TATA MEMORIAL CENTRE
ADVANCED CENTRE FOR TREATMENT, RESEARCH AND EDUCATION IN CANCER
Kharghar, Navi Mumbai- 410 210
www.actrec.gov.in
Phone No : 91-22-27405000

No. ACTREC/ADVT/ 154 /2024 **9th October, 2024**

ADVERTISEMENT FOR A POST DOCTORAL POSITION AT CRI ACTREC

Applications are invited from highly motivated and eligible candidates for post-doctoral positions at the Cancer Research Institute, ACTREC for the advertised projects. The applicant must have obtained a PhD degree from a recognized University. Those who have submitted their thesis and are awaiting the award of the degree are also eligible to apply. However, such candidates, if selected, will be offered a fellowship equivalent of a Senior Research Fellow until they obtain their degree. **The position is for 1 year. The selected candidates will be encouraged to apply for extramural grants under the mentorship of the PIs**.

The upper age limit for the fellowship is 35 years at the time of the submission of the application. Age will be calculated by taking the last date of application. **Age relaxation of five years will be given to candidates belonging to SC/ST/OBC/Physically Challenged & Women candidates. For other exceptional candidates, age will be relaxed based on the discretion of the competent authority.** Since this fellowship is meant to bring in the best of candidates outside of ACTREC so that the faculty and the fellow are mutually benefited from new expertise and a fresh perspective, the following conditions apply for the internal candidates:

At the time of application, candidates who have graduated from ACTREC should not have completed more than six months after the award of the degree. Candidates who have graduated elsewhere and are working in any of the labs at ACTREC should not have been associated with the lab for more than six months at the time of application. In either of these cases, the fellowship will be awarded strictly for one year within which time the candidate has to find alternative support. No more than one fellowship will be awarded under this clause and the candidates will be subjected to the same selection protocol.

Essential Qualifications and Experience:

- PhD degree from a government recognized University or research institution.
- At least one research article publication in a well reputed international journal.
- Expertise in any one or more of these areas: Molecular Biology, Cell Biology, Structural Biology, Computational Biology, Proteomics and Genomics.
- Candidates must be capable of conducting independent research under the mentorship of the PI, develop their own ideas and design experiments. They should be capable of working in a collaborative environment.

Application details:
Send an e-mail with a full CV and Statement of Purpose following the guidelines [Appendix-1]. SOP is graded and will be an important criterion to shortlist the applicants. Take it seriously. Arrange for two letters of recommendation to be sent to the email ID given with the advertisement. This is an important aspect of the recruitment process. An incomplete application will be rejected.

Fellowship amount and conditions are on par with DST/DBT norms.

Consolidated Salary: Rs. 73,660/- per month. (Rs. 58,000/- + 27% HRA) p.m. The work progress of the candidate will be monitored, and extension will depend on satisfactory progress of the work.

Candidates with provisional certificates and candidates who have cleared the viva voce can apply. The later have to provide an official statement from their Institute confirming the same

Candidates fulfilling these requirements should pre-register by sending their application in the prescribed format with

1. Recent CV

2. Statement of purpose

3. List of key publications

4. Letters of recommendation – Two

5. Contact details of referees - Two

by e-mail to pdf.actrec@gmail.com at latest by 5:45 pm on or before 23rd October, 2024.

The interview dates & venue will be informed by email to the shortlisted candidates only.

No T.A. / D.A. is admissible for attending the interview in person. If needed, candidates have to make their own arrangements for accommodation/ stay in Navi Mumbai. Interviews will also be conducted online.

At the time of the Interview, candidates should bring **original certificates** with photocopies (attested), CV and a recent passport-size photograph.

All correspondence should be strictly made only to pdf.actrec@gmail.com as indicated.

Alpasani

In-charge, Academic & Project Cell

APPENDIX

{1}

Expected Statement of Purpose (SOP):

The Introduction

- Indicate the specific position you are applying for with the advertisement number and date.
- Follow it up with a short description of yourself –'I have submitted my PhD/ I have a PhD in (field) at (name of university); My dissertation is titled (title) and is supervised by Professor (name)'.

Candidature: Why are you the right candidate for this postdoc?

1. Describe your dissertation or current research project. This should cover the broad aim, your key findings and why they matter to the field. **100 words**.
2. Summarize in your own words what you understand about the project aim and the long-term goal of the lab you wish to join as a post-doc. **100 words**.
3. Highlight your qualifications, research experience and knowledge that makes you the best candidate for the post. **150 words**.
4. Propose any ideas you may have that can help or direct the project. **50 words**
5. If you are applying for more than one lab, you can add the specific information for each lab (2-4) in the same letter

PRINCIPAL INVESTIGATORS	WEBLINK OR DETAILS
DR PRASANNA VENKATRAMAN	https://actrec.gov.in/dr-prasanna-venkatraman
DR ABHIJIT DE	https://actrec.gov.in/dr-abhijit-de
DR MANOJ MAHIMKAR	https://actrec.gov.in/dr-manoj-b-mahimkar
DR SANJEEV WAGHMARE	https://actrec.gov.in/dr-sanjeev-waghmare
DR NANDINI VERMA	https://actrec.gov.in/dr-nandini-verma
DR MURALI CHILAKAPATI	https://actrec.gov.in/dr-c-murali-krishna
DR SYED HASAN	https://actrec.gov.in/dr-syed-k-hasan
DR SEJAL PATWARDHAN	https://actrec.gov.in/dr-sejal-patwardhan
DR SHARATH CHANDRA ARANDKAR	https://actrec.gov.in/dr-sharath-c-arandkar
DR SUBIR BISWAS	https://actrec.gov.in/dr-subir-biswas
DR SUNIL SHETTY	https://actrec.gov.in/dr-sunil-shetty

APPENDIX

{2}

Application for the post of 'Post-Doctoral Fellow'

Name			
Address			
Date of Birth			
Whether physically handicapped			
Educational Qualification			
Exam Passed	Board / University	Year	Marks (%)
PhD			
MSc			
BSc			
Relevant Work Experience			
Name & Contact details of 2 referees:			
Any other information			
Date:	**Signature:**		

Detail projects from PIs are as below: -

1. DR V. PRASANNA, PRASANNA LAB

Dissecting the role of Proteasomal chaperone PSMD9 in nucleolar architecture, translation, and p53 homeostasis in Cancer Cells

PROJECT SUMMARY:

Proteasomes are major degradation machineries in most cells. Central to the efficient degradation of proteins by the proteasome is its complex structural design. The proteasome is organized into a central cylindrical proteolytic core (20S) capped at one or both ends by the 19S regulatory particle. Inhibitors of proteasome active sites are anti-cancer drugs used in the treatment of multiple myeloma and to a limited extent in mantle cell lymphoma. These inhibitors have not yielded success in the treatment of solid tumors insofar.

Our efforts over the years established that the seemingly innocuous proteasomal assembly chaperone, PSMD9, is central to the biology of some cancers. We find that PSMD9 impacts proteasome assembly status and subunit connectivity in cancer cells. Additionally, novel functions of PSMD9 in facilitating nucleolar transport of RPs, modulation of structural and morphological integrity of the nucleolus, regulation of MDM2 turnover, p53 activation and cellular survival in response to nucleolar stress have been reported from our studies.

Thereby, PSMD9 as a 'chaperone' seems to play an even wider role in cancer cell biology by influencing subcellular organelle structure and biogenesis. Based on these multiple evidences, we believe that PSMD9, the new kid on the oncology block is an Achilles' heel in (at least) Breast Cancer.

Aim: To understand the role of PSMD9 in modulation of nucleolar architecture. To explore the cross-talk between PSMD9 and nucleolar resident proteins in regulation of ribosome biogenesis. To characterize the role of PSMD9 in maintenance of p53 homeostasis in Cancer Cells.

Skills Required: Sound knowledge in Biochemistry, Structure and Functions of proteins; Molecular Biology and Cell biology tools and Techniques.

2. DR ABHIJIT DE, DE LAB

Understanding HER2 receptor targeted drug resistance mechanisms *in vivo* and possible therapeutic intervention methods

Dr. Abhijit De, PI & SO 'G', Professor, HBNI, Molecular Functional Imaging Lab, ACTREC

HER2-positive breast cancer accounts for 20-30% of all BC cases. This subtype of disease presents moderately aggressive behavior with poor prognosis, causing distant metastasis to critical organs like brain, lung and liver. Targeted therapy of different forms such as antibody-based drugs, small molecule inhibitors or antibody-drug conjugates against the HER2 receptor target has shown some improvement in 5 years survival of HER2-positive patients. These drugs target different parts of the HER2 receptor and able to inhibit HER2 oncogenic activation by preventing receptor dimerization, inhibiting its kinase activity and neutralizing the downstream signaling cascade. However, irrespective of the type of personalized drug used, development of drug resistance is very common against these therapies. Through this project we like to fill out knowledge gap in the biology, which eventually will contribute to find alternative therapeutics to improve clinical outcome in future. Various aspects for drug resistance development are now part of cancer hallmark. Here, we aim to pursue a multi-dimensional study to find specific answer on several key mechanisms that my group is actively working. Onset of new mutation in key structural domains of HER2, activation of compensatory pathway, upregulation of downstream signaling, acquirement of Epithelial-Mesenchymal transitions, CSC enrichment, altered metabolism, etc. are being pursued.

We aim to identify possible cause of HER2 targeted treatment failure by utilizing the breast cancer cell models already developed in the lab, 3D cell model as well as *in vivo* mouse model with application of omics as well as molecularly targeted non-invasive imaging procedures.

3. DR MANOJ MAHIMKAR, MAHIMKAR LAB

Predictive Clinical Features and Molecular Markers for Tumor Response and Treatment Outcomes Post NACT in HPV-negative Oral Cancers

Abstract

Head and neck squamous cell carcinomas (HNSCCs) is a complex and heterogeneous disease regulated at multiple levels and associated with high mortality and morbidity. HNSCCs are related to environmental risk factors, especially excessive tobacco and alcohol consumption. Oral squamous cell carcinomas (OSCCs) are the prevalent forms of HNSCC, representing approximately 90% of all tumors in this region. The high mortality associated with OSCC is related mainly to the locoregional advancement of the disease. Although significant improvements have been made in achieving local control of the disease and increasing the survival rate of patients with primary malignant oral tumors via surgical intervention, physicians face yet another challenge—that of preserving oral functions, such as articulation, mastication, and deglutition, and retaining visual aesthetics for improving HNSCC patients' quality of life. Effective treatment for advanced HNSCC (T3 and T4), but non-resectable tumors involves the use of multidisciplinary therapies, such as multiple chemotherapies (CTs) and radiotherapy (RT). However, most patients present in an advanced stage wherein tumor resection is rendered questionable because of the positive resection margins. The prognosis of such unresectable stage IVA or IVB tumors treated with a non-surgical approach is poor, with median survival ranging from 2 to 12 months. for these locally advanced borderline operable cases where the role of neoadjuvant chemotherapy (NACT) has been postulated as an alternative to the current existing therapeutic modalities. Although NACT provides a promising scenario for managing this patient subgroup, it should be known that response rates to this modality vary from 35-40%. Although NACT has been evaluated over the last decade, the chemoresistance phenomenon and its molecular mechanisms are yet to be studied comprehensively. There exists a need to identify biomarkers that will help us in better therapeutic stratification of these patients. There has been no study focusing specifically on the markers to predict response in oral cavity cancers, which is the aim of the present study.

Rationale

Squamous cancers of the oral cavity account for a major proportion of cancers in the Indian population [1, 2]. The sheer load and morbidity associated with these cancers mandate further evaluation of the disease biology. These Oral cancers are managed by surgery followed by adjuvant therapy (radiation/chemoradiation) and radical chemoradiation when the tumor is deemed unresectable[3]. However, many patients present in an advanced stage wherein tumor resection is rendered questionable in view of the positive resection margins. The prognosis of unresectable stage IVA or IVB tumors treated with a non-surgical approach is poor, with median survival ranging from 2 to 12 months [4-7]. It's for these locally advanced borderline operable cases where the role of neoadjuvant chemotherapy (NACT) has been postulated as an alternative to the current existing therapeutic modalities [8-11]. The aim is to downstage the tumor and provide adequate margins of resection. Although NACT provides a promising scenario for managing this patient subgroup, it should be known that response rates to this modality vary from 35-40%. It means that a significant proportion of patients do not benefit from chemotherapy.
Joshi et al. analyzed T4b oral cavity cancer patients who were offered NACT and then assessed for resectability at the end of 2 cycles of chemotherapy. NACT was safe and can achieve resectability in 30.9% of patients. Patients undergoing resection have much better OS than those who underwent non-surgical local treatment [12]. Patil et al. evaluated 721 patients with stage IV oral-cavity cancer who received NACT, of which 310 patients (43%) had a sufficient reduction in tumor size and underwent surgical resection. NACT led to successful resection and improved overall survival in a significant proportion of technically unresectable oral cancer patients [13]. More recently, Chaukar et al., in a prospective phase-II randomized study on OSCC patients with paramandibular disease needing

segmental mandibulectomy, demonstrated that NACT (docetaxel, Cisplatin, and fluorouracil) plays a potential role in mandibular preservation in oral cancers with acceptable toxicities and no compromise in survival [14].
Although NACT has been evaluated over the last decade, its chemoresistance and the underlying molecular mechanisms are yet to be studied comprehensively. The key clinical question is differentiating between responders (achieve resectability) and non-responders. B-tubulin II, p53, GST, ERCC, HPV, and other molecular markers have been proposed as surrogate markers for NACT responsiveness in head and neck cancer [15, 16]. However, there is a dearth of predictive clinical, pathological, or molecular markers to suggest a response to chemotherapy that will help us in better therapeutic stratification of these patients. No study has been focused specifically on the markers to predict response in HNSCC/ OSCC, which is the aim of this study. This will prevent unnecessary chemotherapy in patients with a 'chemoresistant' genotype, thus sparing patients from toxicities.

Summary

The proposed study aims to understand the interrelationship between molecular changes occurring in oral cancers and their association with clinical outcomes. As a part of treating advanced-stage oral cancers, patients receive chemo and radiation therapy in combination with surgery. Surgery is the best treatment for oral cancers. However, some of the advanced-stage oral cancer cases are inoperable or borderline operable and thus are given neoadjuvant chemotherapy (NACT) so that the tumor can be surgically resected. There may be a response to chemotherapy in some cases and no response in others. Thus, there is a need for biomarkers that can predict the response to chemotherapy. Most past studies have used single biomarkers; comprehensive analysis with multiple markers is lacking. Hence, in this study, we plan to use the battery of clinical, pathological, and molecular biomarkers, which may help better strategize the patients in the future and avoid toxicities to patients.

Aims and Objectives

The present study aims to identify clinicopathological features and molecular markers to predict the response (achieve resectability) to NACT for advanced oral cancers.

Specific Objectives

- To carry out the IHC-based analysis of the markers of DNA damage/ repair, hypoxia angiogenesis, apopotosis in tumor tissues before starting the therapy and at the time of surgery to evaluate the association with treatment response.
- To conduct multiplex ELISA-based analysis of markers of inflammation, hypoxia, and angiogenesis before and after the treatment in serum samples and evaluate their association with clinical outcome.

Relevance and Anticipated Outcome:

Oral cavity cancer is the most common cancer among Indian males and 2nd overall. [17] More than 70% of Oral cancer patients present in locally advanced stages III and IV. [18]. A significant proportion of patients are not resectable and have poor outcomes when treated non-surgical. For these advanced stage patients, NACT is routinely given at our Institute. The long-term outcomes of NACT on borderline operable Oral cancer patients has shown superior 10 year survival among patients undergoing surgery than those who did not undergo surgery (21.8% vs 4.1%, $p < 0.001$). [19] However, the response rates to NACT are variable. Thus, if the present study can find out the biomarkers for chemotherapy response. We will be able to spare a lot of patients from NACT, which will save costs to the patients and country and spare patients from toxicities. So, we anticipate that the findings from our study will help patients receive appropriate treatment.

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4. DR SANJEEV WAGHMARE, WAGHMARE LAB

Title: Investigating the differential epigenetic landscape with effect on cell signaling and metabolic pathways during the differentiation of induced pluripotent stem cells into various lineages

PIs: Dr. Sanjeev Waghmare and Dr. Sanjay Gupta

Background:

Induced pluripotent stem cells (iPSCs) cells are derived from adult somatic cells that have been genetically reprogrammed to an embryonic stem (ES) cell-like state by ectopic expression of ES cell genes. Takahashi and Yamanaka showed that adult cells were reprogrammed into iPSCs by adding four specific transcriptional factors: Oct3/4, Sox2, Klf4, and c-Myc. In more recent studies, it has been observed that DNA methylation plays a role in suppressing genes related to cell differentiation and aiding in the modification of chromatin structure. iPSC generation from the somatic cells by using the Yamanaka factors revealed that DNA methylation, histone modifications, histone variants, and ATP-dependent chromatin remodeling affect transcription factors' ability to bind their recognition elements. Recently, studies from Gupta Lab have shown the differential incorporation of histone isoforms in different tissue types and during cancer development. However, the dynamics of histone isoform alterations in lineage differentiation at various stages of reprogramming are still unknown. Cell signaling pathway such as Wnt/ β-Catenin interacts and regulates the expression of Oct4, Sox2, and Klf4, which is involved in efficient generation of mesodermal progenitors; however, molecular mechanism is obscure. Further, metabolic regulation is crucial during the differentiation of IPS cells in to multiple lineages. However, the metabolic control involved in the regulation is yet to be unraveled.

Hypothesis:

The intriguing plasticity of iPSC during reprogramming is potentially due to the differential incorporation of histone proteins, altering the site-specific post-translational modification, leading to differential chromatin organization and gene expression. Therefore, uncovering the epigenetic landscape, metabolic and cell signaling during different cell lineages during iPSC reprogramming will provide insights into the mechanisms for various cell fate decisions.

Objectives:

1. Characterization of induced pluripotent stem cells and reprogramming into different lineages
2. Identifying epigenetic landscape during differentiation into different lineages, ectoderm, mesoderm, and endoderm.
3. Investigating the differentialial cellular signaling pathways during the process of IPSC differentiation into multiple lineages

Brief Methodology:

- iPSC reprogramming will be achieved in the human adult fibroblast cells (procured from the Hi-media) using the CytoTune™-iPS 2.0 Sendai Reprogramming Kit to generate iPSCs cultured feeder-free on vitronectin-coated culture dishes. *In vivo* and *in vitro* characterization of iPSCs will be performed through embryoid body formation and teratoma formation assays.
- Differentiation of iPSCs into lineages: iPSCs will be differentiated into hematopoietic, neural, and muscle lineages. Further, histone modification and histone isoforms will be assessed during the early, mid, and late stages of differentiation of iPSCs to different lineages. Moreover, RNA sequencing will be carried out to define gene expression profiles.

5. DR, NANDINI VERMA, NANDINI LAB

Title : Identification and exploitation of genetic susceptibilities of ferroptosis for the treatment of therapy-tolerant Triple-Negative Breast Cancer.

TNBC is a very heterogeneous, aggressive, and metastatic disease that has high prevalence in India. The lack of hormone receptors and other targetable molecules like HER2 makes TNBC more difficult to treat. The only option for clinical management is chemotherapy for TNBC patients. More than 50% patients do not respond well to chemotherapeutic agents and show intrinsic or adaptive resistance to therapy resulting in treatment failure. Our earlier work identified that TNBC cells are exceptionally vulnerable to iron-mediated ferroptosis cell death due to their unique molecular state governed by transcriptomes related to metabolism of iron, glutathione and ferroptosis pathways [1]. More importantly, chemotherapy-tolerant persister TNBC cells show an enhanced toxicity to ferroptosis inducing agents, signifying a potential alternative therapeutic option for resistant TNBC cells [2]. However, it is not well understood if there are any genetic grounds of ferroptosis susceptibility in TNBC tumors and if oncogenic and tumor suppressor genes can influence this cell death pathway. Therefore, we want to conduct lentivirus-based molecular screens to identify the tumor-associated genes that might govern the sensitivity to ferroptosis in breast tissue. Findings from this study will enable us to deploy the genetic predisposition in TNBC to effectively eliminate tumor cells by ferroptosis.

Key words: Ferroptosis, TNBC, molecular screen, drug resistance

References:

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6. DR. MURALI CHILAKAPATI, CHILAKAPATI LAB

Raman and Mass spectroscopy studies to understand early molecular level changes in experimental carcinogenesis.

Several Raman spectroscopy studies on oral cancer have been reported by others and us. Our studies have demonstrated the efficacy of Raman spectroscopy, both non-invasive (in vivo) and minimally invasive (serum, saliva, and exfoliated cells), in stratifying healthy, habitué, premalignant, and malignant conditions and have also demonstrated the feasibility of identifying subjects who are prone to recurrence/second tumors. Raman spectroscopy has shown nucleic acid, protein, and lipid changes in cancer cells and tissues. However, it is essential to identify and evaluate the most suitable method- as these approaches vary in the levels of challenges in terms of logistics and patient compliance/invasiveness - for routine clinical practice for oral cancer screening/diagnosis. Therefore, a study using tissue and serum for RS from the same cohort will help identify the most suitable Raman tool to aid in early diagnosis. As there are practical and ethical limitations with the study of early carcinogenic changes in humans at Raman and metabolites, an experimental animal model could prove fit for our purpose of study. Hence, we propose to use the Hamster buccal pouch (HBP), the most widely used model for experimental oral carcinogenesis, for our study. The HBP model proves appropriate use owing to attributes such as cancer progression through stages similar to human oral carcinogenesis and 100% incidence of tumors in 14 weeks on treatment with 7,12-Dimethylbenz(a)anthracene (DMBA).

The present project aims to evaluate the suitability of non-invasive (in vivo) vis-à-vis minimally invasive serum Raman methods in the early identification of carcinogenesis-related changes in the HBP model.

Objectives

- Evaluation of serum and tissue Raman spectroscopy in identifying effective tool in stratifying early carcinogenesis-induced changes in HBP models.
- Understanding spectral signature for biomolecular variations using multivariate tools and metabolomic alterations using untargeted and targeted approaches.

Hence, in the current study, the change in serum metabolic response from the early stage to the advanced stage will provide novel insights into the impact of metabolism on the carcinogenesis process. Nuclear magnetic resonance and liquid chromatography-mass spectrometry will measure the metabolic profile. Changes over time will be assessed using multivariate models and ANOVA, with baseline as the control.

7. DR SYED HASAN, HASAN LAB

Acute myeloid leukemia (AML) therapy, besides requirement of intensive chemotherapy faces unique challenges in Indian context like high prevalence of fungal and multi-drug resistant bacterial infections before and during therapy leading to high incidence of mortality. Less intensive regimens are widely used in India in older/unfit patients and younger patients with infections as a bridge to more definitive therapy. Venetoclax (Ven) with Azacitidine (Aza) are useful options of treatment in India and globally. However, resistance to Ven-Aza is emerging, leading to inferior outcomes. To understand the biology of resistance, we aim: 1) To use single-cell profiling (RNA+ATAC sequencing) to understand the genetic trajectory & clonal evolution in patients progressing on Ven-Aza therapy; 2) To perform whole-genome CRISPR-Cas9 based loss-of-function screening to identify novel therapeutic targets in Ven-Aza resistant AML; 3) To understand the metabolic alterations associated with Ven-Aza resistance

8. DR SEJAL PATWARDHAN, PATWARDHAN LAB

Project title: Deciphering the role of matrisome in cancer progression and therapy response

Principal Investigator: Dr Sejal Patwardhan

The extracellular matrix (ECM) is a crucial element in multicellular organisms, offering physico-chemical signals that regulate cellular and tissue organization and functions. Changes such as, excessive production, degradation, or alterations in ECM composition and topology are implicated in various diseases including cancer. Therefore, a deeper understanding of ECM composition, metabolism, and biology can help identify new prognostic and diagnostic markers, as well as therapeutic opportunities. The matrisome, which is the collection of extracellular matrix (ECM) proteins and associated molecules, plays a pivotal role in deciding the tumor fate. Matrisome of each cancer is unique and dynamic that undergoes multitude of changes in the tumor microenvironment influencing plethora of biological processes including cell adhesion, proliferation, motility, migration, stemness, angiogenesis, immune modulation fuelling the disease progression. Matrisome may also contributes to therapy resistance by acting as a physical barrier to drugs or sequestering the drugs reducing their bioavailibity. Emerging evidence also suggest effects of matrisome on radiation response. However, landscape of matrisome dynamics and its exact role radiation response remains largely intangible. This project aims to characterise the matrisome of breast tumors of different stage and grades across the molecular substypes of breast cancer before and after radiotherapy. The histological, and molecular characterisation followed by omics based analysis will reveal the unique signatures or pattern of matrisome, which will be further validated using various in-vitro and in-vivo tumor models.

9. DR SHARATH CHANDRA ARANDKAR, SHARATH LAB

Title: Understanding the dynamic cross-talk between tumour and cancer-associated fibroblast cells in the tumour microenvironment.

The continuous cross-talk between tumour cells and their surrounding microenvironment will define tumour growth and metastasis outcome. The tumour microenvironment (TME) consists of fibroblasts, immune cells, endothelial cells and extracellular matrix and often plays a crucial role in many solid cancers. Stromal cells constitute a large part of the overall tumour mass in multiple cancers, among which cancer-associated fibroblasts (CAFs) are the most abundant stromal cell population. CAFs are a heterogeneous population of cells known to modulate cancer cell behaviour by secreting various growth factors, cytokines, and miRNA, such as TGFβ, IL-1α/β, PDGF, FGF, etc. These CAF-derived secretory factors, through direct or indirect communications with other components of the TME, exert their functions such as immunosuppression of cytotoxic immune cells and recruitment of tumour-promoting cells, thereby creating a hospitable micro-environmental niche favouring tumour promotion, angiogenesis, ECM remodelling leading to fibrosis and desmoplasia, promoting invasion and metastasis. In the current project, we will decipher the molecular mechanisms underlying the cancer-associated fibroblast generation and their constant interaction with tumour cells. For this, we will use various *in vitro* and *in vivo* methods to understand the impact on tumour-microenvironment.

10. DR SUBIR BISWAS, BISWAS LAB

Title: Developing antibodies for immunotherapy against triple-negative breast cancer.

Despite the discovery and implementation of paradigm-shifting monoclonal antibody trastuzumab immunotherapy for metastatic $Her2^+$ breast cancer for more than 25 years, and later approved for use in early stage $Her2^+$ breast cancer, still there is no reliable antibody preparation available for triple-negative breast cancer (TNBC) which accounts for the largest number of breast cancer-related deaths across the world. Although, breast cancer is considered to be a lesser immunogenic cancer type, T-cell and B-cell infiltration into the tumor epithelium, albeit low, has been observed. In this project, we will first identify immunogenic antigens which exhibit restricted expression in human TNBC tumor tissues. Through identifying and isolating definite tumor-infiltrating B-lymphocytes that produce antibodies which specifically reacts with those TNBC antigens (might be present in other histology), and are commonly present in a significant proportion of patients, we will deduce sequence information of such reactive antibodies and their in vivo tumor-controlling abilities using appropriate patient-derived xenograft animal models. We will also quantify the relative proportions of different antibody isotypes produced the tumor-infiltrated plasma cells and outcome. Finally we will leverage towards recombinant production of such 'human' antitumor antibodies in appropriate human Ig backbone for further validation, clinical trial and optimizing strategies to increase their physiological retention.

11. DR SUNIL SHETTY, SHETTY LAB

Targeting remodelers of protein synthesis in hepatocellular carcinoma

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Protein synthesis and ribosome biogenesis are deregulated in various cancers. Numerous therapeutic strategies have been devised to kill cancer cells by inhibiting protein synthesis (translation). However, cancer cells can utilize alternative routes such as initiation with internal ribosome entry sites or upstream open reading frames to compensate for such translation inhibition. As normal cells do not rely on such alternative translation mechanisms, targeting them can be a potential therapeutic strategy against cancer. Hence, the current proposal intends to target

such alternative translation mechanisms in liver cancer cells. Hepatocellular carcinoma (HCC) is the major form of liver cancer. There are several non-essential remodelers of protein synthesis and ribosome biogenesis that are deregulated in HCC. We will investigate the importance of such factors in HCC cells and check their effect on oncogenic translation. We will use adeno-associated virus (AAV) based approaches to target such alternative translation mechanisms in mice models of HCC and see how effective they are in combating HCC development with or without combination of inhibition of oncogenic pathways such as mTOR. The overall goal of the project is to investigate the gene therapy approach to inhibit oncogenic protein synthesis and decipher its impact on HCC intervention.