MAZUMDAR SHAW MEDICAL FOUNDATION

Annual Report 2021-22

Mazumdar Shaw Medical Foundation
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From the Managing Director's Desk

Mazumdar Shaw Medical Foundation (MSMF) is established to provide philanthropic support, medical outreach and translational research. Our goal is to make advanced healthcare accessible and cutting-edge Medical Science applications affordable. MSMF with Narayana Health has established a unique hospital-based ecosystem for bringing our shared vision to fruition.

Medical science has had the jurisdiction almost entirely for healthcare until now and has made remarkable progress possible. However, there is increasing recognition that physician-clinic-hospital centric healthcare must now make way for a broader Personal-Community- Physician- Hospital model of technology led healthcare. This shift mandates an approach that creates a culture of shared ideation between engineering and medical sciences. The expertise from disease biology encompassing genomic and molecular research, big data analysis, clinical research, etc must be now seamlessly integrated through advanced technology to socioeconomic factors to provide novel solutions of future healthcare.

With this in mind MSMF has created an ecosystem for guided innovation at multiple levels. Mazumdar Shaw Centre for Translational Research (MSCTR), Mazumdar Shaw Technology Business Incubator (MSMF-TBI) and the Mazumdar Shaw Cancer Outreach program (MSCOP) with Narayana Health-Mazumdar Shaw Medical Centre (MSMC) constitute an eclectic, scientific network that provides an optimal setting for novel ideation, entrepreneurship and fast track bench-side discoveries to bedside applications and smart solutions.

Healthcare and the practice of medicine in recent times demands more than addressing the physiological and/anatomical anomalies. The knowledge base that includes the underlying molecular basis of disease conditions and its customization according to the genetic framework of each individual, can be leveraged to develop mandatory adjuncts that can enable precision medicine.

Application of advanced technologies for big data analysis, both molecular and clinicopathological, is now a fast-advancing approach that can intelligently optimize existing information to obtain accurate diagnostics/prognostics. Finally, innovation is the primary strategy that can enable the translation of research findings to healthcare solutions. Fostering entrepreneurship in a healthcare set up will ensure a synergism with the clinicians fastening the process of deriving smart solutions. Given that medicine today demands a comprehensive understanding of all the various stakeholders, the Mazumdar Shaw Medical Foundation has a focus on integrative medicine that includes developing the knowledgebase, and encouraging innovation for its optimal application towards value addition in healthcare.

It is my view that we are embarking on one of the most exciting enterprises where clinicians, scientists and entrepreneurs can work under one roof for addressing healthcare issues by bringing in new tools and strategies in the fast-changing scenario of clinical practice.

Dr Paul C Salins

Managing Director, MSMF

MSMF in 2021-22 - at a Glance

The year 2021-22 has been a challenge for MSMF, as has been for the entire world due to the continued pandemic-enforced lockdown. However, the founding principle and a dedicated research/administrative team made it possible to retain the focus on the primary idea of translational research and philanthropy.

Achievements and Highlights

The Discovery program at MSCTR, MSMF focuses primarily in the field of oncology, our research has focused on leveraging the heterogeneity in tumors at imaging, cellular and molecular level to identify novel diagnostics/prognostics.

During the year, the Oral Cancer Control Program validated a novel auto-fluorescence based imaging system and an Optical coherence tomography (OCT) based platform for screening and early detection. MSMF was also granted the patent for an in-house developed, molecular cytology assay for early detection of oral cancer. Studies cataloguing the tissue and cellular heterogeneity that drive early carcinogenesis/metastasis in various cancers are ongoing as an effort to understand the biology and identify diagnostic/prognostic markers. Molecular profiling and AI_based modeling is being carried out in thyroid malignancies, to accurately diagnose the indeterminate nodules that form 30-45% of the nodules detected by Ultrasound-Guided Fine-Needle-Aspiration Cytology (USG-FNAC). Immunophenotyping in GBM identified CD86 and CD63, cell-surface proteins that correlated among myeloid cells in blood and tumor, as candidate markers of progression. G-protein coupled receptors have been a major area of focus in GBM, public domain data coupled with sh-RNA mediated knockdown of GPR56, indicated an enrichment of proteins/pathways associated with mesenchymal cell transition along with an increase in aggressive behaviour of the cells.

Continued research on the application of 3D GelMA models in glioblastoma, has indicated a differential and more aggressive, drug resistant behaviour of the cells in the model as compared to the 2D system. Further the profiling of these cells indicated an enrichment of treatment-resistant mesenchymal cells, resembling the perivascular and perinecrotic zones of the tumor in contrast to the

neurosphere-derived cells that enrich infiltrative cells. This model is currently being explored in head and neck cancers to evaluate the effect of biophysical signaling on carcinogenesis, drug resistance and progression. In vitro models from patient-derived cells form another major effort; primary cells from oral cancer, GBM, and stromal cells are under development.

Novel therapeutics for immunotherapy are being investigated, with *in vivo* studies indicating that Anti-LCN2 reverses both radio-resistance and drug resistance in the colorectal xenograft model. Further its role in inhibition of ferroptosis through the tumor-niche cross talk is being explored in multiple cancers. Other targets under evaluation include the efficacy of novel BCL2 inhibitors in liquid tumors, molecules that target cross-talk as well as stem cells in head and neck cancers.

COVID-19*:* MSMF in collaboration with Molecular Solutions Care Health (MSCH) and the infectious disease clinic, PCMH Restore Health, has carried out epidemiological studies in COVID (>1 million individuals). The team has established and validated a qPCR screening kit, a RAT kit and an antibody detection kit in collaboration with NeoDx, IISc and Achira labs respectively. A novel fusion protein developed as a SARS-CoV2 virus trap is also shown to be efficacious in the Golden Syrian hamster model (in Collaboration with the BSL3 facility at FNDR, Bangalore), a lead which is being explored further.

New Initiatives undertaken

This year, we have undertaken two new initiatives in MSCTR, as concrete steps towards achieving bench-to-bed translation. A **Product Research Group** has been established with the objective of defining pipelines and to pursue the leads obtained from the Discovery Programs. The focus is on generating diagnostic/prognostic assays, novel therapeutics and *in vitro* patient-derived cell models. Work is underway to develop the first set of therapeutics (Ace2Fc, LCN2) and diagnostics (salivary diagnostics) in the team. **Computational Biology** has always been an integral part of the exploratory research work at MSMF, this year we have carved an independent, core program that would focus on Informatics and Artificial Intelligence. Work is already underway towards developing a pipeline for integrated omics analysis and generating AI-enabled models for GBM and lung cancer. We are also in the process of generating AI-based integrated models in oral cancer and thyroid cancer. In collaboration with Narayana Institute of neurosciences, we are also initiating a **Stem Cell Based Stroke Management**

Program focusing on identifying stem cell-based solutions for stroke patients (Funded by SKAN Research Trusts). Furthering our interests in cancer stem cells, we are also initiating an **Ovarian Cancer program** focusing on stem cells in resistance and relapse of the disease in collaboration with the Department of Gynaecologic Oncology, Mazumdar Shaw Medical Centre, Narayana Health.

As an organization focused on translational research, efforts that would provide immediate bed-side benefits to the patients have always been a priority. **Advanced Diagnostic Research Centre (ADRC)**, at MSMF, focuses on tailoring research to the clinical challenges/needs and developing assays/tests that are accurate, and affordable. This program is being established in close collaboration with the clinical team at Mazumdar Shaw Medical Centre and Narayana Hrudayalaya to cater to the unmet and immediate clinical needs.

The MSMF-TBI, expanded its activities during the year, under the BioNest program. Currently housing 22 incubatees that engage in diagnostics, wearable devices, clinical decision support systems and education, many of them are in the process of carrying out clinical validation studies. Additionally, the team at TBI is also developing a Medical Artificial Intelligence Cloud Infrastructure (MAICI) as a service platform. The outreach wing of MSMF, MSCOP continues to support the underprivileged patients, providing financial, nutritional, counseling and emotional support to more than 50 patients.

MSMF, with the new initiatives and continued work in research, business incubation and outreach, hopes to strengthen its approach of translating benchside discoveries/innovation to bedside solutions in the years to come.

Dr Amritha Suresh

Operational Head, MSMF

Achievements

Grants

Dr Amritha Suresh

1. Multimodal intraoral imaging system for oral cancer detection and diagnosis in low resource setting (Collaboration project with Univ of Arizona, Narayana Health, NIH)
2. Mobile oral cancer screening system for low-resource settings (Collaboration project with Univ of Arizona, Narayana Health, SBIR grant, NIH)

Dr Manjula Das

1. Validation of a RT-PCR kit for the detection of Coronavirus in saliva samples (Industry grant from NeoDx)
2. SolAce: Novel Therapeutics against Coronavirus infection (BIRAC grant under COVID-19 initiative)

Dr Sujan K Dhar

1. Development of an AI-enabled computation model for IDH1 mutation detection from H&E-stained glioma histopathology images, in collaboration with NIMS Hyderabad (approved by ICMR), 2022-25
2. Near AI: predicting response to save lives in lung carcinoma, in collaboration with 64 Codon, Kochi (approved by Kerala Startup Mission), 2022-23

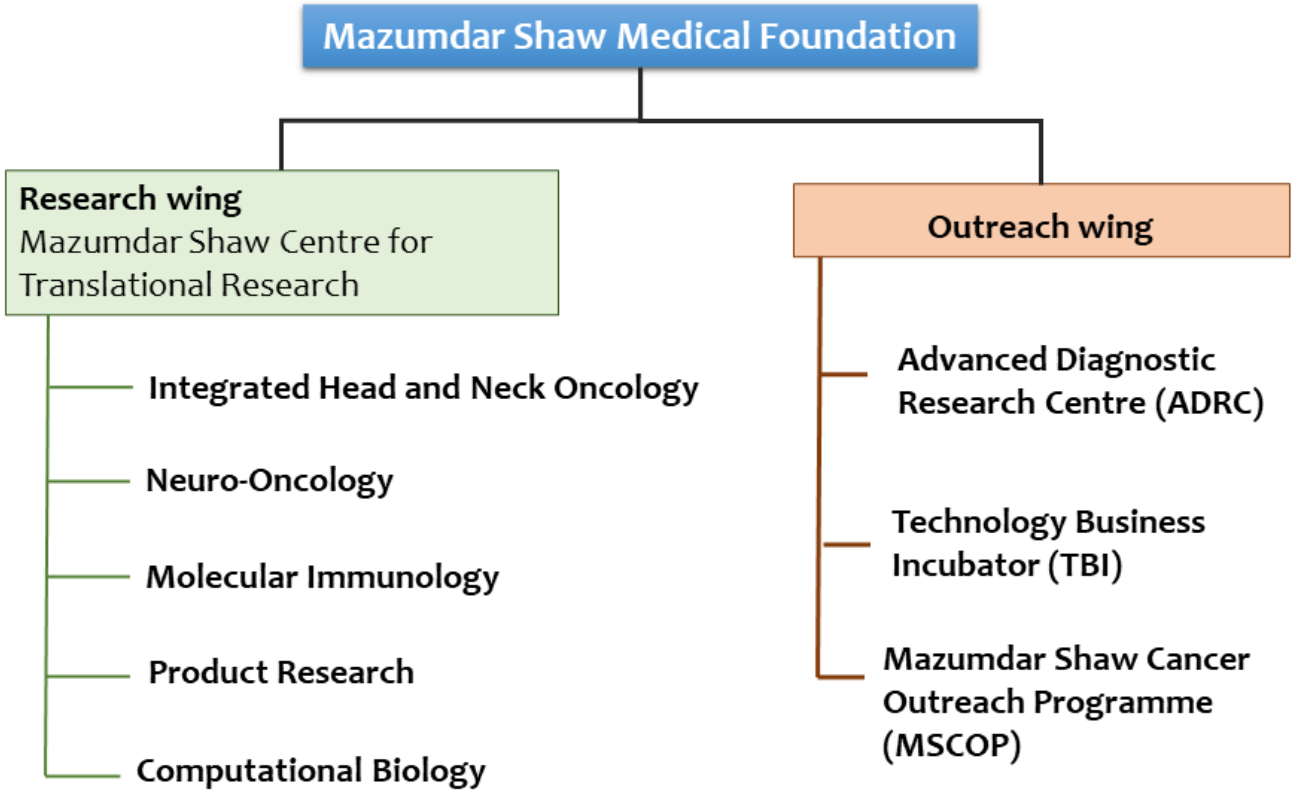
Degree Awarded

PhD awarded to **Ram Bhupal Reddy** from Vellore Institute of Technology (VIT) on the topic *Molecular Prognosticators and Novel Targets in Chemo-Resistant Head and Neck Cancer* under the guidance of Dr Amritha Suresh

PhD awarded to **Simple Mohanta** from Vellore Institute of Technology (VIT) on the topic *Cancer stem cells in oral squamous cell carcinoma: Association with differentiation, recurrence, field cancerization and prognosis* under the guidance of Dr Amritha Suresh

MSMF Structure

MSMF is organized into two broad wings. The research wing is called Mazumdar Shaw Centre for Translational Research comprising research programmes in multiple disease areas. The outreach wing of MSMF caters to broader society including the Advanced Diagnostic Research Center (ADRC), Technology Business Incubator (TBI) and Mazumdar Shaw Cancer Outreach Programme (MSCOP).



Integrated Head and Neck Oncology Program

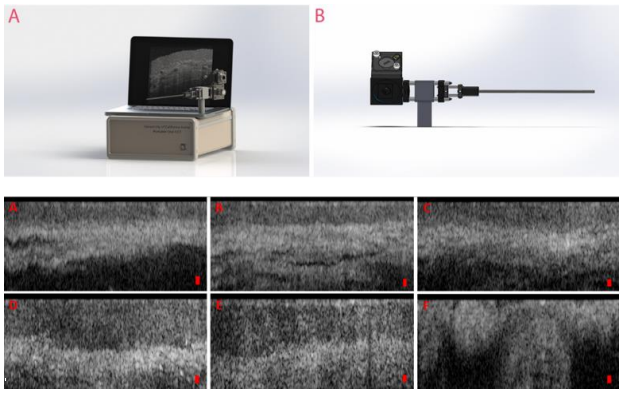
The Integrated Head and Neck Oncology Program focuses on an integrated, multi-disciplinary approach towards addressing two grand challenges of down-staging oral cancer and the possibility of reversing treatment resistance in head and neck cancer. Given that over two-thirds of the patients with head and neck cancer present at advanced stages III/IV, with an overall survival rate of less than 20%, early detection is the key. Secondly, about 50% of all head and neck cancers recur after 'curative intent treatment'. As in the majority of solid tumors, once the disease recurs or develops distant metastasis, there are no curative treatment options. Accurate prognostication, and reversing resistance is hence an immediate need. The team at MSCTR adopts a systems biology approach, exploring the cellular, molecular, biophysical and AI based parameters in tissues, cells and body fluids, such as saliva and blood. Additionally, our cancer stem cell program explores the role of CSCs in the process of tumorigenesis, field cancerization, drug resistance and metastasis.

Research Highlights

- Novel auto-fluorescence based imaging system for oral cancer screening/detection
- Application of OCT in early detection and tumor margin delineation
- Biomarker database for detection of thyroid nodules
- Novel candidate markers for detection, targeting in head and neck cancer
- Biomarker database for nodal metastasis

Oral Cancer Control Program

The Oral Cancer Control Program in the group focused on advancing the technological innovations that can help in improving the surveillance and screening of oral cancer. Additional integrated omic profiling of oral potentially malignant lesions, and deconvolution of the immune landscape are other areas of focus.



The technological innovations that were advanced during the year includes OCT based system, dual modal imaging system including white light and fluorescence and molecular cytology based assay system. *Optical coherence tomography* enables

rapid, real time imaging and frequent patient surveillance and has been in use for multiple clinical conditions. As indicated in the previous years, OCT, a minimally invasive tomographic imaging technology, can be used to non-invasively identify premalignant or malignant changes in the oral mucosa. The mobile OCT imaging system was tested for its performance as a point-of-care oral diagnostic device in an LMIC in a large-scale validation study. It was found that the OCT image processing algorithm performed at or exceeded the performance of visual observer scoring of OCT images. During this year the large scale validation as well as the efficacy of the platform was ascertained (detailed in the later sections). *The dual modality, non-invasive imaging system* for early detection was also validated in a large cohort (n=5000) of patients; our results indicate the efficacy of the system in detecting suspicious lesions when deployed with front-line health workers. *Molecular cytology* has been in focus at our centre during the past years. Systematic review and meta-analysis identified markers that can be carried forward for diagnosis of oral cancer. In an effort to automate the system, our team has undertaken the AI-based analysis of the molecular cytology images. Oral cytology image analysis has multiple challenges such as, presence of debris, blood cells, artefacts, and clustered cells, which necessitates skilled expertise for single-cell detection of atypical cells for diagnosis. We are in the process of developing a semantic segmentation model for Single Epithelial Cell (SEC) separation from fluorescent, multichannel, microscopic oral cytology images and to classify the segmented images. The study is currently ongoing.

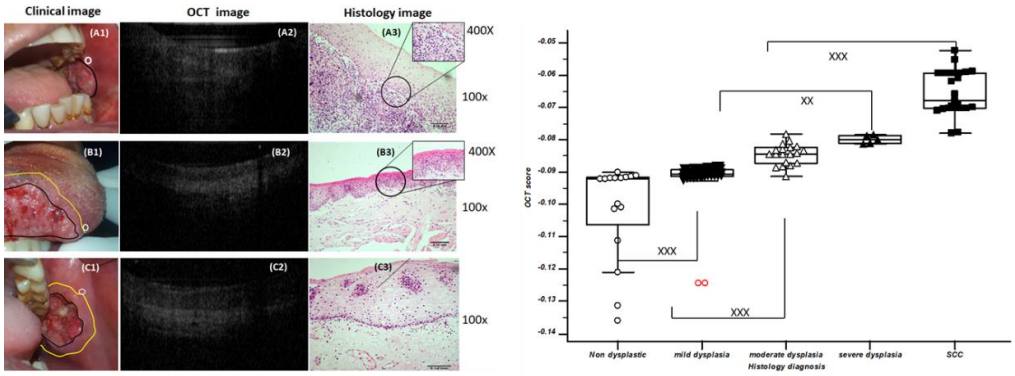
Oral potentially malignant lesions show diverse behaviour in terms of the clinical manifestation (leukoplakia, erythroplakia), histology (grades of dysplasia) and susceptibility for transformation (ranging from ~1.5% to 33%). An effort to characterize the lesions at the genomic/transcriptomic level and generate a comprehensive atlas of the molecular alterations and extracting the tumor microenvironment/immune profile is currently ongoing. This program is in collaboration with KLE Institute of Dental Sciences, Bangalore and Cachar Cancer Hospital and Research Centre, Silchar, Assam.

Cellular/ Molecular Diagnosis/ Prognostication of Head and Neck Cancer

Studies in the field of cellular and molecular prognosis include surgical margin delineation, delineating the basis of nodal metastasis, and cancer stem cells in drug resistance/prognosis.

Surgical Margin Evaluation: We attempted to assess the utility of intraoperative optical coherence tomography (OCT) imaging with automated diagnostic algorithms to improve on the current method of clinical evaluation of surgical margin in oral cancer. OCT

showed an accuracy of 100%, equivalent to histological (κ=0.922, CI= 0.82-1), in detection of malignancy within tumor and tumor margin areas (Images: 122; patients: 14). In comparison, for dysplastic lesions, OCT-based detection showed a sensitivity of 92.5% (CI= 84.4-97.2) and specificity of 68.8% (CI=49.3-89) with moderate concordance with histopathology diagnosis (κ=0.59; CI=0.38-0.81). Additionally, the OCT scores could significantly differentiate squamous cell carcinoma (SCC) from dysplastic lesions (mild/moderate/severe; p≤0.0005) as well as dysplastic lesions from non-dysplastic lesions (p≤0.005). Given the current challenges associated with clinical examination-based margin



OCT images of the oral lesions along with the clinical and histology images. AI-based analysis could delineate the dysplastic lesions

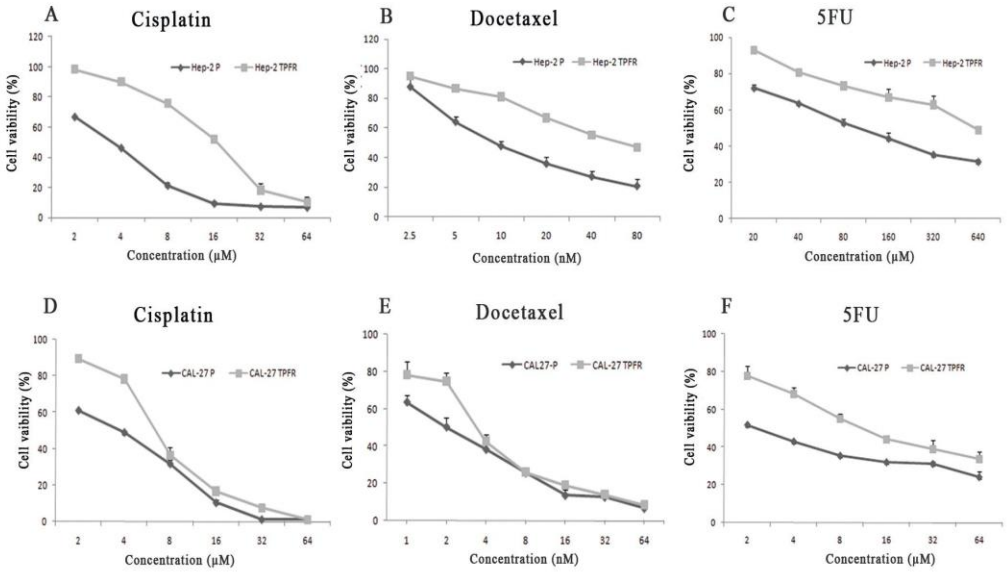
assessment, this study suggests the potential of OCT towards identifying microscopic tumors at the surgical margins and the feasibility of mapping of field cancerization around the tumor. Molecular mapping of surgical margins in oral cancer has been attempted. Literature review followed by patient validation has identified stem cell markers that can help in delineating the margins and were associated with poor disease-free survival (p<0.05). Correlation of the molecular map of field cancerization with the clinical/pathological parameters and prognosis will be a step towards clinical applicability of these markers in mapping the margins and as molecular prognosticators.

Nodal Metastasis in Head and Neck Cancer: One of the major studies currently ongoing (funded by DHR, ICMR) is looking into the underlying molecular and cellular interactions that govern the process of nodal metastasis in oral cancer. An integrated approach including meta-analysis of publicly available datasets, multi-omics profiling and *in vitro/invivo* studies are going on to delineate the mechanisms and identify specific candidate biomarker panels. A comprehensive proteomic profiling is currently ongoing in the tumor and the matched nodes of the patients to delineate the tumor-node interactions underlying nodal metastasis and extra capsular spread. Multiple patient-

derived cultures from primary tumor and lymph nodes are under development as models for mechanistic and biomarker validation.

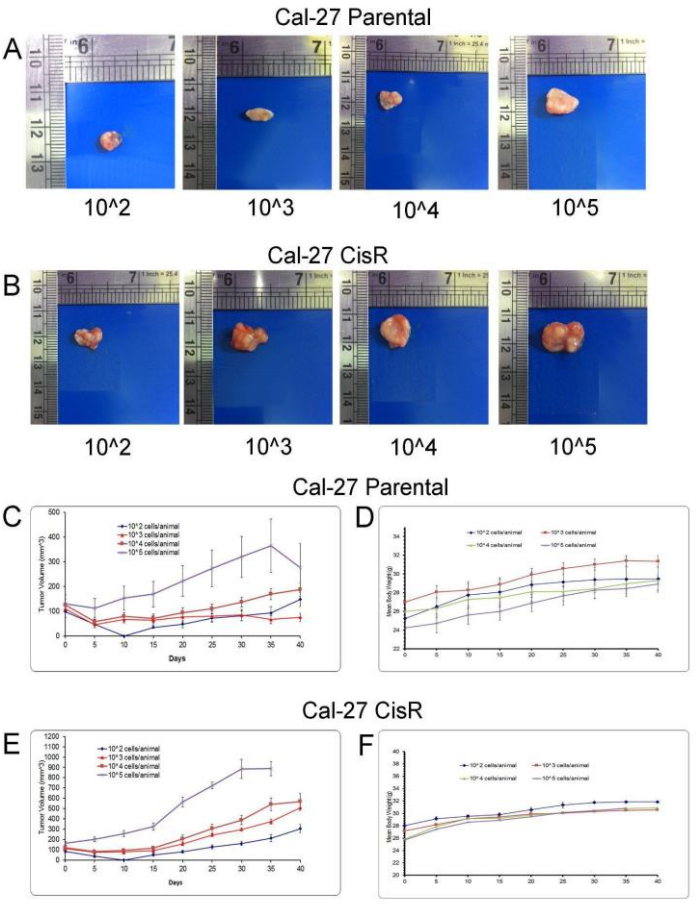
Cancer Stem Cells in resistance and prognosis: CSC-mediated resistance is known to orchestrate the process of disease relapse and our team investigates the underlying mechanisms of the process and the clinical applicability of the targets identified. The role of CSCs during the process of carcinogenesis is not completely worked out; ongoing studies in the lab look at the stem cell populations, their cellular/molecular patterns at different stages of oral carcinogenesis. Previous studies in the lab have led to the establishment of cell lines resistant to taxol, platinum and 5FU (TPF) in combination as well as individually. The resistant cells showed an enrichment of CD44+ cells, increased spheroid formation ($p<0.005$) and migratory capacity ($p<0.05$) indicating that drug resistance is accompanied by the acquisition of a stem cell-based phenotype. An increase in the levels of CSC markers (*CD133, BMI* and *NOTCH1*) known to induce resistance through drug transporters and survival/anti-apoptotic pathways, which are also up regulated in these cells, suggested possible causal mechanisms. Furthermore, both the TPFR cell lines had significantly higher clonogenic survival under different cisplatin concentrations ($p<0.05$) signifying a subset of cells with increased self-renewal capacity with drug resistance. Tumorigenicity assays indicated an increased tumour burden (up to 1.4 fold) with different cell numbers of the Hep-2 TPFR (10^5, 10^4, 10^3 and 10^2) in the *in vivo* xenograft model (3/3 mice). Our findings thus indicate that TPF combination chemotherapy enriches the resident cache of CSCs, ultimately leading to drug resistance. Similar trends were also observed in the single drug resistant cell lines of Cal-27 and Hep-2. Increased expression of stem cell markers (CD44, CD133, NOTCH1, ALDH1A1, OCT4, SOX2) in the single drug resistant cell lines, that correlated with enhanced spheroid/colony formation, migratory potential, and increased in vivo tumor burden ($P < 0.05$). Inhibition of ALDH1A1 in Cal-27 CisR led to downregulation of the CSC markers, reduction in migratory, self-renewal and tumorigenic potential ($p<0.05$)

accompanied by an induction of sensitivity to Cisplatin ($p<0.05$). These leads are currently being followed to validate novel targets in head and neck cancer.



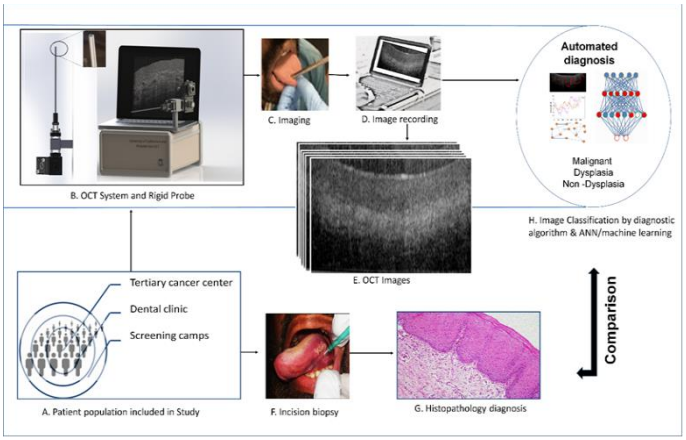
HNSCC cell line models resistant to Cisplatin, Docetaxel and 5 FU

Systematic review followed by comparison with the Cancer Stem Cell database (CSCDb) identified the markers with prognostic significance in oral cancer. Further, we attempted to correlate cancer stem cell markers (CD44 and CD147) with tumor differentiation and evaluate their subsequent effect on prognosis; analysis indicated that differentiation correlated with recurrence and survival ($p<0.05$) in only the patients with $CD44^{high}/CD147^{high}$ cohort. Expression profiling indicated higher expression of cancer stem cell and epithelial–mesenchymal transition markers in SCC029B (poorly differentiated squamous cell carcinoma originated; $p \leq 0.001$), which was further translated into increased spheroid formation, migration, and invasion ($p < 0.001$) as compared to cell line of well-differentiated squamous cell carcinoma origin. This study suggests that CD44 and CD147 together improve the prognostic efficacy of tumor differentiation; *in vitro* results further point out that these markers might be determinant of differentiation characteristics, imparting properties of increased self-renewal, migration, and invasion.



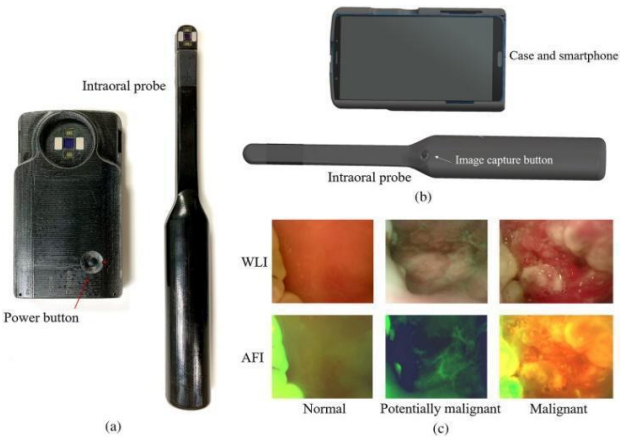
Year at a Glance

Optical Coherence Tomography as a mode for surveillance and detection: Here, we report the validation of a portable OCT device, developed previously by our group, for its efficacy in delineation of OPML (n=121) and malignant lesions (n=75) in community and tertiary care settings. We show that the OCT images analyzed by a MATLAB-based image processing algorithm could distinguish the dysplastic OPML and malignant lesions with a sensitivity of 95% and 93% respectively. Significantly, the ANN-based analysis could delineate high-grade dysplasia with high sensitivity (83%), which in turn can be employed to triage patients for tertiary care referral. [Collaboration with KLE Dental Sciences, UCLA, Irvine, Beckman Laser Institute).



Portable OCT device, the study pipeline and the ANN-based decision making algorithm developed from OCT images for early detection

ANN based classification of oral cancer images for screening: The dataset used in our study was captured among 5025 patients with our customized dual-modality mobile oral screening devices. We trained an efficient network MobileNet with focal loss and converted the model into TensorFlow Lite format. The finalized lite format model is ~16.3MB and ideal for smartphone platform operation. We have developed an Android smartphone application in an easy-to -use format that implements the mobile-based dual-modality image classification approach to distinguish oral potentially malignant and malignant images from normal/benign images. We investigated the accuracy and running speed on a cost-effective smartphone computing platform. It takes ~300ms to process one image pair with the Moto G5 Android smartphone. We



tested the proposed method on a standalone dataset and achieved 81% accuracy for distinguishing normal/benign lesions from clinically suspicious lesions, using a gold standard of clinical impression based on the review of images by oral specialists.

Publications

1. BL, Sunny SP, Heidari AE, Ramanjinappa RD, Lam T, Tran AV, Kankanala S, Sil S, Tiwari V, Patrick S, Pillai V, Shetty V, Hedne N, Shah D, Shah N, Chen ZP, Kandasarma U, Raghavan James SA, Gurudath S, Nagaraj PB, Wilder-Smith P, Suresh A, Kuriakose MA. Validation of a Point-of-Care Optical Coherence Tomography Device with Machine Learning Algorithm for Detection of Oral Potentially Malignant and Malignant Lesions. Cancers (Basel). 2021 Jul 17;13(14):3583. doi: 10.3390/cancers13143583.

Dual Modality device for early detection of oral cancer
2. Kevin Chew Figueroa, Bofan Song, Sumsum Sunny, Shaobai Li, Keerthi Gurushanth, Pramila Mendonca, Nirza Mukhia, Sanjana Patrick, Shubha Gurudath, Subhashini Raghavan, Tsusennaro Imchen, Shirley T. Leivon, Trupti Kolur, Vivek Shetty, Vidya Bushan, Rohan Ramesh, Vijay Pillai, Petra Wilder-Smith, Alben Sigamani, Amritha Suresh, Moni Abraham Kuriakose, Praveen Birur, Rongguang Liang Interpretable deep learning approach for oral cancer classification using guided attention inference network J Biomed Opt. 2022 Jan; 27(1): 015001.
3. Song B, Sunny S, Li S, Gurushanth K, Mendonca P, Mukhia N, Patrick S, Gurudath S, Raghavan S, Imchen T, Leivon S, Kolur T, Shetty V, Bushan V, Ramesh R, Lima N, Pillai V, Wilder-Smith P, Sigamani A, Suresh A, Kuriakose M, Birur P, Liang R. Mobile-based oral cancer classification for point-of-care screening. J Biomed Opt. 2021 Jun;26(6):065003.
4. Song B, Li S, Sunny S, Gurushanth K, Mendonca P, Mukhia N, Patrick S, Gurudath S, Raghavan S, Tsusennaro I, Leivon ST, Kolur T, Shetty V, Bushan V, Ramesh R, Peterson T, Pillai V, Wilder-Smith P, Sigamani A, Suresh A, Kuriakose MA, Birur P, Liang R. Classification of imbalanced oral cancer image data from high-risk population. J Biomed Opt. 2021 Oct;26(10):105001. doi: 10.1117/1.JBO.26.10.105001.
5. Song B, Sunny S, Li S, Gurushanth K, Mendonca P, Mukhia N, Patrick S, Gurudath S, Raghavan S, Tsusennaro I, Leivon ST, Kolur T, Shetty V, Bushan VR, Ramesh R, Peterson T, Pillai V, Wilder-Smith P, Sigamani A, Suresh A, Kuriakose MA, Birur P, Liang R. Bayesian deep learning for reliable oral cancer image classification. Biomed Opt Express. 2021 Sep 20;12(10):6422-6430. doi: 10.1364/BOE.432365. eCollection 2021 Oct 1.
6. Patients' views on a proposed oral cancer screening technology. Orchard A, Sunny SP, Suresh A, Birur P, Kuriakose M, Prabhu S. Br J Oral Maxillofac Surg. 2021 Jun 18:S0266-4356(21)00217-5.

Conferences:

American Head and Neck Society 2021 (Virtual Jul 22-25, 2021)

- ➔ Role of Tumor initiating cells and its fibroblast niche in oral cancer
- ➔ Evaluation of the Immune Landscape by digital cytometry using transcriptomic data from oral pre-malignant lesions **(Best of the topic: Presenter: Vaishnav Vasudevan)**
- ➔ Field validation of smart-phone based portable PoC diagnostic tool with ANN for early detection of oral cancer
- ➔ Deep Learning Algorithm for classification of High Risk Potentially Malignant Lesion using Optical Coherence Tomography
- ➔ Lectin Cytometry as an adjunct to improve USG-Guided FNAC in the detection of malignant thyroid nodules
- ➔ Non-invasive imaging systems in delineating dysplastic OPML from non-dysplastic lesions: A systematic review and meta-analysis.
- ➔ Systematic review and Meta-analysis to identify the immunocytochemical markers effective in delineating benign from malignant thyroid lesions in FNAC samples **(Best of the topic: Presenter: Dr Uma Mohan)**

Patents

Granted: *Molecular marker based oral cytology for detection of potentially malignant and malignant oral lesions*

Grants

1. Multimodal intraoral imaging system for oral cancer detection and diagnosis in low resource setting (Collaboration project with Univ of Arizona, Narayana Health, NIH)
2. Mobile oral cancer screening system for low-resource settings (Collaboration project with Univ of Arizona, Narayana Health, SBIR grant, NIH)

Ongoing Grants

1. Development of Comprehensive Pre-Cancer Genome/Transcriptome Atlas (CPCGA) of oral cavity, ICMR 2019-2023
2. Biomarkers for Nodal Metastasis in head and neck cancer DHR; 2018-2022
3. PARPCytometry- A quantitative and affordable diagnostic system for head and neck cancer diagnostics (In collaboration with CCRC, Kochi) GCE-BIRAC 2019-2020
4. Phase IIb/III study to determine efficacy of Curcumin and Metformin to reduce the incidence of second primary tumors of aero-digestive tract in patients with history of head and neck squamous cell carcinoma (In collaboration with Narayana Hrudayalaya Foundation, HNCOG) NCG 2018-2024

Team

Principal Investigator: Dr Amritha Suresh

Adjunct Faculty: Dr Moni A Kuriakose, Dr Praveen Birur

Oral Cancer Control Program: Dr Sumsum Sunny, Dr Pramila Mendonca, Dr Uma Mohan, Sai Lakshmi, Sowmya C N, Uma M, Srinivas, Dr Shruti Nambiar, Ashwini TM, Reba Elsa Sam

Cellular/ Molecular Diagnosis/ Prognostication of Head and Neck Cancer: Bonney L James, Madhumati HK, Aishwarya RK, Gangotri Siddappa, Dr Uma Mohan, Dr Sumsum Sunny

Interns: Meera Murali, Gopika C, Pavithra Sreenivasan

Collaborators:

Mazumdar Shaw Medical Centre, NH: Department of Head and Neck Surgery, Dr MA Kuriakose, Dr Vijay Pillai, Dr Vivek Shetty, Dr Vidya Bhushan, Dr Yogesh Dokhe; Department of Endocrinology: Dr Subramanian Kannan; Department of Pathology: Dr Rekha PR, Dr Shaestha Naseem, Dr Vidya R

Head and Neck Co-operative group; KLE Institute of Dental Sciences, Dr Praveen Birur; CCHRC, Assam: Dr Ravi Kannan, Dr Rajeev Kumar; CIHSR, Dimapur; Indian Institute of Science: Dr Hardik Pandya, BEES Lab;

University of California: Dr Petra Wildersmith; University of Arizona: Dr Ronguangg Liang; Roswell Park Cancer Institute: Dr Welsey Hicks, Dr William Magner, Dr Subin Surendran

Stem Cell Program

Multiple initiatives are being explored towards applications of stem cells in other disease indications.

Ovarian carcinoma is the fifth most common gynecological malignancy, but leads to the highest case fatality among all gynecological malignancies. High grade serous carcinoma of ovary is the most common histological subtype of ovarian cancers, accounting for 70% of all cases overall. Due to early peritoneal dissemination, the majority of cases present in stage III and IV. The 5-year survival of high grade serous ovarian carcinoma in advanced stage remains less than 30%, which has remained largely unchanged for most patients despite several advancements in surgery and systemic therapy. We are currently initiating a program looking into the role of cancer stem cells in resistance and relapse of ovarian cancers in collaboration with the department of gynaecologic oncology, MSMF, NH.

Stem cell therapeutics are a significant area of research in neurological disorders. MSMF in collaboration with Narayana Institute of Neurosciences, MSMC, NH is establishing a **Stem Cell Based Stroke Management Program.** *Stroke* is emerging as a significant contributor to the disability burden in our country. Neurological recovery after middle cerebral artery strokes remains variable and treatment of impairments are challenging with residual deficits being refractory to existing treatments. The standard of care includes thrombolysis, mechanical thrombectomy, decompressive craniectomy if indicated, early rehabilitation. In stroke, stem cell therapy has been beneficial in animal models but several limitations to apply this treatment clinically have been unmasked in human trials. The program is looking into innovative applications of stem cell-based solutions in stroke management. (The study is funded by the SKAN Research Trust, Bangalore).

Team

Ovarian Cancer Program: MSMF: Dr Amritha Suresh, Dr Durga Prasan, Aishwarya TK

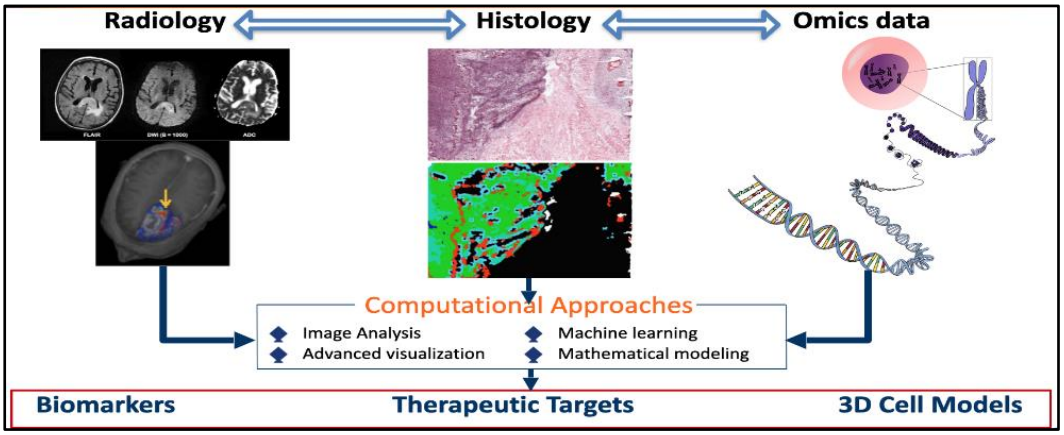
MSMC, NH: Department of Gynaecologic Oncology: Dr Rohit Raghunath Ranade,

Stroke Management: MSMF: Dr Paul Salins, Dr Amritha Suresh, Dr Debprasad Dutta

Narayana Institute of Neurosciences: Dr Thimmappa Hegde, Dr Komal Prasad, Dr Vikram Huded, Dr Srikant Venkatakrishnan

Neuro-Oncology Research Program

The Neuro-oncology Program focuses on the study of low and high grade gliomas, mainly Glioblastoma (WHO Grade IV). We are also initiating some work on Pituitary tumors. Gliomas are one of the most common primary intracranial tumors which comprise 81% of all malignant tumors in adults. Even though brain tumors constitute only 2% of the total cancers, they are the second most leading cause of death in young males (20-39 years) and fifth most leading cause of death in young females in India. They include different histological types (ependymomas, astrocytomas and Oligodendrogliomas) and are of different grades; Grade I, II, III and IV. Grade III and Grade IV (Glioblastoma or GBM) are high grade tumors. Specifically, Glioblastoma is highly heterogeneous and most lethal of all, with median survival in months. The characteristic glioblastoma histological anatomic features reflect specific biological processes, pathways, cell types and microenvironment, all of which add to the tumor heterogeneity. Recently, Gliomas were grouped into two large groups based on the presence or absence of a mutation in the enzyme, isocitrate dehydrogenase (IDH wild and mutant type), the mutant having a better prognosis. Most of the GBMs are IDH wild type. The focus of the neuro-oncology research group is mainly on Glioblastoma, its tumor heterogeneity and micro environment at molecular, imaging, and histological levels using clinical specimens, cell line model, multi-omic analysis and computational approaches. Overall objectives, approach and the specific projects are as described below.

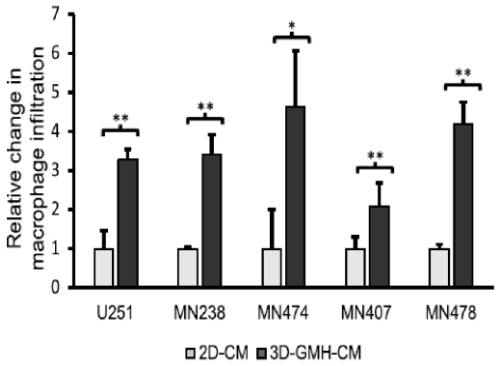


1. Discover, design, and develop clinically feasible biomarker assays that take into account intra-tumor heterogeneity, are representative of the whole tumor.
2. Engineer 3D cell culture models to mimic glioblastoma microenvironment that best reflect the disease and can be used for identification of better therapeutics.
3. Identify novel therapeutic targets

Development and Characterization of *In vitro* 3D cell model for Glioblastoma to study drug response

The conventional *in vitro* models like two-dimensional (2D) cell cultures and neurospheres fail to recapitulate the complexity of the tumor microenvironment, limiting their use to study tumor properties or for studying the effect of drugs. On the contrary, animal models are very expensive and introduce non-native ECM and host cells.

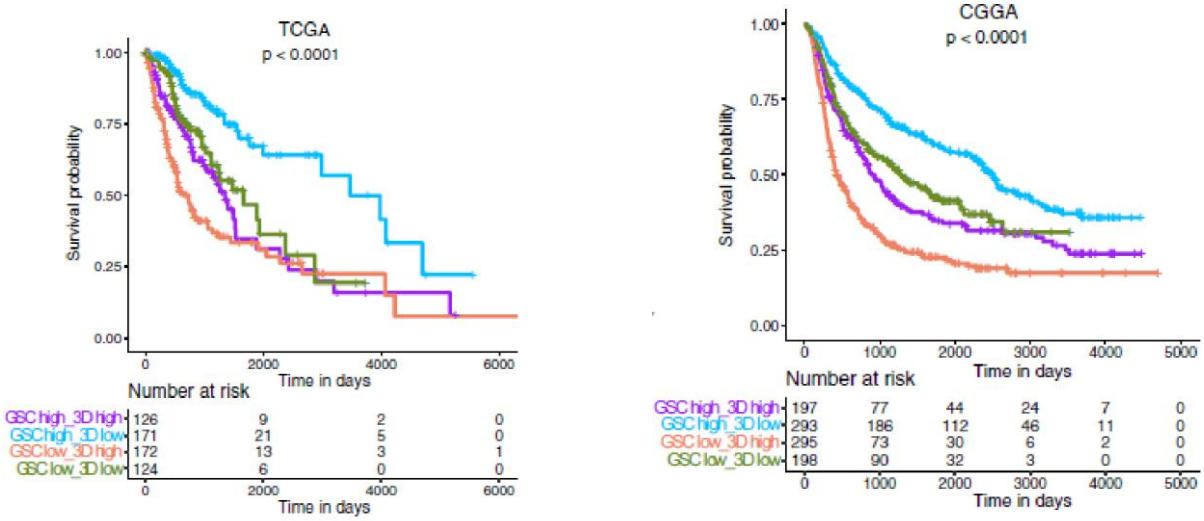
The importance and advantage of scaffold-based 3D cell culture systems over 2D cell cultures or animal models has been discussed in the earlier report (2020-21). They are physiologically relevant, retain the cell-cell and cell-matrix interactions similar to in vivo conditions and have emerged as promising alternative tools to study tumor biology. We have developed a 3D cell system based on gelatin methacrylate (GelMA) hydrogels and are studying them to understand its suitability as a 3D model system to mimic treatment-resistant mesenchymal (MES) type of GBM cells that reside in specific niches of the GBM microenvironment.



Boyden's chamber invasion assay for U937-derived macrophages against CM of U251 cells and patient-derived glioma cells cultured in 2D and 3D-GMH

Using patient-derived GBM cells, we compared both 2D and 3D GelMA hydrogel (3DGMH) systems in terms of their tumorigenic properties using invasion and chemoresponse assays. We observed that cells cultured in 3D-GMH showed higher infiltrative and invasive potential and increased chemo resistance to temozolomide (TMZ) compared to cells cultured on 2 D platform. Further, we analyzed the phenotype of patient-derived GBM cells grown on 3DGMH using in-house RNA-seq integrated with public domain single-cell and spatial transcriptome analysis, which revealed that the 3D-GMH system enriched treatment-resistant mesenchymal cells that were not represented in neurosphere cultures. Furthermore, this MES phenotype resembled the cells found in the perivascular and perinecrotic zones of glioblastoma tumors, in contrast to the neurosphere cultures that enriched cells of the infiltrative edge of the tumor. In addition,

gene expression signatures derived from the transcriptome of GBM cells grown in 3D-GMH showed poor survival association in two large glioma datasets (TCGA and CCGA).



Survival analysis of TCGA and CGGA data sets using 3D-GMH and GSC lists. Based on the median SSGSEA score of 3D-GMH and GSC gene lists, we divided the glioma samples into four categories in TCGA and CGGA data sets. The patients with lower SSGSEA score for 3D-GMH list and higher score for GSC list have significantly better survival compared to patients with higher score for 3D-GMH list and lower score for GSC list (median survival of 3460 days, 95% CI [2988, NA] vs. median survival of 632 days 95% CI [537, 1062] in TCGA and median survival of 2499 days 95% CI [2237, 2982] vs. median survival of 432 days 95% CI [379, 567] in CGGA).

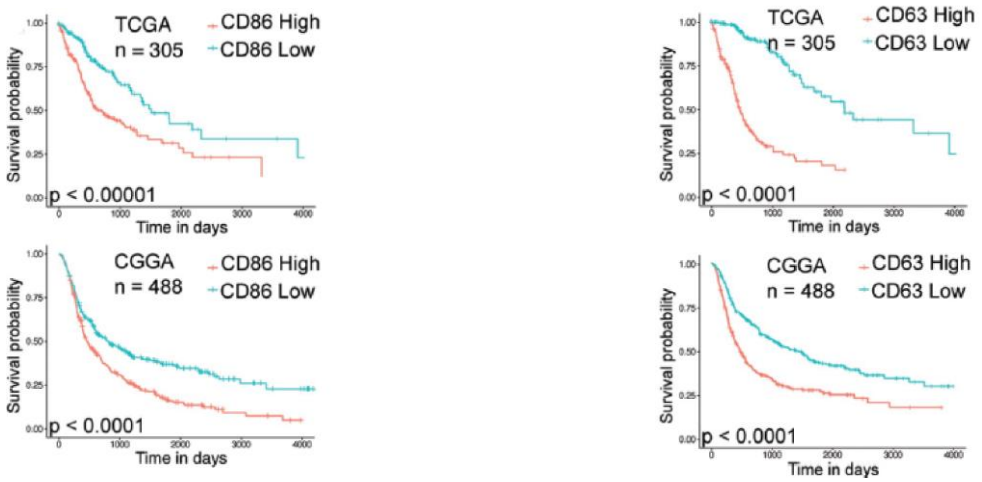
Finally, we showed that cells grown in 3DGMH secreted increased levels of key cytokines as assessed with cytokine array and displayed a higher potential to recruit macrophages using macrophage infiltration assay. So, in this study, we demonstrated the complementary nature of two cell culture methods that mimic glioma cell types found in glioblastoma tumors. Based on the gene expression data from spatially distinct tumor regions, we show that our 3D-GMH model effectively mimics the phenotype of glioma cells that are found in the perivascular and hypoxic niches of the glioblastoma core in situ, in contrast to the neurosphere cultures that enrich cells of the infiltrative edge of the tumor. In conclusion, we propose the 3D-GMH scaffold as a complementary *in vitro* system to study the biology of hypoxia-dependent and independent mesenchymal glioma cells, including understanding tumor-immune cell interactions.

Identification of possible prognostic markers for gliomas using immuno-phenotyping

Gliomas are heavily infiltrated with immune cells of myeloid origin. Past studies have shown that high-grade gliomas have a higher proportion of alternatively activated and suppressive myeloid cells when compared to low-grade gliomas, which correlate with

poor prognosis. However, the differences in immune cell phenotypes within high-grade gliomas (between grade 3 and grade 4 or GBM) are relatively less explored, and a correlation of phenotypic characteristics between immune cells in the blood and high-grade tumors has not been performed. Additionally, myeloid cells of granulocytic origin present in gliomas remain poorly characterized. Herein, we address these questions through phenotypic characterizations of monocytes and neutrophils present in blood and tumors of individuals with glioblastoma (GBM, IDH-wild type) or grade 3 IDH-mutant gliomas.

We characterized the monocytes and neutrophils present in blood and tumors of individuals with IDH-wild type glioblastoma or IDH-mutant grade 3 gliomas using marker-based flow cytometry. We observed that neutrophils are highly heterogeneous among individuals with glioma, and are different from healthy controls. We also showed that CD163 expressing M2 monocytes are present in greater proportions in GBM tissue when compared to grade 3 IDH-mutant glioma tissue, and a larger proportion of granulocytic myeloid-derived suppressor cells are present in grade 3 IDH-mutant gliomas when compared to GBM. Further, we determined if the dexamethasone administration prior to surgery caused any significant changes in the neutrophil proteomic profile, we performed total proteomic analysis of neutrophils from GBM patients with matched samples collected pre- and post-surgery.



Kaplan–Meier survival analysis of TCGA and CGGA data reveals that high expression of two markers, CD63 and CD86, in gliomas is associated with a poor prognosis. Grade 3 with IDH mutation and GBM without IDH mutation samples from TCGA and CGGA data were used for this analysis. Samples were divided based on median expression values of CD86 and CD63 genes.

Data suggested that there were significant differences in the immuno-phenotype of myeloid cells between individuals with gliomas and healthy individuals, which might not

be entirely attributed to the use of steroids. Finally, we demonstrated that the expression levels of CD86 and CD63 showed a high correlation between blood and tumor and suggested that these might be used as possible markers for prognosis. In conclusion, the comparison of the phenotype of myeloid cells between blood and tumor of the same individual has led us to better understand if blood phenotype is a representation of the tumor phenotype.

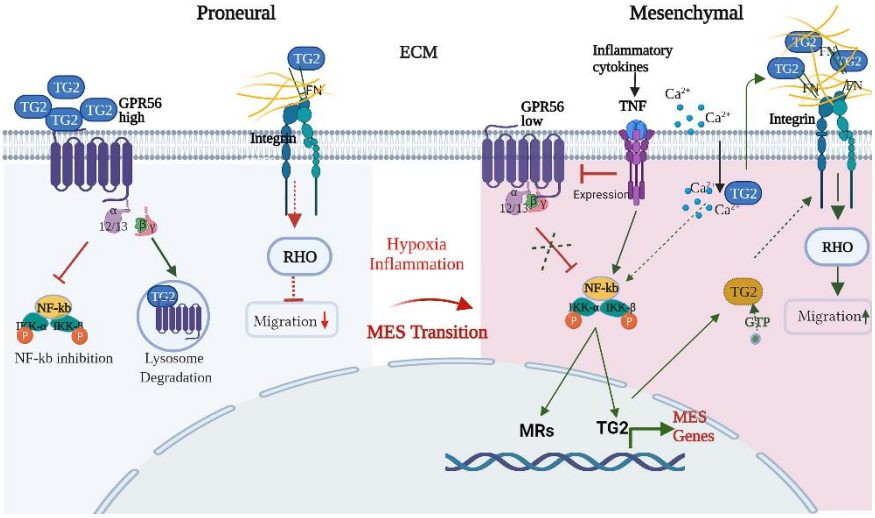
To a large extent, CD86 and CD63 were the only cell-surface proteins whose expression levels correlated among myeloid cells in blood and tumor, suggesting these markers in the blood may be used as prognostic markers for the progression of gliomas.

Study of expression of adhesion GPCR – GPR56 and its functional role in Glioblastoma

G protein-coupled receptor 56 (GPR56/ADGRG1) is an adhesion GPCR with an essential role in brain development and cancer. We had earlier (2020-21) reported that elevated expression of GPR56 was observed in the clinical specimens of Glioblastoma (GBM) and found the expression to be variable across the specimens, presumably due to the intratumor heterogeneity of GBM. We subsequently investigated the link between the heterogeneous expression and functional significance of GPR56 in GBM using public domain data and experimental multi-omics data, including transcriptomics, proteomics, and phosphoproteomics, of GPR56 knockdown U373 GBM cells.

We examined GPR56 expression in public domain spatial gene expression data and single-cell expression data for GBM, which revealed that GPR56 expression was high in cellular tumors, infiltrating tumor cells, and proliferating cells, low in microvascular proliferation and peri-necrotic areas of the tumor, especially in hypoxic mesenchymal-like cells. To gain a better understanding of the consequences of GPR56 downregulation in tumor cells and other molecular changes associated with it, we generated a sh-RNA-mediated GPR56 knockdown in the GBM cell line U373 and performed transcriptomics, proteomics, and phospho-proteomics analysis. Our analysis revealed enrichment of gene signatures, pathways, and phosphorylation of proteins potentially associated with mesenchymal (MES) transition in the tumor and concurrent increase in cell invasion and migration behavior of the GPR56 knockdown GBM cells. Interestingly, our analysis also showed elevated expression of Transglutaminase 2 (TG2), a known interactor of GPR56, in the knockdown cells. The inverse expression of GPR56 and TG2 was also observed in intratumoral, spatial gene expression data for GBM and in GBM cell lines cultured in vitro under hypoxic conditions. Integrating all these observations, we propose a putative

functional link between the inverse expression of the two proteins, the hypoxic niche and the mesenchymal status in the tumor. Hypoxia-induced downregulation of GPR56 and activation of TG2 may result in a network of molecular events that contribute to the mesenchymal transition of GBM cells and we propose a putative model to explain this functional and regulatory relationship of the two proteins.



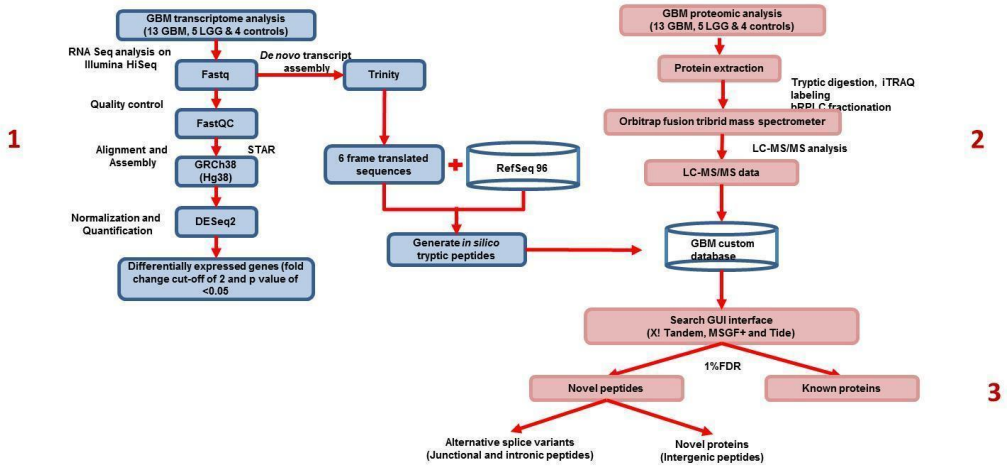
Schematic representation of the interplay of GPR56 and TG2 in regulatory interactions during the mesenchymal transition in GBM. Blue and Yellow circles indicate 'open' and 'closed' conformations of TG2, respectively. Detailed description of the Figure is given in the text. (FN – fibronectin, Ca2+_ - calcium, RHO - Ras homologous, NF-kB - nuclear factor kappa B, IKKa - nuclear factor kappa B inhibitor, alpha, IKKb - nuclear factor kappa B inhibitor, beta, MRs – mesenchymal regulators, GTP - guanosine triphosphate, TNF - tumor necrosis factor-alpha. This schematic diagram was created with BioRender.com.

SPLICE VARIANTS AS BIOMARKERS AND TARGETS

In the earlier (2020-21) report, we discussed the significance of spliced variants of proteins and other novel protein expressions in cells and tissues. Spliced variants, including aberrant forms may be tissue or physiological or pathological condition-specific, and may therefore serve as specific biomarkers of cancer. Alternative and/or aberrant splicing has been reported in several cancers including glioblastoma and has been implicated as an important strategy to attack this highly lethal tumor. Alternative splicing of known protein-coding genes and expression of noncoding sequences of the human genome are increasingly expanding the functional diversity of proteins. These events may be specific to cell type or physiological condition of the cells and may be deregulated in cancer.

As a pilot study, we used the proteogenomic analysis pipeline developed by us and carried out analysis of the breast cancer transcriptomic and proteomic data, available

at The Clinical Proteomic Tumor Analysis Consortium resource, to identify novel peptides arising from alternatively spliced events as well as other non canonical expressions. We used a pipeline that consisted of de novo transcript assembly, six frame-translated custom databases, and a combination of search engines to identify novel peptides. A portfolio of 4,387 novel peptide sequences initially identified was further screened through the PepQuery validation tool (Clinical Proteomic Tumor Analysis Consortium), which yielded 1,558 novel peptides. We considered the dataset of 1,558 validated through PepQuery to understand their functional and clinical significance, leaving the rest to be further verified using other validation tools and approaches.



Proteogenomic analysis and identification of novel peptides. A, a schematic view of the proteogenomic pipeline. Breast cancer transcriptomic and proteomic data from the CPTAC resource was used for the analysis. The pipeline includes de novo assembly of RNA-Seq reads followed by six-frame translation for custom database creation to search against the MS/MS files from the proteomics analysis. The custom database generated for each of the samples was searched against the respective mgf files using the search engines, X!Tandem, MSGF+, and Tide. PeptideShaker was used for integrated identification of the candidate peptides and their corresponding proteins. The known peptides (RefSeq) were then filtered out from the total identifications to get the list of novel peptides. The novel peptides obtained were then validated using PepQuery. The novel peptides validated by PepQuery were categorized into those that map to protein-coding genes, noncoding genes, and uncharacterized ORFs. Numbers shown in brackets represent the number of novel peptides in the respective groups. The different types of novel peptides obtained after ACTG categorization are also shown. The novel peptides mapping to known protein-coding genes were mapped to cancer hallmark genes and further assessed for clinical relevance in breast cancer by carrying out survival analysis.

The novel peptides mapped to the known gene sequences as well as to genomic regions yet undefined for translation, 580 novel peptides mapped to known protein-coding genes, 147 to non–protein-coding genes, and 831 belonged to novel translational sequences. The novel peptides belonging to protein-coding genes represented

alternatively spliced events or 5' or 3' extensions, whereas others represented translation from pseudogenes, long noncoding RNAs, or novel peptides originating from uncharacterized protein-coding sequences—mostly from the intronic regions of known genes. Seventy-six of the 580 protein-coding genes were associated with cancer hallmark genes, which included key oncogenes, transcription factors, kinases, and cell surface receptors. Survival association analysis of the 76 novel peptide sequences revealed 10 of them to be significant, and we present a panel of six novel peptides, whose high expression was found to be strongly associated with poor survival of patients with human epidermal growth factor receptor 2–enriched subtype. Our analysis represents a landscape of novel peptides of different types that may be expressed in breast cancer tissues, whereas their presence in full-length functional proteins needs further investigations.

We are presently modifying the pipeline to incorporate higher rigor and confidence in such identifications and analysing in –house generated transcriptomic and proteomics data on GBM.

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1. Gelatin methacrylate hydrogels culture model for glioblastoma cells enriches for mesenchymal–like state and models interactions with immune cells. Nameeta Shah, Pavan M. Hallur, Raksha A. Ganesh, Pranali Sonpatki, Divya Naik, Komal Prasad Chandrachari, Ralph B. Puchalski & Aditya Chaubey. *Scientific Reports* (2021) 11:17727
2. Immuno-phenotyping of IDH-mutant grade 3 astrocytoma and IDH-wildtype glioblastoma reveals specific differences in cells of myeloid origin. Jayashree V. Raghavan, Raksha A. Ganesh, Pranali Sonpatki, Divya Naik, Arivusudar Everad John, Priyanka Arunachalam, Darshat Shah, Hari P. S., Akhila Lakshmikantha, Shibu Pillai, Komal Prasad Chandrachari, Kiran Mariswamappa, Sathyanarayana Lale, Nameeta Shah, and Siddharth Jhunjhunwala. *Oncoimmunology* (2021) 10:e1957215
3. Multi-Omics Analysis of Glioblastoma and Glioblastoma Cell Line: Molecular Insights Into the Functional Role of GPR56 and TG2 in Mesenchymal Transition. Raksha A. Ganesh, Pranali Sonpatki, Divya Naik, Arivusudar Everad John, Gajanan Sathe, Akhila Lakshmikantha, Komal Prasad Chandrachari, Lea Bauer, Vera Knäuper, Daniel Aeschlimann, Krishnan Venkatraaman, Nameeta Shah and Ravi Sirdeshmukh. *Frontiers in Oncology* (2022) 12:841890.
4. Proteogenomic Analysis of Breast Cancer Transcriptomic and Proteomic Data, Using De Novo Transcript Assembly: Genome-Wide Identification of Novel Peptides and Clinical Implications P. S. Hari, Lavanya Balakrishnan, Chaithanya Kotyada, Arivusudar Everad John, Shivani Tiwary, Nameeta Shah and Ravi Sirdeshmukh, Mol Cell Proteomics (2022) 21(4) 100220.

Patents / Deliverables

- CNS cancer repository (302 samples, Glioma: 186 samples)
- 3D GelMA hydrogel model mimicking the perivascular and perinecrotic zones of glioblastoma
- Glioma assays (MGMT methylation, IDH1 mutation, 1p19q co-deletion)
- Panel of mesenchymal biomarkers for post-surgery surveillance of GBM
- Panel of novel peptides associated with poor prognosis of Her2 enriched breast cancer

Team

Principal Investigators: Dr Ravi Sirdeshmukh

Research Scientist: Dr Atanu Ghorai

Post-Doctoral Fellow: Dr Arivusudar M

Ph D Student: Raksha Ganesh

Project Staff: Chaithanya Kotyada, Divya Naik, Hari PS, Pranali YS, Darshat Shah

Intern: Avishek Biswas

Alumni : Dr Nameeta Shah

Molecular Immunology

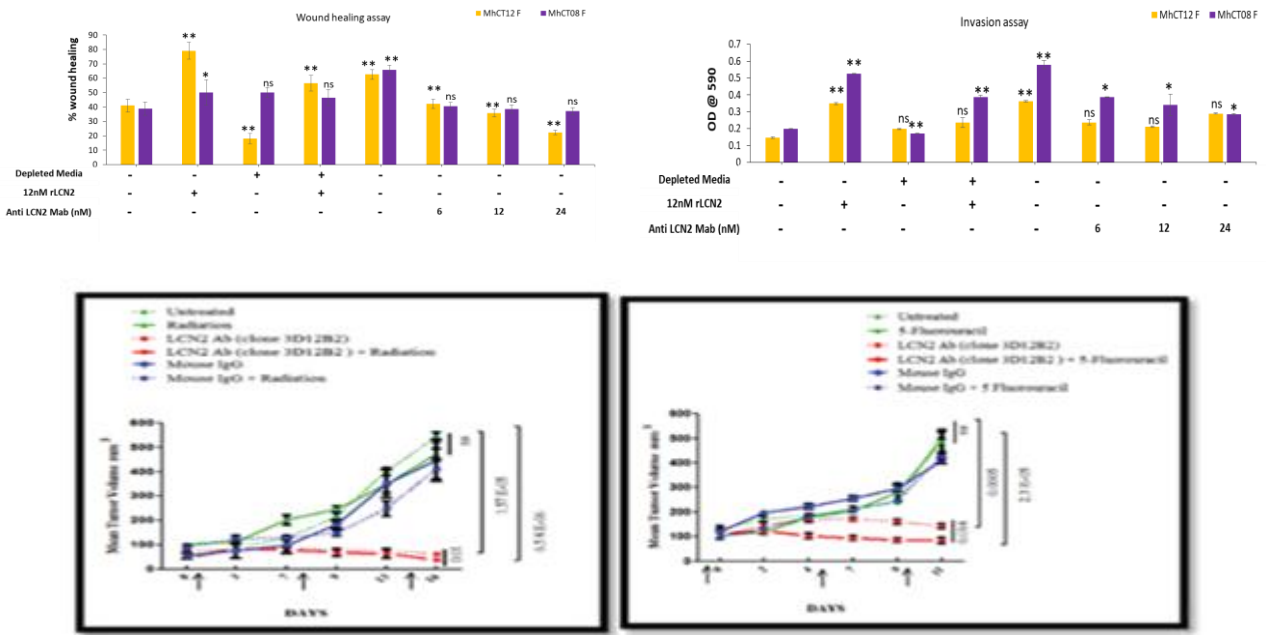
Over the last two decades there has been a paradigm shift in our perception of cancer. As we know now, neoplasia contains an abundant and heterogeneous non-transformed component like stromal, endothelial and immune cells. The host immune system can recognize and react against (pre-) malignant cells as they transform, proliferate and evolve. Apoptosis is one such method of 'reaction' where the 'bad' cells are made to commit suicide. The group concentrates on developing anti-cancer therapy by

- Targeting the suppressors of apoptosis among many suppressor pathways
- Stimulating the immune system to recognize cancer cells as foe

Targeted Suppression of Immune Evasion

Lipocalin 2 (LCN2), an important molecule in the innate immune-pathway has been implicated in various cancers too. Role of LCN2 in inhibition of ferroptosis and therapy resistance through tumor-microenvironment cross talk is being explored in the following neoplasia in our lab in collaboration with Dr Sorab Dalal (ACTREC):

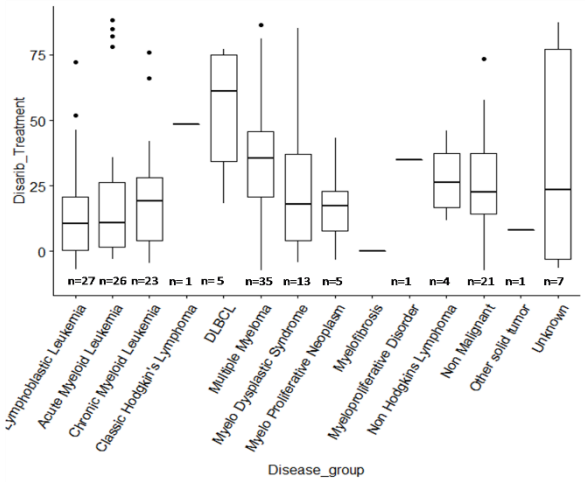
- Head and Neck Cancer
- Colorectal Cancers



Anti-LCN2 reverses radio resistance and drug resistance in a xenograft model

Techniques employed are primary mammalian culture, recombinant protein and monoclonal antibody technology. We have stabilized several patient-derived epithelial

and fibroblast lines and are exploring the crosstalk between each other through targeted experiments in which the one cell line is treated with conditioned media from the culture of the other and changes in gene expression are measured using sequencing..



BCL2, an anti-apoptotic molecule has emerged as one of the hottest targets in liquid cancer. However, the magic bullet, Venetoclax, often fails despite high expression of the target, ie BCL2. Is it because of the co-expression of Myc1, MCL1 or BCL-X ? We are trying to find out by checking the efficacy of BCL2 inhibitors (including a novel small molecule synthesized by Dr Sathees Raghavan at IISc) on patient derived ex-vivo cultures with our clinical collaborator, Dr Sharat Damodar.

Publications

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Myeloma Patient Leading to Acute Kidney Injury. Kargar 14:274–278 (DOI:10.1159/000510046 (IF. 1.08)

6. Nazia Chaudhary, Bhagya Shree Choudhary, Sanket Girish Shah, Nileema Khapare, Nehanjali Dwivedi, Anagha Gaikwad, Neha Joshi, Jinsy Raichanna, Srikanta Basu, Murari Gurjar, Smitha P.K, Avanish Saklani, Poonam Gera, Mukta Ramadwar, Prachi Patil, Rahul Thorat, Vikram Gota, Sujan K. Dhar, Sanjay Gupta, Manjula Das, and Sorab N. Dalal, Lipocalin 2 expression promotes tumor progression and therapy resistance by inhibiting ferroptosis in colorectal cancer (2021) International J of Cancer 149:1495-1511 (IF 5.45) DOI: 10.1002/ijc33711

Grants

1. Exploring Novel BCL2-specific Inhibitors against Leukemia and Lymphoma (DBT 2018-2022)
2. Biodesign Bioengineering Initiative Phase II (Towards Deciphering the Interaction between Diabetes and Cancer), DBT, 2018-2022
3. Development of A Microfluidics Based Point-Of-Care Device For Intra-Operative Detection Of Metastatic Lymph Nodes In Oral Cancer; DST, 2019-2022
4. Deciphering the tumor immune heterogeneity of Head and Neck Squamous Cell Carcinoma (HNSCC) in Indian patient population: A pilot Study; Industry grant by Bristol Myers Squibb Research Centre, 2016-2018

Team

Principal Investigator: Dr Manjula Das

Ph D Student: Nehanjali Dwivedi, CA Divya

Project Staff: Nidhi Shukla, Kunal Biswas, Sakshi Sinha

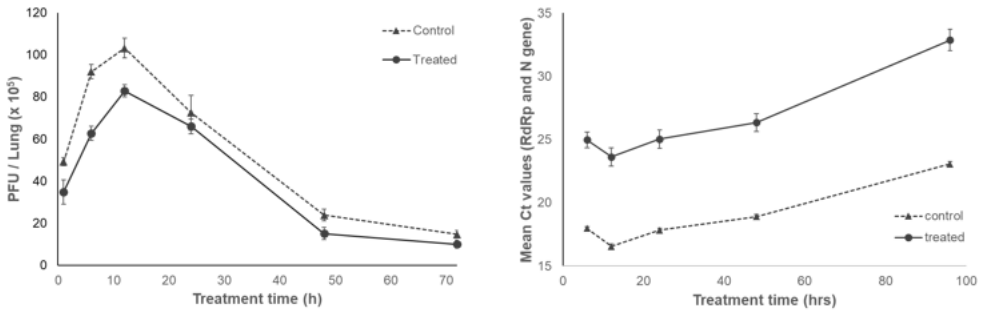
Intern: Aatreyee Basu, Deepika Sreeraman, Aishwarya Chitoor, Kiruthiga R

COVID-19 and MSMF

The thin silver lining on the large dark cloud of COVID-19 pandemic is the knowledge of Virology, immunology, epidemiology and molecular detection that has emerged. During the pandemic MSMF has plunged into the COVID-science through Epidemiological studies: more than 1 million individuals have been screened for the virus in collaboration with the ICMR approved diagnostic lab Molecular Solutions Care Health (MSCH) and the infectious disease clinic - PCMH Restore Health.

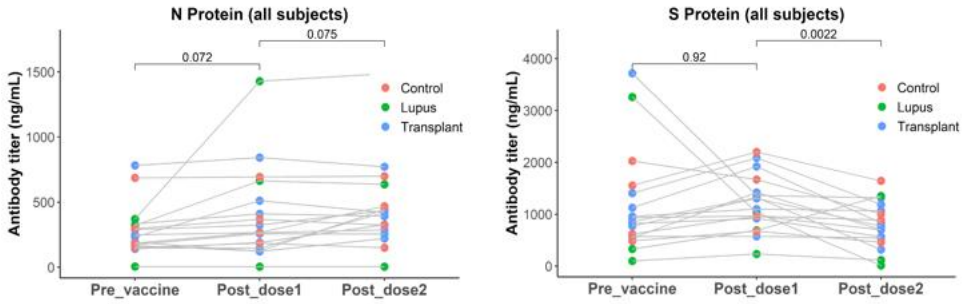
Validation of diagnostic kit: A qPCR screening kit, a RAT kit and an antibody detection kit has been validated in collaboration with NeoDx, IISc and Achira labs.

Therapeutics development: mAce2-Fc, a novel fusion protein has been developed to trap the SARS-CoV2 virus in circulation itself. and shown to be efficacious and safe in Golden Syrian hamsters at a BSL3 facility (FNDR, Bangalore). The project has been funded by DBT/BIRAC.



mAce2-Fc lowers the viral load in SARS-CoV-2 infected hamster models

Survey of Immune status: A survey has just begun to test the B cell and T cell immunity status of the symptomatic and asymptomatic patients and their HLA status.



Titre against SARS-CoV-2 spike protein and nucleocapsid protein before and after vaccine doses

Patent

Compositions and methods for treating coronavirus infection with different levels of disease severity. Number 202041036866 Dated 20 Aug, 2020

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2. IL-6 and IL-10 as predictors of disease severity in COVID19 patients: Results from Meta-analysis and Regression Sujan K Dhar, Vishnupriyan K, Sharat Damodar, Shashi Gujar and Manjula Das (2021) Heliyon (2021 Jan 29 [cited 2021 Feb 2]; e06155) (IF. 1.650)
3. Inflammation and hypercoagulopathy are predominant risk factors of severity in COVID-19 patients with Diabetes Mellitus: Summary of a Meta-analysis Sujan K Dhar, Kartik Sachdeva and Manjula Das (2021) Diabetes & Metabolic Syndrome: Clinical Research & Reviews (15:639 - 642) (IF. 1.940)

Collaboration

- Molecular Solutions Care Health, Bangalore
- Infectious Disease Clinic, PCMH Restore Health, Bangalore,
- Foundation for Neglected Disease Research, BSL3 facility

Grants

- Validation of a RT-PCR kit for the detection of Coronavirus in saliva samples (Industry grant by NeoDx), 2020-2022
- SolAce: Novel Therapeutics against Coronavirus infection, BIRAC grant under COVID-19 initiative, 2020-2021

Team

Principal Investigator: Dr Manjula Das

Members: Dr Smitha PK, Pushkarni Suresh, Kunal Biswas, Suprabuddha Dutta, B Naga Pushpa

Clinical Collaborators: Dr Rammohan Bhat (NH), Dr RK Prasad (PCMH Restore Health)

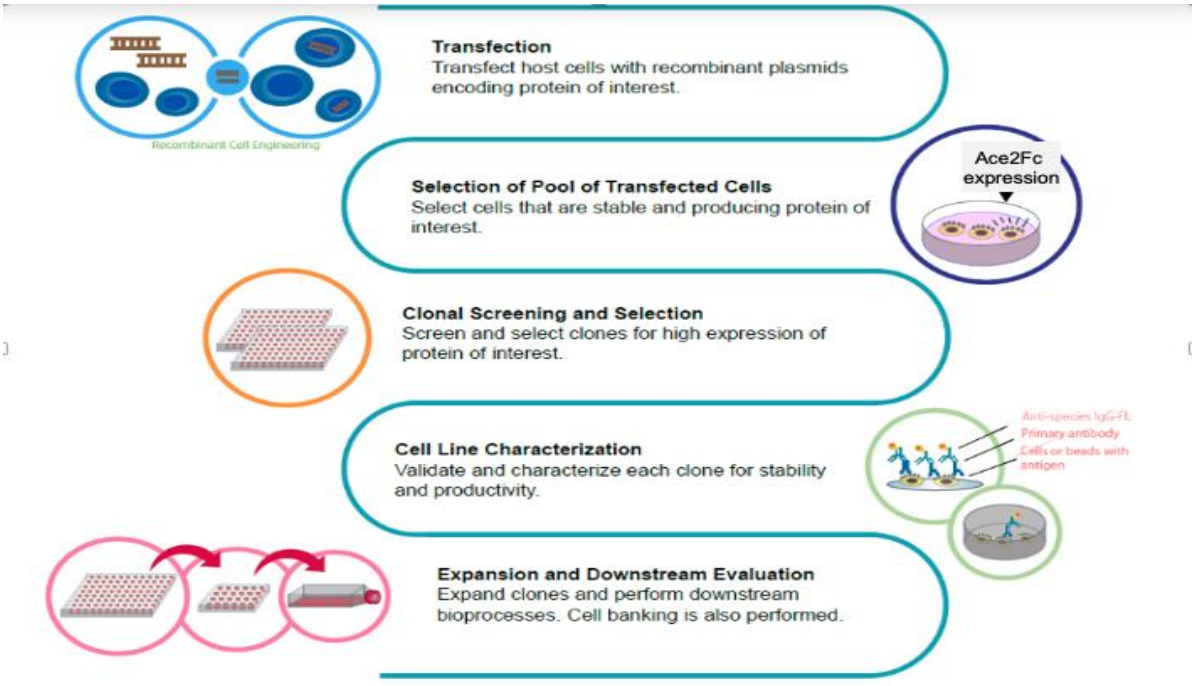
Product Research Group

Effective translation of any discovery to the clinic requires it to be developed into an appropriate product such as a diagnostic reagent or kit or a therapeutic molecule. The Product Research Group (PRG) at MSMF was established at MSMF during 2021-22 to augment this requirement. Currently the PRG team is pursuing the following product leads in collaboration with other discovery groups.

Ongoing Projects

Development of Stable cell line expressing Ace2Fc therapeutic protein (in collaboration with Molecular Immunology)

Strategies to abrogate binding of SARS-CoV2 spike protein (S) to Ace2 host receptors are of utmost importance to prevent disease transmission and control pandemic. A recombinant, catalytically active, mutant Ace2 (mAce2-Fc) could serve as a decoy strategy to trap and neutralize SARS Cov2 and hence can be a potential therapeutic product. Efficacy of this molecule in reducing SARS-CoV-2 viral load in the lung was demonstrated in Syrian Golden Hamster models. The molecule also showed pharmacokinetic behaviour with accepted bioavailability by intranasal administration in hamsters as well by intravenous injection in mice. Beyond Covid-19, this molecule can also be repurposed for treatment of progressive renal hypertension.



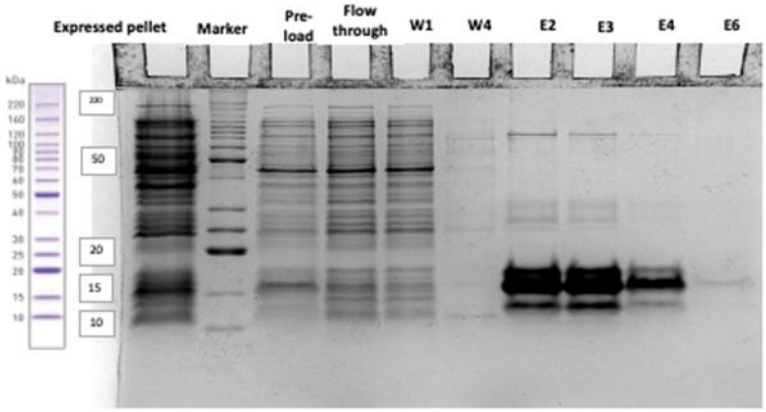
Steps for mAce2-Fc-expressing stable cell line development

Currently a stable cell line expressing Ace2Fc protein is being developed using HEK293 cells. This cell line will be used for continued production of the therapeutic protein.

Development of recombinant Anti-Lipocalin 2 antibody (in collaboration with Molecular Immunology)

In another study, efficacy of Anti-Lipocalin 2 antibody to combat therapy resistance in colorectal cancer was demonstrated earlier. This was a mice antibody developed using the hybridoma technology. PRG has initiated a project to develop a recombinant version of the antibody by isolating the heavy and light chain sequences and inserting them in an appropriate vector. The construct thus created will be used to transfect cell systems and a stable cell line expressing recombinant LCN2 antibody will be developed.

Development of S100P detection Assay (in collaboration with Integrated Head and Neck Oncology)



S100P is a protein marker of diagnostic relevance in many forms of cancer. As mentioned in the previous report, our previous study had shown that the level of S100P, along with other markers, can be used as a marker for saliva-based diagnosis of oral cancer. The present project aims to develop the recombinant S100P protein, and using the protein as an antigen to develop polyclonal antibodies against S100P. These reagents will be used for detection of elevated S100P in oral cancer samples.

Team

Research Scientist: Dr Smitha PK

Project Staff: Suprabuddha Dutta, Pushkarni Suresh

Intern: B Naga Pushpa

Computational Biology

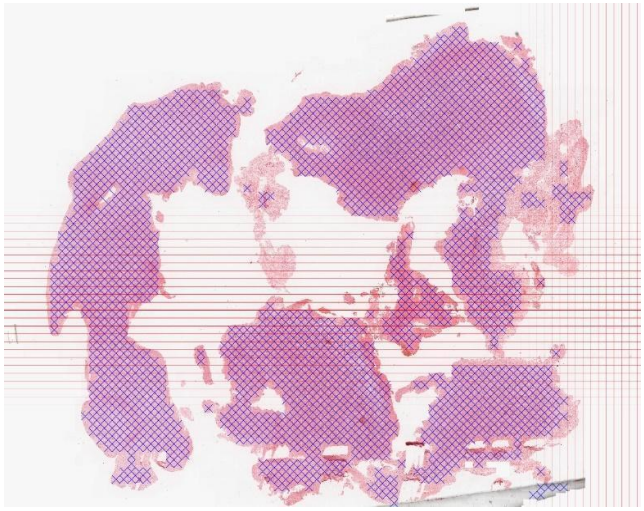
Realm of Computational Biology extends beyond conventional bioinformatics to learn and use models of biological systems developed from experimental data. In the context of a clinic, the experimental data includes clinico-pathological parameters, molecular omics data (genomics, transcriptomics, proteomics etc) and medical images such as histopathology and radiology. The Computational Biology group was established recently with a mandate to utilize computational and statistical techniques including Machine Learning (ML) and Artificial Intelligence (AI) algorithms for processing such data and generate hypothesis that can be further validated and translated to clinic in the form of a diagnostic or a prognostic test.

Artificial Intelligence for analysis of Histopathology Images

Histopathology images, in particular the haematoxylin and eosin (H&E) stains, are collected as part of routine pathology practice to assist in diagnosis of tumours. Though visual inspection of H&E stains by pathologists reveals important information of cell types, morphology and other events, their molecular subtypes or prognostic indicators are unlikely to be uncovered. However, application of neural network-based algorithms had indicated such correlations in multiple cancers. Computational biology group has initiated a couple of projects in this field in collaboration with other organizations.

Detection of IDH Mutation in Brain Tumours: In tumours formed in glial cells around neurons, mutations observed in the isocitrate dehydrogenase (IDH) family of genes appear to be significantly linked with an improved prognosis. Detection of this mutation, primarily by Immunohistochemistry using mutation-specific antibodies is common clinical practice to decide the therapeutic course. However, the IHC is often limited to detect only the most commonly observed mutation whereas the non-canonical mutations are often missed out. In this study, in collaboration with pathologists from NH, Bangalore and NIMS, Hyderabad we are developing an AI-based computational model that can categorize the histopathology images into IDH-mutant and IDH-wildtype molecular subtypes. Once developed and validated, this model can supplement the IHC test for sensitive detection of IDH mutation.

Prediction of Immune Checkpoint inhibitor therapy response in Lung Carcinoma: The recent introduction of immune checkpoint inhibitor (ICI) drugs have seen phenomenal success in extending patient survival across multiple types of cancer. In particular, for lung carcinoma, survival of patients on ICI therapy is sometimes extended beyond 5



years. However, ICI therapy does not seem to work for all patients and currently used tests like PD-L1 expression, tumour infiltrating lymphocytes and tumour mutation burden do not have prediction accuracy beyond 40%. In this project, we plan to use AI algorithms on histopathology images collected from lung carcinoma patients across multiple centres to create a classification model. Once developed, this model is expected to suggest a probability of success of ICI therapy based on the histopathology images.

Collaborative Projects on multi-omic Integration

Advent of high-throughput technologies have enabled collection of molecular data at genomic, transcriptomic and proteomic level that can provide further insights into the disease, However, assimilation and integration of such data remains a challenge computationally. Currently we are working on following such integration projects in collaboration with discovery teams at MSMF.

- Proteogenomics integration in glioblastoma to discover novel protein variants (initiated by Neuro-Oncology group in collaboration with IOB, Bangalore)
- Genomics and transcriptomic atlas of Oral potentially malignant lesions (initiated by Integrated head and neck oncology group in collaboration with other clinical partners).

Grants

- Development of an AI-enabled computation model for IDH1 mutation detection from H&E-stained glioma histopathology images, in collaboration with NIMS Hyderabad (approved by ICMR), 2022-25
- Near AI: predicting response to save lives in lung carcinoma, in collaboration with 64Codon, Kochi (approved by Kerala Startup Mission), 2022-23

Team

Research Scientist; Dr Sujan K Dhar

Intern: Anuradha Panigrahi, Vijeta D Joshi

Technology Business Incubator

We are India's first hospital-based incubator to bring together clinicians, scientists, engineers, entrepreneurs, and researchers under one umbrella. The Technology Business Incubator (TBI) has a vast network of the most innovative, creative, and seasoned experts in the venture space. TBI organizes one-on-one meetings, and venture capitalists, creative directors, legal guides, and serial entrepreneurs share their insight, experience, and advice in order to help you take your own venture further, faster.

- **MISSION:** Our Mission is to create a powerful interactive environment for inspiring entrepreneurs and scientists to the everyday challenges faced by highly accomplished clinicians and to educate healthcare personnel to identify and leverage opportunities emerging in engineering sciences.
- **VISION:** The Vision of BIRAC-Mazumdar Shaw Medical Foundation-TBI is to be a global ecosystem for innovations in health care and nurture the development of novel technology for making advanced healthcare accessible and affordable.
- **FOCUS:** To instill a culture of eclectic, broad bandwidth thinking and imaginative ideation within a busy, evidence-based hospital medical practice to accelerate start-ups to rapidly optimize Medical Technology solutions. Provide exposure to the latest advanced applied medical technology within a hospital and community environment.

The BioNEST is located at the Narayana Health City, Bommasandra. The ecosystem includes a super-specialty flagship cardiac hospital - the Narayana Institute of Cardiac Sciences, one of the largest cardiac hospitals in the world with 32 dedicated Cardiac Operation Theatres and 6 Digital Cath Labs including a Hybrid lab, capable of performing both interventional cardiac procedures as well as complex heart surgeries. The dedicated 80-bed pediatric cardiac ICU is the largest in the world. Standing alongside the dedicated Cardiac hospital is the Mazumdar Shaw Medical Center which is an advanced multispecialty hospital that offers advanced cancer care facilities through the Mazumdar Shaw Cancer Center. The center is a 675 bedded hospital dedicated to all medical and surgical specialties except the Heart. The faculty of clinicians are truly World Class and bring together very eclectic expertise and interests. In addition to this, the health city also houses the Narayana Nethralaya – a specialist eye hospital and Sparsh Hospital for Accidents, Orthopedics.

The Bionest program at MSMF is one of the most unique programs, being India's first Hospital-based facility providing a perfect ecosystem for startups involved in healthcare to interact and validate their innovations. The activities as committed in the GLA commenced with our regular promotional activities of Webinars, Blogs, and updating of the website making it easy for start-ups to know and understand the MSMF-BIONEST program. In this effort, our partner Villgro also assisted by taking care of some of the promotional activities. Simultaneously MSMF also initiated the construction of the physical, dedicated innovation center space along with the Prototyping lab, Mechanical, and Electronics labs. Vendor shortlisting for the equipment was in progress. The formation of the Scientific and Investment committee was also completed. Host contribution of seed fund of Rs 1cr was being planned as a commitment from Villgro as a partner in the MSMF-BIONEST program.

TBI Incubatee Profile

Currently the TBI houses 22 incubatee companies engaged in the diverse space of diagnostics development, application of Internet-based technologies, devices including wearables, clinical decision making system development and education in and around a clinic. Seven of the incubatee companies have already received funding from BIRAC to take forward their innovations. Association with MSMF TBI enables interaction of incubates with the clinicians at NH to bring the necessary clinical perspective in development. Here are profiles of some of the incubatee companies at TBI.

TUTLE helps students and professionals in making a career choice and supports them with affordable learning resources to prepare for healthcare or life sciences jobs. We can help teach doctors and teaching hospitals by designing the courses, hosting them on our LMS platform, and promoting the courses in India.
http://www.tutletest.com

SIAMAF Healthcare is developing magnetic nanotechnology for radiation-free and affordable cancer diagnosis and therapy. SIAMAF brings innovative solutions for cancer staging, screening, localization, imaging, and hyperthermia using advanced magnetic sensing technology and functionalized magnetic nanoparticles.
https://siamaf.com/

Thermaissance is a nanotechnology-based technical textiles startup that reduces various healthcare-associated and community-acquired infections. We make medical textiles such as scrubs, gowns, patient clothing, lab coats, etc using fabrics scientifically proven to be effective against enveloped viruses, gram-positive and negative bacteria, MRSA, VRE, CRE, and mucor species. https://www.thermaissance.com/

Fastsense Diagnostics primarily focusses on affordable and preventive healthcare. We are trying to solve a basic problem that is early diagnostics of life-threatening diseases. In MSMF we are developing portable diagnostic kits for Neonatal Sepsis.
http://www.fastsensediagnostics.com

TERALUMEN is India's first Terahertz company, developing compact medical systems using multispectral Terahertz and Fluorescence technologies combined with Artificial Intelligence for accurate diagnosis of cancer margin intraoperatively.
https://www.teralumensolutions.com/

Oxyliv (White Owl Healthcare) works on a vision to bring in indigenous solutions to empower low-resource healthcare settings to treat the patients more effectively with lesser admissions requiring critical care. Our aim is to reduce the inappropriate use of oxygen delivery to the patient in respiratory distress and to improve quality and efficacy of respiratory support through an affordable and portable titrated air-oxygen therapy device.

Ominar Innovations is committed to develop home based kidney screening devices for knowing (early detection) Kidney related damage using few drops of urine sample. Our technology is Smartphone based that detects 'Urinary Protein to Creatinine Ratio' (UPCR) test using AI/ML programming in 5- 10 minutes. https://ominarinnovations.com/about/

FARCAST Biosciences has the unique distinction of processing over 22,000 live tumor tissues across 17 cancer indications. We strive to work together with our partners in evolving and improving our Farcast™ TiME (Tumor immune Microenvironment) platform.
https://www.farcastbio.com/

Ashva WearTech: Fitness is a wearable technology that captures clinically relevant data in chronic knee injuries for assessment and progress monitoring, with potential for remote monitoring in near future.
https://www.ashvaweartech.com/

64 CODON is a bio-science company catalyzing research with an in-house commercial biobank. We have created a unique network of partner hospitals and laboratories to collect tumor samples.
http://64codon.com/

SCANBO is a data driven medical diagnostics company that aims to provide portable point of care devices that can perform various tests, digitize this data and make it available for sharing in real time with relevant stakeholders. The device will be a boon for primary care screening.
https://www.scanbo.com/

iKanekt is an innovative company, is a brain child of Industry stalwarts in the field of Clinical Research. Clinical Trial Process and Document Management (CTPM) from iKanekt is a SaaS application that provides a structured workflow to efficiently manage the entire process of Clinical Trials at the same time providing transparency, visibility, and control to the stakeholders managing the trials.

iKure is a tech driven, rapidly growing, revenue positive social enterprise meeting rural health care and prevention needs through a unique combination of health outreach initiative, skills development, and technology intervention. We are looking to the future of disease prevention and wellness for rural, semi-urban and urban people in India. https://www.ikuretechsoft.com/

SUNFOX: With the aim of creating innovative technologies for a better and sustainable future, Sunfox visions to bring the reliable technologies related to Biomedical Instrumentation, IOT and other engineering domains is serving the Indian markets and International clients with fervour.
https://www.sunfox.in/

SPARC Life Technologies has been conceptualized with the intent of addressing the problems that the digital lifestyle has brought upon human health and performance.
https://www.sparclife.co/

VisBio Technologies has developed Smart ColpoSpec, a head-mounted colposcope and an operating tool for examination, tele-consultation and surgical procedures in cervical workflow and an assistive tool to detect cervical pre-cancer.

ANATOMECH has developed a Compression Wearable & Portable Medical Device based on shape memory material technology (platform) for lifelong management of secondary lymphedema (medical condition). https://www.anatomech.co/

Promotional Activities conducted by TBI

Under the BIONEST program, we have launched a new initiative, 'Mentor Clinic' which is a pro-bono initiative for a one-on-one mentoring session between an entrepreneur interacting with an expert clinician. In this conversation of 30 minutes the entrepreneur can seek guidance related to their start-up, roadblocks and other challenges without compromising. confidentiality. In 2021-22, we have organized 12 such mentoring sessions involving reputed clinicians from NH.

We also publish monthly blogs, which is either an interview with domain experts around the topic to get insights on the subject or a write up with elaborate details on current social impact of start-ups. In the current year, the topics of our blogs ranged from issues related IPR, digital marketing and scale up to social impact of business and involvement with philanthropic organizations. Our webinar sessions, in which leaders of the MedTech eco-system share their experiences and knowledge with growing enterprises have been very popular within the community. The most recent webinar was on the journey of a diagnostics developer in India who has made their mark in the eco-system by rapidly developing indigenous test kits to handle the Covid-19 challenge. Other webinars also showcased similar organizations offering insights and learning for the incubatees.

In-house Research and Innovation Activities

Scientists in TBI are developing a Medical Artificial Intelligence Cloud Infrastructure (MAICI) as a software as a service platform. The platform is used for storing different data and information for a patient and providing a diagnostic aid to the doctors. As of today, India doesn't have a robust system like the USA's Electronic Health Record system, for which MAICI is the solution. MAICI isn't only meant for information storage – it also provides data processing platforms and easy access to information for different institutions. For example, doctors will only see relevant medical records for the patient, whereas the government sees the information on the number of citizens who visited a doctor and trends in diseases. The first responders only see the information on an allergic reaction to certain medication and a summary of medical history. A research institute only gets the relevant information they are subscribed to and hides the personal details of the patient.The advantage of MAICI, being deployed on existing cloud platform scalability, is instantaneous. The team required to support and maintain is extremely small compared to existing infrastructures, as we don't own any physical servers and clusters. MAICI is the future of data collection as it can be implemented in a clinic or a large-scale hospital chain.

Visits of International and National organizations to TBI, MSMF

Visit by Swissnex – consulate general of Switzerland

Discussion with NEC Global, Japan on AI in healthcare

Vist by atDose, Japan to discuss on drug delivery applications

Visit by Adichunchunagiri Medical College Research Team

Visit by Toronto Business Development Centre (TDBC) team

Signing of Memorandum of Understanding between TDBC and MSMF

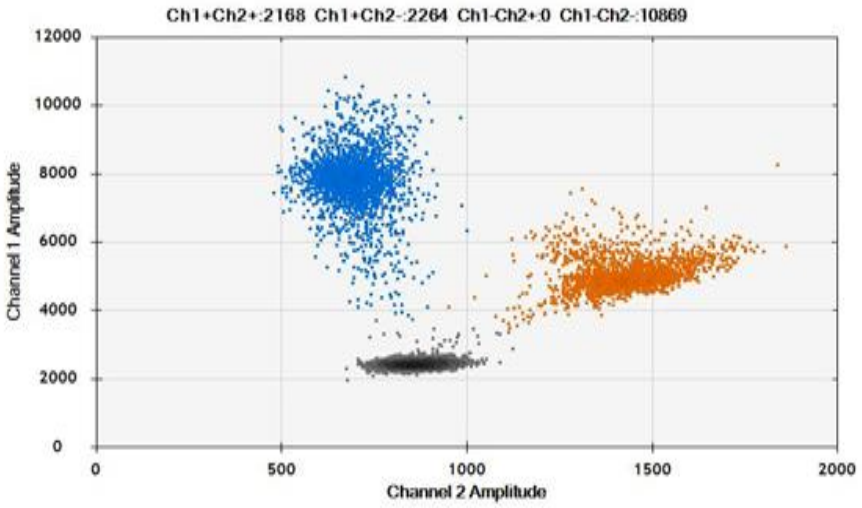
Advanced Diagnostic Research Centre (ADRC)

Advanced Diagnostic Research Centre (ADRC) was started in 2022 to develop a robust ecosystem geared up to meet the demands of today and anticipate tomorrow's challenges of paradigm shift in the way diagnostic solutions are offered. Research team at ADRC works in tandem with the clinicians to identify unmet diagnostic needs and translate them to diagnostic tests of the present and future, through collaborative research in molecular biology, cell biology and data analytics. Major driver of the research is to establish tests that are reliable to clinicians and affordable to patients. Most of the tests offered by ADRC have been developed in-house and were adopted to the clinic after extensive validation. Current test panels of ADRC include molecular diagnostics for brain tumour and transplant biology.

Tests for Brain Tumour Diagnosis

We are currently developing a panel of molecular tests that are recommended by the 2021 WHO guidelines for characterization and classification of brain tumors. Following two tests are already developed and currently undergoing validations in the clinic.

- IDH1 Mutation detection by ddPCR, developed using home-grown primers on the ddPCR platform, is found to be more sensitive than IHC. Also in addition to the most commonly observed R132H mutation, our assay detects other non-canonical IDH1 mutations such as R132C and R132 S for which there are no detection kits available in the market.



- 1p/19q co-deletion assay developed using Fluorescent in-situ hybridization platform is another important prognostic test for lower grade glioma.

In addition to above, we are also developing assays to detect IDH2 mutations, EGFRvIII variant and TERT promoter mutations which are important markers for classification of brain tumours.

Pre- and post-transplant test panels

Narayana Health city is one of the largest centres of transplantation, considering bone marrow, heart & lung, kidney and liver transplants together. ADRC aims to become the largest NABL accredited diagnostic centre for providing tests for transplantation. The donor sera can be stored for 10 years to check development of donor specific antibody post transplantation.

In ADRC we routinely offer the Donor-Specific Antibody Assays (DSA) and the more sensitive LIFECODE single antigen assay (LSA) that are routinely used for bone marrow transplant patients to monitor post-transplant donor specific immune response. We are expanding usage of these assays to solid organ transplant patients including kidney and heart.

Full typing result

	Allele 1	*Allele 2*
HLA-A	**02:03:01:01**	**24:07:01:01**
HLA-B	**13:01:01:03**	**52:01:01:01**
HLA-C	**04:03:01:01**	**12:02:02:01**
DRB1	**12:02:01:01**	**15:02:01:02**
DQB1	**03:01:01:07**	**06:01:01:01**
DPB1	**04:01:01:01**	**26:01:02**

We have also standardized a high-resolution HLA genotyping service for transplant matching. Based on the Next Gen Sequencing platform, this assay focuses on six loci (HLA-A, HLA-B, HLA-C, DRB1, DQB1 and DPB1). Results of the genotyping is used routinely for bone marrow transplant cases and can also be used as guiding information for other solid organ transplants.

With the increased size of HLA genotype data from both donors and patients, we are building a registry which in the long run would help to identify most frequently observed alleles in the local population and their potential disease association. In future, consensus HLA protein sequences can be derived from this registry to develop DSA assays, which will be more specific to the relevant populations than antibodies in imported kits.

Grants

- Establishment of a NABL Accredited Laboratory for Performing Clinical Immunogenicity Testing (approved by BIRAC, DBT)
- Engineering conditionally replication-competent SARS-CoV-2 viral molecular clones and evaluation of cross-variant neutralization, in collaboration with JNCASR, Bangalore (approved by BIRAC, DBT)

Mazumdar Shaw Cancer Outreach Program

Philanthropic wing of Mazumdar Shaw Medical Foundation continues to support the underprivileged patients, enabling them to have healthier and happier lives. MSCOP serves as a ray of hope for many families in the successful completion of their treatment. This is facilitated using a two prong approach, both treatment and financial support to the sick and needy.

Activities of MSCOP include;

- Providing financial assistance to underprivileged families.
- Organizing activities for children in pediatric oncology wing
- Daily nutritional supplement support program
- Drug discounts for needy patients
- Providing cancer awareness in rural villages
- Liaise with various organizations for the benefit of patients
- Emotional support to patients and their families
- Counselling patients and caregivers

Financial assistance to underprivileged families:

Support provided to number of patients in 2021-22			
Category	New Patients	Patients availed Drug discount	Patients supported
Adult	13	35	17
Pediatric	44	38	48

Patients come from different backgrounds with different levels of financial issues and the treatment cost varies depending on the diagnosis and severity of the illness. Patients and families coming from underprivileged backgrounds find it difficult when the treatment estimation is high. MSCOP provides them financial assistance to reduce their burden. Depending on the assessment of the patient and their background, the patients receive funds to complete their treatment successfully. MSCOP also provides oncology drug discounts to patients who cannot afford higher value medicines for a lower cost to help with their regular and follow up treatments.

Daily nutritional supplement support program

Nutrition is very essential for healing of the body and immune system during oncology treatments. During the course of treatment, patients suffer from lack of nutrition as they are unable to afford healthy eating habits. MSCOP provides nutritional supplements in the form of almonds, cookies and fruits on a daily basis for patients who come to 'Day Care' for chemotherapy and supportive care treatments. Approximately 700 patients benefit from the nutritional support program at MSMF.

Emotional support and counselling to patients and their families:

Understanding the stress and pressure a patient and family goes through during the treatment is crucial in providing emotional strength during the course of treatment. MSCOP provides counselling to needy patients helping them cope with treatments. Counselling support is also availed by caregivers who are constantly with patients leaving aside their normal way of life.

Providing cancer awareness in rural villages

An outreach program was conducted for 'Breast Cancer Awareness' month in partnership with Purpose Driven Foundation in Melnedungal village, Tamil Nadu. Women in the community found the session very enlightening and helpful. As part of the awareness campaign, Breast Self-Exam was also taught to them.

Testimonials

Our beneficiaries also have a few words to say.

Pratheeksha

'I love to draw' says Pratheeksha; a 12 year old girl who always loves to read books and draw. She tells us that it keeps her happy and engaged in spite of her ongoing treatment and a long recovery period ahead of her.

Pratheeksha is diagnosed with left distal femur Osteosarcoma (a type of bone cancer) which required 4 cycles of chemotherapy, surgery followed by another 6 cycles of chemotherapy. She recently underwent surgery and is currently getting her 6th cycle of chemotherapy. MSMF sponsored her surgery and is continuing to support her treatment by sponsoring her medicines and other required tests.

"We don't know what we would have done if not for MSCOP's timely support for the treatment. We are very thankful for all the help and for supporting my daughter to complete her treatment without any hassle"; says Pratheeksha's father.

Iniya Sri

My name is Manimegalai. I have two children; my daughter's name is Iniya Sri who is 3 years old. My husband Kumar is a Lab Technician and earns Rs 25,000 per month and he is the only breadwinner of the family.

Our life changed in December 2020 when we heard that my daughter Iniya has been diagnosed with 'Acute lymphoblastic leukemia'. All our dreams came crashing down and we never imagined a day like this would ever come in our lives. We did not know what it was and had no idea how we were going to afford treatment for her. Doctors advised 6 cycles of chemotherapy to be given immediately and we sought help from many people and started her treatment but it was not enough. We sold all the assets we had and it was still not enough. A day did not go by thinking how we were going to afford her treatment and was just hoping for a miracle.

We came across MSMF through the doctor who was treating our child and he suggested that we could seek help. Once we started getting help from MSMF, our burden was greatly reduced and we felt that we have got our daughter back. No words can express the kind of relief we experienced when we were told that MSMF had extended their help for Chemotherapy and follow-up. There were times I did not have any money to buy medicines and cried not knowing what to do. After MSMF started to help, we got medicines at a lower cost with an oncology drug discount.

"MSMF was a God sent angel to me at the right time to help my daughter's treatment and I'll forever be grateful and thankful for the help".

Prathviraj

"I was devastated on hearing that Prathvi was diagnosed with Osteosarcoma. I hardly knew what to do and how to go about his treatment. He's our only son and for him to get such sickness was beyond what I could comprehend. We left everything we had and came to Bangalore for his treatment. The doctors here gave us hope that it is treatable and started the treatment immediately. Then came another added concern, the cost of the treatment. We couldn't afford it after his second chemotherapy was completed. We approached many

organizations, friends and families, other government institutions for funds and didn't get the help we expected. We came across Mazumdar Shaw Medical Foundation and approached them to help with his treatment. After a thorough assessment, they decided to help with his surgeries and post-surgery care.

MSCOP was a helping hand when I had no one to support me. Because of their support, my son was able to get two surgeries done without any hassle and he is on his road to recovery." said his mother.

Prathiviraj is a 17 yr old male diagnosed with Osteosarcoma with metastasis in his lungs. He has undergone two surgeries and is currently on his 1st cycle Chemotherapy post-surgery with 7 more cycles to complete. Prathvi is very smart and loves to play games like "Minecraft " and is tech-savvy. He is an artist who creates beautiful astonishing arts.

In doctors' words

"The Foundation's help is great. Many patients are getting benefited through fund allocations. Patients also receive discounts in medicines which helps them to continue their follow-up treatment regularly".

Dr. Shobha B

Consultant Paediatric Haemato-Oncologist & BMT
Mazumdar Shaw Medical Centre – Narayana Health City

"I have seen many patients who were able to get treated only because of the foundation's support. They always express how grateful they are to receive the funds and complete the treatment intended without any struggle".

Dr. Pragnya Coca

Consultant Medical Oncologist
Mazumdar Shaw Medical Centre – Narayana Health City

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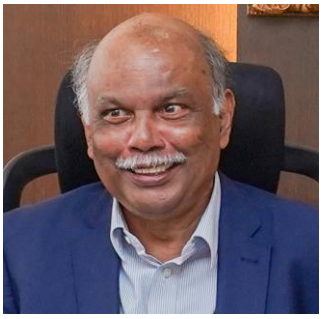
Executive Management



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