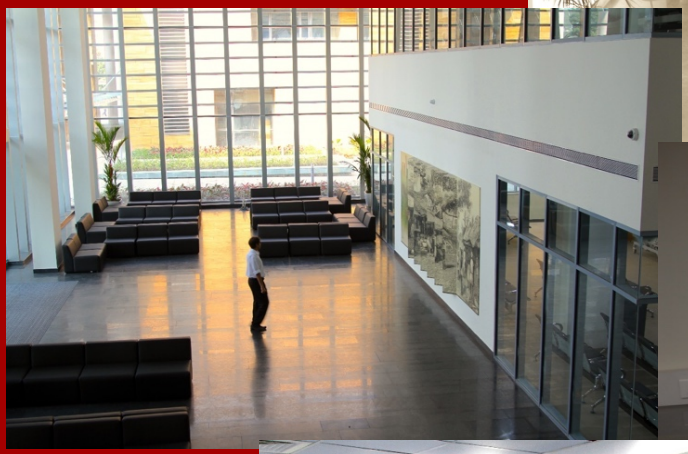
TATA TRANSLATIONAL CANCER RESEARCH CENTRE

Kolkata, India



Annual Scientific Report 2018

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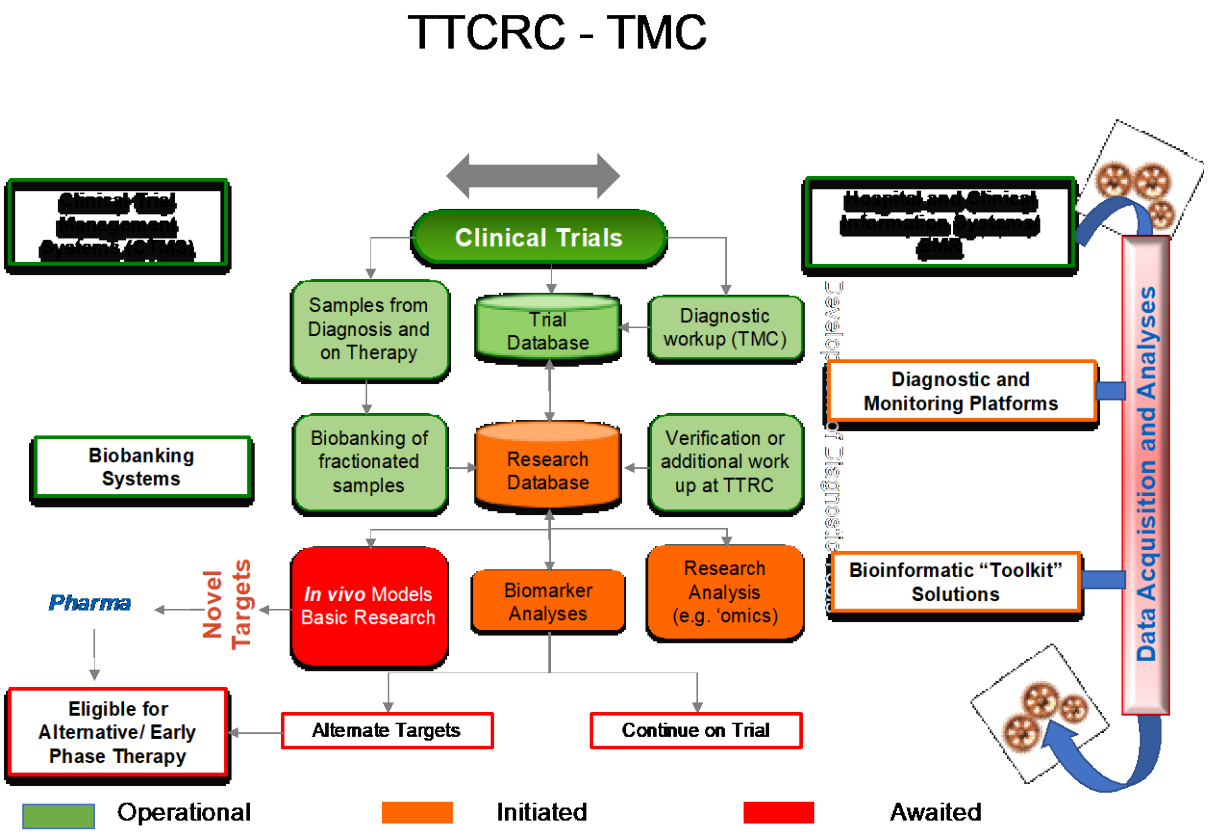
Tata Translational Cancer Research Centre (TTCRC) – An Overview

The Tata Translational Cancer Research Centre(TTCRC) is a dedicated research facility embedded within the Tata Medical Center. Initiated in 2014, it moved into dedicated facilities in April 2018. TTCRC creates an environment for clinicians, scientists and researchers to work together within a cancer hospital. The purpose is to develop innovative partnerships capable of delivering novel solutions for patients with cancer in India. Our work is open source and we freely share data and resources that are generated through our research.

To facilitate research groups, TTCRC has a modular design, shown below, with each module designed to provide core support for researchers. This includes project design, implementation and analysis. A dedicated biorepository and clinical research unit (CRU) underline downstream core activities. These include high throughput genomics, proteomics and microscopy platforms. Data driven engines link data generated from the laboratory with patient information.



The Director's Desk

2018 is a landmark year for TTCRC, as we complete 4-years of existence from conception in 2014. We spent 2014-18, housed in the HLA-Lab (courtesy Drs Biswas & Mishra) and moved into dedicated facility spread over 3 floors in April 2018. In a short while, we have set up dedicated facilities for next generation sequencing, high throughput microscopy and now a QTRAP mass spectrometer.

With the increased availability of space, we were finally able to begin to recruit to existing vacancies. So in 2018, we welcomed Manash and Sayan to CRU; Shivani and Ritam to the Biobank; Jaydeep and Avisek to cellular biology and Arunima to proteomics; Anindyajit and Sangramjit to informatics and Sukanya to the administrative setup. Mayur had two new recruits, Rashmi and Piyali who joined genomics along with Satyam. Mou and Arindam have moved onto greener pastures and we thank them for their work in getting us to where we are now.

From a research perspective, Jasmeet and Asima were awarded India Alliance Fellowships, joining Arunabha, Pritha and myself. I received an exceptional fellow award as well from India Alliance. We had a number of excellent visiting speakers and hosted a visiting team from the University of Manchester.

The work of the genomics lab underpins management of high risk leukaemia patients. Shekhar has been working in collaborative links with IIT-Kharagpur and Indian Statistical Institute to develop novel analytical tools to analyse outpatient Physician and patient compliance. He is co-supervising a IIT-KGP PhD student, Tushar Mungle, with Profs Sangeeta Bhattacharya and Jayanta Mukhopadhyay investigating physician compliance. Professor Kironmoy Das of ISI is helping in developing tools to correlate this data with patient outcome. The long standing collaboration with TCS life sciences has established pipelines for targeted exomic and RNA sequencing. An integrated platform capable of data capture, integration and innovative analysis have been created and installed, and a new version of the clinical trial management system is undergoing testing. There are proposed national collaboration in gall bladder cancer, establishing centralised clinical research units and a centralised small animal facility. International collaborations have resulted in a number of publications this year in Ph^+ and relapsed acute lymphoblastic leukaemia. Arunabha is currently training in the clinical Proteomics facility Whetton at the University of Manchester. Pritha is also to spend a year working with Patricia Muller, CRUK-Manchester Institute. TTCRC has made good progress since 2014 and has great potential.

Many challenges lie ahead. A closer integration with the hospital is required so more clinicians/researchers are able to take advantage of the core facilities. We need to secure a stable long term funding strategy, recruit PIs and establish a graduate training program.

Finally, we join in with all our colleagues on congratulating Dr Mammen Chandy on being awarded the Padma Shri. He has established the standards we have to aim for!

The Associate Director's Desk

2018 was a watershed year for TTCRC. The year saw TTCRC's transition from a virtual organisation to a tangible bricks-and-mortar entity. Two floors were constructed atop the hospital's 2-storey LDU building and the southern halves of the second and ground floors were additionally repurposed to house the research centre. Purpose-built laboratories have been developed in the second and third floors, while office and meeting spaces have been created in the fourth and ground floors. The specifications for the laboratories were inspired by observations and inputs from a wide range of high-quality research facilities, nationally and internationally. The research facilities include specialised areas for advanced analyses (genomics, proteomics, microscopy, cell sorting, informatics) and shared spaces for molecular and cell biology studies.

From the first draft of the design drawings (August 2013), construction of the research centre has been a decidedly hands-on experience, demanding the active participation of all in the research group. It has been an exacting enterprise, has involved a steep learning curve, and has required close communication and obsessive attention to detail at all stages of construction. A silver lining has been the esprit-de-corps arising from this shared sense of mission, something that will hopefully endure and intensify as the research centre grows. The success of this enterprise would not have been possible without the extraordinary support of the many people involved in this project, both within the TMC fraternity and from outside - no words can do justice to their contributions. I would like to especially acknowledge the invaluable support from the Tata Consultancy Services, including from the Infrastructure Planning & Development team at TCS Gitanjali Park (Mr Kaushik Basu, Mr Sanket Mitra and Mr Parijat Mukherjee).

The actual hard work begins now. The management and operation of the research facility will need to be streamlined to ensure optimal use of resources. Information systems are being developed to enable this. The specialised research facilities will need to be developed so as to be able to support research projects within and outside the institution. A strategy for sustainable operation and cost-efficient management of the research centre will need to be crafted. In all this, we will need to stay true to the vision of high-quality, internationally competitive, impactful, open-access research. These are the formidable challenges that will occupy our energies in the years ahead.

TTCRC construction timelines

2013

August: First draft of drawings for the research centre in the LDU

2015

March: Invitation to bid for building works

Nov: Building works begin

2016

Jan – Dec: Building work continues

June: Visit to NCBS Bengaluru to view research facilities

2017

July: Delivery of modular laboratory furniture (Waldner GmbH)

July: Delivery of Featherlite office furniture (temporarily housed at Premashraya)

July: First consignment of laboratory equipment (flow cell sorter, ultracentrifuge)

Sep: Laboratory furniture installation works begin

Dec: Near-completion of mechanical, electrical and plumbing works

2018

Feb: Installation of equipment for high-throughput genomics

Feb: Research group moves into TTCRC (initially occupying the second floor)

March: Office space millwork near-complete; research group moves to the office floor

March: Conference room functional

April: Completion of laboratory millwork

June: Cell sorter relocation and installation

Aug: Equipment for mass-spectrometry proteomics

Sep: High-content microscopy system

Dec: Ground floor lobby lift to upper floors operational

2019

Jan: Ground floor space near-complete

Dr. Shekhar Krishnan
Paediatric Oncologist
CRU Head

Prakriti Roy
CRU Data Analyst

Manash Pratim Gogoi
CRU Data Manager

Sayan Chaterjee
CRU Data Manager

Mou Das
Clinical Trial Manager
Till 2018

Saikat Pal
TCS

Bindu Abraham
TCS

Tushar Mungle
IIT Kharagpur

Clinical Research Unit

The Clinical Research Unit (CRU) in TTCRC established in November 2013 and over the years played a major role in coordinating clinical studies linked with the translational research. The team includes CRU Head, Clinical Trials manager, Data Analyst, Data Managers and seconded personnel from Tata Consultancy Services (TCS).

Multicentre Clinical Trial in Childhood ALL

Started with the multicentre Pre Trial study for the InPOG-ALL-15-01 ICiCLe-ALL-14 in august 2013 followed by ICiCLe-ALL-14 Trial, the first national multicentre randomised controlled trial in Childhood acute lymphoblastic leukaemia launched in October 2016 with the aim of Improving outcome by using modernised standardised risk stratified therapy which is locally accessible and cost effective to the patients. Till now over 3000 patients have been enrolled in the study within the country. Preliminary analysis showed survival rates of 90% with low intensity treatment for a group of patients with low risk disease conforming that risk stratification is the most effective method for better outcome and is effective in reduction of treatment related deaths and relapses.

Maintenance Therapy

The CRU supervises the maintenance phase of therapy in children with ALL receiving treatment at TMC. The aim is to optimise the antimetabolite drugs. In collaboration with IIT-Kharagpur we have audited practice and developed monitoring tools and to optimise maintenance dosing. We are working towards development of app based system for dosing advise and computerised dosing algorithm system. The unit also contributes towards laboratory studies in ALL, such as genetic characterisations and therapeutic drug monitoring.

Relapsed ALL

A strategy for managing children with relapsed ALL has been piloted and developed. The protocol, named TMC ALLR1, is being developed as a multicentre registry study within the Indian Pediatric Oncology Group (InPOG).

Data Development

The CRU works closely with the TCS in the development of the tools needed for various clinical and laboratory studies such as Clinical Trials management system (CTMS) supporting the data management for the trial which enables remote data entry, data capture, trial randomisation and decision support. A Data Management System (IDM 4.0) is being developed for TMC ALLR1. Working with TCS, we are using data extraction tools like Apache cTakes to mine data from Hospital Management System. Data discovery tools like i2b2 as cohort creation tool and Kibana as data visualisation tool are being evaluated for future studies.

TiMBR- The Biorepository

Dr Shivani Bhagwat
Administrative Lead

Soumosree Tapadar
Biobank
Technologist

Ritam Siddhanta
Biobank
Technologist

Tata Medical Center biorepository (TiMBR) is a centralized facility of Tata Medical Center (TMC) catering to the unique heterogeneity of cancer. It provides an interface between high quality clinical samples and diverse research objectives. Holistically designed infrastructure, workflows, SOPs, LIMS and quality checks exhibit its competence. It has a dedicated and trained workforce, specialized processing and storage facility possessing - 80 freezers, liquid nitrogen (LN) storage and supply tanks to support long term sample preservation. It is stationed in proximity to hospital's LN plant to manage any unforeseen deficit.

IRB approved projects and ethically consented patients are recruited and biomaterial is collected based on pre-analytical standards. Based on ISBER guidelines, surrogate time points have been implemented to offset processing delays. Information accession between hospital management system (HMS) and Labvantage 6.0.1 (Laboratory information management system; LIMS) creates comprehensively pseudo-anonymization of biospecimen. LIMS supports operation management including processing logs, compliance reports, workflows and traceability of stored samples. Lately, it helped resolve unfiled and unknown samples kept at unspecified locations and discrepancies of non-uniform sample processing. Implementation of standard workflow for every project, electronic sample requisition, material transfer agreement, regular internal audits are now in place to make the operations consistent and eventually been linked to LIMS as well.

TiMBR is a project based repository where samples are accessed through research collaborations. In 2018, more than 2000 patients were recruited under ten active studies across six departments at TMC. Key areas of research at TiMBR includes paediatric oncology, gynaecological (ovarian & cervix) malignancies, breast oncology, adult haematology, Head & neck oncology and radiation oncology.

The facility houses more than 15,000 sample derivatives. It comprises 2D barcoded tissues (FFPE, SNAP frozen and in RNA later), plasma, serum, cell blocks, cell pellets, DNA, RNA, cryo MNCs and paired normal tissues for unbiased study cohorts. Periodic quality checks and stringent checkpoints accredit the quality of samples being used for in-house translational research. Recently, a gall bladder cancer project has been initiated where epidemiological database, sample flow, processing SOPs and documentation has been initiated to support active biobanking of excess material.

With growing sample size and number of projects, expansion of infrastructure, upgradation of Labvantage 8.3 and development of hub and spoke model is in place to facilitate inter-hospital and academic institution research collaborations. The use of a of web-based LIMS solutions will allow the us to participate in national and international biobank networks.

Dr Mayur Parihar
Haemato-pathologist and Head Cytogenetics

Dr Tanvi Gupta
Fellow

Arun SR
Scientific Officer

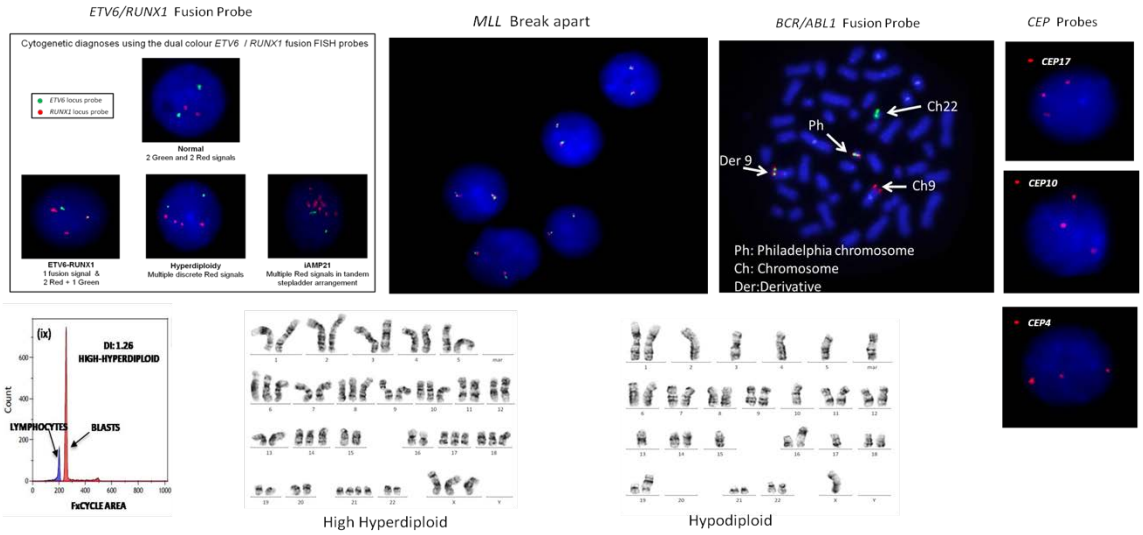
Sumanta Patel
Scientific Officer

Sipra Rani Patel
Scientific Officer

Pranay Gurung
Scientific Officer

Cytogenetics

Cytogenetic strategy



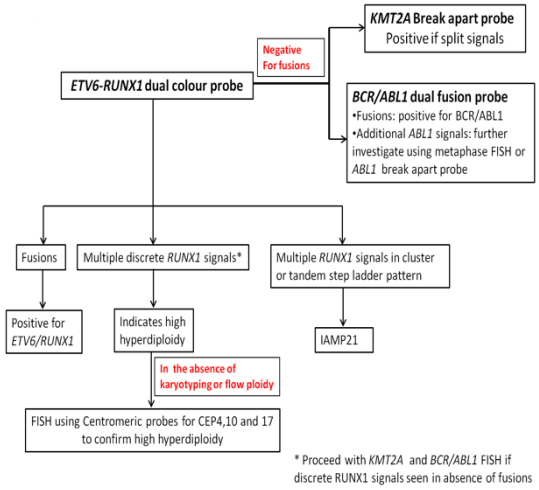
High Hyperdiploid

Hypodiploid

The Cytogenetics team at Tata Medical Center/TTCRC has been working to provide low cost, efficient, sensitive and effective solutions not only for the patients being treated at Tata Medical Center but also for other centres.

As a group we have been working to improve outcomes in childhood leukaemia through risk stratified therapy based on genetic characterisation of tumor cells and response to treatment. The Cytogenetic Lab at Tata Medical Center is the reference lab for the National trial on childhood Acute Lymphoblastic Leukaemia (InPOG-ALL-15-01 ICiCLe-ALL-14 trial).

As there is a lack of established cytogenetic laboratories and trained cytogenetics personnel in India cytogenetic strategy based on fluorescent in situ hybridisation (FISH) was developed to categorise patients with B-cell precursor ALL (BCP-ALL) as Standard, Intermediate or High Risk (SR, IR, HR). FISH testing was chosen as the technique is easily learnt, does not require live cells, is relatively inexpensive and allows transport of

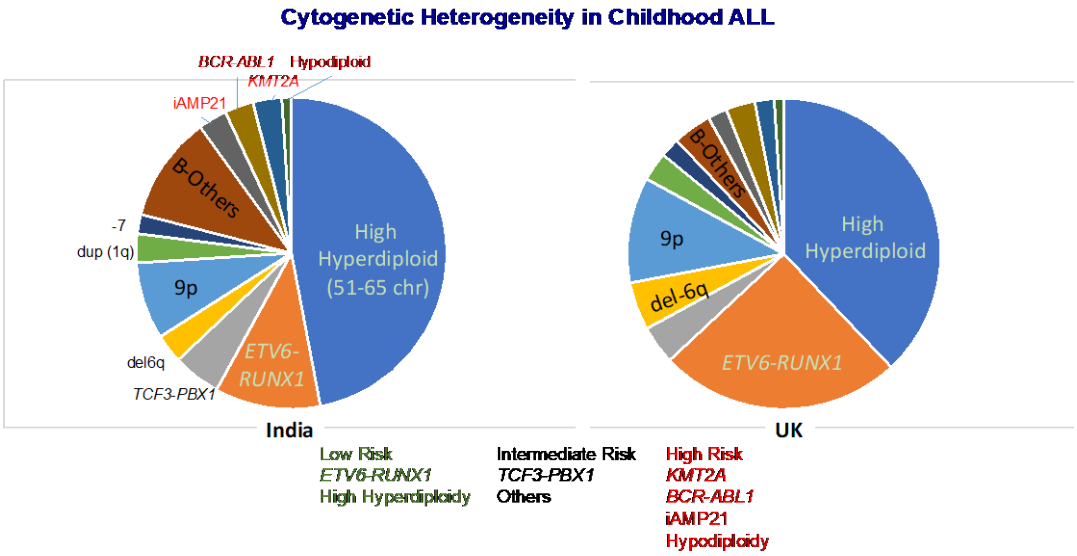


samples for testing to referral laboratories. FISH microscopy images can also be reviewed centrally to ensure standardisation and diagnostic accuracy across treatment centres. A 3-probe FISH testing strategy has been established to identify the principal genetic subtypes in BCP-ALL. Our experience demonstrates the utility of this approach in providing modern standardised diagnostic services for ALL in resource-limited settings. TTCRC has been instrumental in helping other centres set up

FISH based analyses for childhood ALL across the country.

Analyses of the ICiCLe patient cohort, identified an increased proportion of patients with High-Hyperdiploid (HeH) and B-other karyotype when compared with reports from the west. Given the numbers of patients, we also observed that HeH and B-others comprised the largest group in relapsed ALL and a many of these patients were not identified as high risk MRD at the end of induction. Along with the genomics group we have further characterized the HeH and B-other patients.

We investigated whole genome copy number alterations (CNAs) using the CytoScan HD array (ThermoFisher, USA). Along with identification of prognostically important intra-gene deletions (e.g., *IKZF1*) we have identified a constellation of copy number alterations and fusions in the B-other cohort. Early observations from high density SNP array analysis shows a distinct and heterogeneous pattern of copy number alterations in high hyperdiploid BCP-ALL compared to reports in western patients. Our ongoing studies are focused on correlating these variations with observed variations in treatment response in children with ALL treated on the InPOG-ALL-15-01-ICiCLe-ALL-14 clinical study to further optimise genetic risk stratification.



Dr Debdutta Ganguli
Administrative Lead

Dr Binuja Verma
TCS Life Science Sr. Scientist

Dr Satyam Banerjee
Post-Doc Fellow

Debparna Saha
Research Assistant

Rubina Islam
Research Assistant

Piyali Sarkar
Research Assistant

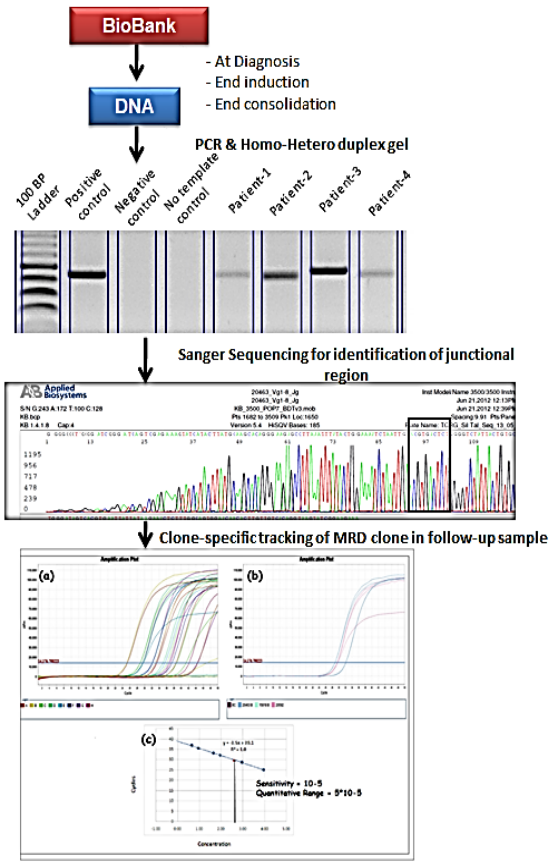
Genomics Laboratory

TTCRC provides a core genomics facility for both laboratory and clinical research. The genomics lab works in close cooperation with the CRU.

Minimal Residual Disease (MRD)

After successfully optimising the protocols at our centre, we joined the Euro-MRD consortium in Nov 2015, taking part in the bi-annual quality control rounds held every year for continued accreditation.

Representative figure showing PCR-MRD



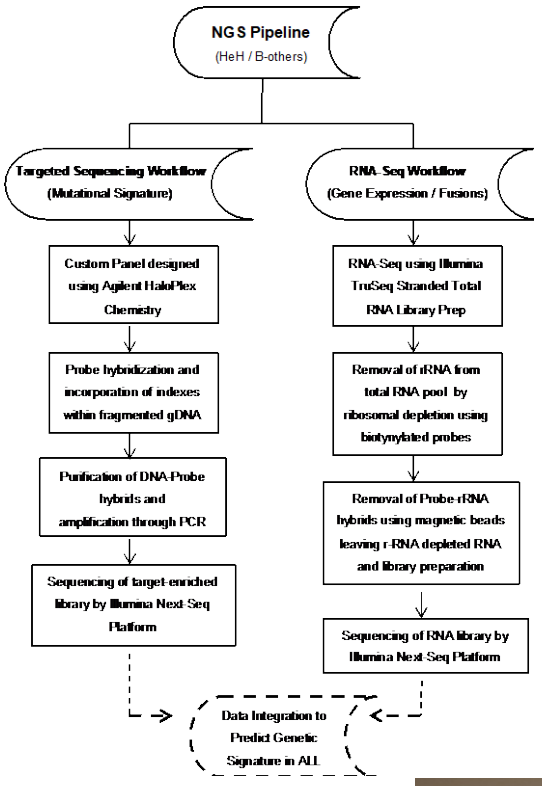
based MRD workflow: (a) Amplification plot of informative clonal marker using serial dilutions of diagnostic DNA, (b) PCR-MRD quantification of follow-up time point, (c) Standard curve defining quantitative range and assay sensitivity.

Over the last year, we have retrospectively evaluated the PCR-MRD vs flow-MRD findings on 55 BCP-ALL patient samples banked. MRD $\geq 10^{-4}$ is interpreted as high by both approaches. In about one-third of patients analysed as negative by flow-MRD, Ig/TCR is able to detect disease at below the 10^{-4} threshold. The clinical significance of this observation will need prospective evaluation. Currently the PCR-MRD is being done in real time for patients on TMC ALLR1 who are eligible for transplantation.

Targeted Exome Sequencing

In close collaboration with cytogenetics, we designed a targeted panel of 95 genes using the Agilent Sure Design software based on all reported mutations in BCP-ALL patients as reported in PubMed and reported on the St. Jude - Washington University Pediatric Cancer Genome Project. Our probe design included 102966 amplicons covering 1.977 million bases; all coding exons, intron-exon bounderies and average 1000 bp upstream promoter and 3'' UTR sequences within selected genes. The target regions were captured using Agilent HaloPlex High-Sensitivity Target Enrichment kit. The unique feature of this HaloPlex High-Sensitivity technology is the presence of more than a million unique 10-nt sequences or molecular barcodes embedded within each probe for higher sensitivity of detecting mutations present at below 1% allele frequency in a genetically heterogeneous sample. The enriched DNA fragments were amplified by PCR followed by deep paired-end sequencing using Illumina (Illumina, San Diego, CA, USA) Next-Seq 550 platform. A

total of 32 HeH and 30 B-other samples have now been analysed.



RNA-Sequencing

We have standardized a workflow for whole transcriptome sequencing approach using Next-Seq 550 to identify the gene-expression signatures and novel fusion transcripts in these patients. TruSeq stranded Total RNA library prep kit (Illumina) was used for whole-transcriptome library preparation. Paired-end sequencing was performed using the Illumina Next-seq 550 platform with 75– or 150- bp reads. We are supported by our in-house bioinformatics team as well as the TCS LifeSciences for developing bioinformatics pipeline to analyze the high-throughput omics data. The future goal is to integrate the RNA-Seq data with mutations and copy number variations to predict the significantly altered pathways in Indian ALL patients.

Dr.Anindyajit Banerjee
Post-Doc Fellow

Sangramjit Basu
Bioinformatics Technologist

Amit Saxena
Head, TCS Genomics Initiative

Abhishek H. Iyer
TCS

Computational Biology

Computational biology at TTCRC is a collaboration between TCS and TTCRC. This is facilitated by a dedicated server link between TCS, Noida and TTCRC Kolkata. In 2018, we set up the server facility in close association with the IT group at Tata Medical Centre.

Targeted Exome Sequencing

The analysis workflow for Targeted Exome Sequencing has been standardised. This includes correcting mapping fragment reads around indel locations followed by variant calling from multiple tools like SureCall, MuTect2, HaplotypeCaller, VarScan2 and Vardict. The process of variant calling in hyperdiploidy population can be problematical due to inconsistent zygosity and contributions from sub-clonal population. To this end we examined each of the putative mutations in Integrated Genomic Viewer (IGV).

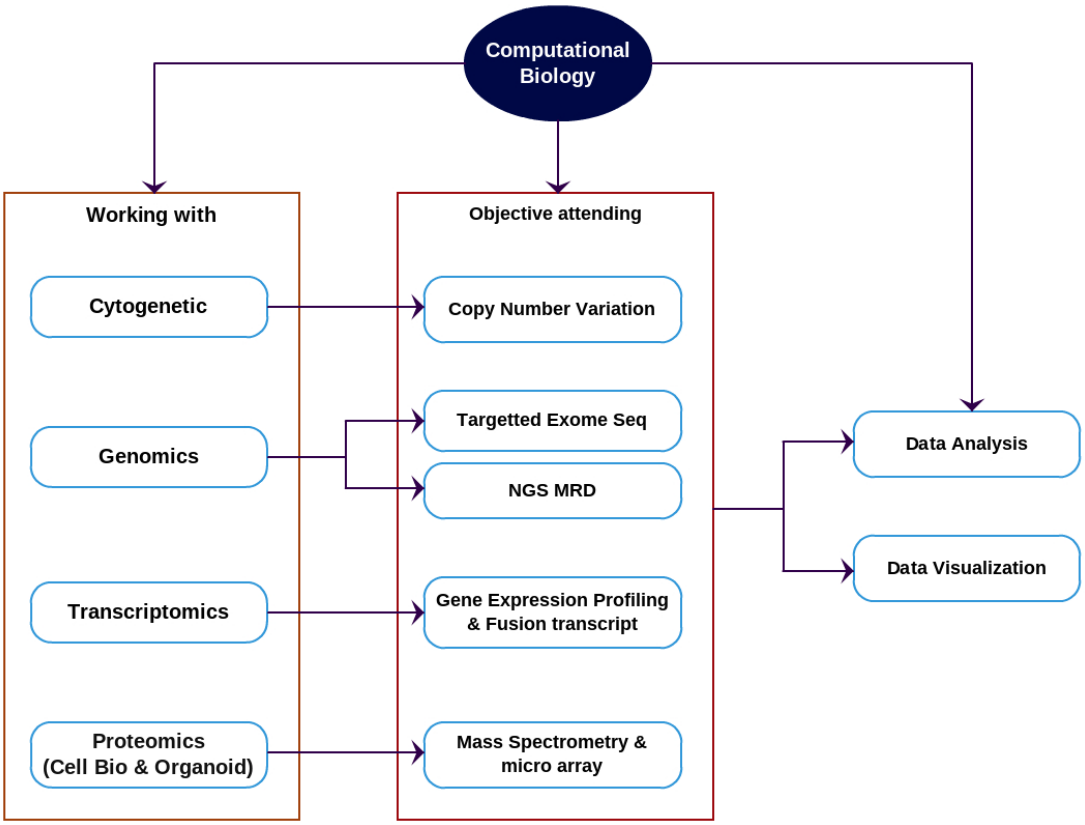
RNA Sequencing

The RNASeq pipeline consists of both direct transcript quantification and quantification of transcript through genomic locus expression following transcript match. The genomic method is mediated by New Tuxedo pipeline wherein the mapping to genome is done using Hisat2 and the transcript assembly and quantification is done using StringTie2 and the Differential Gene Expression is done using BallGown/DESeq2 or optionally using FPKM values using in-house scripts. The direct quantification method is done using Salmon/Kallisto. Though these methods are quick and useful for known transcript quantification, these are not very dependable for novel gene or splice variant detection/quantification and that is where the Tuxedo pipeline is valuable.

The RNASeq data is being used to call the variants in the mutations called from TES genomics data. The bioinformatics team have also used data from SRA NCBI archive to exercise and establish workflow to carry out analysis of ChIP-seq and Methylation-Seq data. The team have also established pipelines to work with genomic data produced from Nanopore MinION platform which will primarily be useful for the detecting genic rearrangement for MRD detection group and for detecting Fusion-transcripts with high confidence.

High Throughput Microscopy and Proteomics

Currently data is being generated by a high throughput microscopy system which requires the development of analytical tools. A Absciex QTRAP is to generate SWATH data for correlation with RNAseq.

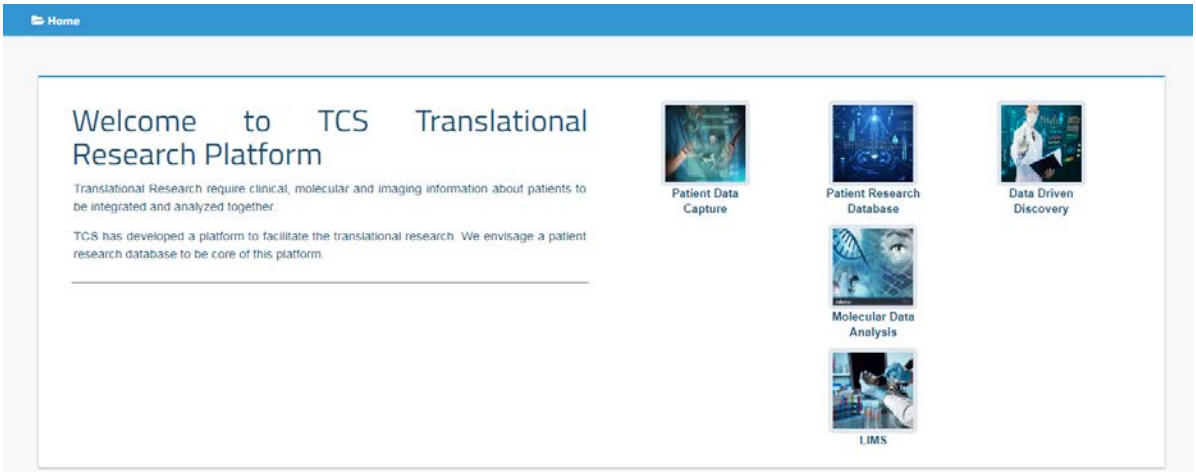

Computational Biology
Working with
Cytogenetic
Genomics
Transcriptomics
Proteomics (Cell Bio & Organoid)
Objective attending
Copy Number Variation
Targetted Exome Seq
NGS MRD
Gene Expression Profiling & Fusion transcript
Mass Spectrometry & micro array
Data Analysis
Data Visualization

Amit Saxena
Head, TCS
Genomics Lab

Anju Goel
Program Manager,
TCS Life Sciences

Divya Narayan
Program Manager,
TCS Life Sciences

TCS @ TTCRC



TCS is contributing to accelerate research initiatives by deploying platform and solutions for Translational Research. The Translational Research Platform allows for collecting and integrating clinical research data , molecular data , patient Electronic Medical Records (EMR) followed by cataloguing of data and creation of research database. The platform further has functionality to capture research hypothesis and generate hypothesis based patient cohorts . Specific concepts extracted from the research database can be used for exploratory analysis and visualisation or pattern mining and analytics for validating any scientific hypotheses.

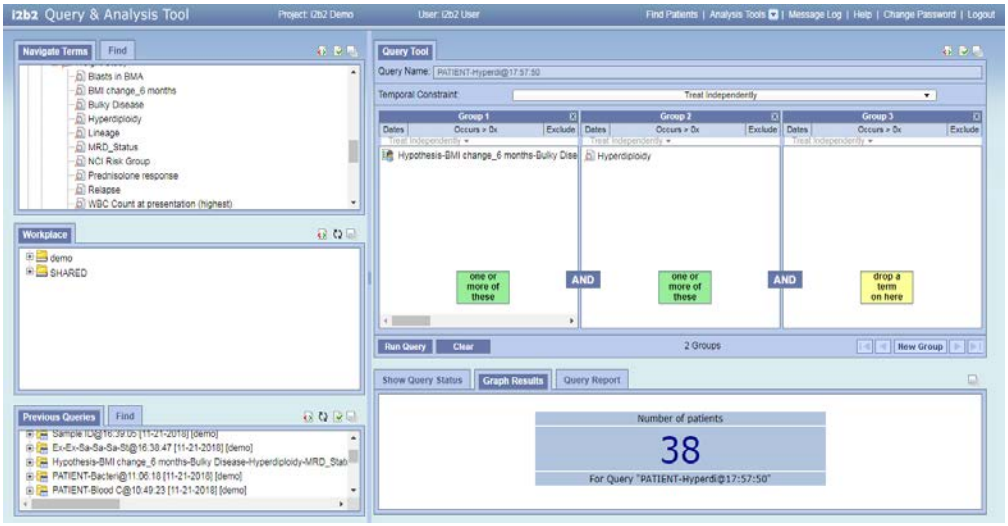
TCS has also provided support to enable necessary IT infrastructure including server configuration for genomic data processing, platform deployment and a 50Mbps ILL link to its Noida center.

Core functionalities of the Translational Research Platform include integration of clinical and molecular data into a patient research database, hypothesis management and discovery analytics using features of natural language processing (NLP) and machine learning. The platform integrates molecular data from genome sequencing with phenotype and clinical information from EMR and clinical trials.

Functionalities and solutions implemented as components of Translational Research Platform:

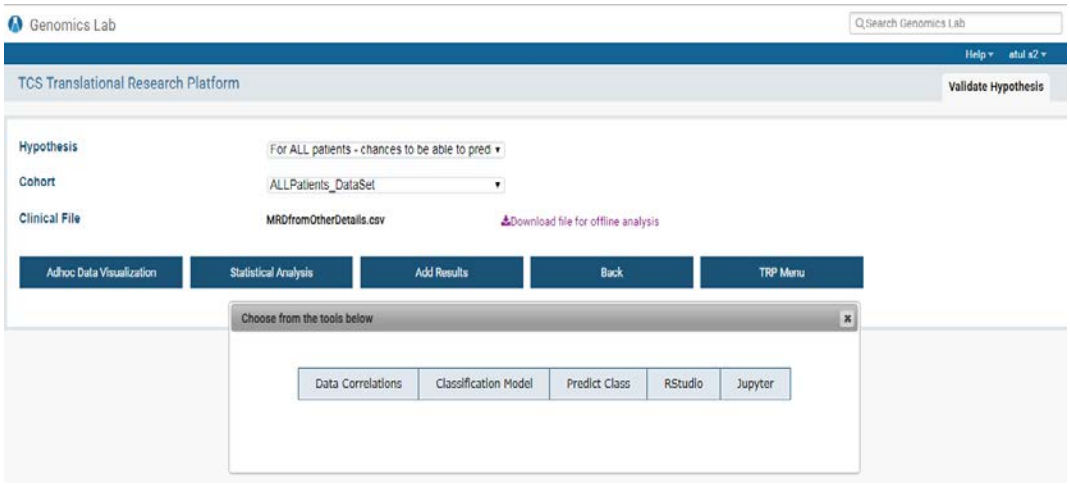
1. **Data Ingestion System** developed and deployed to extract data from electronic medical records in TMC's HMS system and upload into the research database as per the needs of clinicians / researchers.
2. **HMS mirror** setup for TTCRC to facilitate clinical data extraction from HMS
3. **i2b2*:** Implementation of open source i2b2 so that data extracted from EMR is integrated into i2b2 and is available for query through i2b2 web client and workbench. I2b2 is used for patient cohort creation, where queries can be performed on patient clinical and molecular data together as well download data necessary for proving a hypothesis.

4. **NLP based extraction** implemented using cTAKES™. Extract information from unstructured data sources like reports and doctors notes e.g. FISH, Karyotype, Immuno-phenotype, Ultrasound and Chest X-Ray reports, Examination and Advice texts.



5. Kibana: Stack of ELK* (Elasticsearch, Logstash, Kibana) implemented for visualization and analysis of extracted patient cohorts / concepts. Kibana has been used for visualization of integrated clinical and molecular data as well.

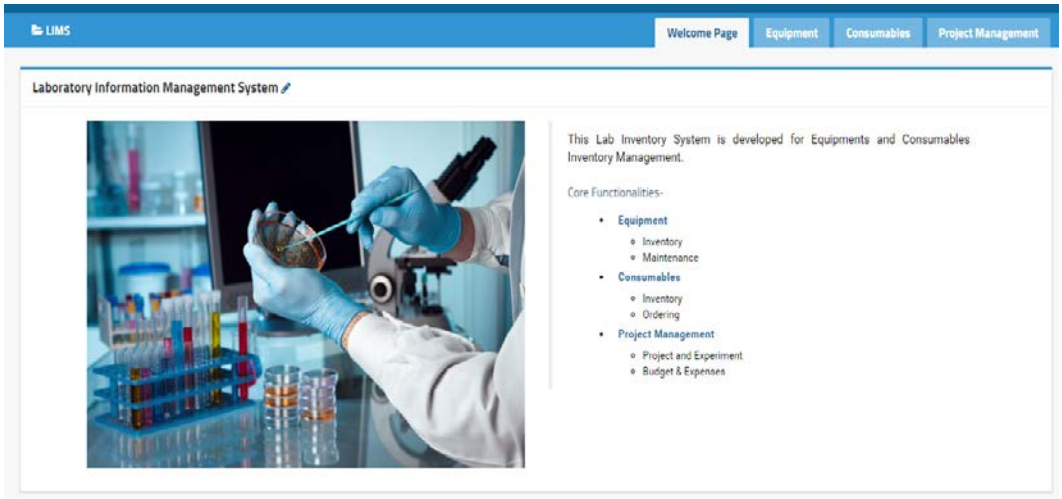
6. Data Driven Discovery – One touch Analytics Platform within TRP: Module catering to data analytics needs of researchers integrated within TRP to work in both Hypothesis driven as well as Data Driven modes.



7. LIMS: Deployment of Equipment & Consumables Inventory Modules. Complete details of Equipment Demos, Installation, Calibration, SOPs, Routine Maintenance, Equipment Breakdown, Incident management, Equipment Repair and

Equipment AMC details, etc. can be maintained and referred to as per need.

Dashboard showing status of various pending/ongoing activities is made available. Project wise Consumable requirements and usage can be maintained. Stock of all lab consumables can be maintained and reports indicating levels below minimum stock required can be generated for critical items.



8. **Patient Cohort Creation:** Capability allows scientific users to mine clinical findings from EMR and other real world data sources to extract patient cohorts for hypothesis testing. Also, allows for cohort creation based on molecular data along with clinical data.
9. **Search & Visualization:** Allows for scientific community and relevant stakeholders to perform enterprise search on raw, curated and analytical assets (includes data and metadata) and create adhoc visualizations for better insights.
10. **Discovery Analytics:** This includes analyzing extracted datasets using functionalities of basic and advanced statistical modeling, predictive analytics and exploratory analysis with tools like R (R Studio and EZR) & Jupyter.
11. **Clinical Trial Management :** For clinical trial management TCS has deployed IDM platform for **ICiCLE trial** where TCS IDM 3.0 is being used at 5 centers and ~ 1000 patients enrolled currently in existing trial. Some of the features of IDM include :
    a. Complex eCRF's and edit checks
    b. Block level randomisation
    c. Dashboards for site level and all India coordinator level with enhanced user requested reports.
    d. JIRA tool implementation done for better monitoring and faster ticket resolution.
    e. Separate Platform Support team for L1 / L2 ticket resolution.
    f. Development activity of TCS IDM 4.0 platform for new trial development on relapsed ALL

patients is completed and UAT is in progress.

Some of the ongoing projects where components of TRP have been used include hypothesis related to HD MTX Infusion Episodes Management, extraction of drug dosages for improvement in ALL maintenance therapy, Project on Gall Bladder Cancer, Hypothesis related to Effect of Weight Gain on the outcome of treatment for ALL patients etc.

** i2b2 (Informatics for Integrating Biology and the Bedside, http://www.i2b2.org)*

** ELK : Open source Elasticsearch, Kibana and Logstash*

etc.

India Alliance Wellcome-DBT Fellows

Dr Arunabha Chakrabarti
IA Early Career Fellow (2016)

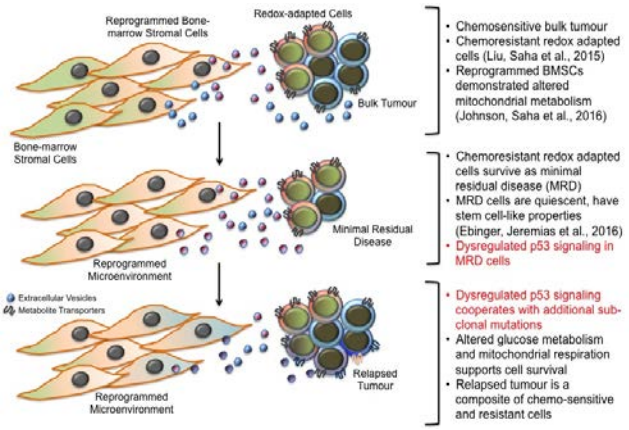
Dr Pritha Paul
IA Early Career Fellow (2017)

Dr Jasmeet Sidhu
Clinical Research Fellow
IA Early Career Fellow (2018)

We are delighted to host Wellcome DBT India Alliance Early Career Fellows in three consecutive years.

Dr Arunabha Chakrabarti (2016) is presently at the CRUK-MI facility at the University of Manchester from June 2018 for one year. Here, he is developing leukaemia cell lines with different Ikaros status (wild type IK1 and isoforms IK6 carrying deletion of exon 4-7) by using CRISPR-CAS9 based sgRNA for *IKZF1* for knock down Ikaros in leukaemia cells and introducing the isoforms of interest in those cell lines. He will also perform experiments on the Sciex 6600 Mass Spectrometer in Prof. Anthony D. Whetton's lab at the University of Manchester, where he will earn to run and analyse SWATH proteomics. His research focus is to understand the differential proteogenomics characterisation of Ikaros altered BCP-ALL subtypes and their response to therapy.

Dr Pritha Paul (2017) is working on *TP53* alterations, present in about 2-3% of children with acute lymphoblastic leukaemia (ALL) at initial diagnosis, but increases to ~13-15% at relapse and have been identified as the most significant sub-clonal mutation associated with recurrent therapeutic failure in ALL. These patients most often relapse early on-therapy. Another group of patients with similar clinical phenotype of early relapses, despite wild-type *TP53*, supports the hypothesis that common aberrant signalling pathways regulated either epigenetically in *TP53* wild-type or by gain-of-function in *TP53* altered ALL cells have an unexplored role in therapeutic failure addition, recent publications have offered insights into how the microenvironment influences cancer cell behaviour and in turn is influenced by the cancer cells to create a favourable niche. She will be travelling to CRUK-MI in Manchester in March 2019, to work with Dr Patricia Muller.



Dr Jasmeet Sidhu (2018) has been awarded with an early career fellowship last year and concentrating to start her research work as per proposal. Initially she was a Post-Doctoral Fellow in Cell Biology Team. Her research interest includes optimisation of L Asparaginase (Asnase) used in treating childhood ALL and identifying alternative induction agents in genetic subgroups prevalent in Indian children.

Proposed approaches to decrease post-induction minimal residual disease (MRD) burden

Dr Anindita Dutta
Administrative Lead

Avisek Banerjee
Post-Doc Fellow
Metabolism

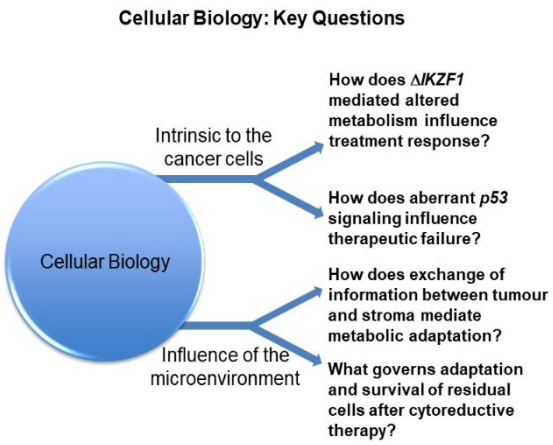
Dr Arunima Maiti
Research Assistant
Tumour stroma

Jaydeep Das
Research Assistant
Metabolism

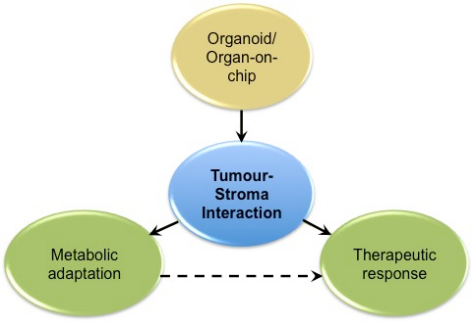
Priyanka Bose
Research Assistant
Therapeutic response

Cell Biology Laboratory

Cell Biology facilities have been developed at TTCRC from April 2018. We have a dedicated tissue culture facility, organoid laboratory and high throughput fluorescent microscopy. Facilities for cell transduction will be developed in 2019. To complement genomics, a high throughput mass spectrometer has been installed. Our work is focused on the interactions within the tumour microenvironment.



Organoid Culture



We are developing primary tissue organoids from patients, starting with ovarian and gall bladder cancer. We intend to generate both tumour organoids as well as tumour-on-chip for phenotypic drug discovery.

We are working with collaborators at IIT-Mumbai and the University of Manchester to develop biomimetic substrates and microfluidic systems to support organoid development.

Extracellular Vesicles

Our previous work has demonstrated that a variety of extracellular vesicles are exchanged between stroma and tumour cells within the leukaemic microenvironment. We have developed processes to isolate extracellular vesicles from cell culture and body fluids. Characterisation has confirmed release of exosomes by released cancer cells (Figure 1). We have observed that exchange of extracellular vesicles between tumour Stroma interaction in ovarian cancer (Figure 2 & 3). We are investigating the effect of vesical exchange in disease progression and therapeutic response.

Metabolism

In ALL we are investigating the functional aspects of mutations and copy number alterations, identified by the genomics team as present in high risk patients. We hypothesise that the metabolic changes that occur as a result of these genetic aberrations and leads/cause variations in therapeutic response.

Phenotypic Drug Assay

A phenotypic drug discovery system has been set up using a high throughput microscope (Figure 4). This is system is being developed both for direct drug assay as well as for studying the behaviour of cells within their microenvironment.

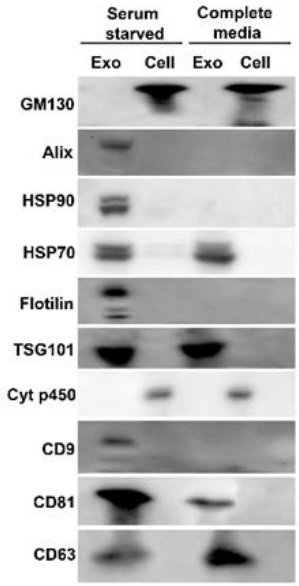


Figure 1: *Characterisation of cancer cell derived extracellular vesicles*. Exosomes were isolated from ovarian cancer cell, SKOV3, cultured either in exosome free FBS (complete media) or serum starved media. Following lysis of both SKOV3 cells and its secreted exosomes at indicated conditions, cell extracts were analysed by Western blot with antibodies against GM130, Cytochrome (Cyt) p450 (as negative controls for exosome lysates) and other indicated antibodies to check enrichment of targeted proteins within the released exosomes corresponding to the cell lysates.

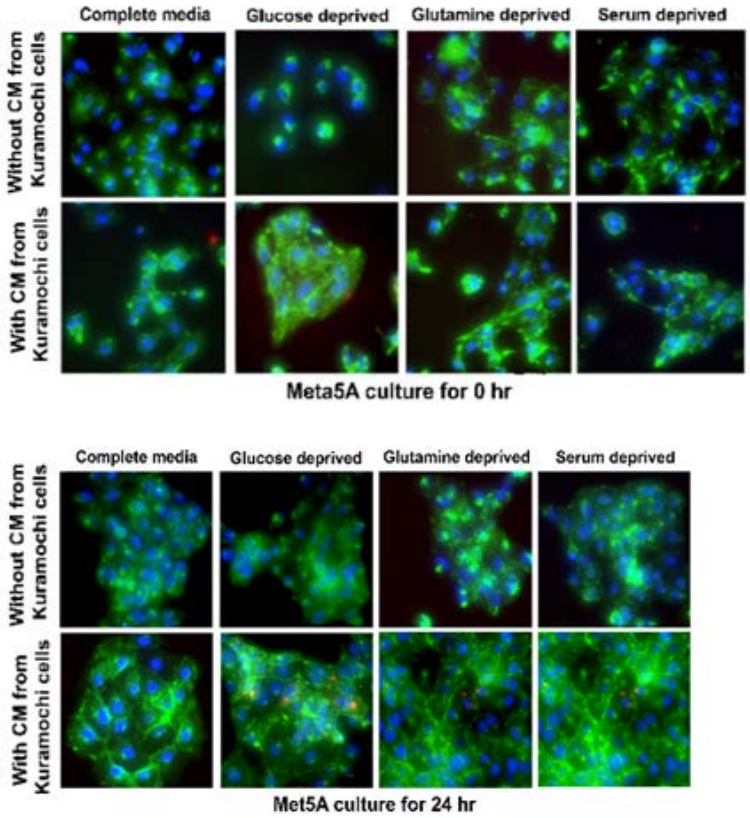


Figure 2: *Vesicles released from ovarian cancer cell line Kuramochi are taken up by normal mesothelial cells (Met5A)*. Kuramochi cells cultured in exosome free FBS were labelled with PKH-red fluorescent dye (Red). Vesicle containing conditioned media (CM) at indicated conditions from cancer cells were collected at 72 hours and incubated with Met5A (Green) cells for indicated time points. Fluorescence

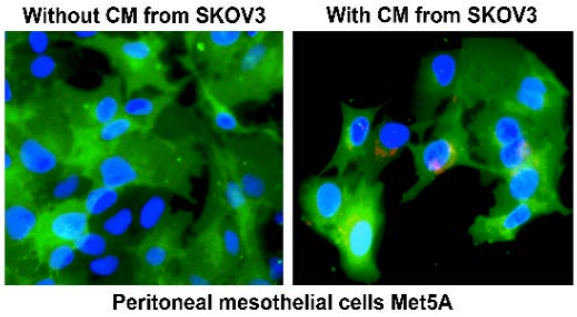


Figure 3: *internalisation of cancer cell derived vesicles by stromal* cell. Vesicles released from ovarian cancer cell line, SKOV3, are taken up by normal mesothelial cells (Met5A). SKOV3 cells cultured in exosome free FBS were labelled with PKH-red fluorescent dye (Red). Conditioned media (CM) containing extracellular vesicles from cancer cells are fed to mesothelial stromal cells. Internalisation of vesicles (Red) by stromal cells (Green) are observed after 24 hr.

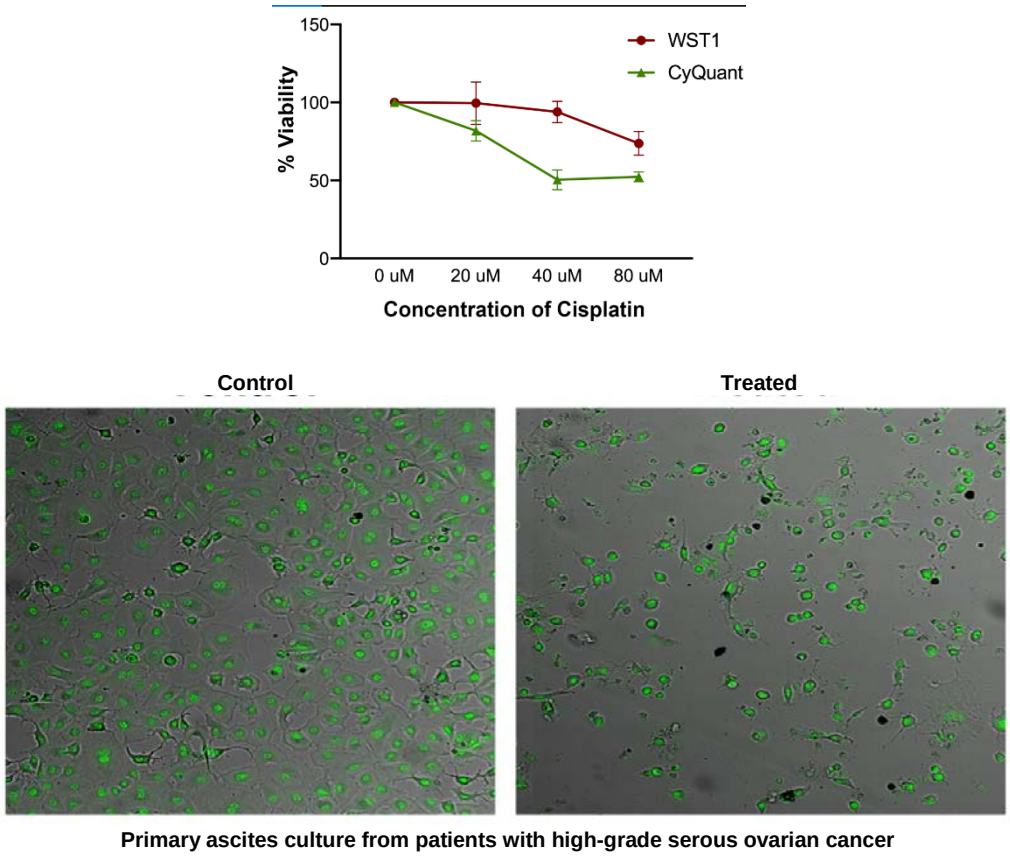


Figure 4: *Phenotypic drug assay in patient derived ascitic fluid culture*. Primary cells from patient with high-grade serous ovarian cancer were treated with indicated doses of cisplatin for 72 hours. Total nuclei were quantified using high-throughput fluorescence image analyser (ImageXpress). In parallel plates, anti-proliferative effect of cisplatin was measured by metabolic assay (top). Representative images of control and cisplatin treated cells are shown (bottom).

Dr. Ruma Dey Ghosh
DHR Woman Scientist

Akash Bararia
Biobank Technician

Head & Neck Cancer

Our research interest is focused on translational research for patient benefit. We are working around the development of biomarkers for oral cancer that will make diagnosis more precise, offer tailored therapy, and reduce the burden of over treatment and improve outcome. Currently I am working on oral squamous cell carcinoma (OSCC) to understand the clinical impact of different non-coding RNAs in different stages of cancers specifically, initiation, progression, and metastasis. We are trying to explore their regulatory effect on stem cell biology and drug resistance mechanisms which ultimately result differential prognostic outcome.

Oral cancer is the leading cause of cancer-related death in Indian male population. OSCC develops from epithelial lining of the mucosal surfaces of the oral cavity. Surgery is first-line of treatment, whereas radiotherapy and chemotherapy are used as adjuvant therapies in OSCC. Still the detection and prediction of disease-risk is not an easy thing and post-operative treatment strategies are determined mainly on the basis of histopathology report and tumour-staging. If fails, the general time to recurrence is within 24 months after treatment. Currently, there is no molecular biomarker for the prediction of OSCC-patient's risk (failure: recurrence and metastasis) analysis.

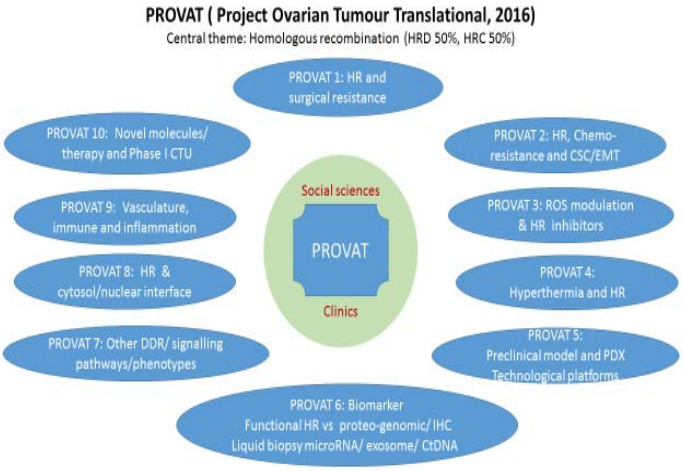
Our prediction is that the changes in the molecular-profile of malignant-tissues could produce a common detectable/testable molecular-profile in blood and other body fluids. Therefore, altered level of these analysts in circulation could be used as molecular-biomarker to predict patients-prognosis in OSCC. It will help clinicians to provide high efficiency treatment-strategies for OSCC.

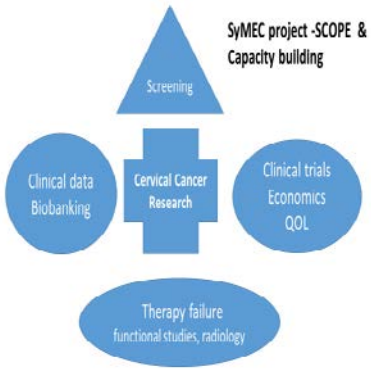
As miRNA are known to be very stable-molecule in circulation, we are exploring the idea that the tumour-associated cell-free miRNAs from peripheral blood plasma will allow us to predict OSCC patient prognosis at diagnosis. In our current investigation we are aiming to develop new miRNA biomarkers by analysing a patient cohort for the detection of disease risk with accurate subcategorization at diagnosis to provide appropriate treatment for OSCC patients. Subsequently, we are also trying to understand the miRNA mediated molecular pathways which may involve in the OSCC-prognostication.

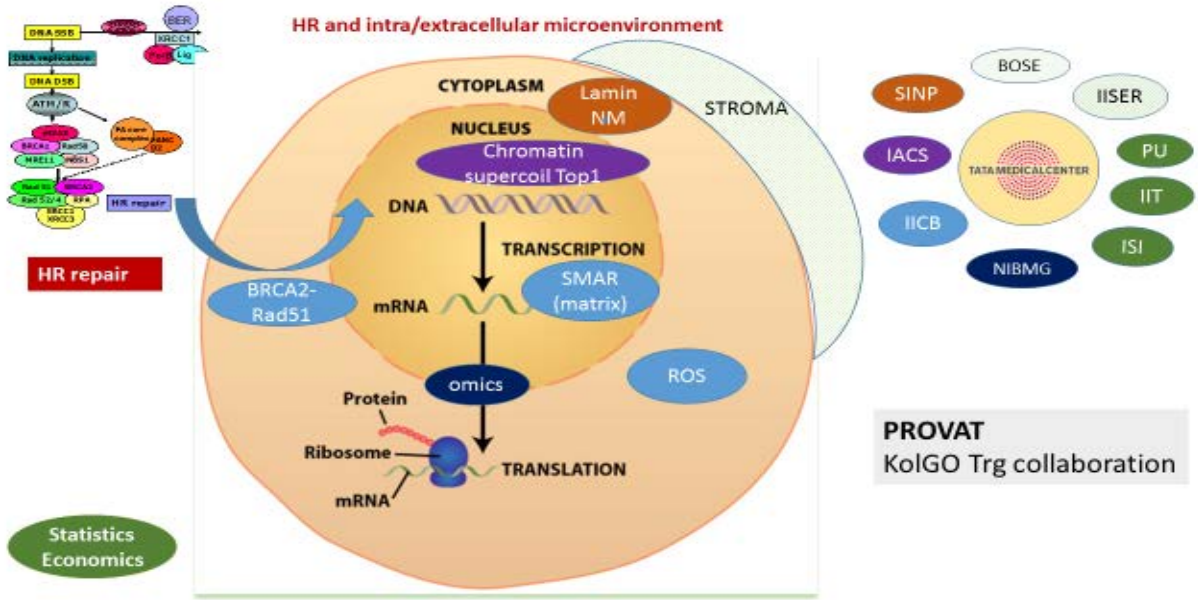
Dr Asima Mukhopadhyay
Senior Consultant and Academic Lead in Gynaecological Oncology
IA Fellow (2018)

Gynaecological Oncology

The key areas of clinical and lab research include: I. Establishing cytoreductive surgical services in ovarian cancer in low resource settings (optimizing surgical tools/techniques and quality assurance) and ii. Therapeutic applications of homologous recombination (HR)/BRCAness in Gynaecological Cancers. Her previous research led to a discovery that 50% of epithelial ovarian cancers are HR deficient and respond to PARP inhibitors; she is a contributor to the Newcastle Drug development and Discovery team that has led to FDA approval of the PARP inhibitor currently known as Rucaparib. Her current work at TTCRC and at Newcastle University focuses on generation of 2D and 3D primary culture models in ovarian and cervical cancers, estimation of functional homologous recombination status in primary culture models, study of tumour-stromal interaction/intra/extra-cellular micro-environmental differences in HR stratified tumours and developing therapeutic targets/ tailored surgical approaches in HR stratified cancers. Her research group in TMC/TTCRC currently has 34 members (clinical and lab research) and is working on the PROVAT (project ovarian translational) group of studies (PI) in ovarian cancer and SyMEC (Systems Medicine Cluster) project (Co-I) in cervical cancer. She is the founder of the Kolkata Gynaecological Oncology Trials and Translational Research Group which focuses on development and conduct of regional academic clinical trials/ studies and participation in major International collaborative group trials.






HR and intra/extracellular microenvironment
CYTOPLASM
Lamin NM
STROMA
NUCLEUS
Chromatin supercoil Top1
DNA
TRANSCRIPTION
SMAR (matrix)
mRNA
BRCA2-Rad51
omics
ROS
Protein
Ribosome
TRANSLATION
mRNA
HR repair
Statistics Economics
BOSE
SINP
IISER
IACS
TATA MEDICAL CENTER
PU
IIT
IICB
ISI
NIBMG
PROVAT
KolGO Trg collaboration

Dr. Susri Ray Chaudhuri
Administrator Operations

Sukanya Guha
Administrative Assistant

Administration

This year had been a very rich learning experience for me as part of the administrative team that provides the necessary infrastructure and services to facilitate the running of the Institute. It involves coordinating and planning very closely with the departments of Finance, Purchase, IT, Estates, Logistics, Health & safety and HR. The responsibility also includes involvement in all aspects of administration, communication and act as the primary point of operational contact within the Institute for both TTCRC and TMC.

Scientific Operations and General Administration

The office provides administrative support to the Director in order to facilitate the day-to-day running of the Institute. The team is also responsible for producing a variety of scientific communications for the Institute including TTCRC, TCS and Margdarshi Annual Reports.

In addition, the department has assisted the organisation for several events over the course of the year, including the successful Annual Review of the Institute on December 2018. Administrative support is provided for the internal seminar series called Radium, which has continued to be a great success in 2014-2018, hosting around one seminar per week. The seminars serve to foster collaboration and encourage positive interaction within the wider scientific community. We aim to provide a platform for a wide spectrum of national and international speakers deliberating unique aspects of their scientific research.

The administration team is responsible for planning, coordinating and implementing the entire infrastructure of the LDU-TTCRC unit and make the new office and lab setup operational on the year 2018. It involves rigorous engagement with multiple vendors and suppliers, coordinating the logistics, setting and monitoring of the deadlines, managing the occasional slip-ups and facilitating a state of art infrastructure.

Finance

The administration team carries the responsibility of coordinating with the finance in preparation and placing the budget on the table of the Director. It involves management of funds from the various sources and in ensuring that the funds are purposefully utilised. The team supports the research groups by providing effective and efficient professional advice when preparing the financial viability of new research proposals and contracts.

Human Resources

Over the past year, the administrative team has successfully coordinated with the HR department to deliver a high quality proactive service to the Institute and its staff. The admin team has provided the relevant information to the staff on all employment related matters advice and guidance to managers and staff on all employment-related matters such as recruitment, policy guidance, and best practice methods in concurrence with the HR department.

During 2017-18, 14 individuals were interviewed and appointed to facilitate the work of the Institute. Also, the smart

objective based appraisal of the TTCRC staff were organised and implemented this year.

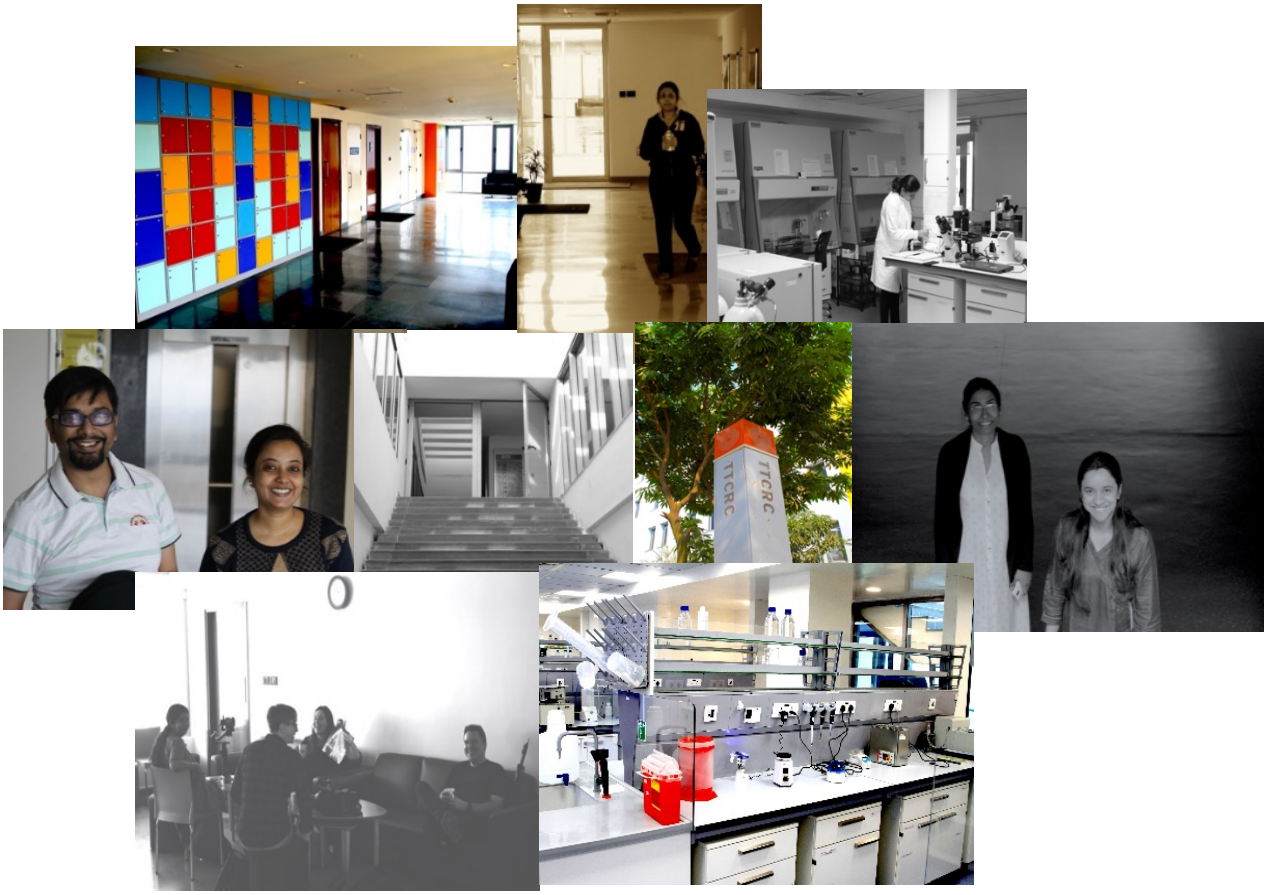
The transport network for the staff working late for Biobank sample processing and for the invited speakers were also organised in coordination with the HR department.

Information Technology

The administration team has worked in tandem with the IT team in providing a full catalogue of IT services based on which our researchers depend for most aspects of their work. In 2018 we have introduced our new storage solution and server facility.

Logistics (store)

This year the admin team along with the TMC logistics team had to deal with new challenges including the relocation of the team to the LDU-TTCRC Building. In the later part of the year we were able to establish small stores in the TTCRC building to deliver an efficient and effective service providing support for the research carried out. This includes the ordering, PO generation, indenting, issue acceptance and stock maintenance. We continue to make savings by procuring in bulk from suppliers and achieving the economies of scale and thereby guaranteeing a stable stock.



External Radium Speakers and Visits

The internal seminar series called Radium which take place on every Wednesday at 8.30am is a bridge between the TTCRC researchers, clinicians and national and international researchers working in the field of cancer biology. We have enjoyed the scientific interaction throughout the year and with an excellent set of internationally renowned speakers visiting the Institute. Following are the details of Invited speakers in the year (2017-2018).

1. **Dr. Asit Manna (National Cancer Institute, NIH, USA)**

   Multi protein complexes involved in TCR-mediated signalling: composition & cooperativity

   4th Oct 2017

2. **Dr Santasree Banerjee (Dept of Human Medical Genetics, R & D Group, Beijing Genomic Institute, China)**

   Next Generation Sequencing & Cancer

   11th Oct 2017

3. **Dr Debabrata Biswas (Wellcome-DBT Intermediate Fellow, Priniciple Scientist, IICB Kolkata)**

   Mechanistic understanding of role of MLL-Fusion and Fusion partner protein in Transcriptional regulation leukemogenesis.

   18th Oct 2017

4. **Dr Sandip Paul (Structural Biology & Bioinformatics Division, IICB,Kolkata)**

   Adaptive Evolution in Human Microbiome

   13th Dec 2017

5. **Dr Dipanjan Choudhury (Harvard School, Dana Farber Cancer Institute)**

   Micro RNA in Cancer Biology

   20th Dec 2017

6. **Dr Sounak Bakshi (Dept of Cell & Molecular Biology, Karolinska Institute, Stockholm, Sweden)**

   Alpha-Synuclein Moduletes Retinel Iron Homeostasis by RPE

   17th Jan 2018

7. **Prof Nicola Curtin (Newcastle University, UK)**

   Exploiting DNA Damage Response in Gynaecological Cancers

   31st Jan 2018

8. **Dr Kaushik Biswas (Associate Prof, Division of Molecular Medicine, Bose Institute,Kolkata)**

   Understanding The Role of ganglioside Gm2 in Tumorigenesis

   7th Mar 2018

9. **Dr Kaustabh Kumar Maity (CSIR-NIIST, Trivandrum)**

   Emerging Trends in Diagnostic & Theraputic Molecular & Nano Carrier Probes for Cancer Management

   11th Apr 2018

10. **Dr Saikat Chakrabarti (Indian Institute of Chemical Biology, Kolkata)**

    Analysis of Bio-Molecular Interactions: An Integrative Approach

    25th Jul 2018

11. **Dr Partha Sarathi Choudhury (Kyoto University)**

Fighting cancer by unleashing

1st Aug 2018

12. **Dr Sagar Sengupta (NII New Delhi)**

    Usage of Multiple Mechanisms to Maintain Genome Stability

    31st Oct 2018

13. **Dr Amit Dutt (Scientist F, ACTREC, Mumbai)**

    Translating Cancer Genomics to Medicine in Gall Bladder and Lung Cancer

    19th Dec 2018

Visit by University of Oxford
Jan 2018

Inauguration of 3rd Floor lab
April 2018

Visit by Dr Sagar Sengupta & Prof. Nicola Curtin, Oct 2018

Annual Review Dinner TTCRC, Dec 2018

Visit by Dr Rob Wynn, Nov 2018

Visit by Team of scientists from University of Manchester, Dec 2017

Publications - TTCRC

1. Catriona Parker, **Shekhar Krishnan**, Lina Hamadeh, Julie A E Irving, Roland P Kuiper, Tamas Révész, Peter Hoogerbrugge, Jeremy Hancock, Rosemary Sutton, Anthony V Moorman, **Vaskar Saha**. Outcomes of patients with childhood B-cell precursor acute lymphoblastic leukaemia with late bone marrow relapses: long-term follow-up of the ALLR3 open-label randomised trial. **Lancet Haematol. 2019** Feb 27; S2352-3026(19)30003-1

2. Biondi A, Gandemer V, De Lorenzo P, Cario G, Campbell M, Castor A, Pieters R, Baruchel A, Vora A, Leoni V, Stary J, Escherich G, Li CK, Cazzaniga G, Cave H, Bradtke J, Conter V, **Saha V**, Schrappe M, Grazia Valsecchi M. Imatinib treatment of paediatric Philadelphia chromosomepositive acute lymphoblastic leukaemia (EsPhALL2010): a prospective, intergroup, open-label, single-arm clinical trial. **Lancet Haematol. 2018**;5(12): e641-e52.

3. **Mukhopadhyay A**, Drew Y, Matheson E, Salehan M, Gentles L, Pachter J, Curtin N. Evaluating the potential of kinase inhibitors to suppress DNA repair and sensitise ovarian cancer cells to PARP inhibitors. **Biochemical Pharmacology. 2018** https://doi.org/10.1016/j.bcp.2018.10.011

4. Satyavarapu E, Das R, **Mandal C**, Mukhopadhyay A, Mandal C. Autophagy-independent induction of LC3 through oxidative-stress reveals its non-canonical role in anoikis of ovarian cancer cells. **Cell Death & Disease. 2018;** 9:934.

5. Sayantani Sarkar Bhattacharya, **Chandan Mandal**, Reinhard Schwartz Albiez, Suman Kumar Samanta & Chitra Mandal. Mahanine drives pancreatic adenocarcinoma cells into endoplasmic reticular stress mediated apoptosis through modulating sialylation process and Ca2+-signalling. **Scientific Reports. 2018**; 8:3911 DOI:10.1038/s41598-018-22143-w

6. Basu P, **Mukhopadhyay A**, Konishi I. FIGO Cancer Report 2018: Targeted therapy for gynaecological cancers: Toward the era of precision medicine. **Obstetrics and Gynaecology 2018**; 143 (2): 131-36

7. **Mukhopadhyay A**, Bizzarri, N, Bradbury M; Sinha S, Bhaumik J, Helm C. W*. Metastatic Involvement of Lesser Sac in Advanced Epithelial Ovarian Cancer. **International Journal of Gynecological Cancer. 2018**; 28 (2): 293-301

8. **Avisek Banerjee**, Barun Mahata, Arjun Dhir, Tapan Kumar Mandal, Kaushik Biswas. Elevated histone H3 acetylation and loss of the Sp1-HDAC1 complex de-repress the GM2- synthase gene in renal cell carcinoma. **JBC. 2018** doi/10.1074/jbc. RA118.004485

9. **Parihar M**, Singh M, **Islam R, Saha D**, Mishra DK, **Saha V, Krishnan S**. A triple-probe FISH screening strategy for risk-stratified therapy of acute lymphoblastic leukaemia in low-resource settings. **Pediatric Blood & Cancer. 2018** Dec;65: e27366.

10. Chauhan J, Dasgupta M, Luthra T, Awasthi A, Tripathy S, **Banerjee A**, Paul S, Nag D, Chakrabarti S, Chakrabarti G, Sen S. Design, synthesis and biological evaluation of a novel library of antimitotic C2-aroyl/arylimino tryptamine derivatives that are also potent inhibitors of indoleamine-2, 3-dioxygenase (IDO). **Eur J Pharm Sci. 2018** Nov; 124:249-265.

11. Bhattacharya R, **Ray Chaudhuri S**, Roy SS. FGF9-induced ovarian cancer cell invasion involves VEGF-A/VEGFR2 augmentation by virtue of ETS1 upregulation and metabolic reprogramming. **Journal of Cellular Biochemistry. 2018** Oct; 119:8174-8189.

12. Lu H, Bowler N, Harshyne LA, Craig Hooper D, Krishn SR, Kurtoglu S, Fedele C, Liu Q, Tang HY, Kossenkov AV, Kelly WK, Wang K, Kean RB, Weinreb PH, Yu L, **Dutta A**, Fortina P, Ertel A, Stanczak M, Forsberg F, Gabrilovich DI, Speicher DW, Altieri DC, Languino LR. Exosomal αvβ6 integrin is required for monocyte M2 polarization in prostate cancer. **Matrix Biol. 2018** Sep; 70:20-35.

13. Biondi A, Cario G, De Lorenzo P, Castor A, Conter V, Leoni V, Gandemer V, Pieters R, Stary J, Escherich G, Campbell M, Attarbaschi A, Li CK, Vora A, Bradtke J, **Saha V**, Valsecchi MG, Schrappe M.Long-term follow-up of Pediatric Philadelphia Positive Acute Lymphoblastic Leukemia treated with the EsPhALL2004 study: high white blood cell count at diagnosis is the strongest prognostic factor. **Haematologica. 2018** Sep; 10:3324.

14. **Ray Chaudhuri S**, Ghosh S, Roy A, Swarnakar S. Protective role of black tea flavonoids against ethanol-induced gastropathy via matrix metalloproteinase pathway. **Indian Journal of Clinical Biochemistry. 2018** Aug; 30:1-16.

15. Mitra T, Prasad P, Mukherjee P, **Ray Chaudhuri S**, Chatterjee U, Roy SS. Stemness and chemoresistance are imparted to the OC cells through TGFβ1 driven EMT. **Journal of Cellular Biochemistry. 2018** Jul; 119: 5775-5787.

16. Ahmad B, **Banerjee A**, Tiwari H, Jana S, Bose S, Chakrabarti S. Structural and functional characterization of the Vindoline biosynthesis pathway enzymes of Catharanthus roseus. **J Mol Model. 2018** Feb; 24:53.

17. Song HY, Rellinger EJ, Park SH, **Paul P**, Qiao J, Vasilopoulos A, Ozden O, Gius D, Chung DH. Inhibition of Sirtuin 6 Induces Neuroblastoma Differentiation. **Anticancer Res. 2018** Feb; 38:647-654.

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19. **Paul P**, Rellinger EJ, Qiao J, Lee S, Volny N, Padmanabhan C, Romain CV, Mobley B, Correa H, Chung DH. Elevated TIMP-1 expression is associated with a prometastatic phenotype, disease relapse, and poor survival in neuroblastoma. **Oncotarget. 2017** Jul 28; 8:8260982620.

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21. McGinn OJ, **Krishnan S**, Bourquin JP, Sapra P, Dempsey C, **Saha V**, Stern PL. Targeting the 5T4 oncofoetal glycoprotein with an antibody drug conjugate (A1mcmmaf) improves survival in patient derived xenograft models of acute lymphoblastic leukemia. **Haematologica. 2017** Jun; 102:1075-1084.

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23. Johnson SM, Dempsey C, Parker C, Mironov A, Bradley H, **Saha V**. Acute lymphoblastic leukaemia cells produce large extracellular vesicles containing organelles and an active cytoskeleton. **J Extracell Vesicles. 2017** Mar; 6:1-12.

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27. Revathi Rajagopal, Sayyidatul Abd-Ghafar, Dharmendra Ganesan, Anita Zarina Bustam Mainudin, Kum Thong Wong, Norlisah Ramli, Vida Jawin, Su Han Lum, Tsiao Yi Yap, Eric Bouffet, Ibrahim Qaddoumi, **Shekhar Krishnan**, Hany Ariffin, and Wan Ariffin Abdullah. Challenges of Treating Childhood Medulloblastoma in a Country with Limited Resources: 20 Years of Experience at a Single Tertiary Centre in Malaysia. **Journal of Global Oncology. 2017** Apr; 3(2): 143–156.

TTCRC - The Organizational Structure

Director TTCRC: Prof Vaskar Saha
Associate Director TTCRC: Dr Shekhar Krishnan

Research Team TTCRC

(I) Clinical Research Unit

Dr Shekhar Krishnan

Mou Das
Prakriti Roy
Manash Pratim Gogoi
Sayan Chatterjee
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