promoted to Associate Professors with tenure in the past year. Our best wishes for the growth and continued success of their programmes!

We are delighted to welcome new colleagues across all sections and levels of appointment to our administrative team. A special note of acknowledgement for Mr. K Ramanathan, who took over as Head Administration and Finance, from Mr. Pawan K Pahwa who proceeded on deputation early in 2021, after a short but effective period in the post at inStem. We thank Mr. Pahwa for his commitment and sterling contributions to the growth of this still young institute and wish him the very best. Under Ramanathan's leadership and the energies and commitment of the relatively new sections heads Anup Kumar and Amit Sarkar, as well as hires across sections, the administration now brings strength and stature not only to the administrative management of inStem but also shoulders responsibilities across the Bangalore Life Science Cluster (BLiSC).

A warm welcome to the new recruits in the Technical Cadre, where we look forward to colleagues joining us in the coming months.

New appointments in the scientific cadre added to the positives of the past year. On behalf of all at inStem and the BLiSC, we welcome Deepti Abbey (Stem Cell Core); Sucharita Bose (Cryo EM and EM); Gurbind Singh (CGMP Facility, CSCR); Nirpendra Singh (Mass Spec Facility); Sandhya Rani (Microscopy Core, CSCR) and Mahesh Sahare (MGEF). Our best wishes to Mohankumar Murugesan and Sarvanabhavan Thangavel, who join the Cell & Gene Therapy effort at CSCR, (the translational unit of inStem at CMC Vellore), to launch their careers on the independent investigators track, building on efforts of past years. We look forward to Diya Binoy Joseph and Sudarshan Gadadhar joining the faculty at inStem, in 2022. Last but not the least, it gives me great pleasure to announce that Dr Rakesh Mishra (former director CCMB) is the new Scientific Director of the Tata Institute for Active Genetics and head of the collaborative Centre at inStem. Our warmest appreciation for the efforts of Prof Suresh Subramani who has steered the activities of the TIGS-Centre at inStem and laid deep foundations for the partnership, which will only strengthen in the years ahead.

Speaking of partnerships, inStem with NCBS continue their contributions to the SARS-CoV-2 testing effort, having tested close to 200,000 samples since April 2020. We are also active partners in the INSACOG programme, as a primary node for sequencing samples from Tamil Nadu, Karnataka and Pondicherry and have established an archive of precious biological resource that also anchors these efforts at the COVID19 biorepository at inStem. This bioresource serves as repository of clinical studies based in Baptist Hospital, NIMHANS and St. John's Research Hospital in Bangalore. These and related activities are described in page 42 of the report.

Many were recognized for contributions in specific domains. Praveen Vemula received the DBT Biotech Product, Process Development & Commercialization Award 2020, Bhavana Muralidharan was awarded the Har Gobind Khurana Innovative Young Biotechnologist Award 2020 to support her research. Sunil Laxman was selected to the EMBO Global Investigator cohort 2020 and Tina Mukherjee and her long-time collaborator Prof Angela Giangrande, were recognized by a Fellowship from the University of Strasbourg's Institute for Advanced Study.

In other efforts, inStem has leveraged the online webinar mode to strengthen and expand connections with our stakeholders. The Science Setu webinar series *Discovering Possibilities*, is now a fixture on the calendar of events since April 2021. The bimonthly talks showcase the developments in laboratories in the country and generate awareness of career and training opportunities for students in biology. This series enjoys active participation by UG and PG students from colleges in Karnataka, Tamil Nadu and Kerala. The "Mechanisms to Medicine" series connects our students and postdocs to cutting-edge ideas at the interface of basic science, industry research and clinical application. The monthly talk series was initiated in September 2021 and is generously funded by the TTK Prestige, *Science without Boundaries* grant. The webinars feature leaders in their fields from India and around the world and we are very grateful that the speakers commit time (often at the oddest hours in their time zones!) to extended discussions with subsets of students and postdocs after their presentations. Finally, look out for a new series that connects the doctoral students and postdocs from laboratories across India. The Early Career Seminar Series starts in the coming months bringing exciting talks from this community using the online platform!

We look ahead to renewing partnerships with institutions in Bangalore under the aegis of URJIT umbrella and building new engagements through the health science cluster of the DBT Autonomous Institutes. Even as we negotiate the realities of day-to-day life, still shadowed by the pandemic, our new appointments and renewed interactions, allow us to look forward with enthusiasm and energy. We return to our creative efforts to take the possibilities of new discoveries to the path of translation, remaining responsive to the needs of today as we set new directions for tomorrow.

Apurva Sarin
October 2021

2

Administration Report

inStem has completed twelve 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, 2021

Description	Details
Core grants received (Rs. in Crore)	38.72
EMG grants received (Rs. in Crore)	21.64
Number of Active grants (Nos)	92
Staff (incl. Contractual & Outsourced employees- Nos)	222

Funding has been affected due to Covid-19 pandemic during 2020-21.

Important administrative events that occurred during 2020- 2021 are as follows:

- Hindi Week and Vigilance Awareness Week were observed in September 2020
- Planned Activities pertaining to Swachh Bharat Abhiyan was also observed during 2020-21
- Oath to abide by the Constitution was taken during November 2020
- Online RTI replies (RTIMIS) and online Grievance redressal (CPGRAMS) were implemented during the year
- 777 Purchase Orders for 906 indents valued at Rs. 17.50 Crore were issued
- Status of vacancy positions (number) of various posts (as on March 31, 2021)

Cadre	Approved	Filled	Vacant	Advertised
Scientific	42	13	29	16
Admin	22	13	19	09
Technical	27	07	20	12
TOTAL	**91**	**33**	**58**	**37**

- 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 it's research facilities operational
- Vaccination was provided in co-ordination with MOHFW & DBT to all the frontline workers from 27.01.2021

The following important meetings were conducted during 2020-21 in the normal course of its activities:

Sl. No.	Meeting	Date
1	26th Finance Committee	17.09.2020
2	27th Finance Committee	15.03.2021
3	27th Governing Council	29.04.2020
4	28th Governing Council	25.09.2020
5	19th Governing Council	24.03.2021
6	12th AGM inStem Society	19.02.2021

The following audits were conducted during 2020-21:

Sl. No.	Type of Audit	Date
1	Statutory audit FY 2019-20	June-July 2020

The following employees joined inStem during 2020-21:

Sl. No.	Name	Designation
Scientific Staff		
1	Deepti Abbey	Scientist-D
2	Sucharita Bose	Scientist-D
Technical Staff		
1	Thiyagarajan M	Senior Technical Officer
2	Rakshith Komalan H K	Senior Technical Officer
3	Umesha T	Technical Officer
4	Naresh Kumar Yadav	Technical Officer
Administrative Staff		
1	Ramanathan K	Senior Admin. Officer
2	Anup Kumar	Administrative Officer (Estt)
3	Amit Kumar Sarkar	Administrative Officer(Services)
4	Manish	Junior Management Assistant
5	Anand G	Clerk
6	Gnanasampanthan S	Clerk

The undersigned joined inStem as Senior Administrative Officer w.e.f. November 26, 2020.

Shri Pawan Kumar Pahwa, Chief Administrative Officer proceeded on deputation to UIDAI w.e.f. 26.03.2021 and undersigned has taken over charge as Head-Administration.

Ramanathan K
Head-Administration,
inStem

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Multi - Institutional Programmes

Accelerator Program for Discovery in Brain Disorders using Stem Cells (ADBS)

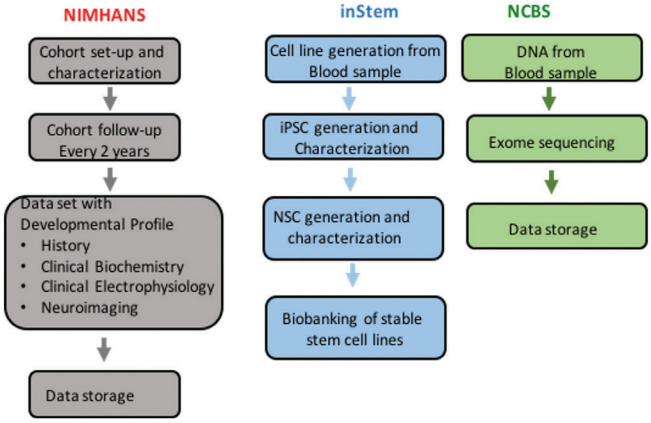
Summary

The Accelerator program for Discovery in Brain disorders using Stem cells (ADBS) is a venture to understand the genetic and cellular basis of severe mental illness by harnessing the power of modern human genetics and stem cell technology. The programme is a collaborative initiative of three institutions from Bengaluru, India – the Institute for Stem Cell Science and Regenerative Medicine (inStem), National Centre for Biological Sciences (NCBS) and the National Institute for Mental Health and Neurosciences (NIMHANS). This programme uses modern stem cell technology to create cellular models of the brain derived from human subjects with a strong history of severe mental illness. The overall goal is to uncover the genetic, cellular and molecular basis of mental illness and relate these to clinical findings.

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

The ADBS programme focuses on five major forms of severe mental illness (SMI): schizophrenia, bipolar disorder, obsessive compulsive disorder, substance dependence and dementia. All of these disorders are known to have an inherited basis. However, despite their high heritability, to date few genetic correlates that could account for of this high heritability have been identified. In order to study these disorders, in collaboration with the Department of Psychiatry, NIMHANS and NCBS, inStem has assembled a prospective cohort of families with a strong family history of SMI. Three distinct but interactive lines of analysis are ongoing: (i) The families have been clinically studied in depth to understand changes in structure and function at multiple levels of brain organization; they will now be 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) 100 induced pluripotent stem cell lines are established from affected individuals in these families and unaffected controls. These lines are being used to generate cellular models and mechanistic aspects of cellular neurobiology that lead to disease. (iii) Next Generation Sequencing and family-based bioinformatics analysis is being used to uncover the genetic basis of SMI. (iv) Genome editing technologies for the analysis of genetic variants using stem cell derived models of brain cells have been developed.

The multiple types of data generated by the programme are being 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 have been assembled into a biorepository that will allow the sharing and use of this resource to drive discovery biology in the area of SMI. The ADBS programme has instituted mechanisms to facilitate the sharing of data and resources generated through its activities.



Novel Approaches to Haematological Diseases (NAHD) Program

Summary

The programme Novel Approaches to Haematological Disorders (NAHD) at CSCR and CMC Vellore, 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 haemoglobin diseases in the population at risk in India, this collaborative initiative blends these efforts with a community outreach programme 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 with several subcomponents. These are summarised below.

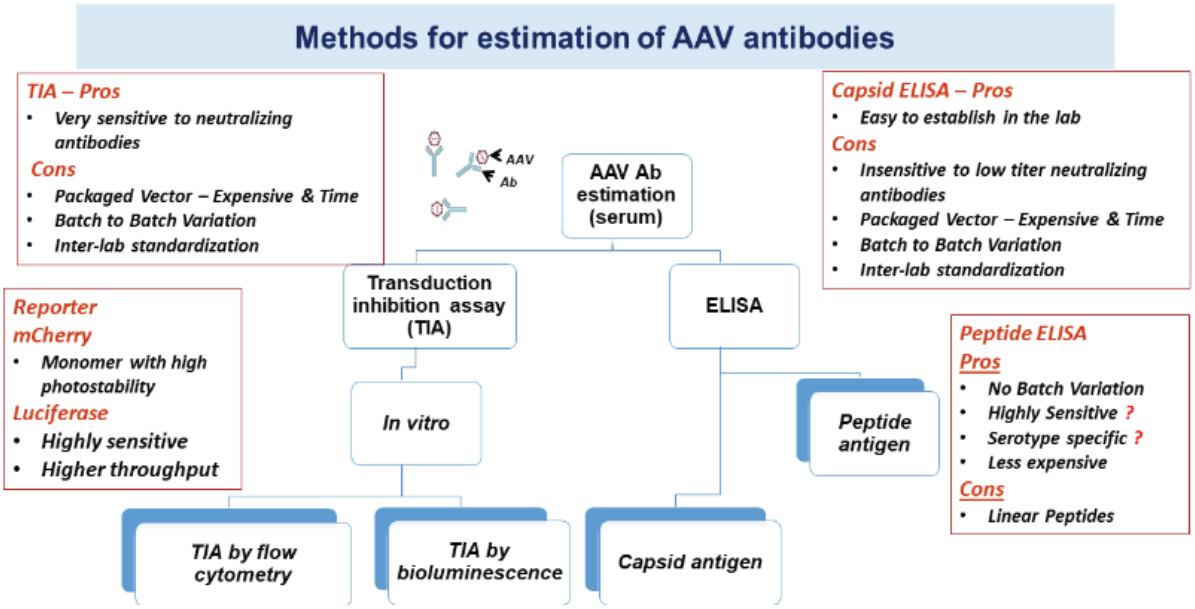
Gene Therapy

I. 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. The delay in initiating the clinical trial has been due to our inability so far to get cGMP grade vector manufactured at affordable cost. We now have a very exciting new possibility of manufacturing this in India at CSCR itself in an extended cGMP facility, which has been custom extended for this purpose. Our collaborators at Emory University have established a new GMP facility through their company - Expression Therapeutics [ET]. A team of senior GMP scientists have been recruited for process development and some engineering runs before transferring the technology to CSCR. A suitable team has been put together to take responsibility for this manufacturing within the CSCR GMP facility. The construction of state of art cGMP facility is at the verge of completion, depending to some extent on the current COVID19 pandemic situation and regulatory approvals.

Haemophilia A: An ongoing collaboration with Emory University has also led to the development of an alternative gene therapy product - a haematopoietic stem cell based lentiviral vector mediated gene therapy product for the treatment of Haemophilia A. This is a novel approach - first in-human proposed clinical trial 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 the major haemoglobin disorders. The product has been tested in pre-clinical mouse models for safety and effecacy (Doering et al Human Gene Therapy. 2018; 29:1183).

For the proposed clinical trial, all pre-clinical experiments have been completed including transfer of technology to CSCR / CMC, Vellore for the final product to be administered to the subjects in this trial – the autologous haematopoietic stem cells harvested from three patients with severe Haemophilia were transduced with the lentiviral vector with the FVIII gene. This was carried out as required by the RCGM and CDSCO and with appropriate approval of the institutional committees. An investigational new drug (IND) proposal had therefore been filed in both India and USA for this clinical trial to be undertaken in August, 2018. This proposal has been approved by CDSCO for a phase 1 clinical trial in July, 2021. We will now proceed to import the necessary clinical quantities of the cGMP lentiviral vector for the manufacture of the final drug product – the transduced autologous haematopoietic stem cells from the patient (subject) for the clinical trial.



II. 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, in collaboration with the University of Florida, USA.

Both binding and neutralizing antibodies are being assessed Kannangai from Department of Clinical Virology, CMC, Vellore and Sanjay Kumar and Alok Srivastava from CSCR, 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.

III. 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. We are 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 programme is use of gene editing for reactivation of foetal haemoglobin production. This work is being carried out by Saravanabhavan Thangavel and Mohankumar Murugesan using CRISPR-Cas9 technology in collaboration with the University of California.

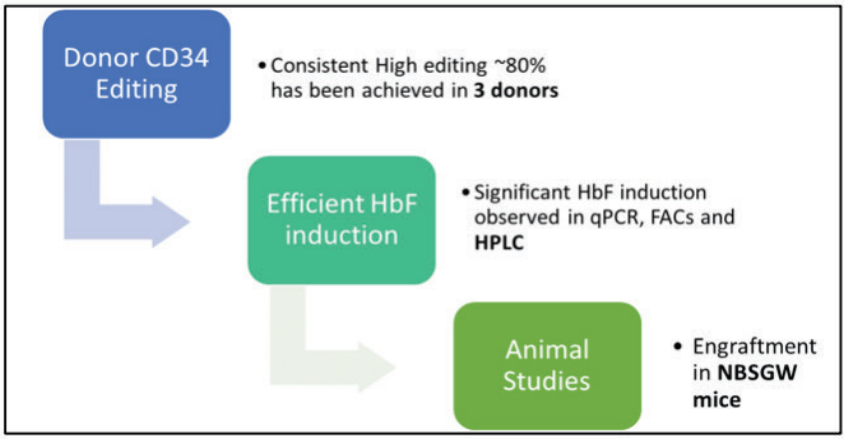
Saravanabhava Thangavel's laboratory is attempting to recapitulate HPFH like deletions in the haematopoietic stem and progenitor cells (HSPCs) of SCD and thalassemia patients, targeting a region that is conserved among many HPFH deletions. These deletions have been introduced in the HSPCs with an efficiency of >70% and it is observed that when edited HSPCs are differentiated into erythrocytes they express high levels of foetal haemoglobin. Gene edited cells have been transplanted into NSG mice and NBSG-W mice and it is observed that the cells engraft and re-populate in mouse bone marrow.

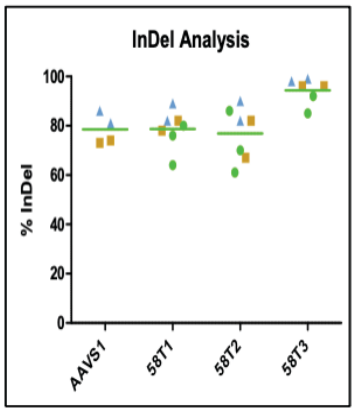
Mohankumar Murugesan's laboratory is focused on using different genome editing strategies for the treatment of beta haemoglobinopathies and haemophilia. The recent study by CRISPR Therapeutics and Vertex Pharmaceuticals (NEJM, 2020) emphasizes the promising effect of genome

editing BCL11a enhancer in β-thalassemia and sickle cell disease patients and have reported that therapeutic levels of foetal haemoglobin ameliorate clinical symptoms. We have identified a new target in the BCL11a enhancer region, which has shown robust induction of foetal haemoglobin comparable to the clinical trial target with better in vitro erythroid differentiation potential (comparable to that of control).

II. **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.





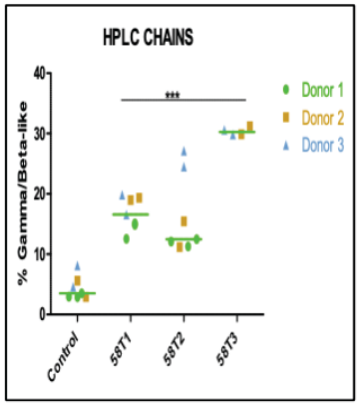


Figure: Targeting specific regions of BCL11A enhancer at the functional core of +58 DHS in human CD34+ cells

Applications of Induced Pluripotent Stem Cell (iPSC) Technology

I. **Disease Modelling for Erythroid Disorders:**

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

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 have established a feeder-free, xeno-free and integration-free protocol to generate GMP grade iPSCs. So far, iPSCs from 20 donors with top 10 HLA haplotypes have been generated. 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.

Control of Sickle Cell Disease & Thalassemia Major in Odisha Programme – Creating a Model for India

The project aims to reduce the burden of these diseases in the affected populations in Odisha through he combined effort of Ministry of Health, Odisha, NHM Odisha, Christian Medical 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 Haemoglobin 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 programme for the control of these major haemoglobin disorders in India to be carried out at this scale. Novel technologies have been developed for screening haemoglobin disorders 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. The ***Behavioural Change & Communication*** component is being coordinated by Shantidani Minz. In the past one year, BCC has reached 83 towns and 779 villages, 1410 panchayats, 65 blocks and 335 peripheral health facilities in 5 districts. Although the BCC activities were severely hampered by the COVID-19 lock down situation, BCC activities are in full pace to cover the remaining 25 districts in Odisha. The ***Training*** component is coordinated by Jiji Mathews together with Kuryan George and Alok Srivastava. Towards increasing capacity and capability for treatment, training workshops were conducted at different levels (State / Regional / District levels) for doctors / other healthcare workers of Odisha to train them in management of these disorders and effective implementation of the field program. ***Data Management*** is coordinated by Venkata Raghava. Android app and web-based application to facilitate data management were developed this year. Training of field staff to use the app and data entry is completed.

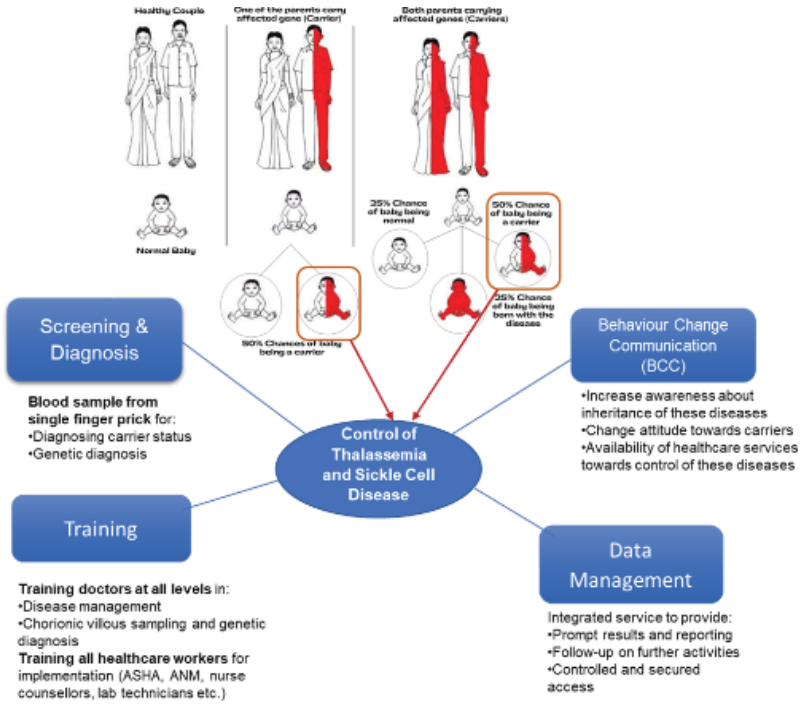


Figure: Pictorial representation of the programme (Control of Thalassemia and Sickle Cell Disease in Odisha)

Program in Chemical Biology and Therapeutics (PCBT)

Summary

The Program in 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.

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. Third, solubility of Bractoppin (~70uM) hindered co-crystallization. Therefore, structure guided optimization of potency, PPB and solubility led to Bractoppin analogues, 2088 and 2171. Among them, 2171 had 10 fold improved solubility and slightly improved potency of IC50 50nM in vitro. Co-crystallization and soaking efforts are in progress to obtain the BRCA1-tBRCT:2171 complex structure.

In cells, compound 2171 inhibits 16Gy ionizing radiation induced BRCA1 foci recruitment, inhibits Homologous Recombination Repair (in DR-GFP Assay) and abrogates ionizing radiation induced G2-M arrest in a dose dependent manner at lower concentrations compared to Bractoppin. Further, 2171 had favorable PPB **(Table 1)**. These results, together with its *in vitro* and in-cell potency offer encouragement that these approaches will yield potential candidates for future development.

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

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

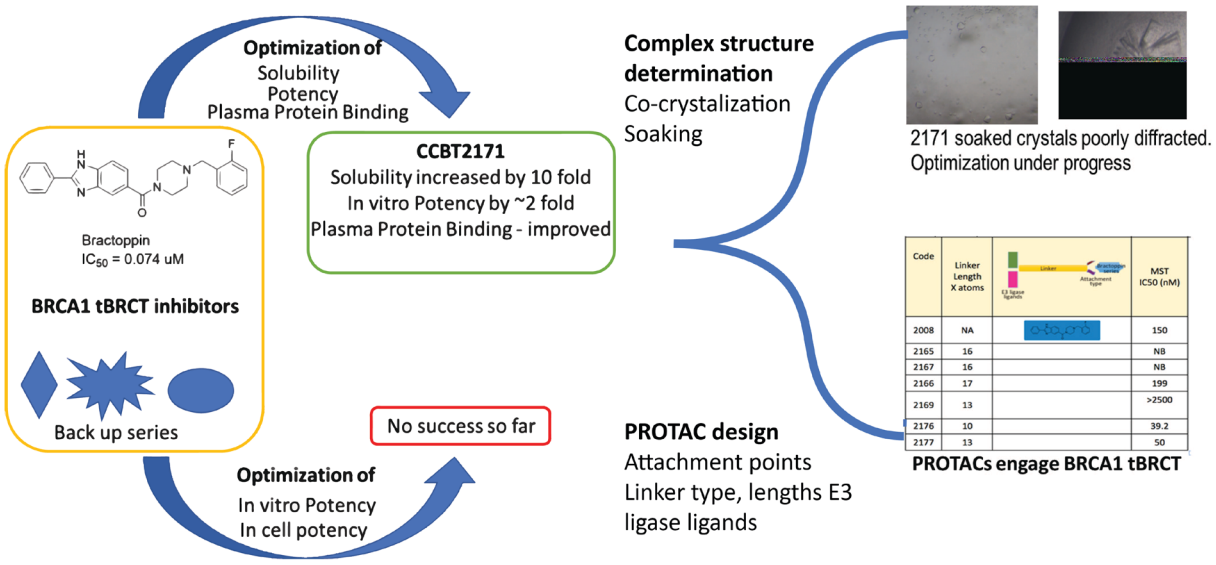
* % Unbound is the percent of free fraction of test compound in total plasma following 4 hrs dialysis.

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, clusters of compounds that are chemically distinct from Bractoppin were expanded and tested for *in vitro* potency and selectivity. The best examples of different cluster compounds were tested for their cellular potency, where BRCT overexpression and Bractoppin showed inhibition of BRCA1 recruitment, while none of the back-up series compounds had significant effect. These results suggest that the compounds were not potent enough to have in-cell potency. Though the results were disappointing, it has propelled us towards strategies for identifying new scaffolds.

We have in parallel embarked upon targeting other phosphopeptide-recognizing domains like 14-3-3, in collaboration with the Venkitaraman lab at the MRC Cancer Unit, Cambridge. FOXO3a is a tumour suppressor that is typically inactivated in a subset of cancers by post-translational modification. FOXO3a is retained in the cytoplasm by 14-3-3ε through the activation of the PI3K/Akt pathway and is unable to translocate to the nucleus and carry out transcription of genes involved in cell cycle arrest and apoptosis. Our collaborators have identified a bioactive peptide, 9J10, using novel PROTEINi technology, that binds to 14-3-3ε and inhibits its interaction with FOXO3a, thereby allowing the possibility of reactivating FOXO3a as a strategy for the treatment of cancer. To identify small molecule inhibitors of the 14-3-3ε/FOXO3a interaction, two parallel strategies were followed: i) High throughput screening and ii) Structural elucidation of 14-3-3ε complexed with 9J10/FOXO3a phosphopeptides. Six compounds showed effective dose dependent inhibition and engaged the target. We determined the first crystal structures of 14-3-3ε complexed with FOXO3a/9J10 phosphopeptides at a resolution of 1.85Å and 3.16Å respectively. Together, these results provide scope for developing novel 14-3-3ε small molecule inhibitors that could reactivate FOXO3a in the cell-based assays developed in Cambridge.

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 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.



Tata Institute for Genetics and Society – Centre at inStem (TIGS-CI)

Genetics at the fulcrum of human health and agriculture

Genetics is the foundation of all biology. It is the basis of diversity of life forms, inheritance of traits, and how the environment shapes and influences this diversity. Recent unparalleled technological advances in our ability to read and manipulate genomes has fueled a new era in biology. It has pushed the boundaries of our understanding of biology itself, and in turn we have leveraged it to improve human health, agriculture and livestock. Today, we live in times where rapid advancements in genetics and genomics have immediate implications for our society.

The Tata Institute for Genetics and Society (TIGS) was established in 2016 as the result of visionary philanthropic support from the Tata Trust. In recent times, Tata Trusts have forged various alliances with academic institutions in India and abroad to sponsor and catalyze advanced research and to improve the quality of life in resource-constrained communities in India and perhaps throughout the developing world. inStem provides exceptional opportunity to undertake ground-breaking research into the stem cells and their utility in creating disease models, as well as their applications to drug discoveries, the development of cell therapies and new technologies for the larger benefit of society.

In this context, a major, new collaboration between inStem and TIGS, the TIGS-CI is setup on such a strong foundation in the ecosystem of Bangalore Life Science Cluster. The Centre focuses on the broad applications of genetics, genomics and genome editing for beneficial and ethical societal impact in the fields of health (more specifically rare genetic diseases and infectious disease) and agriculture, supported jointly by inStem and TIGS. This collaboration brings some of the most recently-developed science and technologies to inStem to address key fundamental and applied questions to scale in its thriving intellectual environment and its quality infrastructure which allows the collaboration to be as good as that possible anywhere.

In its vision to use genetics and genomics technologies to address the needs of our society, we focus on various areas. Among the areas that the center addresses are that of vector biology, infectious diseases, and environmental surveillance. A world class insectary and associate IBSL3 facility has been established jointly to accelerate efforts in these areas. Crop improvement is another core area of the centre where our target is to use CRISPR-Cas9 mediated genome editing technology to introgress disease- and herbicide-tolerance traits. A state-of-the-art greenhouse facility will support these activities. More recently, we have initiated an effort to address various aspects of rare genetic disease including diagnostics and therapeutic interventions to make these, otherwise unaffordable options, accessible to our society.

In summary, we pivot on modern technologies of genetics and genomics to understand and address the most pressing and urgent needs of our society. We plan to include a One Health theme which will incorporate vector and pathogen surveillance and antimicrobial resistance. We will explore rare genetic disorder by developing novel diagnostic methods and therapeutics. Ours is a unique model in Indian science – we are embedded in an intellectually vibrant campus and are supported by philanthropic funding. Our development in the short time of our existence demonstrates that this new model of research in India works and should be emulated widely.

Theme Reports

4

BDDM

Brain Development and Disease Mechanisms

Raghu Padinjat (Theme Coordinator)

Sumantra Chattarji

Bhavana Muralidharan

Brain Development and Disease Mechanisms

Summary

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

The theme is 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. Bhavana Muralidharan's laboratory aims to understand chromatin-level control of brain development in health and in disease. At the fundamental level, we would like to explore the crosstalk between different chromatin complexes and tease out the interactions at the molecular level to understand the fine-tuning of gene expression of downstream targets and ultimately bring in-depth molecular insight into the dynamicity of the developing brain. To achieve this, a mouse model of cortical development is used to define detailed molecular mechanisms of

individual genes of interest. 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 programme from clinically dense families with SZ and BPD. Using 2D and 3D cerebral organoid cultures combine CRISPR-Cas gene editing the cellular and molecular origins of neuropsychiatric disorders is modelled in a dish.

The Accelerator program for Discovery in Brain disorders using Stem cells (ADBS) programme, 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 programme 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 at 3 year intervals. (ii) Induced pluripotent stem cell lines (iPSC) and neural stem cell lines have been established from affected individuals in these families and unaffected controls. (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 programme have been assembled into an integrated database to facilitate the uncovering of 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 programme has instituted mechanisms to facilitate the sharing of data and resources generated through its activities.

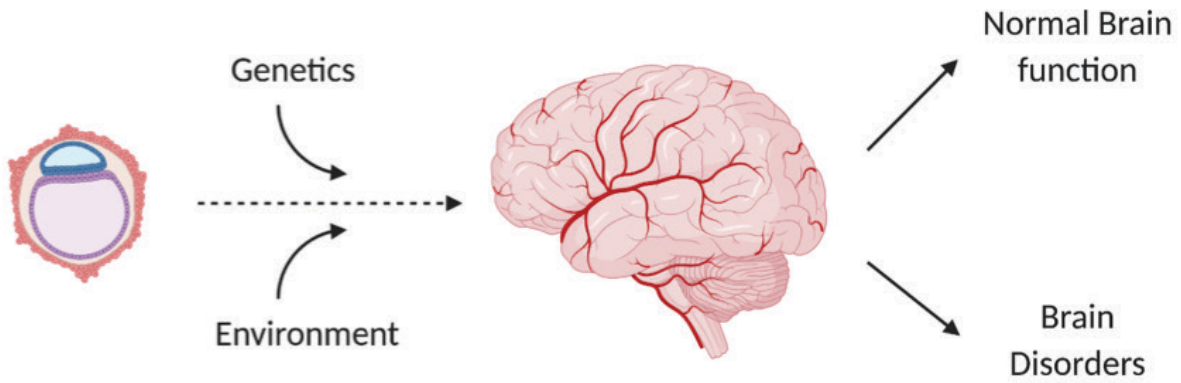


Figure: During development specific cells in the human embryo divide and differentiate to give rise to the adult human brain. These developmental events are influenced by both genetic and environmental factors and these can lead to either normal brain (Image created with BioRender.com)

5

Centre for Inflammation and Tissue Homeostasis

Colin Jamora
(Theme Coordinator)

Srikala Raghavan

Centre for Inflammation and Tissue Homeostasis

Summary

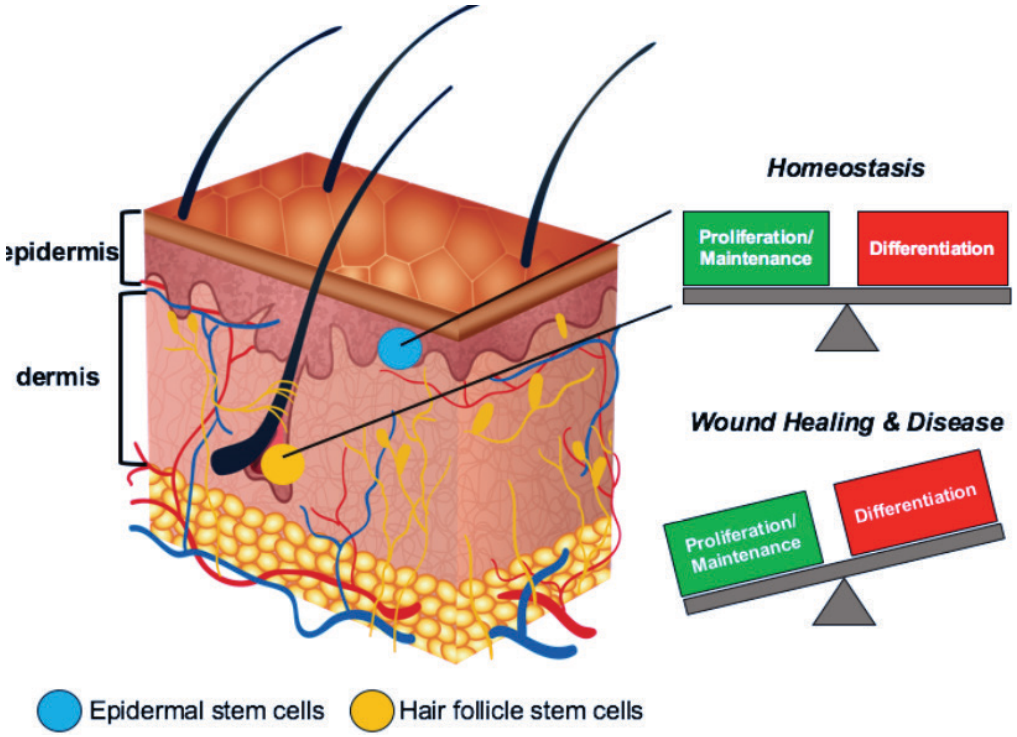
The focus of the Centre for Inflammation and Tissue Homeostasis (CITH) is on the crosstalk between cells within a tissue that guides organ development, regeneration and repair. CITH investigators have coalesced around the use of the mammalian skin as a powerful model system to gain a mechanistic understanding of the processes of tissue regeneration and repair. The skin and its appendages is one of the few organs in the body that constantly regenerates throughout the lifetime of the animal and, because of its vital role as the body's main barrier from the external environment, has evolved a remarkable capacity to rapidly heal itself when damaged. The laboratories are making contributions to the understanding of how stem cells within a tissue interact with other types of cells or its local environment to promote tissue health and aid its restoration following injury. The ultimate goal is to utilize the basic understanding of these processes to design new therapies for a broad spectrum of diseases marked by defective stem cells and chronic inflammation such as eczema, diabetic wound healing, and cancer.

Owing to the constant regeneration of its different components, the skin is home to numerous depots of stem cells that are on call to replace other cells lost through natural turnover, aging, injury, or disease. In particular, the theme focus on two epithelial stem cell populations: the epidermal stem cells, which replenishes the epidermis that turns over every three weeks; and the hair follicle stem cells that are responsible for generating a new hair when it falls out (Figure 1). This requires an intricate balance of maintaining a pool of stem cells for future use, while withdrawing some of them from the bank in order to differentiate and replace the epidermis or hair follicle. In addition to the continuous decision of stem cells to proliferate or differentiate, emergency conditions such as wound healing requires that the stem cells become acutely activated so they can contribute to the repair of the damaged skin. Consequently, the fine balance between stem cell maintenance and proliferation with differentiation under homeostatic conditions can be altered in response to emergency situations such as the need to rapidly repair tissue injury. Interestingly, many common inflammatory diseases of the skin such as psoriasis and eczema (and even cancer) disrupt this intricate balance in favor stem cell proliferation often resulting in uncontrolled cell growth (hyperplasia). Thus, an understanding of the physiological regulation of the stem cell's decision to proliferate or differentiate can provide therapeutic insights into how to treat a multitude of diseases.

Over the past year the laboratories have described two important processes that govern this stem cell balance within the skin. One of these processes is a mechanical signal that informs the hair follicle stem cells whether they should divide. Until they are called upon, stem cells are normally in a "sleep mode" known as quiescence. The cues that transition stem cells from quiescence to an activated mode is a subject of intense study as it has implications in both normal physiological functions as proper regeneration or it can lead to disease when the stem cells are hyperactivated. We found that hair follicle stem cells in their niche sense the physical forces endowed by the adhesions they make with adjacent stem cells. When the tension is relieved from these intercellular contacts, the hair follicle stem cell interprets this as a signal to begin proliferating.

A second process was discovered of how differentiation of the stem cells in the epidermis were blocked to maintain their "stemness". Interestingly, a protein normally associated with the extracellular matrix surrounding the cells was found to be able to reinforce the characteristic features of stem cells and also make them resistant to cues that would normal induce their differentiation. This is not only an important mechanism for maintaining a stable pool of epidermal stem cells, but this same process is usurped by cancers to maintain cancer stem cells (CSCs). This finding is particularly notable as CSCs are thought to be the lynchpin for tumor growth and metastasis as well as the cause of relapse after chemotherapy. Consequently, substantial efforts in academic and biotech labs have been searching for avenues to eliminate these CSC as a means of halting

the spread of the cancer. A major roadblock in this endeavor has been the lack of a target in these CSC that is crucial for their pro-tumorigenic functions. Our discovery of a protein that is critical in maintaining the stemness of the CSCs has revealed an attractive therapeutic target for the control of cancer progression.



6

CBDT

Cardiovascular Biology and Disease Theme

Sivaraj Sivaramakrishnan (Theme Coordinator)

James Spudich (Theme Coordinator)

Minhaj Sirajuddin

Dhandapany Perundurai

Cardiovascular Biology and Disease Theme

Summary

Our research plan leverages the multidisciplinary expertise of the Cardiovascular Biology and Disease (CBDT) theme investigators to gain insights into the functional genomics of HCM in the Indian population. Whereas, mutations in sarcomeric proteins have been a major thrust of research worldwide, there is limited information on HCM mutations in signaling proteins that regulate the effects of established cardiac therapeutics. Our goal is to focus on leveraging our combined expertise to identify and characterize biochemically, structural-wise and molecular functions related to HCM mutations in a signaling protein, Protein Kinase Cα (PKCα), a master regulator of cardiomyocyte signaling.

Hypertrophic cardiomyopathy (HCM) is a disease condition that afflicts 1 in 500 individuals worldwide. HCM manifests as the abnormal thickening of heart muscle, resulting in the constriction of ventricle size and consequent reduction in volume of blood pumped by the heart. HCM usually stems from genetic mutations in proteins in cardiac myocytes, the cells that drive heart contraction. While the molecular mechanisms underlying HCM in the North American and European patient populations are at advanced stages of scientific enquiry, the genetic basis of HCM in the Indian subcontinent remains vastly unexplored. CBDT is focused on dissecting the molecular basis of HCM in the Indian subcontinent, with the goal of translating basic scientific research into the personalized targeting of cardiovascular disease.

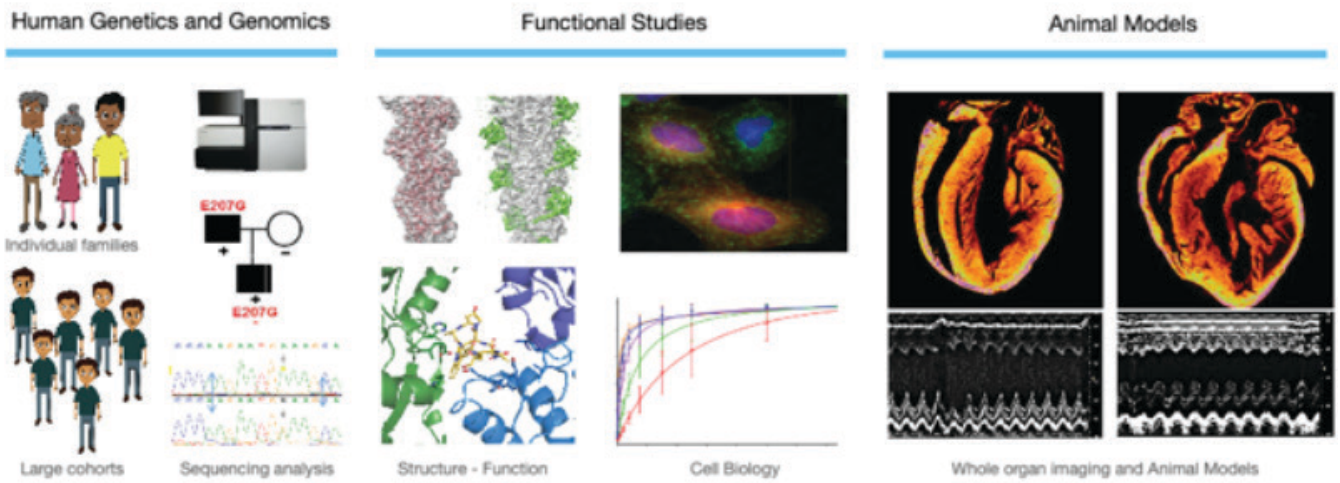
Dhandapany Perundurai brings expertise in human genetics and experience in identifying and characterizing the genetic basis of cardiomyopathies in the South Indian population. Sivaraj Sivaramakrishnan is a biomedical engineer who has designed innovative biosensor technologies to probe protein conformation and function in live cells. Minhaj Sirajuddin is a structural biologist with expertise in X-ray crystallography, light and cryo-electron microscopy. James Spudich is a world-renowned biophysicist with an extensive record of single molecule approaches to study enzyme function. The CBDT theme has established an integrated workflow that streamlines dissection of the molecular basis of HCM in South Indian populations (Figure 1). This includes (1) the identification of genetic variations in HCM targets such as PKCα (Perundurai); (2) physiological studies using cardiac myocyte cell lines and model organisms (Perundurai); (3) biosensors in cells to map protein interactions (Sivaramakrishnan); (3) high-resolution structural biology and microscopy to study molecules and structures related to heart (Sirajuddin); (4) single-molecule biophysical techniques to probe enzymatic function (Spudich).

In an ongoing attempt to unravel new candidate genes, the Perundurai laboratory performed exome sequencing in 25 patients with HCM, in India, who are negative for known causes. The standard in-house pipeline and systemic analysis in these unrelated patients, resulted in the identification of two novel mutations in a gene encoding **PKCα**, in two different patients, leading to the amino acid changes p.E207G and p.V566L. iPSCs were generated from patient fibroblasts bearing the E207G PRKCA mutation, differentiated into cardiomyocytes and subsequently purified by cell sorting using the cardiomyocyte-specific cell surface marker SIRPα.

A transgenic mouse with the mutation (E207G) observed in patients has been generated. Histological analyses of mouse hearts have revealed a massive HCM with the hallmarks of hypertrophy, including increased fetal gene expression. The left ventricular chamber dimensions in diastole (LVID-d) and fractional shortening were significantly greater than those in the control animals. In addition, the heart tissue obtained from these mice showed increased ERK activity suggesting a gain-of-function effect. To determine whether cardiac changes activated by the E207G variant of *PKCα* (PKC) can be reversed by silencing ERK, *PKC* transgenic mice were treated with an ERK inhibitor (PD325901- MEKi). Recent promising findings suggest that cardiomyopathy triggered by the *PKC* variant can be rescued by MEKi.

The Sirajuddin laboratory had determined cryoEM

structures of F-actin bound to small molecule toxins (phalloidin), peptides (lifeAct), proteins (Utrophin) and bundling proteins (nexilin) at near atomic resolution. Using this established structure elucidation pipeline, the laboratory will determine high-resolution structures of full-length PKCα, to elucidate mechanisms of PKC *dys*function during HCM. The existing low-resolution mechanistic *PKC*α models fail to illuminate PKCα dysfunction during pathological conditions. With the advent of CryoEM, there is a renaissance in revisiting macromolecules that were previously not amenable for structural characterization using X-ray and NMR approaches. The National Cryo-EM laboratory located at inStem and jointly managed institutions in the Bangalore Life Science Cluster will be pivotal to these efforts. Overall there is a severe dearth of molecular information with respect to full-length PKCα and its regulation by regulatory factors. Moreover, the kinase domain of PKC isoforms such as PKC-gamma, -delta and -epsilon are conserved however with variations in the regulatory domains. A comparative structural analysis of PKC isoforms with regulatory domains is also lacking in the field. Therefore, the aim is to determine high-resolution structure of full-length PKCα and other isoforms using cryoEM single particle reconstruction methods. In this regard, the has established methods to purify full-length PKCα from insect cells and baculovirus expression system and is in the process of optimizing grid freezing conditions for cryoEM data collection. Expanding the scope and depth of the analysis of molecular functions, the Sivaramakrishnan laboratory has developed a kinase toolbox of FRET-based sensors that can be employed to map the protein-protein interaction landscape of PKCα. The kinase toolbox uses a platform technology, termed systematic protein affinity strength modulation (SPASM). The laboratory has broadly utilized this technology to probe GPCR conformation, GPCR-G protein interactions, and the activity state of downstream effectors including adenylyl cyclase and protein kinase C. Using the SPASM sensors, the lab is bringing its expertise to characterise PKC dysfunctionin HCM. Collectively, the interdisciplinary CBDT labs standardised a template to leverage and accelerate a comprehensive HCM research in India.



7

Integrative Chemical Biology

Praveen Kumar Vemula

Ashok Venkitaraman (Theme Coordinator)

Dasaradhi Palakodeti

Integrative Chemical Biology

Summary

The broad vision of the theme is to develop systems and chemical biology based approaches to study complex cellular processes, for mechanistic insights into disease progression. 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. The 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 with strong translational and clinical implication in disease biology. Based on core expertise, two major research programmes have emerged within the theme.

1. Use of chemical approaches to dissect and modulate biological processes.

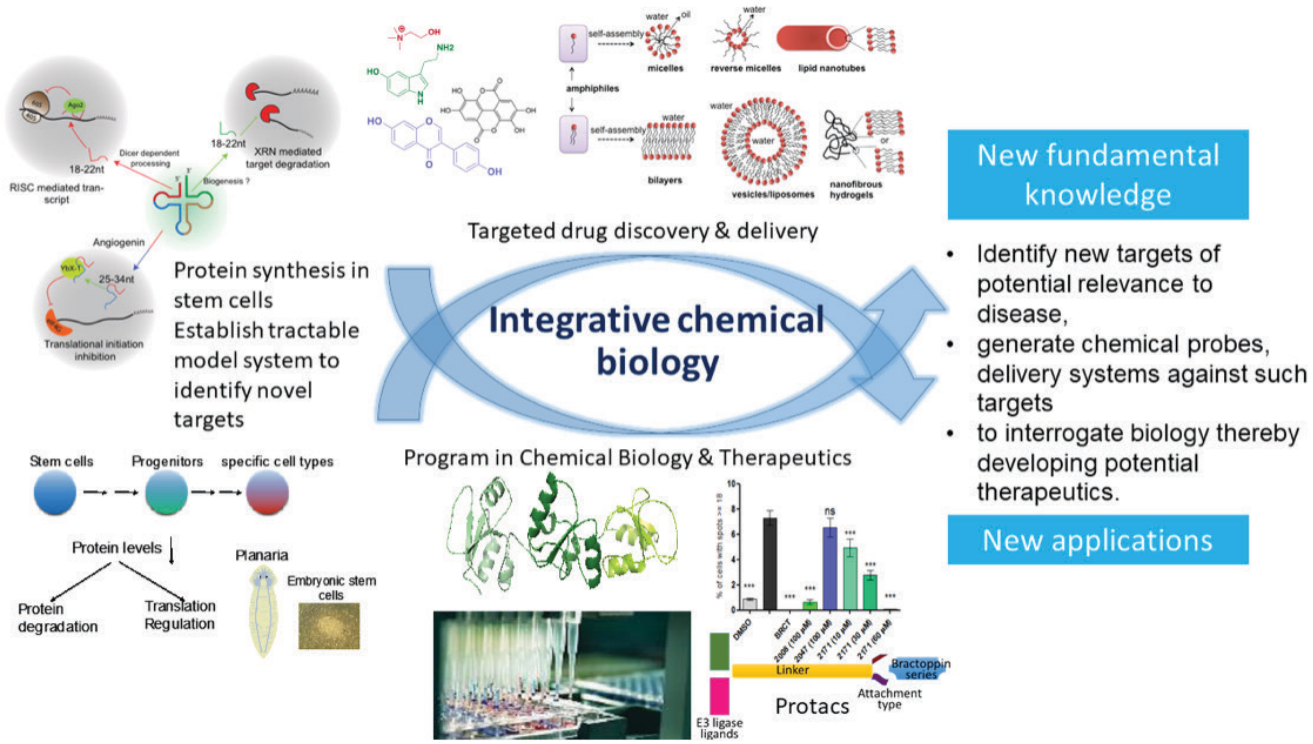
Chemical-based approaches to obtain insights into RNA biology. Dasaradhi Palakodeti's laboratory has a long-term interest in studying RNA mediated regulation of gene expression. Combining rigourous biophysical and biochemical characterizations, the group is the first in the world to report novel roles for newly described RNA species in stem cells with implications for regenerative biology. The group showed a previously described novel class of small RNAs known as tRNA derived small RNA (tsRNAs) in pluripotent stem cell populations, and went on to demonstrate roles in stem cell function. Molecular and biochemical studies show that these tsRNAs and their associated proteins repress translation of specific transcripts critical for maintenance of stemness, thereby, facilitating differentiation. A specific inhibitor was synthesized to block the function of Angiogenin, an endoribonuclease critical for the biogenesis of a specific class of tsRNAs. Inhibition of Angiogenin led to the increased differentiation of embryonic stem cells suggesting the role of Angiogenin and its associated tsRNA in the maintenance of stem cell fate. Currently, research is underway to characterize the regulatory factors including post-transcriptional modification of tRNAs and associated proteins in tsRNAs biogenesis and function.

Expanding the druggable proteome using Chemical Biology. Using innovative approaches to modulate intracellular signalling pathways disrupted in disease investigators in the program on chemical biology and therapeutics (described in detail elsewhere in the Annual Report), 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 BRCA1 tBRCT domain, which selectively blocks BRCA1-dependent signals triggered by DNA damage. We have made strong progress in developing first-in-class drug-like Bractoppin series by applying multiple new strategies including Bractoppin SAR optimization, PROTAC design, Backup series optimization, and Fragment based ligand discovery. Bractoppin series optimization yielded CCBT2171 with improved potency, solubility and Plasma protein binding compared to Bractoppin suggesting its potential to be taken forward for in-vivo studies while Co-crystallization of BRCA1 tBRCT:2171 complex is underway. Alternatively, Bractoppin series PROTAC exploration yielded PROTACs that bind to BRCA1 tBRCT with good *in vitro* potency, and are currently being evaluated for in-cell efficacy. Overall, our efforts in targeting BRCA1 tBRCT with small molecules shows promise. Similarly, our collaboration with the Venkitaraman lab at the MRC Cancer Unit, Cambridge to tackle another phosphopeptide-recognizing domain, 14-3-3ε protein, led to the identification of selective small molecule inhibitors of the 14-3-3ε/FOXO3a interaction and structural elucidation of 14-3-3ε complexed with a novel phosphopeptide. Thus, our success in discovering selective small-molecule inhibitors exemplifies our versatility in addressing the challenges posed to modulate novel targets to enlarge the druggable proteome.

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

Establishing a tractable model system to identify novel targets for disease intervention. Planaria is one of the most well studied models of regeneration worldwide. Genome wide RNAi screens coupled with transcriptome analysis identified several genes that could trigger the process of regeneration in these animals. Recent work from the Palakodeti laboratory has begun to explore the possibility of modelling human diseases in Planaria. The group had identified key roles for conserved RNA processing enzymes - polyA binding proteins (PABP) and RNA helicases – in the maintenance of the integrity and organization of epidermal and muscle tissue in planaria. Their work has also identified factors such as microRNAs, signaling pathways and patterning genes that trigger the formation of the neurons and organization of the brain. Many of the pathways revealed in these studies are known, from the work of others, to have essential roles in development of the human brain and mutations associated with neuro-developmental disorders. This holds out the promise of identifying novel regulators or targets relevant to human disease by relatively unbiased approaches, that can be realised with planaria. Having established methods to isolate and establish culture conditions to sustain stem cells outside planaria, the group is poised to perform knockdown screens and biochemical assays to identify (evolutionarily conserved and other) pathways, essential for maintenance of stemness and differentiation of specific tissue lineages.

Establishing a platform for small molecule based targeted drug discovery. A novel library of small molecules has been developed, which mimic the structure of gut metabolites. Using these molecules, Praveen Vemula's laboratory has uncovered a new role for gut metabolites in repairing epithelial barrier dysfunction. These findings have led to improved understanding of disease progression and enabled the development of potential drugs that restore/ re-establish a broken gut barrier. Barrier dysfunction plays a vital role in diverse disease pathologies, including inflammatory bowel diseases, alcohol liver disease, and non-alcohol liver disease and contributes to a huge social health burden. Therefore, the capability to modulate barrier dysfunction using new chemical entities could significantly impact new therapeutics for barrier dysfunction-associated diseases. Recently, the team has demonstrated that alcohol consumption, either binge or chronic forms, led to the breaking of the gut barrier in contexts which culminate in alcohol liver disease. Furthermore, in studies performed in preclinical models of disease, a small molecule-mediated overexpression of tight junction proteins in the gut epithelial cells resulted in the repair of the gut barrier, which reduced the pathology associated with alcohol liver disease. The team is currently investigating the potential therapeutic efficacy of this small molecules platform for the treatment of other barrier dysfunction-associated diseases.



8

RCF

Regulation of Cell Fate

Apurva Sarin
(Theme Coordinator)

Sunil Laxman

Arvind
Ramanathan

Tina Mukherjee

Arjun Guha

Regulation of Cell Fate

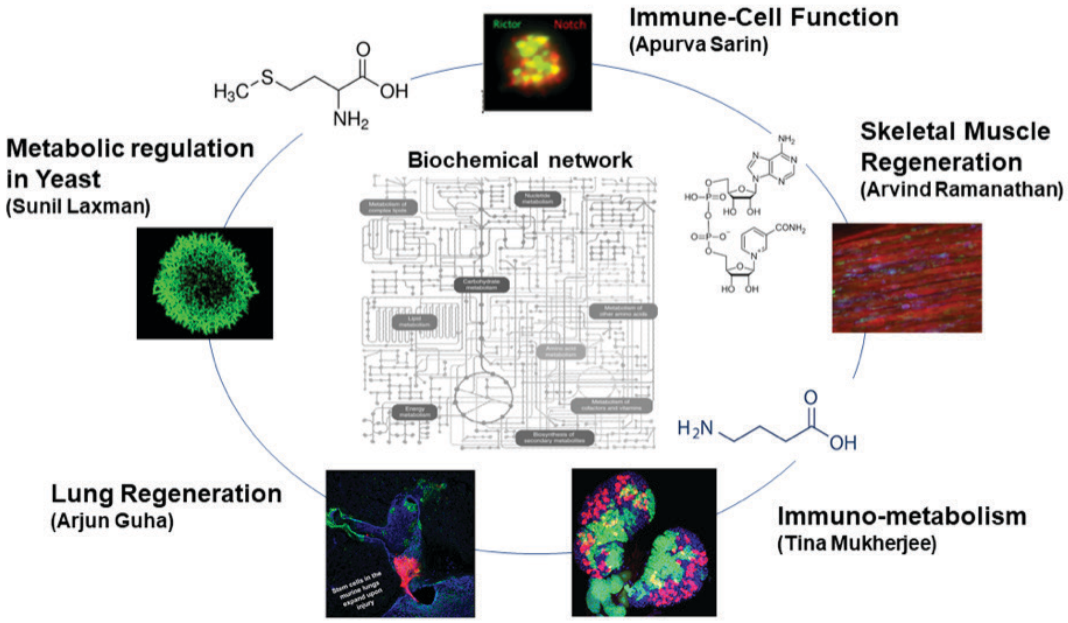
Summary

Decision-making processes during cell state changes determine the long-term growth/developmental trajectories and require the integration of cell-extrinsic and cell-intrinsic networks, impinging on downstream signaling, metabolic and transcriptional/translational circuitry. In adult organisms, the maintenance and restoration of homeostasis involves the active balancing of cell populations. Perturbations of homeostasis due to cell turnover, injury, infections or the deletion of damaged/defective cells are reset by the activation of tissue-resident, specialized stem/progenitor cells. The dynamic modulation of cellular repertoires in complex tissues requires a diverse set of distinct cell fate decisions that are shaped by the local microenvironment as well as systemic cues. The "Regulation of Cell Fate" theme has focused its efforts on understanding responses to physiological, pathological and environmental challenges, to tissue homeostasis through the inter-connected investigation of metabolic control of cell fate. The groups use diverse array of model systems including budding yeast, *Drosophila* and mice, attempts have been initiated to identify systemic influences and signaling cascades through the lens of metabolism. The application of these to contexts of biomedical relevance is an immediate goal for the theme's future endeavours.

The past year has seen the strengthening of linkages between the laboratories of Laxman & Sarin; Guha & Mukherjee as well as Laxman & Ramanathan, in attempts to address questions on cell fate regulation in various tissue and cellular contexts. These efforts speak to a core thematic direction, unifying signaling and metabolic mechanisms in the regulation of cell fate. The investigators work on the following experimental models: Nutrient sensing and metabolic control of cellular behavior, [Sunil Laxman, in budding yeast, Arvind Ramanathan and Apurva Sarin, in isolated cells and mice]; Metabolic control of blood cell homeostasis [Tina Mukherjee, in *Drosophila*]; Airway epithelial homeostasis and senescence and repair in muscle [Arjun Guha and Arvind Ramanathan, respectively]. The laboratories employ genetic, biochemical and systems-level approaches toward dissecting signals that maintain homeostasis, and perturbations of these to amplify the signals that orchestrate effector responses. The aforementioned perturbations include injury, exposure to cytotoxic chemicals, infectious/allergenic agents, hypoxia and nutrient deprivation or excess. Given the importance of understanding causal events that drive distinct cell fates (differentiation, proliferation, survival and death) in biology and human disease, we have established tractable systems and identified specific niches (regulatory T-cells, hematopoietic stem cells, lung stem cells, muscle aging and repair), where disparate cues control cell identity and fates. The theme brings together investigators with expertise in metabolism, signaling, cell biology as well as physiology to develop comprehensive approaches to address these questions.

Some of the highlights of our efforts in the past year are summarised in the following section. Across the laboratories, metabolic-control check points in specific developmental processes or transitions that cannot be easily explained using simpler paradigms of transcriptional/signaling control, have been identified. Sunil Laxman's laboratory has leveraged capabilities they have established in the laboratory, to measure levels and fluxes of metabolites to show that methionine is a hub-metabolite that rewires glucose and mitochondrial metabolism by signaling via the nutrient responsive transcription factor gcn4/ATF4. This has set the stage for a joint programme with Apurva Sarin's laboratory, in exploring a requirement for methionine, which is, intriguingly, tuned by Notch signaling in T-cell fate determination. Using the metabolite measurement platform Arvind Ramanathan's laboratory is focusing on the role of hub metabolites in aged cells and skeletal muscle cells. His laboratory has identified the role of fatty acid derived prostaglandins in regulating signaling pathways like HRas, as a mechanism of promoting cancer. The laboratory is also studying the role of hub metabolite and enzyme cofactor NAD+ in regulating skeletal muscle homeostasis in response to disuse and in muscle regeneration. Tina Mukherjee's group has made strides in developing a comprehensive

framework to define non-immune function of innate immune cells. These have been demonstrated in the maintenance of systemic homeostasis in response to environmental and metabolic stimuli using *Drosophila.* Further, a detailed understanding of the role for the neurotransmitter GABA, functioning as a metabolite in immune cells and controlling the response to infection in *Drosophila* has also emerged from her laboratory. The implications of conserved functions in vertebrate immune cells are just one exciting outcome of this work. Arjun Guha's laboratory has bridged the role of environmental stress signaling in regulating cellular fate using the mouse lung's response to injury and in the maintenance of homeostasis. His laboratory has uncovered a possible role for the Fragile X Mental Retardation Protein (FMRP) in the pulmonary oxidative stress response using FMR1 knockout mice, which were available for the analysis of FMRP in neurodegenerative disorders by other groups on campus. Using these mice, his laboratory has shown that FMRP protects the airways in mice, and potentially in humans, from the cytotoxic effects of aromatic hydrocarbons that cause oxidative and genotoxic stress. Employing *Drosophila,* his laboratory has focused on mechanisms regulating cell cycle checkpoints during normal development and regeneration. Overall, the theme has integrated different scales of biology, from single cells to the organismal level, and established approaches to interrogate the role of metabolic and environmental signals in both the maintenance, and restoration of homeostasis in contexts of injury, disease and aging.



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A translational unit of inStem

CSCR *Centre for Stem Cell Research, CMC Vellore*

Shaji R Velayudhan

Srujan Marepally

Alok Srivastava (Head)

Mohankumar K Murugesan

Sanjay Kumar

Vrisha Madhuri

Sarvanabhavan Thangavel

Sunil Martin

Centre for Stem Cell Research, CMC Vellore

Summary

The Centre for Stem Cell Research (www.cscr.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 to find solutions for current medical needs in the country. Three thematic multi-individual, multi-disciplinary and multi-institutional research programmes are described below.

Musculoskeletal Regeneration

This programme is coordinated by Vrisha Madhuri and includes Vikram Mathews, Nihal Thomas, Srujan Marepally, Mohan Kumar, Alok Srivastava, Dolly Daniel, Lilly Verghese. The major focus is on clinical and preclinical translation related to physis, articular cartilage, bone, and muscle regeneration, with a focus on two major areas. 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 foetal liver derived mesenchymal stem cells (MSC). 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 uses culture-expanded muscle derived stem cells for the treatment of urinary sphincter incontinence. The second focus is on cell-free therapy for cartilage and bone regeneration using biomolecules. In collaboration with multidisciplinary groups from SCTIMST, Trivandrum, Kerala 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 animal and cellular models. These 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.

Another research programme under the same theme is led by Elizabeth Vinod and includes Upasana Kachroo, Solomon Sathish Kumar, Soosai Amirtham Manickam, Abel Livingston, Viju Daniel Varghese, Alfed Job Daniel. The major focus is on the characterization of cartilage-derived progenitors and studying potential implications for cartilage regeneration using in-vitro and in-vivo conditions.

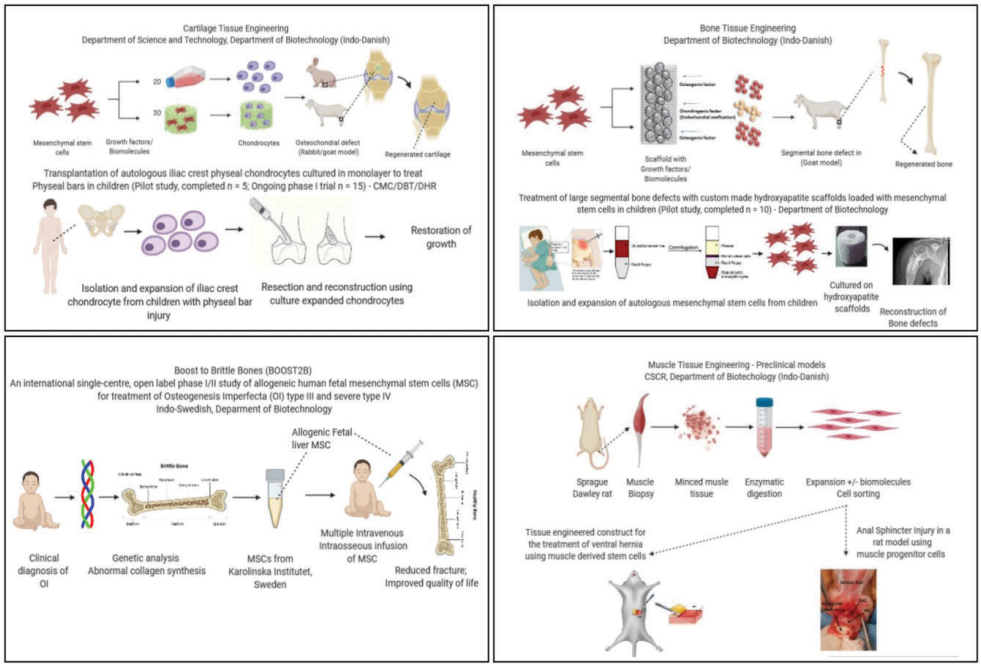


Figure: Regenerative strategies using cell-based and cell-free therapy for musculoskeletal disorders

The work involves the characterization of soluble factors derived from these progenitors and assessing their potential for cultivating directly injectable therapeutic molecules. Another outcome is the creation and validation of osteoarthritic models in animals and the development of novel histological processing techniques for the assessment of chondrogenesis.

Gene Therapy

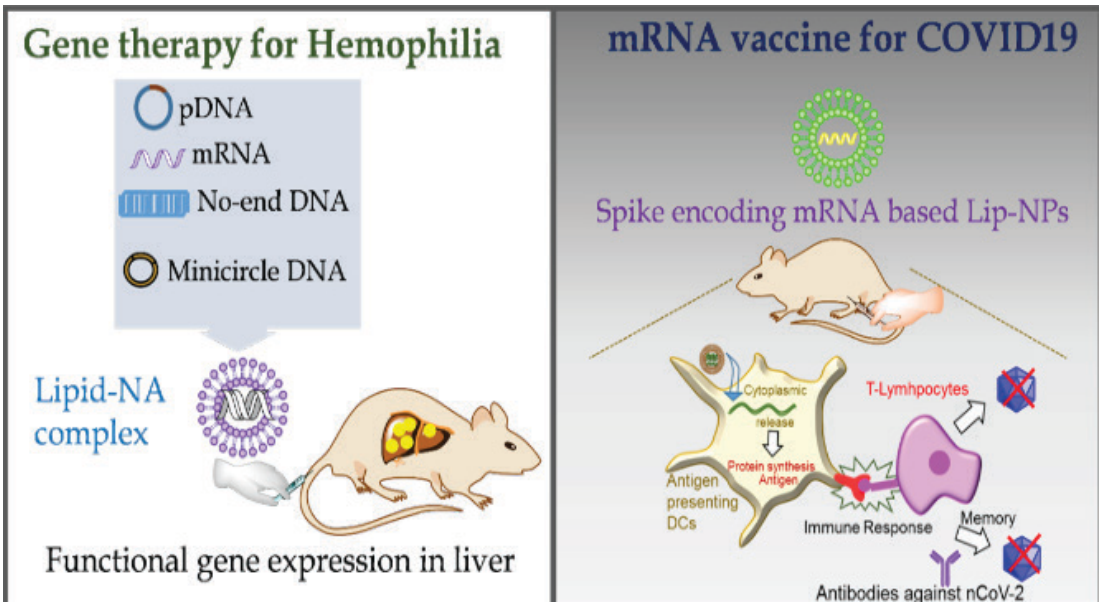
A major focus of research at CSCR is on gene therapy. The goal is to capitalize on recent advances in the world towards gene therapy of monogenic haematological disorders, and make them accessible to patients in India. Several scientists and physicians are involved with this work, which is coordinated by Alok Srivastava and includes R V Shaji, Saravanabhavan Thangavel, Mohankumar Murugesan, Srujan Marepally, Sunil Martin and Gurbind Singh at CSCR, several Faculty from CMC, Vellore as well as other collaborators.

Haemophilia: This involves two major areas at present. The first is directed towards haemophilia where two programmes 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 in a major initiative for the first time 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. Here the lentiviral vector is ready and the final gene therapy product with the autologous stem cells will be manufactured at site in India. With approval from CDSCO in place, this should be initiated very soon.

The second part of the gene therapy programme involves gene therapy for major haemoglobin disorders. Here again, 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. These have tested in cellular and animal models and are now close to clinical translation. This programme is a collaboration with Emory University, USA as well as 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-CoV-2 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 an 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 (details in the NAHD report) 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 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.

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. Newer areas of research are being established to assess antitumor functions of NK cells, γδ T cells and αβ T cells with the specificity and robustness of Chimeric Antigen Receptors (CARs). The area of immune cell therapy is being coordinated by Sunil Martin.

Cellular Reprogramming and its Applications - Disease Modelling 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 disease modelling and haplobanking. Towards the former, reprogramming technology has been applied to the develop disease models of various bone marrow failure syndromes – Fanconi anaemia, Diamond Blackfan anaemia and congenital dyserythropoietic anaemia. 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).

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Bhavana Muralidharan

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Colin Jamora

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inStem Awards/Honours
April 2020 – July 2021

- Dr. Bhavana Muralidharan, selected for the Har Gobind Khorana Innovative Young Biotechnologist Award (HGK-IYBA)-2020.
- Dr. Praveen Kumar Vemula, is a recipient of the 'DBT-Biotech Product, Process Development & Commercialization Award-2020.
- Dr. Anusree Mahanta, a postdoctoral fellow at inStem won the award for the best talk at the Young Scientist Conference-2020.
- Dr. Sunil Laxman, is one of nine life scientists in 2020 selected to the European Molecular Biology Organization's Global Investigator Programme.
- Dr. Tina Mukherjee awarded the Fellowship from University of Strasbourg Institute for Advanced Studies (USIAS)-2021.
- Dr. Aswathy BS, Dr. Kavitha Govarthanan and Dr. Raja Lakshmi S, awarded the MK Bhan-Young Researcher Fellowship Program (YRFP)-2021.

Patents applied for

1. ***Title:*** Compact liposomal vehicle for delivery of large molecules
   Inventors: Srujan Marepally, Saravanabhavan Thangavel and Alok Srivastava (CSCR)
   Application no.: 202041010160
   Filing date: 09.03.2020, India

2. ***Title:*** Microtubule marker
   Inventors: Minhajuddin Sirajuddin, Balaji M Rao and Shubham Kesarwani
   Application no.: 202041014818
   Filing date: 03.04.2020, India

3. ***Title:*** Germicidal fabric technology to create antiviral/antibacterial masks, PPEs and cloths
   Inventors: Praveen Kumar Vemula, Mahendra K Mohan, Sandeep Chandrashekharappa and Siju C.
   Application no.: Know-How Knowledge
   Filing date: 12.04.2020, India

4. ***Title:*** Compositions and methods for reactivating developmentally silent genes
   Inventors: Mohankumar Murugesan and Alok Srivastava (CSCR)
   Application no.: 202041020165
   Filing date: 13.05.2020, India

5. ***Title:*** A biosensor, a kit and application thereof
   Inventors: Arati Ramesh, Akash Gulyani, Geen George, Siladitya Bandyopadyay, Sreesa Sreedharan and Anirudh Chakravarthy Srinath
   Application no.: 202041030231
   Filing date: 15.07.2020, India

6. ***Title:*** Substituted Lithocholic Acid and Methods Thereof
   Inventors: Srujan Marepally, Porkizhi Arjunan, Gokulnath Mahalingam, Praveen Kumar Vemula and Alok Srivastava
   Application no.: 202041047355
   Filing date: 29.10.2020, India

7. ***Title:*** Methods and systems for determining viruses in biological samples using a single round based pooling
   Inventors: Manoj Gopalkrishnan, Ajith Rajwade, Dasaradhi Palakodeti and Sandeep Krishna
   Application no.: 202021051801
   Filing date: 27.11.2020, India

8. ***Title:*** Recombinant Milk Proteins
   Inventors: S. Ramaswamy, Sanchari Banerjee and Kanaga Vijayan
   Application no.: 202141001050
   Filing date: 09.01.2021, India

9. ***Title:*** Molecular markers for infection-induced lung damage;
   Inventors: Neha Vyas (St. John's Research Institute) and Apurva Sarin (inStem)
   Application no.: 202141029243
   Filing date: 29.06.2021, India

10. ***Title:*** Formulation, Lipid Compounds And Methods Thereof
    Inventors: Srujan Marepally and Alok Srivastava
    Application no.: 202141033290
    Filing date: 23.07.2021, India

Granted patents:

1. ***Title:*** Compounds As Fluorescent Probes, Synthesis And Methods Thereof
   Inventors: Akash Gulyani, Sufi Oasim Raja and Gandhi Sivaraman.
   Patent no: US 201903759
   Granted Date: 20.10.2020, USA

10 COVID - 19 Response

COVID-19 Response at inStem

The COVID-19 pandemic has had 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 management, and development of interventions to prevent viral infection. As the pandemic was taking hold in India, 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. These efforts leveraged the local ecosystem, which includes the NCBS-TIFR and C-CAMP at Bengaluru. Altogether, the large breadth of programmes contribute significantly in the national efforts to combat SARS-CoV-2 and mitigate its detrimental impact on society.

TESTING, DIAGNOSTICS & TRACKING

COVID-19 Testing Laboratory

The testing laboratory located in a separate floor in the inStem building, began activities in April 2020. The laboratory, not only meets the highest standards for safety and ethical management of information, but also emphasizes the overall well-being of the volunteers and staff who undergo routine medical checkups and have access to support programmes. The testing facility has since tested ~ 190,000 samples from throughout the state of Karnataka. These efforts have been buoyed by support from the DBT and the State Government, as well as generous philanthropic support enabling free-of-cost RT-PCR based testing for SARS-CoV-2 for a large number of people from disadvantaged and marginalised communities.

Diagnostic kit evaluation and optimisation

As a natural extension of the infrastructure and trained personnel to handle samples and to conduct COVID-19 testing efficiently, inStem has received designation from the ICMR-NIV to serve as a validation centre for new testing kits developed by academic and biotechnology laboratories. The validation centre at inStem will use 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) programme, which aims to locally build a large capacity of COVID-19 molecular diagnostic kits and reagents. Thus far, the inStem group has assisted 15 companies in the development and optimization of 45 kits that are based on multiple technologies including RT-PCR, LAMP, and CRISPR on nasopharyngeal swab and saliva samples.

C-CAMP InDx ATMANIRBHAR BHARAT

INSACOG (Indian SARS-CoV-2 Genomics Consortium)

inStem is one of the original designated Regional Genome Sequencing Laboratory (RGSL) and 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, which has achieved its initial goal of completing the sequencing of 1000 SARS-CoV-2 genomes. INSACOG, locally managed by Dasaradhi Palakodeti at inStem and Uma Ramakrishnan at NCBS 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. Till date the laboratory has sequenced more than 3000 viral genomes since it began activities in May 2021.

COVID19 Bioresource

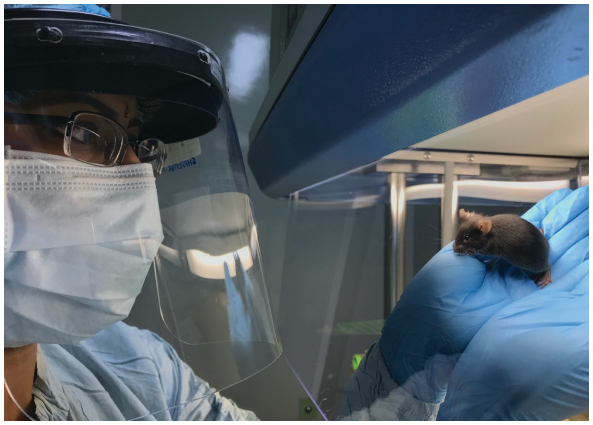
inStem is one of the five dedicated biorepositories established by the Department of Biotechnology for clinical and viral samples linked to the coronavirus disease (COVID-19). The purpose of this biorepository is to share biological materials from infected patients with clinicians and researchers from the academia and industry to accelerate innovations to combat the pandemic. Starting off with the storage of nasopharyngeal and oropharyngeal swab samples, the biorepository has teamed up with Hospitals in Bengaluru to expand the collection to include serum (blood), saliva, PBMCs and bronchioalveolar lavages. Though initially projected to collect up to 400 samples in the first year, over 9 months over 1400 samples are already archived. 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. Thus far, the biorepository samples have been used by an academic laboratory to develop a new RNA based biosensor to detect multiple variants of SARS-CoV-2 from swabs as well as saliva (**doi:** https://doi.org/10.1101/2021.01.08.21249426). In addition the biorepository has been an important resource in the development of a saliva testing kit from Kryamed that is now under consideration for FDA approval.

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 accurately 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 employed state-of-the-art infrastructure and highly skilled personnel to rapidly deploy these resources to generate mouse models of COVID-19 infection. Three so-called "humanized" mice were generated in a period of five months, 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 characterisation 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. Consequently, we are now poised to provide a powerful mouse model to researchers throughout India in a process that bypasses the administrative hurdles of importing live animals from overseas.



Animal BSL-3 (ABSL-3 Facility)

An animal BSL-3 facility is being established in which challenge studies using the mouse models can be performed to test new vaccines and therapies. This project is currently in design phase and is slated to be able to perform most preclinical studies from investigators in academia and industry. In addition to meeting strict regulatory requirements for work with contagious, airborne pathogens, the facility will be equipped with a state-of-the art whole animal imaging system that will allow tracking of potential treatments in a live animal. Ongoing plans includes seeking support to obtain the capability to humanize the inflammatory response in the animals to more faithfully recapitulate the pathophysiology of SARS-CoV-2 symptoms in infected patients.

COVID 19 Disease Amelioration

There are team-based projects currently underway aimed at blocking the infection of humans by SARS-CoV-2:
Scientists from inStem (Arjun Guha, Anandi Karumbati and Praveen Vemula) and NCBS (Satyajit Mayor, Vardharajan Sundaramurthy, and Vinothkumar K Raghunath) amongst others, are working to repurpose FDA-approved drugs for the inhibition of SARS-CoV-2 entry into cells. The central hypothesis is that drugs that inhibit endolysosomal acidification in cells will prevent viral entry by preventing fusion of the viral envelope with the endolysosomal membrane. The primary screen for drugs that inhibit endolysosomal acidification has identified 38 compounds from the 1280-compound library. Of these, 15 compounds have shown promising results in blocking SARS-CoV-2 infection. One compound, Niclosamide, was observed to be a potent inhibitor of viral entry and results were published in PLoS Pathogens (https://doi.org/10.1371/journal.ppat.1009706). The drug is now in Phase II trials to evaluate efficacy, safety, and tolerability to treat COVID-19 patients.

11 Science Outreach and Communication at inStem

inStem's science outreach and communication efforts focus primarily on engagements with schools and colleges through webinars, Open Days and school or college visits, as well as more opportunistic participation in diverse programmes that facilitate interactions with the lay public. Owing to the COVID-19 pandemic, digital modes of communication were leveraged in the past year and have allowed a wider reach, albeit without the more personal interactions that were possible earlier. In the sections that follow a few events from our repertoire of outreach activities are highlighted.

Engagement with Schools, Undergraduate Colleges and our Communities

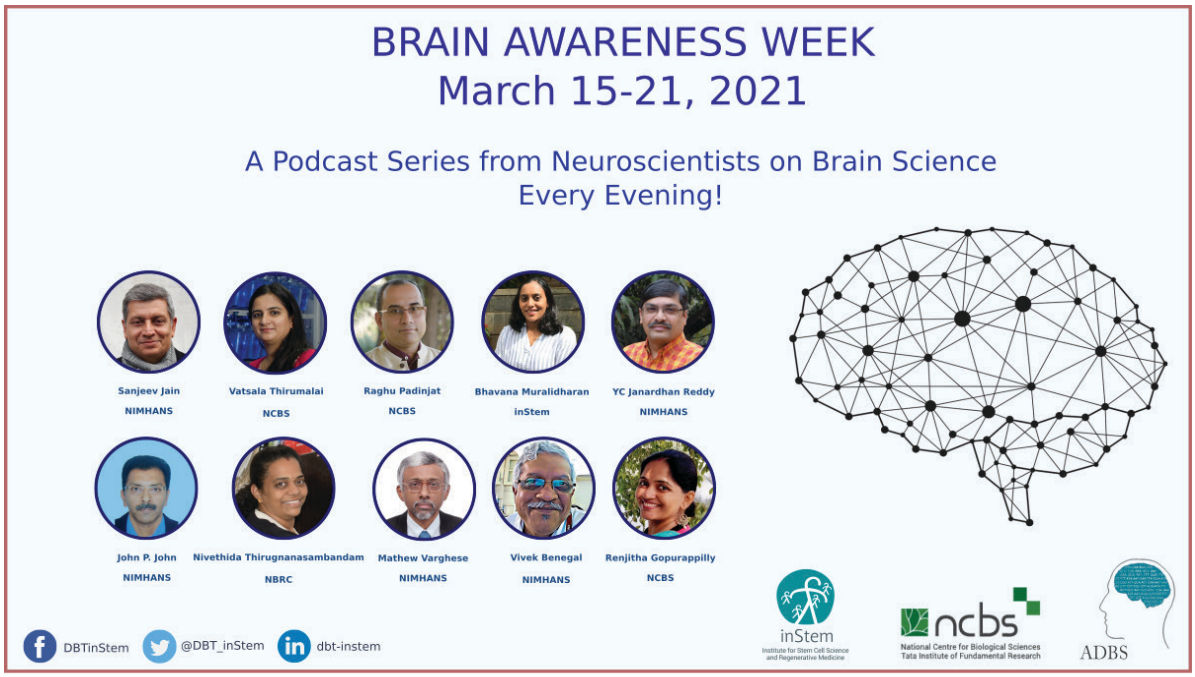
The Science Setu programme, called *Discovering Possibilities* is a celebration of India@75, Azadi Ka Amrit Mahotsav, under the aegis of the Atmanirbhar Bharat campaign. This is an online interactive series, which includes lectures on current, contemporary areas of research being undertaken in laboratories in India, and presented in a format accessible to students in colleges. Attracting an enthusiastic audience of 150-175 participants, the sessions, which began in April 2021, have touched on areas ranging from the 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 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, Chennai
- St. John's college, Anchal, Kollam.

Earlier in the year, in an outreach event to celebrate International Women's Day 2021 (#IWD2021) we collaborated with CARE India. This event connected young women scientists from inStem laboratories with school students from the Ponneri and Kattumannarkoil regions in Tamil Nadu. Communicating in the vernacular, Drs. Anandi Karumbati and Shridhivya A.R., from the 'Program on Chemical Biology and Therapeutics' (PCBT), inStem and NCBS spoke on *'What is science'* and *'Journey of a drug in the human body'*. Along similar lines, Sujanthi E. and Dr. Rajalakshmi Srinivasan, engaged with students from Srimushnam and Chinnambedu Govt. schools, Tamil Nadu. The speakers narrated their personal journeys and the motivations to pursue a research career. Further, they also spoke about the facilities on campus, scholarships, funding agencies and various organizations that empower and encourage women to consider STEM as a career option.

On the occasion of National Science Day, a webinar titled *'Future of Science, Technology, and Innovation: Impact on Education, Skills, and Work',* which featured speakers from on academia and industry was organised on February 27, 2021. Praveen Vemula, inStem, Vatsala Thirumalai, NCBS, and Naren Chirmule, CEO, Symphony Tech Biologics, shared insights on the importance of fundamental science and curiosity in transitioning to translational outcomes and technology development. The talks, which drew upon the speakers' personal journeys in science and research in distinct domains, illustrated how the convergence of various disciplines including chemistry, biology, physics and engineering enable new discoveries. This webinar was attended by students and faculty from colleges in Bangalore, Ujire, Mangalore, and Kollam and included an interactive and extended Q&A session with many comments on the chat box and lively participation from the audience.



Brain Awareness Week, organised by Dr. Bhavana Muralidharan was celebrated from March 15-21, 2021 via a series of podcasts with scientists from DBT-inStem, NCBS-TIFR, NIMHANS and DBT-NBRC. Scientists spoke on a wide range of topics related to the brain such as mental illness, addiction, Parkinson's disease, non-invasive treatment methods, brain imaging, personalized medication for mental illness. In addition, the possibilities of utilizing iPSCs (induced pluripotent stem cells) in diagnosis and treatment of brain disorders with a special focus on modelling brain disorders-in-a-dish and the ADBS programme was also covered. The campaign was primarily driven through our social media handles and the podcasts were hosted on our SoundCloud account.

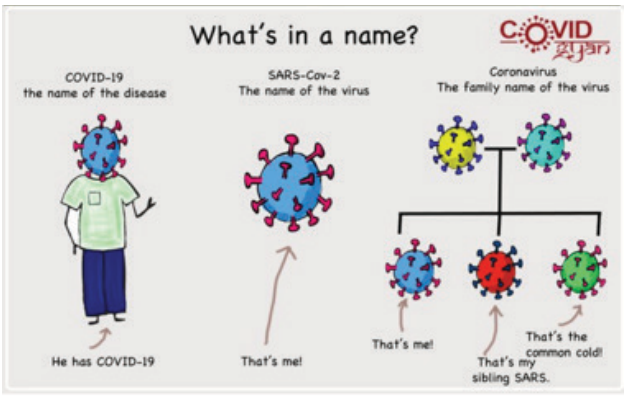
The Science Café is a monthly series of curated science talks by scientists associated with the Bangalore Life Science Cluster (NCBS, inStem, and C-CAMP), to initiate interactions with their local residential communities. Science Café transitioned to an online mode with sessions hosted and live streamed on The BLiSC YouTube channel. The December 2020 Science Café, featured Sunil Laxman, inStem, who spoke about *'Life in the Extreme'.* Another series, 'The Human Body: InsideOUT' curated for high school and college students featured scientists who talked about one human body part associated with their research. inStem scientists Bhavana Muralidharan and Arvind Ramanathan presented in this series, with talks entitled '*Exploring the brain: Its birth and function'* and *'Skeletal muscle – life's mover and shaker!'* respectively. These sessions attracted close to 200 participants and included quiz polls along with Q&A session to facilitate audience participation.

Digital Exhibits and Conferences

The past year has been 'the year of digital exhibits and virtual conferences'. inStem participated in the 6th India International Science Festival 2020 (IISF 2020) from December 22-25, 2020, which was organized by the Council of Scientific and Industrial Research-National Institute of Science, Technology and Development Studies (CSIR-NISTADS). Anusree Mahanta, a postdoctoral fellow at inStem, won the award for the best talk at the conference. inStem participated in the 2nd edition of the Global Bio India 2021— a three day mega international conglomerate of biotechnology stakeholders from March 01-03, 2021; organized by the Dept. of Biotechnology, India and Biotechnology Research Assistance Council (DBT-BIRAC) with Confederation of Indian Industries (CII), Invest India, and Association of Biotechnology Led Enterprises (ABLE) as event partners. Our virtual booths at #IISF2020 and #GlobalBioIndia2021 showcased videos on inStem and on-campus COVID testing efforts along with posters on the various thematic programmes at inStem and our translational unit at CSCR, to highlight the multi-institutional, collaborative and multidisciplinary nature of our efforts.

COVID19 Outreach

A national crisis like the COVID-19 pandemic calls for clear and simple explanation of issues at hand. Scientists, in particular, we participated in efforts to generate informed awareness in the general public on the scientific basis of the disease, as well possible solutions to mitigate its spread. This task was assisted using graphical science i.e. merging art with science. The informative graphic novel ***'Bharath and Fatima learn about COVID 19',*** created by Arvind Ramanatha, inStem in collaboration with Sonia Sen, TIGS-Centre at inStem, is one such contribution posted on the multi-institutional, multi-lingual COVID-Gyan website. The comic is based around two children Bharath and Fatima and their education on COVID-19, the immune system, and vaccines, with their uncle Raman who is a scientist. This graphic novel has been also translated into Hindi and Marathi.



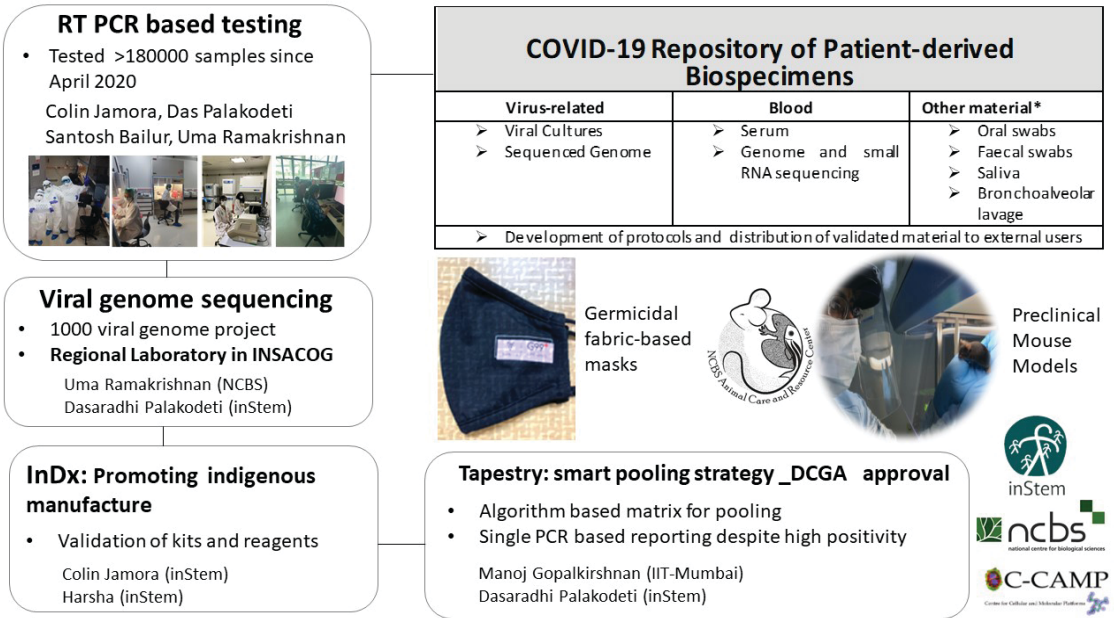
Our social media handles have been critical in designing and running the 'social campaigns' in these uncertain times of COVID-19. The **#Unite2FightCorona** has been a major effort, which began in Oct-Nov 2020. Through various in-house contents such as posters, artwork, and photographs and videos in English, Hindi and Kannada, we emphasized on the three basic rules that are critical to limit the spread of infection: #WearAMask, #HandHygiene, and #PhysicalDistancing. We have also campaigned to raise awareness of the importance of vaccination. Sriram Varahan, a postdoctoral fellow at inStem presented a webinar titled *'COVID: What has it taught us really?'* to high school students of P.S. Senior Secondary School, Mylapore, Chennai on Oct 17, 2020.

In November 2020, the **#AskMeAnything** session hosted Dasaradhi Palakodeti, inStem and Manoj Gopalkrishnan, IIT-Mumbai who spoke about their collaborative venture – the ***'Tapestry Pooling'*** for effective COVID testing. In this unique session, the speakers primarily addressed the questions from the audience over a panel discussion. The algorithm developed by Manoj Gopalkrishnan and Sandeep Krishna, NCBS-TIFR, Bangalore has been experimentally tested – involving matrices of increasing complexity and samples of known status – by Dasaradhi Palakodeti.

Participation in National Outreach Initiatives

The pan-institutional COVID-Gyan website (www.covid-gyan.in) launched in April, 2020 still serves as a national hub to bring together a collection of resources in response to the COVID-19 outbreak. As a part of the COVID outreach effort, inStem has actively supported, and contributed to, this website with other research institutions from across the country. The website can be accessed in 13 Indian languages and the content ranges from infographic to scientific articles, webinars, and podcasts.

The 6th DBT webinar held on Nov 20, 2020, organized in association with DBT-India Alliance Wellcome Trust, focused on the responses of DBT Autonomous Institutes to the COVID-19 pandemic. This included the Institute for Stem Cell Science and Regenerative Medicine (inStem), National Brain Research Centre (NBRC), and Rajiv Gandhi Centre for Biotechnology (RGCB). The panelists for the webinar were the directors of inStem, NBRC and RGCB.



LIST OF STUDENTS DEFENDED/AWARDED THESIS (1-8-2020 TO 31-7-2021)

1. **Name of the student:** Preeti Madhav Kute
   Registered University: Sastra
   Thesis guide: Ravi Muddashetty
   Thesis title: NMDAR mediated translation at the synapse is regulated by MOV10 and FMRP
   Date of the thesis award: 05/09/2020

2. **Name of the student:** Nishan B S
   Registered University: Sastra
   Thesis guide: Akash Gulyani
   Thesis title: Complex Light Sensing in Simple Eyed Flatworms Reveals New Sensory Paradigms
   Date of the thesis awarded: 31/10/2020

3. **Name of the student:** Radhika Rao. A
   Registered University: Sastra
   Thesis guide: Shravanti Rampalli
   Thesis title: Understanding the Role of Histone Methyl Transferases in Development and Aging.
   Date of the thesis award: 15/04/2021

4. **Name of the student:** Amrutha K
   Registered University: Sastra
   Thesis guide: Arjun Guha
   Thesis title: Mechanism Regulating Developmental G2 arrest in Drosophila
   Date of the thesis award: 29/10/2020

5. **Name of the student:** Nitya Nandkishore
   Registered University: Sastra
   Thesis guide: Ramkumar Sambasivan
   Thesis title: Role of Anterior Signals in Cardiopharyngeal Mesoderm Developement.
   Date of the thesis award: 12/08/2020

6. **Name of the student:** Ananya Mukherjee
   Registered University: Sastra
   Thesis guide: Akash Gulyani
   Thesis title: Visualizing Spatio Temporal protein Activation and dynamic signal integration with engineered fluorescent Biosensors
   Date of the Thesis exam: 16/07/2021

7. **Name of the student:** Aritra Misra
Registered University: Manipal
Thesis guide: Ramkumar Sambasivan
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 the thesis award: 05/03/2021

8. **Name of the student:** Bhakti Vyas
Registered University: Manipal
Thesis guide: Ramkumar Sambasivan
Thesis title: Genetic program regulating vertebrate mesoderm development along anterior-posterior axis.
Date of the thesis award: 17/02/2021

9. **Name of the student:** Sudhriti Dastidar
Registered University: Manipal
Thesis guide: Ravi S. Muddashetty
Thesis title: Bioenergetics of glutamate receptor-mediated protein synthesis
Date of the thesis award: 24/02/2021

10. **Name of the student:** Shubham Kesarwani
Registered University: Manipal
Thesis guide: Minhaj Sirajuddin
Thesis title: Spatial and temporal organization of microtubule posttranslational modifications
Date of the thesis award: 24/05/2021

INSTEM LEADERSHIP COMMITTEES 2020 -2021

DIRECTOR
Prof. Apurva Sarin

SOCIETY

Dr. Renu Swarup, *Secretary to the Government of India, DBT, New Delhi - President*
Prof. Apurva Sarin, *Director, inStem, Bengaluru*
Dr. Alka Sharma, *Advisor & Scientist G, DBT, New Delhi*
Mr. B. Anand, *Addl Secretary & FA, DBT, New Delhi (till March 2020)*
Ms. Jyoti Arora, *Special Secretary & FA, DBT, New Delhi (April- September 2020)*
Shri. Vishvajit Sahay, *Addl Secretary & FA, DBT, New Delhi (October 2020- till date)*
Shri. Chandra Prakash Goyal, *Joint Secretary (Admin), DBT, New Delhi*
Prof. K. VijayRaghavan, *Principal Scientific Adviser to the Govt. (Signatory to MoA)*
Dr. Kiran Mazumdar Shaw, *CMD, Biocon India Ltd., Bengaluru (Signatory to MoA)*
Prof. H. Sharat Chandra, *Hon. Director, Centre for Human Genetics (Signatory to MoA)*
Prof. Jyotsna Dhawan, *Emeritus Scientist, CCMB, Hyderabad (Signatory to MoA)*
Prof. Satyajit Mayor, *Centre Director, NCBS-TIFR, Bengaluru (Signatory to MoA)*
Prof. P. Balaram, *Molecular Biophysics Unit, IISc, Bengaluru (Signatory to MoA)*
Prof. S. Ramaswamy, *Visiting Professor, inStem, Bengaluru (Signatory to MoA)*
Prof. Goverdhan Mehta, *CSIR Bhatnagar Fellow, Bengaluru*
(Signatory to MoA)
Prof. J. V. Peter, *Director, CMC, Vellore*
Mr. Pawan Kumar Pahwa, *Head-Admin & Finance, inStem, Bengaluru (Non-member Secretary till 24th March 2021)*
Mr Ramanathan K, *Senior Admin Officer, inStem, Bengaluru* (*Non-member Secretary, 25th March 2021 onwards)*

GOVERNING BODY

Dr. Renu Swarup, *Secretary to the Government of India, DBT, New Delhi - Chairperson*
Prof. Apurva Sarin, *Director, inStem, Bengaluru*
Mr. B. Anand, *Addl Secretary & FA, DBT, New Delhi (till March 2020)*
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Shri. Chandra Prakash Goyal, *Joint Secretary (Admin), DBT, New Delhi*
Dr. Alka Sharma, *Advisor & Scientist G, DBT, New Delhi*
Dr. Niloo Srivastava, *Scientist 'E', DBT, New Delhi (Up to September 2020)*
Dr. Kalaivani Ganesan, *Scientist 'E', DBT, New Delhi* **(From October 2020)**
Prof. Satyajit Mayor, *Centre Director, NCBS-TIFR, Bengaluru*
Prof. Upinder S Bhalla, *Dean, NCBS, Bengaluru*
Prof. J. V. Peter, *Director, CMC, Vellore*
Prof. Alok Srivastava, *Head- CSCR, CMC Vellore*
Prof. Sandeep Trivedi, *Director, TIFR, Mumbai (up to September 2020)*
Prof. S. Ramakrishnan, *Director, TIFR, Mumbai (from March 2021)*
Prof. Gagandeep Kang, *Former Executive Director, THSTI, Faridabad (Presently Professor, CMC Vellore)*
Prof. Soniya Nityanand, *Professor and Head, Dept. of Hematology, SGPGI, Lucknow*
Prof. Jyotsna Dhawan, *Emeritus Scientist, CCMB, Hyderabad*

Dr. Dinakar Salunke, *Director, ICGEB, New Delhi*
Dr. B. S. Ramakrishna*, Director, SIMS Institute of Gastroenterology, Chennai*
Prof. Mammen Chandy, *Director, Tata Medical Centre, Kolkata*
Prof. S. Ramaswamy, *Visiting Professor inStem, Bengaluru*
Prof. Colin Jamora, *inStem, Bengaluru*
Mr. Pawan Kumar Pahwa, *Head-Admin & Finance, inStem, Bengaluru (Non-member Secretary till 24th March 2021)*
Mr Ramanathan K, *Senior Admin Officer, inStem, Bengaluru (Non-member Secretary, 25th March 2021 onwards)*

SCIENTIFIC ADVISORY COMMITTEE

Prof. Azim Surani, *Wellcome Trust, Cancer Research UK, Gurdon Institute, University of Cambridge, UK*
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Prof. Upinder S. Bhalla, *Dean, NCBS, India*
Prof. Apurva Sarin, *Director, inStem, India*

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Shri. B. Anand, *Addl Secretary & FA, DBT, New Delhi (till March 2020)*
Ms. Jyoti Arora, *Special Secretary & FA, DBT, New Delhi (April to September 2020)*
Shri. Vishvajit Sahay, *Addl Secretary & FA, DBT, New Delhi (October 2020 to till date)*
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Mr. Pawan Kumar Pahwa, *Head-Admin & Finance, inStem, Bengaluru – Member Secretary (till 24th March 2021)*
Mr Ramanathan K, *Senior Admin Officer, inStem, Bengaluru -Member Secretary (From 25th March 2021)*

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

Qualified 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 2021, and the Income and Expenditure 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, except for the effects of the matter described in the Basis for Qualified Opinion section of our report, the accompanying financial statements give a true and fair view of the financial position of the Institute as at 31st March 2021, and of its financial performance for the year ended in accordance with the Accounting Standards issued by the Institute of Chartered Accountants of India (ICAI).

Basis for Qualified Opinion
Rs.2,10,80,931 has been accounted as consumables under Core projects (reflected in Income & Expenditure account) by transferring them from EMG projects (reflected in Schedule 3) without approval from the grant sanctioning authorities i.e. Department of Biotechnology. The basis and supporting for such transfer was not available for our verification. Hence the effect of the same on the deficit, grant utilization and balance of grants could not be ascertained.

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 of Ethics issued by ICAI and we have fulfilled our other ethical responsibilities in accordance with the Code of Ethics. We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our opinion.

Other Matter

We have not audited the financial statements of the Vellore branch, whose financial statements reflect total assets of Rs.2.69 crore, total revenue of Rs.6.99 crore and excess of expenditure over income of Rs.0.10 crore for the year ended as on 31-03-2021. 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 with generally 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.

• 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:**21214431AAAAGG3445**

Place: Bangalore
Date: 09-10-2021

File No.InStem/G/110/20-21/

UTILISATION CERTIFICATE

(Towards establishment of Institute for Stem Cell Science and Regenerative Medicine for the financial year: 2020-21 (01-04-2020 to 31-03-2021)

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 2019-20 quoting DBT letter No. & date in which the authority to carry forward the said amount was given: : Rs.23,79,91,475/-

5. Amount received from DBT during the financial year 2020-21 (Please give No. & date of sanction orders showing the amountpaid):

1	No. BT/PR7972/MED/14/1208/2006	09.06.2020	Rs. 5,94,37,840/-
2	No. BT/PR7972/MED/14/1208/2006	09.06.2020	Rs 46,33,000/-
3	No. BT/PR7972/MED/14/1208/2006	09.06.2020	Rs. 63,25,000/-
4	No. BT/PR7972/MED/14/1208/2006	20.08.2020	Rs. 2,75,62,160/-
5	No. BT/PR7972/MED/14/1208/2006	20.08.2020	Rs. 1,59,65,000/-
6	No. BT/PR7972/MED/14/1208/2006	20.08.2020	Rs. 2,17,72,978/-
7	No. BT/PR7972/MED/14/1208/2006	28.10.2020	Rs. 2,00,00,000/-
8	No. BT/PR7972/MED/14/1208/2006	28.10.2020	Rs. 8,76,89,000/-
9	No. BT/PR7972/MED/14/1208/2006	28.10. 2020	Rs. 2,00,00,000/-
10	No. BT/PR7972/MED/14/1208/2006	26.02.2021	Rs. 1,35,94,022/-
11	No. BT/PR7972/MED/14/1208/2006	26.02.2021	Rs. 8,52,00,000/-
12	No. BT/PR7972/MED/14/1208/2006	19.03.2021	Rs. 2,50,00,000/-

6. Other receipts/interest earned, if any on the DBT grants: : Rs. 95,98,760/-

7. Total amount that was available for expenditure incurred during the financial year (Sl.No. 4, 5, and 6): : Rs.63,47,69,235/-

8. Actual expenditure incurred during the financial year (Statement of expenditure is enclosed) : Rs.53,53,20,971/-

9. Unspent balance refunded, if any (Please give details of Cheque No. etc.) : Rs.1,20,04,132/- refunded vide DD No.23754 dated 20.05.2020.
: Rs. 23,51,856/- refunded vide Bharatkosh
: Rs.59,02,151/- refunded by CSIR

10. Balance amount available at the end of the financial year:(as on 31.03.2021) : Rs. 7,91,90,125/-

11. Amount allowed to be carried forward to the financial year 2021-22 vide letter no. & date : Rs. 7,91,90,125/-

CERTIFICATE

Certified that the amount of **Rs. 53,53,20,971/-** mentioned against col.8 has been utilized on the project/scheme for the purpose for which it was sanctioned and that the amount of **Rs.7,91,90,125** /-remaining unutilized at the end 31.03.2021 will be adjusted during the year 2021-22.

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

This Certificate has to be read with the attachment enclosed and this certificate is subject to the comments in the attachment.

For B. P. RAO & CO.
Chartered Accountants
FRN 002116S
Partner

(Prashanth. C)
Partner
(M.No.214431)
UDIN 21~~214431AAAA~~214431AAAAG52742
09-10-2021

(Raju Verma)
inStem Accounts

(Ramanathan K)
Head Admin. & Finance

(Prof. Apurva Sarin)
Director

प्रो:अपूर्वा सरीन / Prof. Apurva Sarin
निदेशक / Director
स्टेम कोशिका विज्ञान और पुनर्योजी औषधि संस्थान
Institute for Stem Cell Science and Regenerative Medicine (inStem)
जैव प्रौद्योगिकी विभाग, भारत सरकार के अधीन स्वायत्त संस्थान
(An Autonomous Institute under Department of Biotechnology, Govt. of India)
जीकेवीके पोस्ट, बेल्लारी रोड / GKVK Post, Bellary Road
बेंगलूरु – ५६० ०६५ / Bengaluru-560 065

inStem

INSTITUTE FOR STEM CELL SCIENCE & REGENERATIVE MEDICINE, BANGALORE
STATEMENT OF EXPENDITURE FOR THE PERIOD FROM 01.04.2020 TO 31.03.2021

(Amount in Rs.)

Sl.No.	Particulars	Unspent balance as on 01.04.2020 as per Audited SOE & UC	Grants received from DBT during the period 01.04.2020 to 31.03.2021	Other receipts/interest earned , adjustments, if any, on the DBT	Total	Expenditure incurred (excluding commitments) from 01.04.2020 to 31.03.2021	Interest Refunded	Balance as on 31.03.2021
1	2	3	4	5	6=3+4+5	7	8	9=6-7-8
	INSTEM :							
A	GIA - Capital							
(i)	Equipments & Accessories	14,52,70,283	3,00,00,000		17,52,70,283	14,35,61,311	-	3,17,08,972
	Total (A)	**14,52,70,283**	**3,00,00,000**	-	**17,52,70,283**	**14,35,61,311**	-	**3,17,08,972**
B	GIA - Salary							
(ii)	Manpower	3,40,52,018	4,50,00,000		7,90,52,018	7,07,82,155	-	82,69,863
	Total (B)	**3,40,52,018**	**4,50,00,000**	-	**7,90,52,018**	**7,07,82,155**	-	**82,69,863**
C	GIA - General							
(iii)	Recurring Expenses	68,99,769	21,48,89,000	-	22,17,88,769	20,17,03,751	-	2,00,85,018
	Total (C)	**68,99,769**	**21,48,89,000**	-	**22,17,88,769**	**20,17,03,751**	-	**2,00,85,018**
D	Other receipts	-	-	-	-			-
E	Interest Earned	1,43,55,988	-	69,23,018	2,12,79,006	-		**2,12,79,006**
F	Interest Refunded	-	-		-	-	1,43,55,988	**-1,43,55,988**
	GRAND TOTAL (A+B+C+D+E+F) - INSTEM	**20,05,78,058**	**28,98,89,000**	**69,23,018**	**49,73,90,076**	**41,60,47,217**	**1,43,55,988**	**6,69,86,871**
	CSCR Vellore :							
G	GIA - Capital	8,69,891	3,00,00,000		3,08,69,891	2,80,40,438		28,29,453
H	GIA - Salary	99,16,558	2,22,90,000		3,22,06,558	2,68,05,463		54,01,095
I	GIA - General	-53,71,356	4,50,00,000	17,026	3,96,45,670	3,83,31,680		13,13,990
J	Interest Earned	59,02,151	-	26,58,716	85,60,867	-		85,60,867
K	Interest Refunded			-	-	-	59,02,151	-59,02,151
	GRAND TOTAL (G+H+I+J+K) - CSCR	**1,13,17,244**	**9,72,90,000**	**26,75,742**	**11,12,82,986**	**9,31,77,581**	**59,02,151**	**1,22,03,254**
	GRAND TOTAL - INSTEM + CSCR	**21,18,95,302**	**38,71,79,000**	**95,98,760**	**60,86,73,062**	**50,92,24,798**	**2,02,58,139**	**7,91,90,125**
	instem							
A	GIA - Capital							
i	Building & Services	2,60,96,173	-		2,60,96,173	2,60,96,173		-
	GRAND TOTAL (INSTEM+CSCR+BUILDING)	**23,79,91,475**	**38,71,79,000**	**95,98,760**	**63,47,69,235**	**53,53,20,971**	**2,02,58,139**	**7,91,90,125**

Subject to our comments in the attachment enclosed

For B. P. RAO & CO
Chartered Accountants
(Prashanth. C)
Partner (M.No.214431)

Partner
FRN 003116S
UDIN 21214431AAAAG52742

(Raju Verma)
inStem Accounts

(Ramanathan K)
Head Admin. & Finance

(Prof. Apurva Sarin)
Director

प्रो॰अपूर्व सरीन / Prof. Apurva Sarin
निदेशक / Director
स्टेम कोशिका विज्ञान और पुनर्योजी औषधि संस्थान
Institute for Stem Cell Science and Regenerative Medicine (inStem)
जैव प्रौद्योगिकी विभाग, भारत सरकार के अधीन स्वायत्त संस्थान
(An autonomous Department of Biotechnology, Govt. of India)
जीकेवीके पोस्ट, बेल्लारी रोड / GKVK Post, Bellary Road

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

Attachment to Utilization Certificate of M/s. Institute for Stem Cell Science and Regenerative Medicine for the Financial Year 2020-2021

This certificate is subject to the following:

1. The certificate is to be read along with Independent Auditor's Report dated 09-10-2021 on the Financial Statements of the Institute for the year ended 31-03-2021 where we have issued a qualified opinion. The qualification pertains to transfer of consumable expenses to the extent of Rs 2,10,80,931 from EMG Projects to Core Projects. This expenditure has been included in the certificate as utilization.

2. The Institute has paid Rs 2,16,00,000 to CMC, Vellore for building construction. The same is accounted as advance in the books of accounts, pending receipt of construction bills. The said amount has been included by the Institute as expenditure incurred during the financial year in the certificate.

3. The Institute has paid Rs 2,60,96,173 to NCBS against claim by contractors in respect of the Institute's building construction. The same is accounted as advance in the books of accounts. The said amount has been included by the institute as expenditure incurred during the financial year in the certificate. Also refer Note No 1.5 under Schedule 25 to the financial statements

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

Prashanth. C
Partner
M No:214431

Place: Bangalore
Date: 09-10-2021

UDIN 21214431AAAAGS2742

Also At:
No.14/C, 5th Main, Yadavgiri, Mysore – 570 020. Ph. 2515929, 2514880
2nd Floor, No. 3, Nathan Street, Near Prashanth Hospital, Harrington Road, Chetpet, Chennai 600 031. Phone : 044-28361457, 28362457..
"Shanthi", No.12/62, 1st Floor, Reservoir Street Cross, Basavanagudi, Bangalore - 560 004. 080- 2662 2101/2662 2201

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, 2021

(Amount -Rs)

RECEIPTS	CURRENT YEAR	PREVIOUS YEAR	PAYMENTS	CURRENT YEAR	PREVIOUS YEAR
I. Opening Balances			I. Expenses		
a) Cash in hand	21,943	-	a) Establishment Expenses	9,75,87,618	10,86,94,603
b) Bank Balances			b) Administrative Expenses	24,00,35,431	35,03,23,002
i) in current accounts	4,07,52,806	8,39,53,501		**33,76,23,049**	**45,90,17,605**
ii) in deposit accounts	39,38,15,116	36,21,67,415	**II. Payments made against projects**	**20,50,44,932**	**25,80,00,963**
iii) in savings accounts	13,75,12,740	5,97,39,232	**III. Investments made**		
	57,21,02,605	**50,58,60,148**	a) Out of Earmarked/End. Funds	-	-
II. Grants Received			b) Out of own funds		
a) From Govt. of India	38,71,79,000	67,20,00,000	**IV. Increase in Current Assets**	**-**	**95,27,687**
b) From State Govt.		-	**V. Capital Expenditure**		
	38,71,79,000	**67,20,00,000**	a) Purchase of fixed assets-Projects	1,25,70,172	6,02,15,533
III. Project Receipts-Projects	**24,02,55,533**	**28,42,64,231**	b) Exp. On Building	10,87,569	6,57,81,543
IV. Increase in Current Liab	**-**	**8,59,69,337**	c) Exp on Equipments & Furnitures	10,16,48,053	16,84,55,690
V. Decrease in Current Assets	**-3,44,69,790**			**11,53,05,794**	**29,44,52,766**
VI. Interest Received			**VI. Refund of surplus money/Loans**	-	-
a) On Bank deposits	1,97,10,847	2,51,53,906	a) To the Govt. of India	2,02,58,139	-
b) on Loans, Advances etc.		-	a) To the Govt. of India-EMG	1,77,03,787	-
	1,97,10,847	**2,51,53,906**		**3,79,61,926**	**-**
VII. Other Income (Specify)	**1,26,88,726**	**1,98,54,002**	**VII. Finance Charges (Interest)**	-	-
VIII. Amount Borrowed	-	-	**VIII. Decrease in Current Liabilities**	**7,99,38,445**	
IX. Any other receipts	-	-	**IX. Closing Balances:**		
			a) Cash in hand	1,224	21,943
			b) Bank Balances		
			i) in current accounts	6,34,81,240	4,07,52,806
			ii) in deposit accounts	30,60,03,848	39,38,15,116
			iii) in savings accounts	5,21,06,464	13,75,12,740
				42,15,92,775	**57,21,02,605**
TOTAL	**1,19,74,66,921**	**1,59,31,01,626**	**TOTAL**	**1,19,74,66,921**	**1,59,31,01,626**

Vide our report of even date

For B. P. RAO & CO.

Chartered Accountants

FRN 003116S

(Prashanth. C)

Partner (M.No.214431)

UDIN 21214431AAAAGG3445

Place: Bangalore

Date : 09-10-2021

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

(Raju Verma)

Accounts

(Ramanathan K)

Head Administration & Finance

(Prof. Apurva Sarin)

Director

प्रो:अपूर्वा सरीन / Prof. Apurva Sarin
निदेशक / Director
स्टेम कोशिका विज्ञान और पुनर्योजी औषधि संस्थान
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(An under Department of Biotechnology, Govt. of India)
जीकेवीके पोस्ट, बेल्लारी रोड / GKVK Post, Bellary Road

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, 2021

(Amount- Rs.)

Particulars	Schedule	Current Year	Previous Year
INCOME			
Income from Projects - to the extent of expenditure included	3	20,50,44,932	25,80,00,963
Income from Sales and Services	12	69,43,703	94,11,509
Grants/Subsidies	13	32,71,79,000	41,20,00,000
Fees/Subscriptions	14	-	-
Income from Investments	15	-	-
Income from Royalty, Publications etc.	16	-	-
Interest earned	17	1,02,46,635	1,24,65,062
Other Income	18	57,45,023	1,04,42,493
Increase/(decrease)in stock of Finished goods and works-in-progress	19	-	-
TOTAL (A)		**55,51,59,293**	**70,23,20,027**
EXPENDITURE			
Establishment Expenses	20	9,75,87,618	10,86,94,603
Other Administrative Expenses	21	24,00,35,431	35,03,23,002
Expenditure on Grants/Subsidies etc.	3	20,50,44,932	25,80,00,963
Interest	22	2,02,58,139	-
Depreciation (Net Total at the year -end -corresponding to Sch.8)		35,82,81,599	37,97,91,972
TOTAL (B)		**92,12,07,719**	**1,09,68,10,540**
Balance being excess of Expenditure over Income (A-B)		**-36,60,48,426**	**-39,44,90,513**
Less- Transfer to Capital Reserve - equivalent to depreciation charges	2(1)	35,82,81,599	37,97,91,972
Less- Transfer to/from General Reserve - Recurring Grant Account	1(B)	-77,66,827	-1,46,98,541
Balance being surplus/deficit carried to Corpus/Capital Fund			
SIGNIFICANT ACCOUNTING POLICIES	24		
CONTINGENT LIABILITIES AND NOTES ON ACCOUNTS	25		-

Vide our report of even date

For B. P. RAO & CO.

Chartered Accountants

FRN0031165

(Prashanth. C)
Partner (M.No.214431)
UDIN 21214431AAAAGG3445
Place: Bangalore
Date : 09-10-2021

(Raju Verma)
Accounts

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

(Ramanathan K)
Head Administration & Finance

(Prof. Apurva Sarin)
Director

प्रो:अपूर्वा सरीन / Prof. Apurva Sarin
निदेशक / Director
स्टेम कोशिका विज्ञान और पुनर्योजी औषधि संस्थान
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(An under Department of Biotechnology, Govt. of India)
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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, 2021

(Amount- Rs.)

Particulars	Schedule	Current Year	Previous Year
CORPUS/CAPITAL FUND AND LIABILITIES			
CORPUS/CAPITAL FUND	1	19,49,13,202	24,54,15,651
RESERVES AND SURPLUS	2	2,71,29,78,550	2,95,59,54,355
EARMARKED/ ENDOWMENT FUNDS	3	28,15,04,212	26,71,03,358
SECURED LOANS AND BORROWINGS	4		-
UNSECURED LOANS AND BORROWINGS	5		-
DEFERRED CREDIT LIABILITIES	6		-
CURRENT LIABILITIES AND PROVISIONS	7	5,74,60,894	13,73,99,339
TOTAL		**3,24,68,56,858**	**3,60,58,72,703**
ASSETS			
FIXED ASSETS	8	2,76,02,44,676	3,00,32,20,481
INVESTMENTS - FROM EARMARKED /ENDOWMENT FUNDS	9	-	-
INVESTMENTS - OTHERS	10	600	600
CURRENT ASSETS, LOANS, ADVANCES ETC.	11	48,66,11,582	60,26,51,622
MISCELLANEOUS EXPENDITURE		-	-
TOTAL		**3,24,68,56,858**	**3,60,58,72,703**
SIGNIFICANT ACCOUNTING POLICIES	24		
CONTINGENT LIABILITIES AND NOTES ON ACCOUNTS	25		

Vide our report of even date

For B. P. RAO & CO.

Chartered Accountants

FRN003116S

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

UDIN 21214431AAAAGG3445

Place: Bangalore

Date : 09-10-2021

(Raju Verma)
Accounts

(Ramanathan K)
Head Administration & Finance

(Prof. Apurva Sarin)
Director

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

प्रो:अपूर्वा सरीन / Prof. Apurva Sarin
निदेशक / Director
स्टेम कोशिका विज्ञान और पुनर्योजी औषधि संस्थान
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बेंगलूरु – ५६० ०६५ / Bengaluru-560 065

In Memoriam

Vinod Kumar
8.05.1982-2.05.2021

We remember our colleague Shri Vinod Kumar.
Facility Assistant, BLiSC Animal Care and Resource Centre.

In Memoriam

Nataraj L
1.06.1979 - 10.10.2021

We remember Shri Nataraj L
Staff, Canteen services

He participated in many sports events on the campus and led the teams that he played with to great success.

New Hires
Scientific Staff

Mohankumar Murugesan
Scientist E, CSCR, inStem
• PhD, Liggins Institute, University of Auckland, Auckland, New Zealand.
• Post-Doctoral Research, St. Jude Children's Research Hospital, Memphis, TN, USA.

Sarvanabhavan Thangavel
Scientist E, CSCR, inStem
• PhD, International Centre for Genetic Engineering and Biotechnology (ICGEB), Trieste, Italy.
• Post-Doctoral Research, ICGEB, Trieste, Italy and Department of Biochemistry and Molecular Biology, Saint Louis University, St. Louis, USA.

Gurbind Singh
Scientist D, cGMP Facility, CSCR, inStem
• PhD, Indian Institute of Science, Bangalore
• Post-Doctoral Research, Stempeutics Research Malaysia

Sucharita Bose
Scientist D, Cryo-EM and Electron Microscopy Facility
• PhD, Purdue University
• Post-Doctoral Research, InStem

Deepti Abbey
Scientist D, Stem Cell Core
• PhD, Indian Institute of Science, Bangalore, a
• Post-Doctoral Research, St Jude Children's Research Hospital, Memphis and University of Pennsylvania, Philadelphia USA.

Nirpendra Singh
Scientist D, Mass Spectrometry and Facilities
• PhD, Ambedkar Center for Biomedical Research (ACBR), University of Delhi.
• Consultant and Head of Facilities, Advanced technology Platform Center at Regional Center for Biotechnology.

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