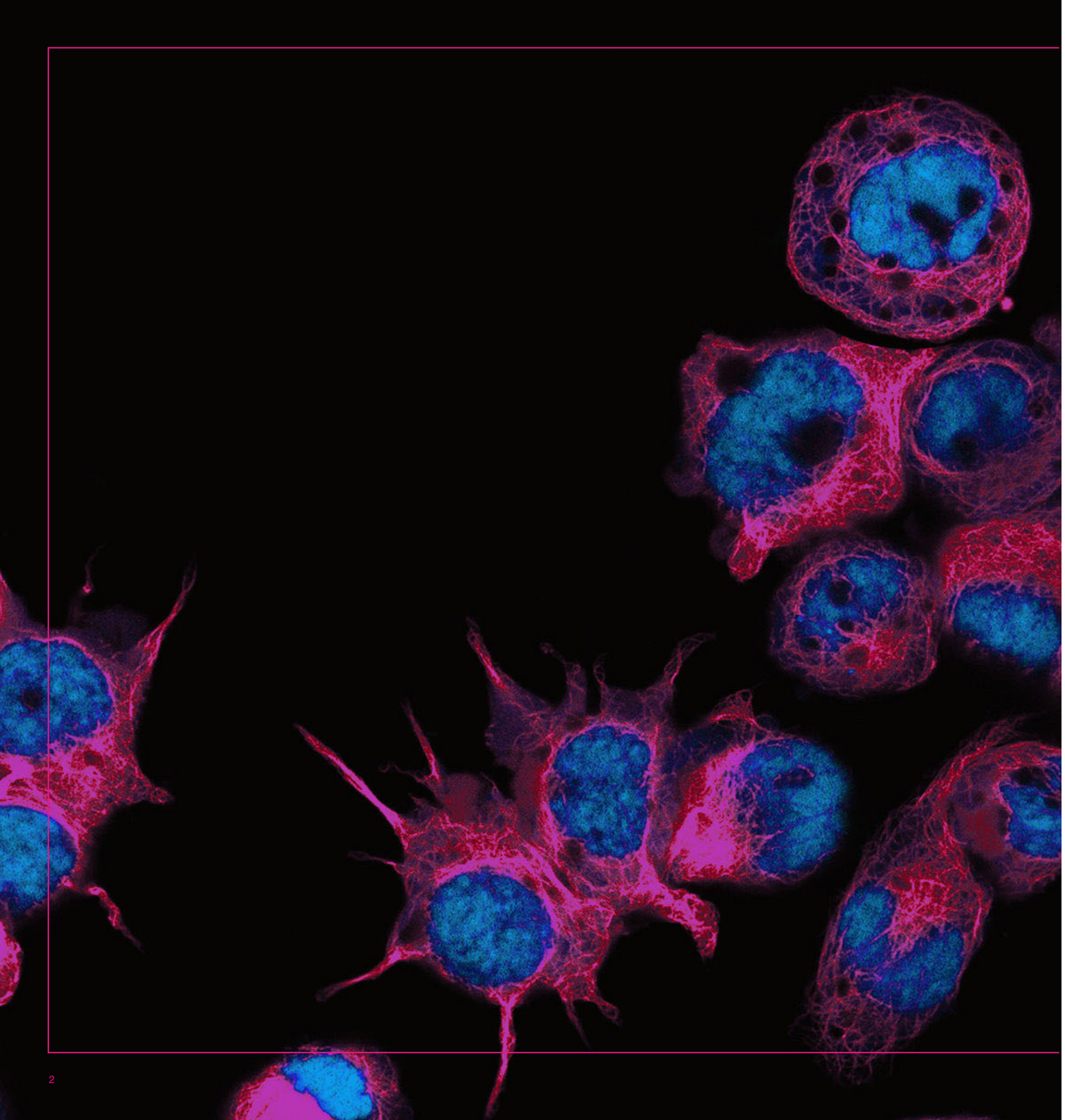
CSI | 2017 ANNUAL REPORT



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DIRECTOR'S FOREWORD

Professor Daniel Tenen
Director, Cancer Science Institute of Singapore
Distinguished Professor in Medicine, National University of Singapore

DIRECTOR'S FOREWORD

2017 marks another exciting year for the Cancer Science Institute of Singapore.

In the past year, CSI has achieved recognitions through numerous awards and honors which our scientists and students have obtained. The impact, breadth and quality of the institute's research is also evident in our list of publications in high-impact scientific journals. This annual report provides a glimpse of the innovation, development and achievements of our scientists' works.

We are a dynamic research institute encompassing basic and translational studies devoted to understanding the pathogenesis and treatment of cancer. The Institute is enhanced through the synergistic collaboration between basic scientists and clinician-scientists. Our team of dynamic scientists have established outstanding national and international reputations in their respective fields. Our research teams are committed to conduct ground-breaking research and produce novel developments in their research.

With two strong multidisciplinary programs, the Cancer Stem Cells & Biology Program and the Experimental Therapeutics Program, our research span the spectrum from laboratory based studies in experimental models to targeted therapies in humans, utilizing the expertise from both programs. Capitalizing on these programs, as well as the study and understanding of RNA biology processes under the RNA Biology Centre (RBC), we continue to focus on specific disease areas of relevance to Singapore.

2017 has seen a steady rise in the number of students enrolling in the CSI PhD Graduate Program in Cancer Biology. This year, we congratulate and celebrate with our 3rd batch of PhD graduates, who are ready to open up new horizons and contribute to the advancement in the cancer research field. We are also excited to have successfully launched our inaugural CSI RNA Biology Scholarship, focusing on RNA biology PhD projects, in the same year.

CSI will continue to strive towards our mission of leading and promoting cancer research in Singapore, and continually foster global scientific partnerships, with a vision to be the premier cancer science institute in Asia and a world leader.

02

FACTS & FIGURES

2.1
RESEARCH FRAMEWORK

DISEASE FOCI:

Aerodigestive Tract Cancers
(gastric, nasopharyngeal, HCC, lung)

Hematological Malignancies
(leukemia, lymphoma & myeloma)

CANCER BIOLOGY & RNA

EXPERIMENTAL THERAPEUTICS

DISEASE OF STRATEGIC INTEREST

Breast & Gynecologic Cancers

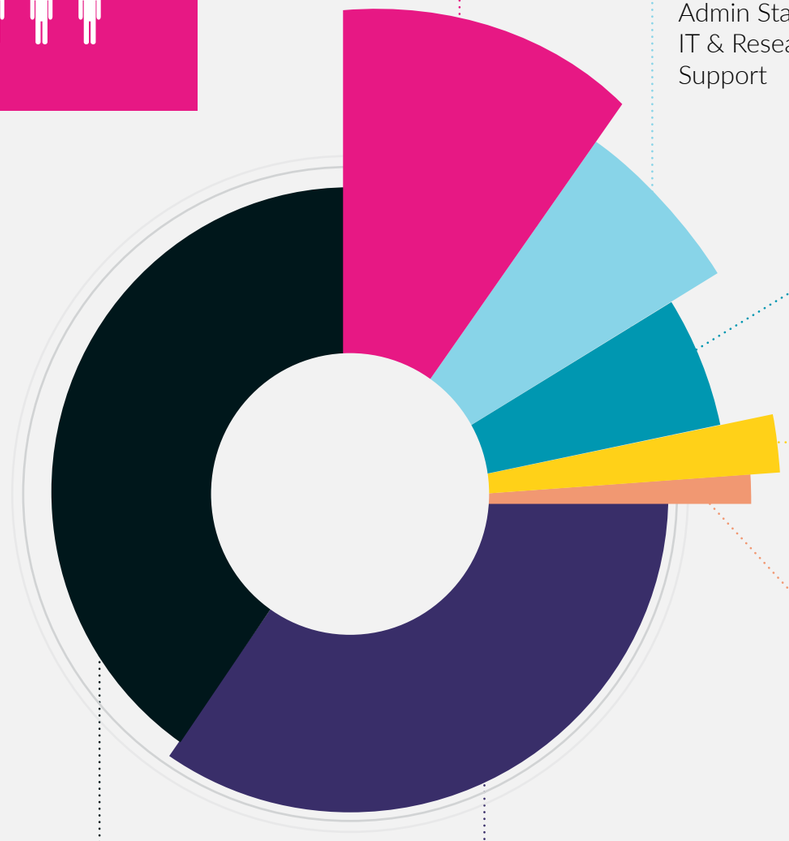
The area of expertise of the Cancer Biology and RNA Program is in gene regulation in cancer, including studies of transcription factors, perigenetics and RNAs in cancer. The projects that the group are working on include: (1) systems biology of ovarian carcinoma: design of new diagnostic and therapeutic strategies, (2) targeting transcription factors in leukemic stem cells, (3) SALL4 in stem cells, leukemia, and liver cancer, (4) gastric cancer stem cells, (5) microRNA of liver cancer stem cells, (6) cancer genome of hepatocellular carcinoma.

On the other hand, the Experimental Therapeutics Program aims to develop novel therapeutics and uncover optimal combinations of drugs for cancer treatment through better understanding of mechanisms of action and drug resistance.

2.2
STAFF STRENGTH

2017

39
FACULTY



21
Principal Investigators

20
Admin Staff, IT & Research Support

12
Principal Associates

4
Facility Heads

2
Special Fellows

78
Research Staff (Research Scientists & Research Fellows)

70
Research Associates/ Assistants & Laboratory Executives/ Technicians & Others

2.3
PUBLICATION HIGHLIGHTS

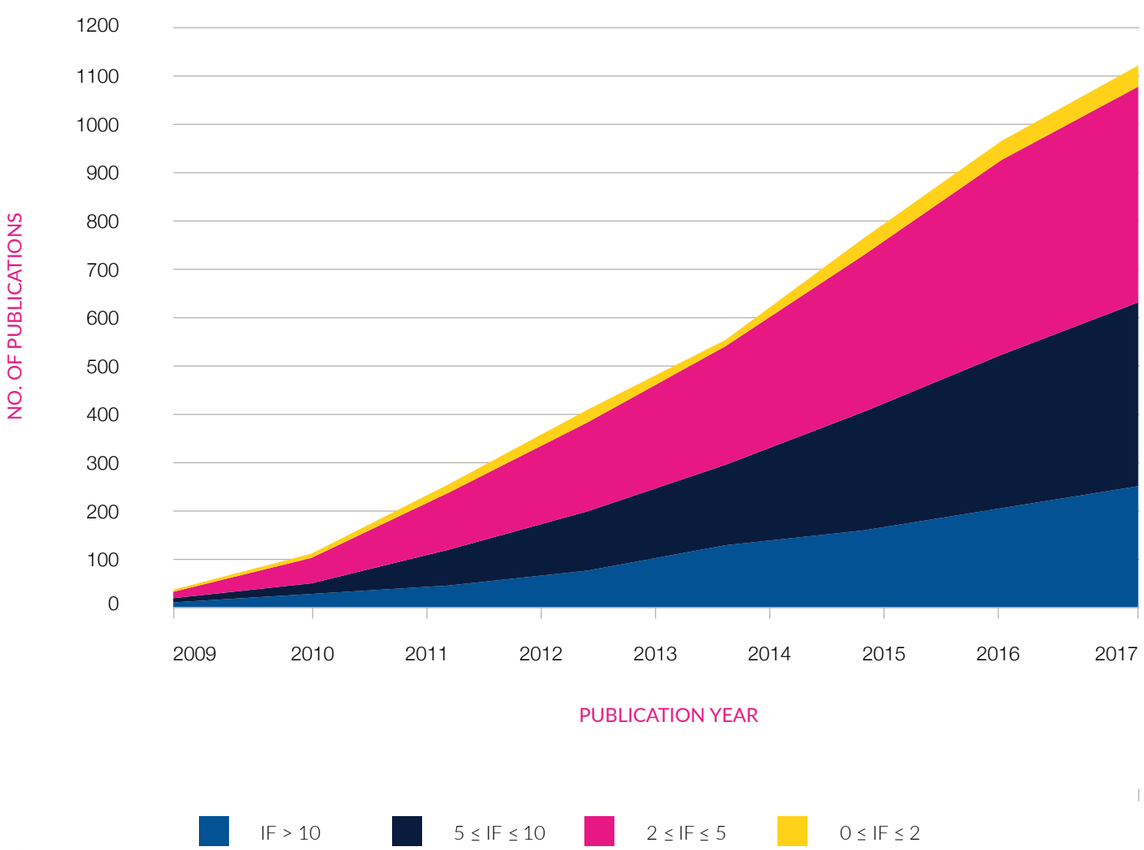
202
Publications

2
Highly Cited Papers

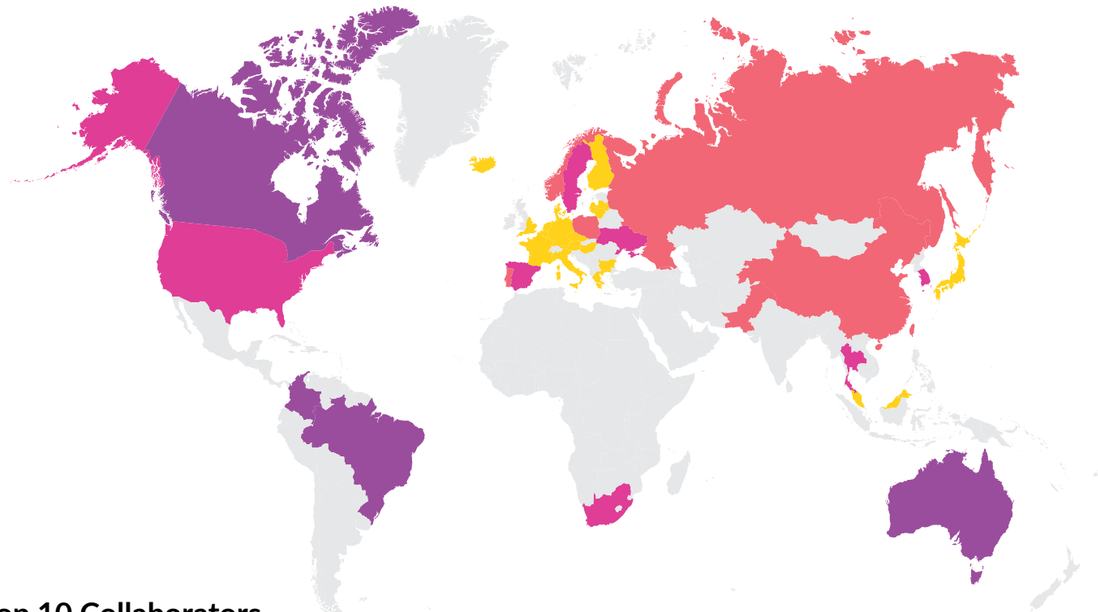
32,851
Citations Received

25
International collaborations

55
Press Releases

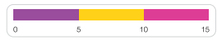


2.4
INTERNATIONAL COLLABORATION



Top 10 Collaborators

01 Singapore
02 USA
03 Japan
04 Australia
05 China
06 England
07 Germany
08 France
09 India



2.5
LOCAL COLLABORATION

01
National University of Singapore (NUS)

02
National University Health System (NUHS)

03
Agency for Science, Technology and Research (A*STAR)

04
Duke-NUS Graduate Medical School

05
Genome Institute of Singapore (GIS)

03

TOP RESEARCH STORIES

These stories highlight the highest impact research of the year in shaping the future of cancer research. Our scientists are committed to foster groundbreaking, novel research that would benefit the global and local scientific communities. The selected publications demonstrate the breadth and quality of the research being undertaken at the institute.

New Model for Gastric Carcinogenesis Studies

Research team led by Prof. Yoshiaki Ito identified gastric stem cells as eR1+ cells in the epithelium of the mouse stomach corpus (main body) and antrum (distal part).

In situ hybridization and immunofluorescence staining revealed a RUNX1 enhancer element, eR1, that marks the eR1+ cells.

In addition to be able to use eR1 to express cancerous mutations in gastric stem cells, the team has also successfully established organoid culture from these stem cells, providing a new model for stepwise gastric carcinogenesis studies.

***Gastroenterology*, January 2017**

Wanted DEAD/H or Alive: Helicases Winding Up in Cancers

A family of RNA helicases known as DEAD/H-box helicases have recently been implicated in various cancer and in the development of cancer drugs. Dr. Alan Prem Kumar and his team offered a summary of recent findings on these RNA helicases.

The group provided a comprehensive overview of the roles and involvement of Dead/H-box helicases reported in adult and childhood solid tumors, leukemia as well as cancer stem cells which have emerged as a hallmark of cancer.

A better understanding of these helicases in cancer makes them attractive drug targets and potential biomarkers.

***Journal of the National Cancer Institute*, January 2017**

Targeted Therapeutic Strategy for Acute Myeloid Leukemia (AML)

Patients with partial tandem duplication of *MLL* (*MLL*- PTD), a subtype of AML, often have a bad prognosis. *MLL*-PTD also occurs more frequently in elderly patients. Prof. Phillip Koeffler and his team provided a detailed mutational profile of *MLL*-PTD which may lead to the development of personalized therapeutic strategies.

The group found that multiple mutations co-occur with *MLL*-PTD and that they are usually acquired in a sequential manner. This study provided important insights for understanding the relative importance of different mutations to define targeted therapeutic strategy for *MLL*-PTD AML patients.

***Leukemia*, January 2017**

New Possibility for Treating Bladder Cancer

In urothelial bladder carcinoma, the most common type of bladder cancer, *KDM6A* (a H3K27 demethylase) is frequently mutated. Researchers led by Prof. Bin Tean Teh have discovered the therapeutic potential of EZH2 inhibition in the absence of KDM6A.

The group demonstrated that IGBP3, a direct KDM6A/EZH2/H3K27me3 target, was upregulated by EZH2 inhibition and resulted in antiproliferative activity in *KDM6A*-null urothelial bladder carcinoma cells.

With no targeted therapy being approved for urothelial bladder carcinoma for the past two decades, these new findings establish new possibility for its treatment.

***Science Translational Medicine*, February 2017**

The Evolution of “Preleukemia”

Prof. Phillip Koeffler imparted a fascinating report on how the term “preleukemia” has not only transformed through many years but also changed our approach and understanding towards managing it.

Preleukemia was viewed as myelodysplastic syndrome (MDS) with a tendency to progress to acute myeloid leukemia (AML). As such, individuals with germline mutations of either *RUNX1*, *CEBPA*, or *GATA2* are described as preleukemic. Previous treatment of a primary malignancy with either an alkylating drug or radiation therapy can also result in a preleukemia that almost always progresses to AML.

This comprehensive review offers better understanding of how preleukemia has evolved and concludes that it might be defined as a condition with modifying mutations in the bone marrow that either cause MDS or cause clonal hematopoietic expansion initially without disease but associated with progression to AML.

***Leukemia*, March 2017**

Insights: How Cancers Evade the Immune System

Focusing on gastric cancer, Prof. Patrick Tan and his team uncovered the relationship between somatic promoters and tumor immunity, providing new insights on how cancers can evade the immune system.

Using NanoChIp-Seq, the group highlighted the important role of somatic promoters in gastric cancer. The group identified alternative promoters in genes such as EPCAM, RASA3 and MET that are of significant clinical and translational implications in gastric tumors.

The epigenomic profiling of the promoter landscape of gastric cancer has allowed better understanding of the mechanisms of gastric cancer development and progression.

***Cancer Discovery*, June 2017**

Exosomes and Cancer

Recent studies have explored the role of nanovesicles, specifically exosomes, in providing a controllable, bioinspired system for targeted drug delivery. Exosomes could thus offer oncologists dynamic new therapeutics in the fight against cancer.

In this review, Prof. Boon Cher Goh's group evaluated the use of exosomes and their current considerable clinical potential, impact and functionalization, and probable ways to overcome clinical challenges.

The group described two exosome-based therapeutic models for future cancer treatment: the trojan horses-like formulations which insidiously deliver anti-tumor contents to target tumor cells; and therapeutic cell-free vaccines that induce the immunological rejection of escaped tumors.

***Trends in Biotechnology*, July 2017**

Better Target for Oesophageal Squamous Cell Carcinoma (OSCC) Treatment

With the known genomic landscape of OSCC, Prof. Phillip Koeffler's group catalogued super-enhancers (SEs) associated master regulators and oncogenic transcripts, leading to a better understanding of OSCC biology and the development of more innovative therapies.

Through the identification of THZ1, a potent anti-OSCC compound, the group found that THZ1-sensitive transcripts were frequently associated with SEs. This establishes the therapeutic merit of targeting SE-associated oncogenic transcription programme for OSCC treatment.

The group also identified a druggable SE-associated oncogene, PAK4, whereby KPT-9274, its small-molecule inhibitor, suppresses OSCC cell viability and induces massive apoptosis.

***Gut*, August 2017**

Super-Enhancers: The Fight against Leukemia

The oncogene TAL1 is found to be highly prevalent in patients with T-cell acute lymphoblastic leukemia (T-ALL). In their search of genes activated by TAL1, Dr. Takaomi Sanda and his team identified a super-enhancer which activates a cluster of *GTPase of Immunity-Associated protein* (*GIMAP*) genes.

The activation of the GIMAP enhancer by TAL1 in developing thymocytes contributes to T-cell leukemogenesis, leading to the development of T-ALL. This presents the possibility of targeting super-enhancers to fight leukemia.

***Leukemia*, August 2017**

New Therapeutic Strategy in Natural Killer/T-Cell Lymphoma (NKTL)

Research team led by Prof. Wee Joo Chng and A/Prof. Siok Bian Ng identified RUNX3 overexpression in NKTL with functional oncogenic properties and revealed a new therapeutic strategy by targeting the inhibition of MYC.

MYC is found to play a role in the transcriptional regulation of RUNX3 whereby treatment with a small-molecule MYC inhibitor (JQ1) causes significant downregulation of MYC and RUNX3. This has led to the reduction in cell proliferation and increased in apoptosis.

The new findings would allow the development of novel therapeutic strategies targeting the modulation of MYC expression, particularly in tumors that are difficult to treat such as NKTL.

***Leukemia*, October 2017**

Non-Editing Side of ADARs Opens Another Door to Target Cancer

Using *METTL7A* (methyltransferase like 7A), a novel tumor suppressor gene with multiple editing site at its 3' UTR, research team led by Dr. Leilei Chen and Prof. Daniel Tenen demonstrated that its expression could be repressed by ADARs beyond their RNA editing and double-strand RNA (dsRNA) binding functions.

The team has also identified a subset of genes – *CCNYL1*, *MDM2*, *TNFAIP8L1* and *RBBP9*, to be regulated by ADARs in a similar RNA editing and RNA binding-independent mechanism.

As such, the functional significance of ADARs is thought to be much more diverse and is of high biological importance.

***Nucleic Acids Research*, October 2017**

04

THE YEAR IN RESEARCH

What we have accomplished

RESEARCH GROUPS

Our community of 22 distinguished and highly talented cancer scientists work in an environment entrenched in a spirit of close collaboration and research freedom. Guided by principles of excellence, creativity, and the unique diversity of experiences, our team takes on a bold and ambitious approach in the pursuit against cancer. Read more to learn about their research and impact.

LEILEI CHEN GROUP

"We are the first group to reveal that RNA editing is dysregulated in hepatocellular carcinoma (HCC), esophageal squamous carcinoma (ESCC), and gastric cancer."

HCC, ESCC and gastric cancer are neither hypo- nor hyper-edited cancers. Instead they display a severely disrupted A-to-I RNA editing balance. The group recently revealed a "driver" RNA editing event in HCC in which increased A-to-I RNA editing activity of the antizyme inhibitor 1 (AZIN1) gene confers a gain-of-function phenotype that is manifested by augmented tumor-initiating potential and more aggressive behavior, which was also observed in ESCC.

A recoding editing of PODXL transcripts mediated by ADAR2 protein was also found to cause a "loss-of-function" phenotype, which contributes to gastric cancer progression. Overall, RNA editing is a novel mechanism in cancer, and careful examination of RNA editing targets will contribute significantly to the understanding of cancer complexity.

Moving forward, the group aims to exploit the causes and functional consequences of RNA editing dysregulation in cancer.

WEE JOO CHNG GROUP

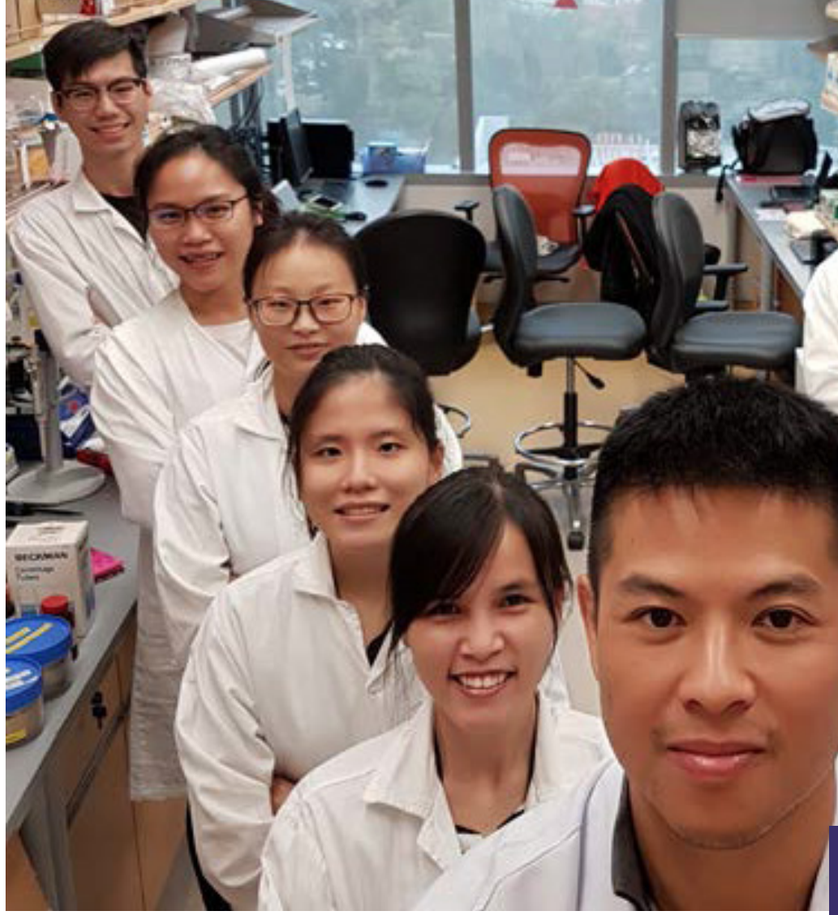
Acute Myeloid Leukemia (AML)

PRL3 is aberrantly expressed in AML and is involved in therapeutic resistance and regulation of stem cell/self renewal function in malignant cells. The group has shown that PRL3 alters expression of miRNA which also alters expression of a set of genes that maintain stem cell properties, suggesting that PRL3 over-expression may lead to acquisition of stem cell characteristics in the tumor cells. Furthermore, the group has also dissected the upstream and downstream signalling networks that regulate the expression of PRL-3 and mediate some of the critical function of PRL-3. In addition, they identified LEO1 and an important substrate of PRL-3 that mediates much of its downstream function via the beta-catenin pathway.

Natural Killer T-cells Lymphoma (NKTCL)

The group's work on miRNA profiling found a lead linking MYC activation to miRNA suppression and over-expression of a number of oncogenes in NKTCL that turns out to be good therapeutic targets. One of the most exciting molecules is EZH2. EZH2 is a histone methyltransferase that is over-expressed in a number of tumors and mutated in some lymphomas. The group has found the oncogenic function of EZH2 is independent of its enzymatic activity. They have also found that EZH2 associates with Pol II to drive active transcription of a separate set of genes that is important for its oncogenic properties. This opens up the study of EZH2 as a transcriptional regulator and the mechanism by which it leads to active transcription.

"Our PRL3 studies in AML and the study of EZH2 in NKTCL are novel and may lead to biomarkers and new therapeutic strategies that may be used clinically."



EDWARD CHOW GROUP

In collaboration with researchers at UCLA, the group is the first to demonstrate the use of nanodiamonds as a drug delivery platform.

By pairing oncogene-specific mouse models of liver cancer and human HCC PDX lines, the group has developed a clear system of studying cancer stem cells (CSCs) biology *in vivo* and *in vitro* and evaluating therapeutic strategies against CSC-driven cancers in both the context of specifically controlled genomic alterations as well as the complex genomic background of human hepatocellular carcinoma (HCC).

The group has also made great strides in the use of their Phenotypic Personalized Medicine (PPM) drug combination optimization platform to identify optimized drug combinations against Bortezomib-resistant Multiple Myeloma as well as uncovering the underlying molecular mechanisms behind these combinations.

"A major objective of our lab is to develop a comprehensive understanding of the mechanisms by which initiating oncogenes promote tumorigenesis."

PIETER EICHHORN GROUP

The group has identified 3 deubiquitinating enzymes, USP28, USP10 and USP26 in the MAPK, PI3K and TGF-β pathways, respectively. They have shown that USP28 directly targets BRAF for degradation and is deleted in 10% of melanoma patients and the loss of this enzyme confers resistance to vemurafenib through the stabilization of BRAF 600E.

A genome screen with the DUB library revealed USP10 as a novel regulator of PTEN, which regulates its localization to plasma membrane. It is proposed that USP10 should be considered as a novel biomarker for resistance to PI3K inhibitors in breast cancer.

In addition, the group also demonstrated USP26 as a novel component of the TGFB negative feedback loop whereby USP26 deubiquitinates SMAD7 resulting in the stabilization of SMAD7.

"Our work focuses primarily on the role of deubiquitinating enzymes in cancer relevant pathways & mechanisms of resistance to targeted therapeutics in breast cancer."

"Our findings will contribute significantly to the understanding of key mechanisms of autoimmunity as well as studies of liver cancer development."

XIN-YUAN FU GROUP

Using several autoimmune animal models, the group has demonstrated that it was neither Th1 nor Th17, but a novel subset of GM-CSF/IL-3 producing cells, that act as the major driver for antigen-specific autoimmunity. They have also demonstrated that STAT5 regulates GM-CSF/IL-3 production, which is essential for inflammatory autoimmunity in animal models representing multiple sclerosis (MS) and rheumatoid arthritis (RA) – this was further validated by clinical data from human patients with MS or RA.

Based on these findings, the group has filed a comprehensive patent on Th-GM for autoimmunity which, along with other intellectual properties, has resulted in the proposal of the setting up of an NUS-spin-off biotech company, with clinical trials planned and to be conducted in USA.

The group has also been working on establishing liver development and cancer models using their newly generated FoxA2 knock in and KO mice, SMAD4 KO as well as liver specific STAT3 KO mice. In particular, FoxA2-GFP knock in mice have been generated and initial characterization revealed that expressed FoxA2-EGFP can serve as a marker for endoderm and liver/ pancreas development *in vivo*.

MELISSA JANE FULLWOOD GROUP

The group's major accomplishments have been to work on understanding 3D genome organization and RNA biology in the context of haematopoiesis and acute myeloid leukemia. Their competitive advantages include strong technical skills in the niche of 3-dimensional genome organization methods and collaborations with clinicians such as Prof. Wee Joo Chng and Prof. Wilson Wang who have generously shared clinical samples, allowing them to understand 3D genome organization and RNA biology in clinical samples.

In addition, taking advantage of the team's deep expertise in 3D genome organization, they have collaborated with Professor Patrick Tan and Professor Vinay Tergaonkar, leading to two co-authorship manuscripts demonstrating the importance of 3D genome organization in cancer, in Nature Communications (Ooi et al.) and Cancer Discovery (Akincilar et al.) respectively.

"We are interested to understand the effects of aberrant gene transcription in cancer and the relationship between RNA and 3D genome organization in cancer. Our goal is to translate our findings into better biomarkers and therapies for the clinic."

BOON CHER GOH GROUP

The group has established several preclinical and translational clinical projects in search of novel drugs for the treatment of cancer. In an exosome study of patients with lung cancer to identify novel protein targets, the group has found that FAM3C, a potential lung cancer biomarker, affects lung cancer cells proliferation, metastasis and drug resistance.

"Our group aims to conduct cutting edge research into development of novel therapeutics for cancer treatment."

The group is also studying a commonly occurring cMET mutation, albeit a germ line mutation, but which occurs in 20% of Chinese/East Asian population and rarely in Caucasians. This study elucidates the role of MET-N375S as an activating mutation that strongly enhance malignant transformation and metastatic potential in lung squamous cell carcinoma (SCC). Mechanistically, the dysregulated interaction with HER2 explains the aggressiveness of the tumours expressing the c-Met mutant. Clinically, MET-N375S could be utilized as a potential predictive biomarker for patients with advanced SCC.

A Phase I/II clinical trial of anti-angiogenic agents to modulate the tumour microenvironment prior to chemotherapy has been initiated to investigate the effects of an anti-VEGF antibody, which is leading to another clinical trial to evaluate the addition of an anti-angiogenic agent to standard chemotherapy for NPC.

RUBY YUN-JU HUANG GROUP

The group has established an 86-gene EMT scoring assay in EOC which subsequently resulted in the conception of the Epithelial-Mesenchymal Transition in Oncology (EpiMeT) program. This provides technological solutions for the void of any quantitative diagnostic test for EMT that can be applied in clinical samples.

Following the initiation of a pilot project with NanoString to analyse the EMT score in archival human ovarian cancer samples, the nCounter Pan-cancer Progression has been launched by Nanostring. A panel of 269 EMT genes as well as several of the group's Generic EMT Signature genes were selected and validated for use.

The team has also established a platform to screen for small molecular weight compounds that might exert a reversal of EMT effect on EOC cells with the Mes molecular subtype, which results from the downregulation of an epithelial transcriptional gatekeeper GRHL2 and can be targeted by a receptor tyrosine kinase AXL.

"Our group aims to become leader in transforming care for epithelial ovarian cancer (EOC) patient towards precision medicine in the Asia-Pacific region."

YOSHIAKI ITO GROUP

Despite multiple reports of stomach stem cell probes, no other group in the world have identified stomach stem cells in all predicted locations. The group's collaboration with Dr. Motomi Osato's group has achieved this by using Runx1 enhancer element, eR1, which drives the expression of Runx1 in hematopoietic stem cells.

Stem cells in isthmus. This is the predicted location of stem cells in corpus (main body) by isotope labeling. The group identified rapidly proliferating stem cells in this location.

Stem cell activity in chief cells. A subfraction of fully differentiated chief cells at the base is also labeled by eR1. The group has evidence that these cells indeed proliferate upon oncogene stimulation.

Stem cells in antrum isthmus. This region was predicted to have stem cells. eR1 also targets the antral isthmus stem cells. Lgr5+ cells are located at the base of antrum. Therefore at least two types of stem cell activities are detected in antrum.

Generation of organoids. Organoids are generated from stem cells. The team is able to generate organoids from eR1+ stem cells. Organoids are useful for a wide range of research purposes

"For the first time in the history of gastric cancer, we achieved the molecular identification of stomach stem cells at all predicted positions."

SUDHAKAR JHA GROUP

Following the discovery of a novel E3 ligase, EDD1, through which E6 destabilizes TIP60, the group has established TIP60 as a potent inhibitor of a viral oncogene-induced tumor formation. They have identified the previously unknown role of TIP60 in repressing the catalytic and rate limiting subunit of the human telomerase complex, hTERT, a key driver for immortalization.

The group has shown significant downregulation of TIP60 in breast cancer patients with poor overall survival and disease-free survival prognoses. This suggests levels of TIP60 as a prognostic marker of breast cancer and the promising strategy to treat cancers through the stabilization of TIP60.

In addition, TIP60 is found to be degraded by adenovirus oncoproteins EIB55K and E4orf6 via a proteasome-mediated pathway - an important process for efficient viral early gene transcription and for changes in expression of cellular genes.

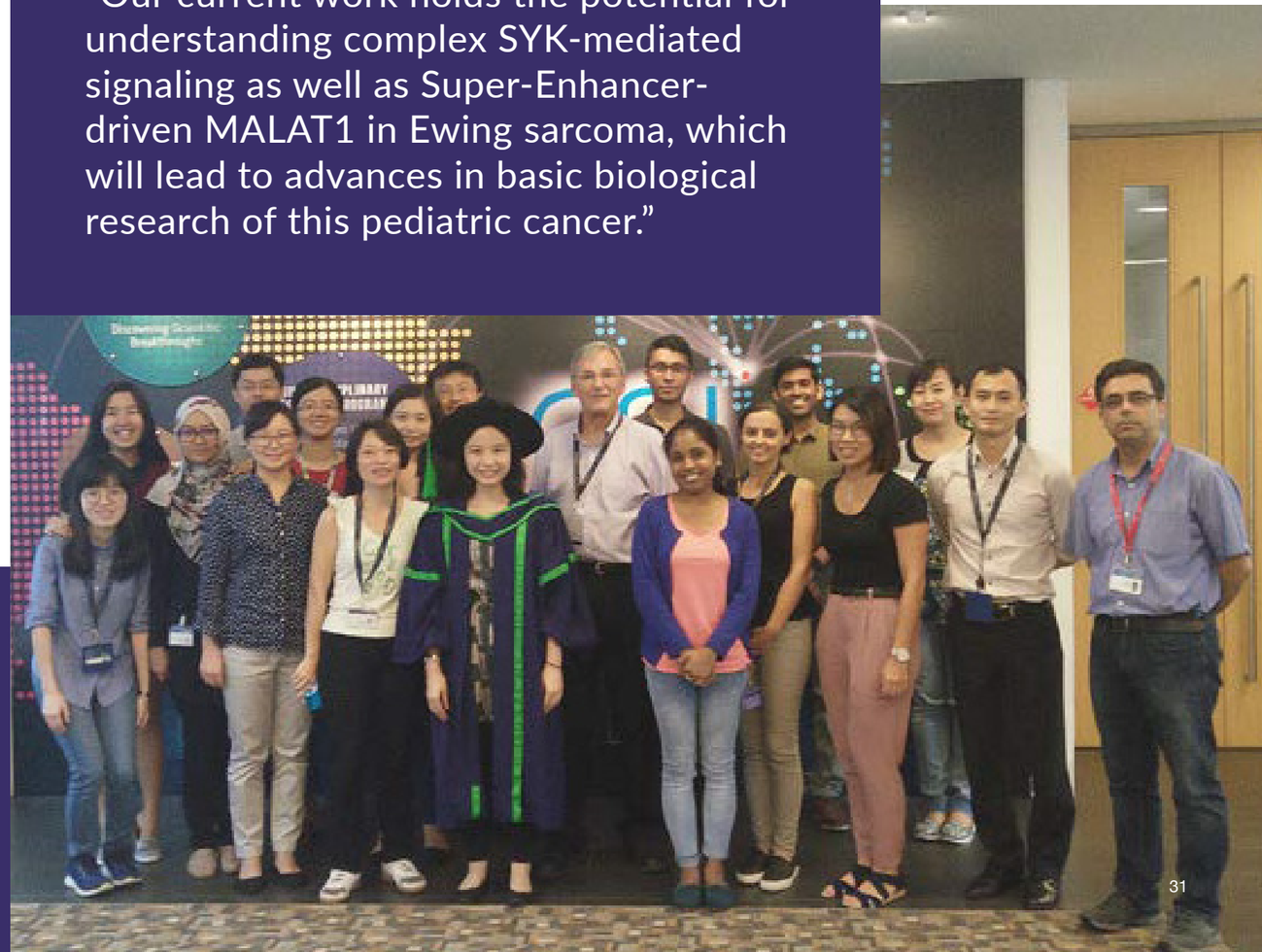
"Our discoveries of the mechanism by which HPV E6 destabilizes TIP60 and the biological significance of TIP60's downregulation are of high relevance in the prevention of cancer."

H. PHILLIP KOEFFLER GROUP

The group has demonstrated that the inhibition of CRM1 promotes cytotoxicity in Ewing sarcoma cells by repressing EWS-FLI1-dependent IGF-1 signaling. Treatment of EWS cells with a combination of KPT-330 and the IGF-1R inhibitor, linsitinib, synergistically decreased cell proliferation both *in vitro* and *in vivo*.

In addition, the group identified spleen tyrosine kinase (SYK) as a candidate actionable target. Transcriptome analysis identified that a long non-coding RNA, metastasis associated lung adenocarcinoma transcript 1 (MALAT1), was dependent on SYK-mediated signaling. Moreover, c-MYC, a SYK up-regulated gene, bound to the promoter region of MALAT1 and transcriptional activated MALAT1, which further promoted the proliferation of EWS cells. The findings identify a novel signaling involving SYK/c-MYC/MALAT1 as a promising therapeutic target for the treatment of EWS.

"Our current work holds the potential for understanding complex SYK-mediated signaling as well as Super-Enhancer-driven MALAT1 in Ewing sarcoma, which will lead to advances in basic biological research of this pediatric cancer."



"We are the first to conduct the study directing NK cell therapy using therapeutic monoclonal antibodies in solid tumors, which is of great significance in the search of cell-based immunotherapy against breast cancer."

SOO CHIN LEE GROUP

In their study using the neoadjuvant breast cancer model, the addition of sunitinib to chemotherapy was found to have normalized tumor vasculature and improved tumor blood flow, providing proof-of-concept of this novel therapeutic strategy.

The group has also initiated a phase Ib/II study to evaluate the use of expanded, activated autologous natural killer cells to enhance the antibody-directed cell cytotoxicity (ADCC) of trastuzumab, which is a therapeutic monoclonal antibody against HER2. The study in metastatic HER2-positive breast cancer has yield favorable preliminary data.

Two new studies evaluating novel agents in the neoadjuvant setting against breast cancer have also been initiated – one using ASLAN001, a novel tyrosine kinase inhibitor with paclitaxel/ carboplatin and the other using lenvatinib, a RET inhibitor with letrozole.

PETER LOBIE GROUP

TFF3: In a collaborative effort with Cambridge University and The University of Bangalore, the group has developed lead candidate small molecule inhibitors of trefoil factor-3 (TFF3) which show marked specificity for TFF3-positive carcinoma cells. The compounds are predicted to bind specifically at the Cys57-Cys57 bond interface of the TFF3 dimer.

Artemin: The group was granted the European patent for Artemin as a target in oncology and has been putting in effort to obtain commercial funding to develop antibody-based inhibitors to Artemin.

hGH: The group also discovered that autocrine hGH correlates strongly with survival outcome, functioning of the TFF3 and BAD phosphorylation inhibitors.

"The research focus of our group remains the characterization of the role of a number of secreted therapeutic targets, and development of inhibitors to such, for the treatment of mammary and other carcinoma."

TAKAOMI SANDA GROUP

The group has identified a novel enhancer controlling the GIMAP genes in T-cell acute lymphoblastic leukemia (T-ALL). These genes are expressed in hematopoietic stem cells and mature T-cells, but are downregulated during the immature stage of thymocytes. Their findings demonstrated that aberrant activation of the GIMAP enhancer contributes to T-cell leukemogenesis.

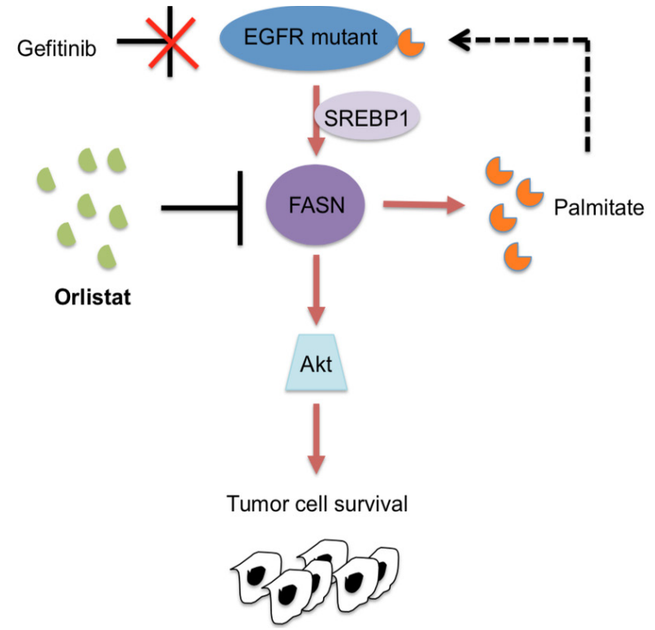
The group has also identified ARID5B as a novel member of the TAL1-induced core regulatory in T-ALL. The forced expression of this gene in immature thymocytes has resulted in thymus retention, radio-resistance and tumor formation. This is the first study showing oncogenic roles of ARID5B in cancer.

"We identified 2 new cancer genes attributed to T-cell leukemogenesis, resulting in adult T-cell acute lymphoblastic leukemia (T-ALL). This has then led to the discovery of novel therapeutic targets based on enhancer profiling."

ROSS SOO GROUP

The group has shown that the persistent signaling by mutated EGFR in TKI resistant tumor cells relies on EGFR palmitoylation, and can be targeted by Orlistat, an FDA approved anti-obesity drug. The inhibition of FASN induces EGFR ubiquitination and abrogates EGFR mutant signaling, triggers cell death, and reduces tumor growths both in culture systems and in vivo. The data provide strong evidence on the functional interrelationship between mutated EGFR and FASN and indicate the fatty acid metabolism pathway as a candidate target for TKI-resistant NSCLC treatment.

Besides, in understanding the significance of immune checkpoint proteins in EGFR-mutant NSCLC, the group has initiated the first study to characterize the expression of PD-L1 in both tumor and immune cells as well as the expression of CTLA-4 and TIM-3 in 90 patients with NSCLC harboring sensitising EGFR mutations. Their findings support the ongoing development of CTLA-4 and PD1/PD-L1 inhibitors in this patient population.



In EGFR mutated NSCLC with acquired TKI resistance, FASN mediates EGFR palmitoylation and is crucial in supporting tumor growth. With limited effective therapeutic options, these pre-clinical data show that FASN is a candidate target for acquired TKI resistant EGFR mutant NSCLC.

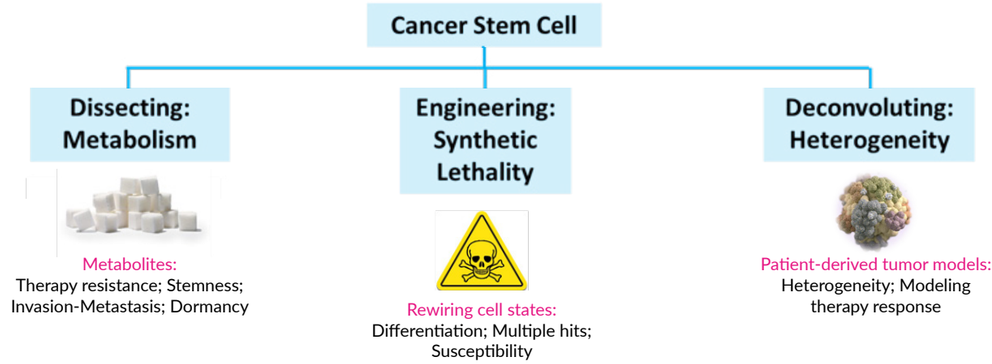
"We have uncovered a novel oncogenic signaling pathway exclusively in mutated epidermal growth factor receptor (EGFR) non-small cell lung cancer (NSCLC) with acquired tyrosine kinase inhibitor (TKI)-resistance."

TOSHIO SUDA GROUP

The group has made significant progress in their continuous study on HSCs and niche cells, particularly in stem cell metabolisms and signaling. They found that the presence of a rapidly responding subgroup of HSCs during stress hematopoiesis which enables on-demand production of Mk/platelet lineages.

In addition, in their study to establish a new disease entity caused by a novel mutation detected in a family of familial platelet disorder (FPD) associated with hematological malignancy, the group discovered a novel mutation in TUBB1, a blood cell-specific microtubule component abundant especially in Mks.

"Our work revealed a close relation between megakaryocytes (Mks) and hematopoietic stem cells (HSCs) and established the concept of the Mk niche that will provide us with further insights into manipulating HSCs for efficient platelet production for the treatment of thrombocytopenia."



WAI LEONG TAM GROUP

One of the grand challenges for cancer treatment is that current therapeutic strategies to treat tumor are ineffective due to therapy resistance and tumor recurrence that are caused by cancer stem cells (CSCs). The lab addresses this important challenge by integrating the fields of cancer, CSC, targeted therapy, and disease modeling, to translate biological findings about CSCs into innovative, targeted cancer therapies.

Advanced multidisciplinary approaches are employed to uncover and interrogate emerging paradigms in CSC biology. This will reveal facets of CSCs that are amendable to rationally designed targeted therapies. High-throughput chemical-genetic screening is further utilized to discover potentially useful agents and gene modulations that can eradicate CSCs. In the long-term, the development of these agents will provide novel therapeutic modalities which can be employed as neoadjuvants for cancer treatment.

Research Themes:

1. Metabolism: What are the metabolites produced and utilized by CSCs? Why are they uniquely important? How do we exploit the metabolic liabilities of CSCs as therapeutic targets?

2. Synthetic lethality: How do we engineer vulnerabilities into CSCs that will cause them to gain susceptibility to therapy? Can we rewire stemness and differentiation programs in cancer cells?

3. Heterogeneity: How do we build clinically relevant models for understanding tumor heterogeneity and better model their response to therapy? How does tumor heterogeneity influence drug response and clinical outcomes?

"We have developed the RAD51 nuclear/cytoplasmic ratio assay which could potentially predict outcomes in ovarian cancer patients following platinum-based chemotherapy."

DAVID TAN GROUP

The group has completed whole genome sequencing of ovarian cancer patient-derived xenografts (PDX) and identified several single nucleotide variants (SNV) in homologous recombination and other DNA repair genes. This will allow further investigation on the correlation between genomic aberrations with the response to PARP inhibitors and platinum chemotherapy.

A preliminary analysis of the RAD51 nuclear/cytoplasmic ratio assay on 30 advanced stage ovarian cancers demonstrated poorer progression-free survival (PFS) outcomes in tumors with high levels of cytoplasmic RAD51 expression. A collaborative study with Prof. Robert Brown at Imperial College revealed the possibility of using the assay for platinum sensitivity.

PATRICK TAN GROUP

In establishing platforms to systematically profile primary tumors and cell lines at multiple genomic levels and to use genomic analysis tools to classify human cancers into more homogeneous subgroups unified by common pathway dysregulation, the group has reported patterns of genetic aberrations in Asian cancers, including RNA-editing processes and super-enhancer landscapes in gastric cancer.

The findings of the RNA-editing project implicates ADAR1 as a potential therapeutic target in gastric cancer. On the other hand, the super-enhancer study identifies, for the first time, genetic alterations associated with non-coding genomic regions in gastric cancer that may represent novel biomarkers.

"Our research group has developed a deep and comprehensive genomic phenotyping program interrogating cancers relevant to Asia and is one of the leaders in applying next-generation sequencing to Asian cancer cohorts."

“Our study has tremendous potential to identify novel oncogenes and tumor suppressors based on their ceRNA crosstalk, which may represent attractive candidates for diagnostic or therapeutic applications of relevance to multiple cancers.”

YVONNE TAY GROUP

While miRNA studies have largely focused on the effect of individual miRNAs on target transcripts, the group has shown that RNA transcripts can co-regulate each other by competing for shared miRNAs, acting as competing endogenous RNAs (ceRNAs) and forming a novel post-transcriptional regulatory layer.

The deconvolution of these post-transcriptional layers of endogenous competitive crosstalk will have wide-ranging implications for the understanding of multiple basic biological systems & pathophysiological conditions including various cancers.

BIN TEAN TEH GROUP

The group is the first to characterize the mutational landscape of several Asian cancers that are relatively uncommon in the West, including gastric cancer, biliary tract cancer, NK/T cell lymphoma, urothelial cancer and phylloides tumors.

They reported frequent RARA point mutations in solid tumors, i.e. in breast fibroepithelial tumors. These point mutations are located in the ligand-binding domain and display altered sensitivities to retinoic acid-mediated transcriptional activation, thus standing out as an attractive target for therapeutics development.

“Our research on fibroepithelial tumors of the breast will pursue both basic & translational science, with the goal of developing effective therapeutics for better health outcomes & eliminating the need for breast surgery which will reduce aesthetic complications & surgical risk.”

DANIEL G. TENEN GROUP

"Our lab is the first to describe mutations and dysregulation of C/EBPα in AML and lung cancer, and these have been used as part of the recent classification schemes in AML."

The role of Tip60 in hematopoiesis

The group reported that Tip60 (Tat Interacting Protein, 60kD) regulates the function of Myc genes for critical biological processes in hematopoietic stem cells (HSCs). This lays the groundwork in the discovery of novel mechanisms underlying the pathogenesis of bone marrow failure or myelodysplastic syndrome, which will eventually leads to development of effective treatments.

The role of Sharp1 in MLL-AF6 AML

By performing gene profile analysis of a large cohort of adult AML patients, the group found SHARP1, a basic helix-loop-helix transcriptional factor that is exclusively upregulated in MLL-AF6 AML and that it is dispensable for normal hematopoiesis. This could serve as a platform for development of novel drug compounds for the treatment of MLL-AF6-positive AMLs.

Reactivation of C/EBPα in AML by targeting acetylation

GCN5-mediated acetylation was found to be the negative regulatory mechanism of C/EBPα transcriptional activity. The group has also demonstrated enrichment of acetylated C/EBPα in human myeloid cell lines and primary AML samples. With that, Prof Tenen's group has established collaboration with GSK to identify novel selective inhibitors of GCN5 as well as to find novel anti-cancer drugs to treat AML and possibly other cancners.

RNA in AML and cancer: methylation and editing

In collaboration with Dr. Polly Chen, the group has detected a marked dysregulation of RNA editing enzymes in two AML subtypes. Significant findings have also been made on the role of RNA in controlling DNA methylation. Active transcription and RNA can bind to and inhibit the ability of DNA methyltransferase I to methylate DNA. These findings demonstrate that RNA/transcription "protects" DNA from methylation, and furthermore RNAs and transcription can be used to induce gene-selective demethylation.

Unravelling Znf143 function

Based on their analysis that conditional knock-out of ZNF143, a zinc-finger transcription factor, in hematopoietic cells causes embryonic lethal phenotype, Prof Tenen's group is the first to generate ZNF143 conditional ko mice to analyze their phenotype. This would eventually uncover the mechanism of how a chromosome structure protein regulates hematopoietic development by affecting global chromosome structure.

Design and synthesis of small molecule C/EBPα inducers

The group has reported that quinazolinones restore C/EBPα expression and/or activity which led to myeloid differentiation of leukemic cells. It was identified that 2-[(E)-2-(3,4-dihydroxyphenyl)vinyl]-3-(2-methoxyphenyl)-4(3H)-quinazolinone (ICCB-280) as a potent inducer of C/EBPα and myeloid differentiation. This would lead to the development of novel therapeutics in acute myeloid leukemia treatment.

CORE FACILITIES

Supports the research groups and operations in CSI, NUS & the wider scientific community in Singapore.

DRUG ANALYSIS AND PHARMACOKINETICS CORE (DAPC)

About the facility

Jointly launched by CSI and National University Cancer Institute of Singapore (NCIS), DAPC aims to provide a state-of-the-art platform for teaching and research communities on pharmacokinetics and drug analysis.

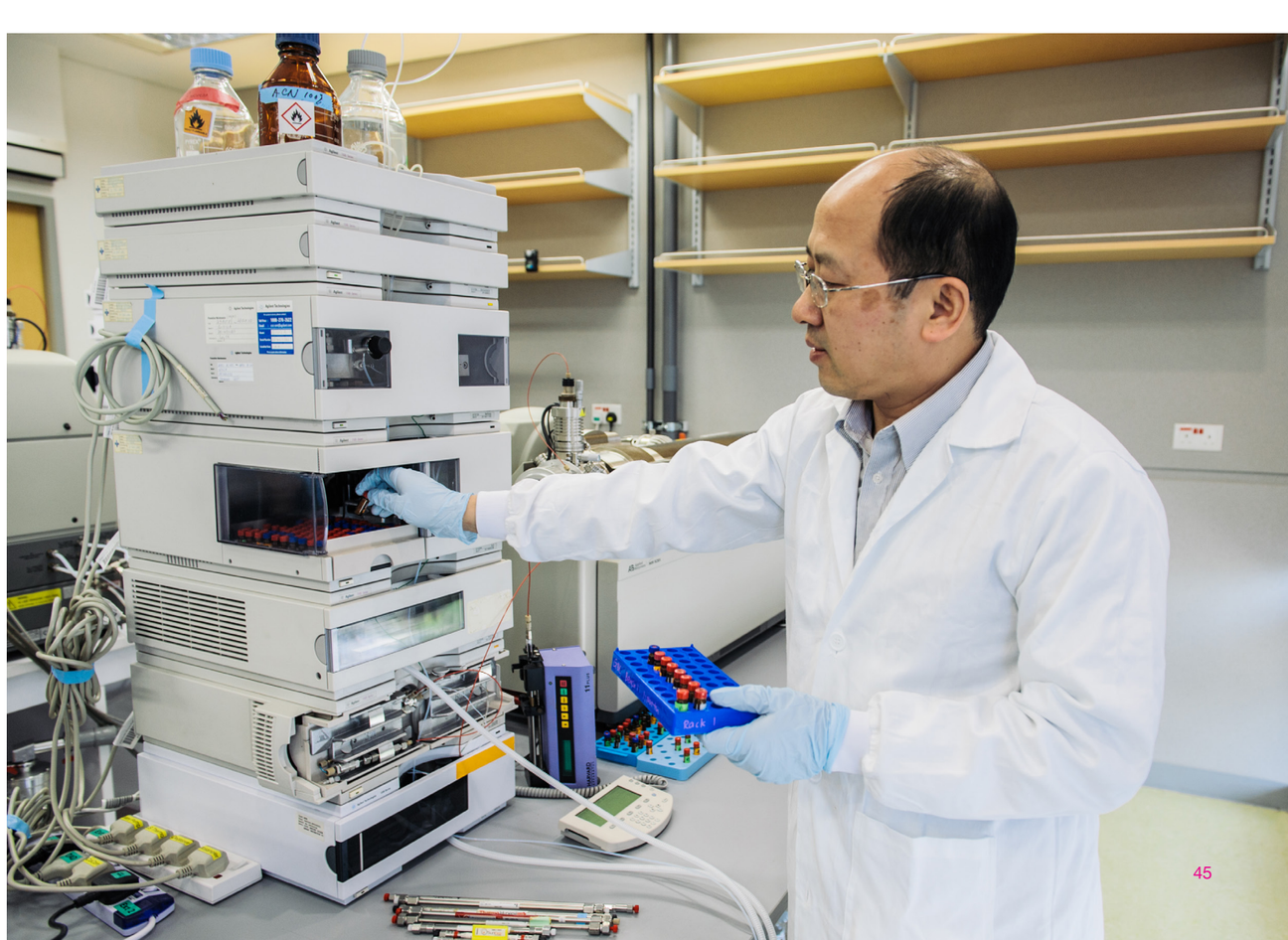
The facility is currently equipped with API 3200 LC-MS/MS, API 4000 LC-MS/MS and an Agilent HPLC-UV/FL system coupled with 1200 fraction collector.

Facility Head
Prof Boon Cher GOH

The facility has the capacity to conduct preclinical and clinical pharmacokinetic studies of current anticancer drugs or novel drug candidates, to assist therapeutic drug monitoring and to initiate drug-drug interaction studies.

Good collaboration has been established with renowned researchers in local and international institutions.

DAPC has also offered training opportunities to NUS students to do their final year projects.



TRANSGENIC AND GENE TARGETING FACILITY

About the facility

The facility provides service and collaborative support to generate genetically engineered animal models for basic and translational life science research.

The facility is equipped with a Leica AM6000 micromanipulator, Eppendorf FemtoJet micro-injector, micro-pipette fabrication devices and tissue culture system.

Facility Head

Dr. Md. Zakir HOSSAIN

The facility has successfully completed various projects:

1. CRISPR/Cas mediated gene targeting

Founder mice for 10 independent lines were generated using CRISPR/Cas9 pathway.

2. Embryonic stem (ES) cell mediated gene targeting

Chimera mice were generated from ES clones for 5 independent lines.

3. Pronuclear DNA micro-injection

Founder mice for 5 independent lines were generated using conventional pronuclear DNA injection.

4. Germ-line rescue and rederivation of mouse model

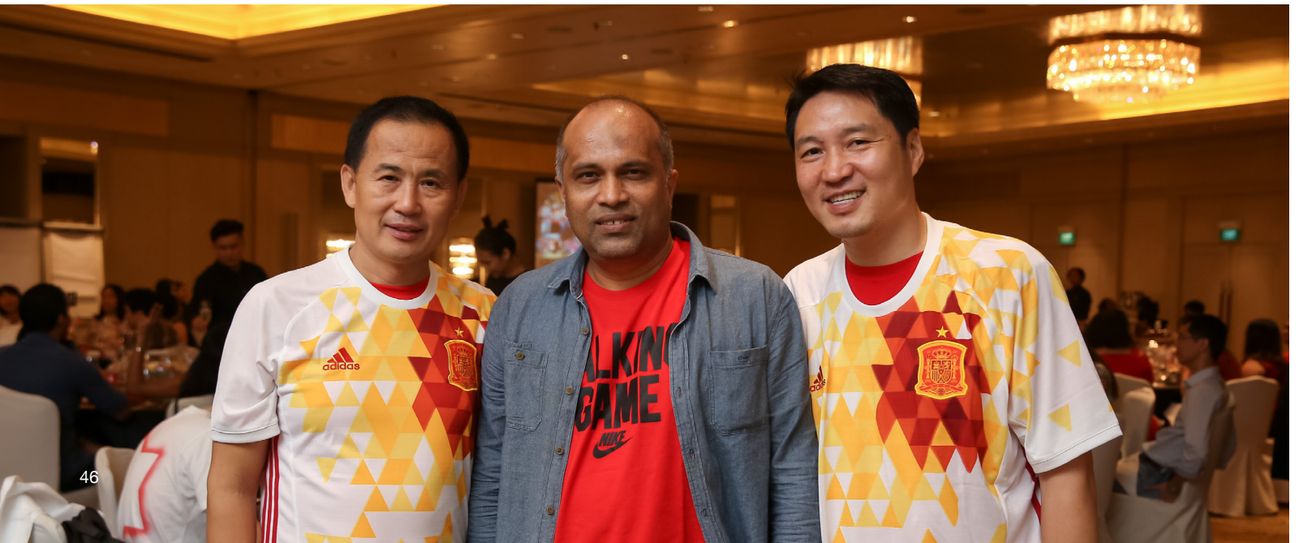
A total of 5 mouse lines were rederived from cryo-preserved sperm and sperm.

5. Cryo-preservation of mouse line

A total of 42 mouse lines were cryo-preserved.

6. Establishment of cutting edge genetic technologies

The facility has adopted rapid and low cost genotyping approaches using T7E1, Surveyor and PAGE assay for the detection of CRISPR/Cas mediated founder mice with high fidelity.



FLUORESCENCE ACTIVATED CELL SORTING (FACS) FACILITY

About the facility

The facility provides cell sorting service for CSI and non-CSI researchers. The facility also organizes seminars, workshops and hands-on sessions for user training and provides technical advices to users.

The facility currently houses FACS Aria, FACS Aria II and LSRII analyzer

Facility Head

Dr. Motomi OSATO

The facility serves a total of 31 laboratories within CSI and 42 non-CSI users.

With the RNA Biology Centre set up in CSI, the facility has begun to provide PrimeFlow RNA assay, which allows flow-based RNA in situ hybridization with single cell resolution.

A total of 23 papers were published and 3 grants were awarded.

LEUKEMIA CELL BANK

About the facility

The facility houses childhood and adult leukemia samples characterized based on leukemia subtypes and biological characteristics including standard morphology, immunophenotyping, cytogenetics and molecular studies.

The facility also stores some samples of other hematological malignancies such as lymphoma and solid tumors are also stored here.

Facility Head
Pediatric Hematology & Oncology
A/Prof Allen YEOH
Adult Hematology & Oncology
Prof. Wee Joo CHNG

The facility has forged strong collaborations with local and overseas academic/health institutions:

- National University Cancer Institute, Singapore
- National University of Singapore
- National University Hospital
- St Jude Children's Research Hospital
- Rigshospitalet, Denmark

Figure 1. An overview on the number of adult haematological malignancies registered at leukaemia tissue bank.

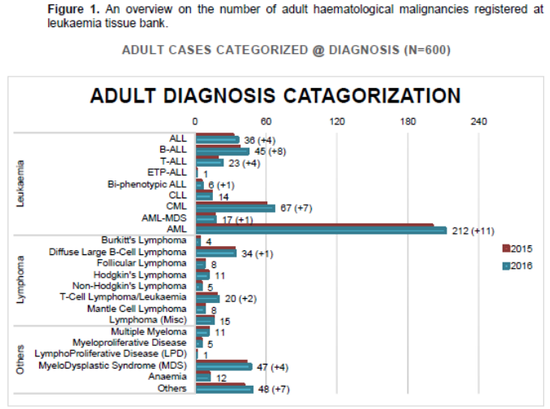
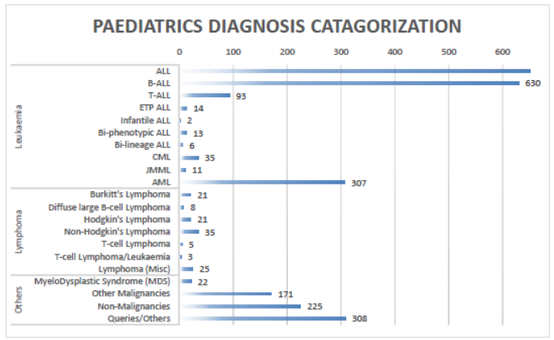


Figure 3. An overview on the number of paediatric haematological malignancies registered at leukaemia tissue bank.



XENOGRAFT CANCER MODELS FACILITY

About the facility

The facility maintains strains of immunocompromised mice for xenograft experiments and creates libraries of patient-derived tumor xenografts that represent clinical heterogeneity.

The facility also provides technical assistance for researchers with their mouse experiments, and perform optional services such as engrafting cell/tissue.

Facility Head
Dr. Shing Leng CHAN

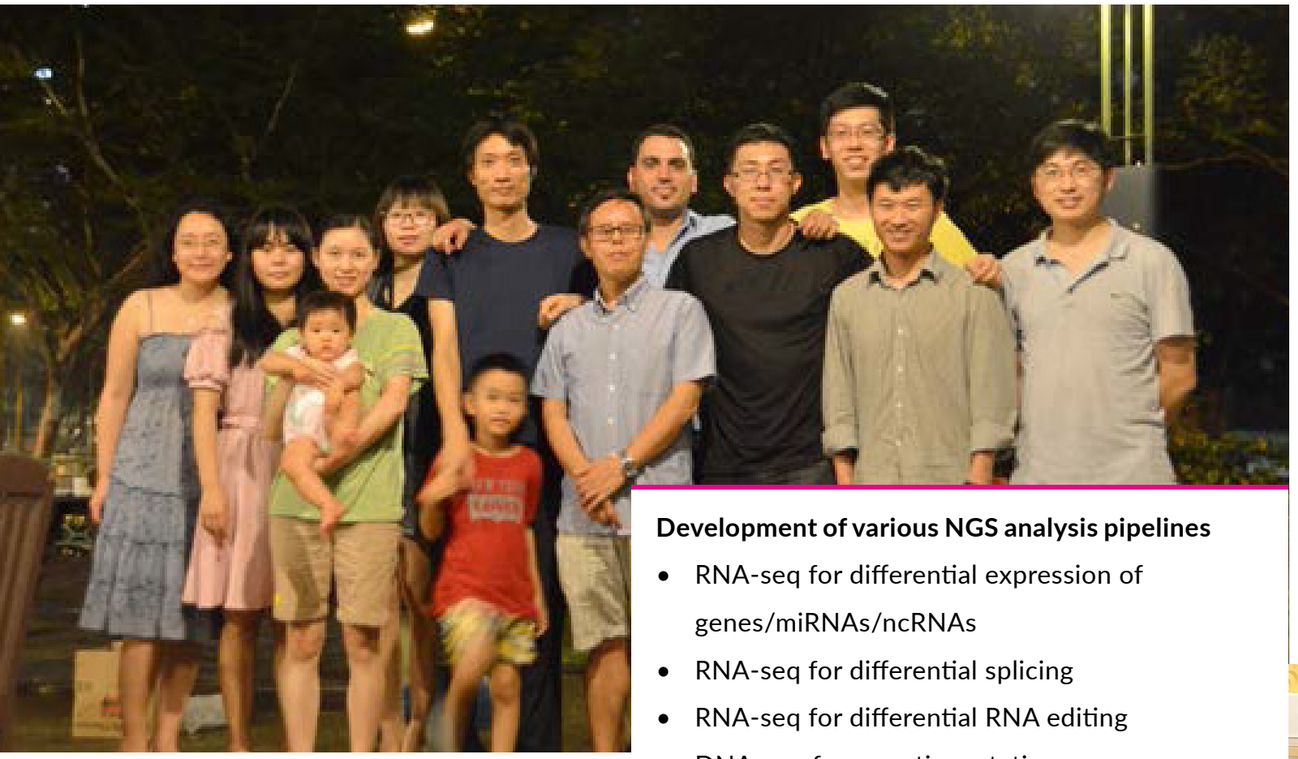
The facility has established various xenograft models:

- 19 lines of intestinal gastric cancer
- 8 lines of diffuse gastric cancer PDX models (subcutaneous and ascites)
- 2 lines of drug resistant model (GAGA3-R and GAGA6-R)

The facility has also successfully derived cell lines from GAGA1, GAGA3, GAGA6, and GC21 xenografts for in *vitro* studies.

An industrial collaboration has been established with Bayer Pharma AG on the *in vivo* efficacy of FGFR2-ADC in FGFR-SMOL inhibitor resistant diffuses type gastric cancer PDX model GAGA-6R (IPA7).

BIOINFORMATICS CORE



Development of various NGS analysis pipelines

- RNA-seq for differential expression of genes/miRNAs/ncRNAs
- RNA-seq for differential splicing
- RNA-seq for differential RNA editing
- DNA-seq for somatic mutations
- ChIP-seq for protein-DNA binding or methylation
- RIP-seq for protein-RNA binding
- 4C-seq for DNA-DNA interaction

Development of an automatic portal for NGS data analysis

Development of an interactive portal for project annotation/between the core and collaborators

Analysis of TCGA and 1000 genome datasets integrated with available clinical data

Data analysis in various collaborative projects with institutions such as CSI, NUS Department of Anatomy and Department of Biochemistry, NTU, IMCB and IMB

About the facility

The Bioinformatics Core analyses, interpretes and integrates large scale genomic data generated from hybridization-based microarrays & next-generation sequences (NGS).

The core also handles MS/MS peptide data and fluidigm single-cell analysis data and various downstream bioinformatics analyses.

Facility Head
Dr. Henry YANG

The Bioinformatics Core has successfully completed various computational and collaborative projects:

COMPUTATIONAL CORE

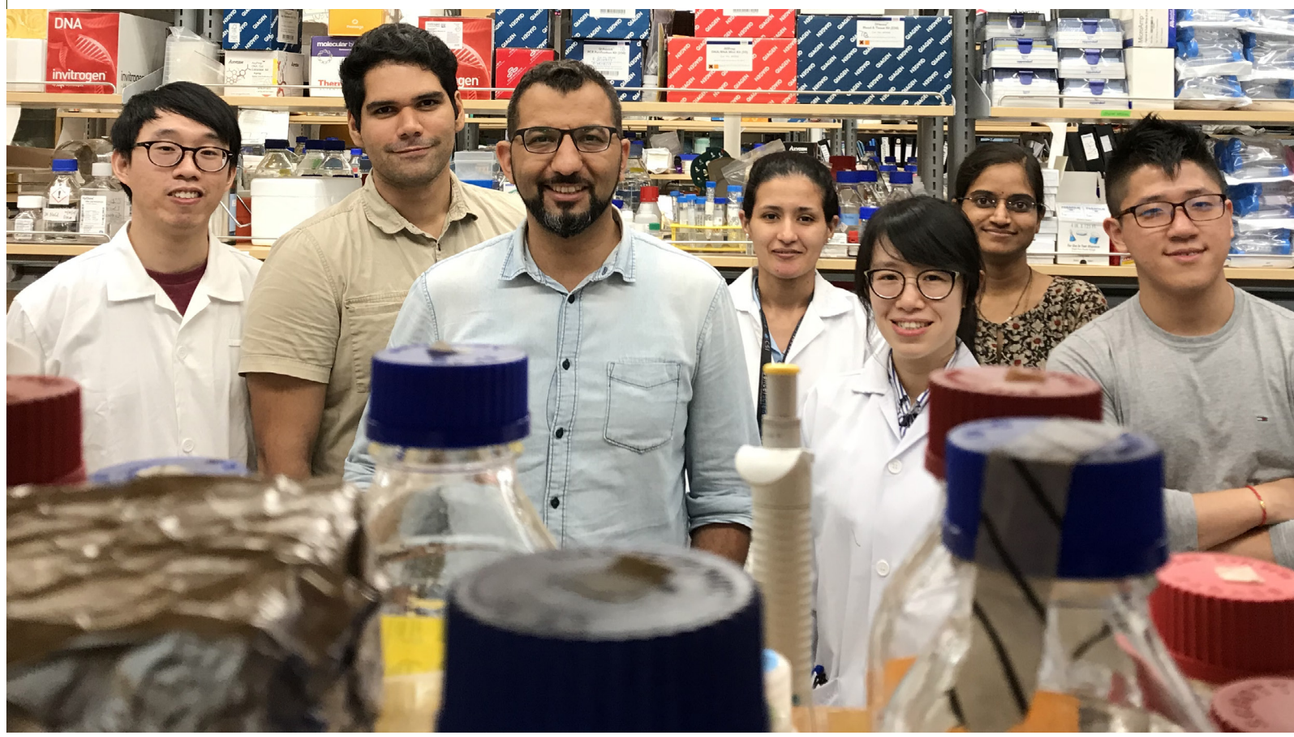
About the facility

The facility provides IT support, centralized IT solutions and services for the institute.

Facility Head
Dr. Touati BENOUKRAF

The facility has implemented various security features to the data storage and file sharing system within the institute.

The facility maintains a centralized server and has been supporting 15 labs in CSI for their computational and storage needs.



MICROSCOPE CORE

About the facility

The facility manages high end microscopes to support the research activities within the institute. The facility also allows supervised use for scientists across Singapore, including those from NUS, SingHealth, Duke-NUS and A*STAR.

The facility contains several imaging systems with different designs and configurations to meet the various research requirements:

- Confocal Microscopes: Nikon A1 and Nikon C1
- High content screening systems: Vectra and Operetta
- Epifluorescence microscopes: Zeiss Axiovert A1/ Zeiss Axioplan 2/ Zeiss Imager M2/ Zeiss Axiovert 200/ Olympus IX71/Nikon TE2000S/Nikon TS100
- Live cell imagers and optical sectioning microscopes: Zeiss Live Cell Observer

Facility Head
Dr. Anand JEYASEKHARAN

The facility maintains and upkeeps the existing microscopes within the institute and conducts various training sessions for staff and students.

The facility has also worked with Olympus to conduct a demonstration on the new FV3000 confocal microscope for consideration in expanding the facility's capabilities and to better serve the needs of the institute.

QUANTITATIVE PROTEOMICS CORE

About the facility

The facility features state-of-the-art quantitative mass spectrometry and support researchers in their proteomics workflow.

The facility offers the following applications:

1. DNA/RNA sequence/structure-specific pull-downs
2. Protein-protein interaction studies based on immunoprecipitations
3. Whole proteome analysis
4. Identification of post-translational modifications

Facility Head
Dr. Dennis KAPPEI

The facility has established standard workflows with the arrival of the Q Exactive HF mass spectrometer.

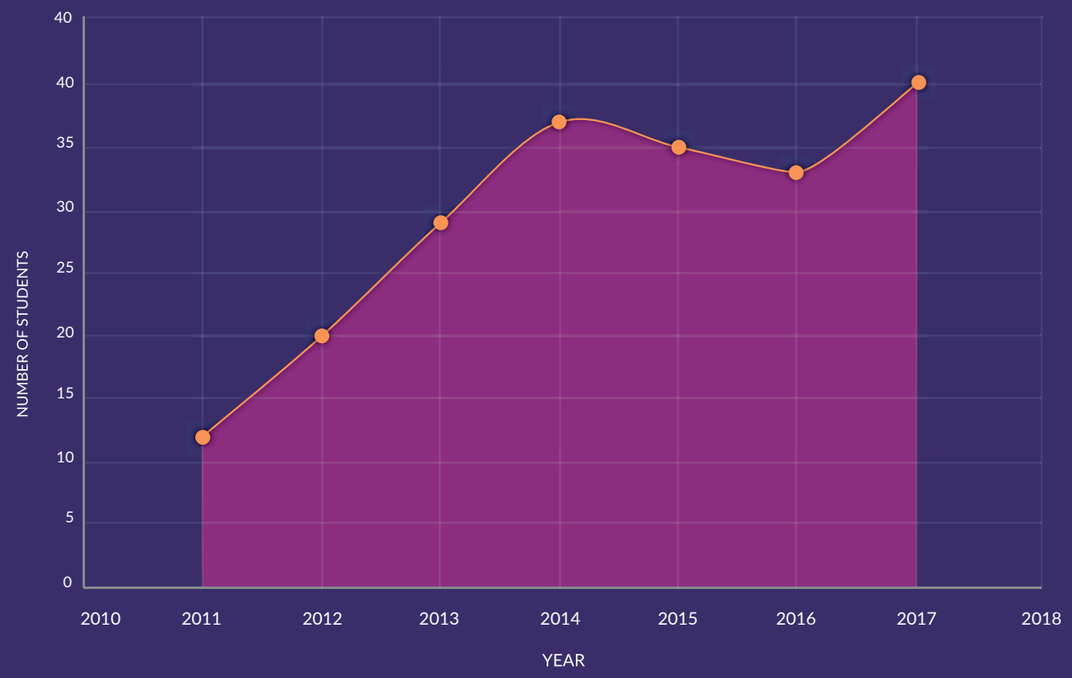
The facility has supported 18 research groups at CSI, Duke-NUS, GIS, NUS Department of Biochemistry and CREATE in providing the researchers with SILAC reagents and measuring proteomics samples. They are also involved in the experimental planning with these researchers.

05

EDUCATION

5.1
CSI GRADUATE PROGRAM

No. of Students in the PhD Graduate Program in Cancer Biology



2017

56
Applied

7
Admitted

33
Existing Students

5.2
2017 GRADUATES

Tan Ming
Establishing an Epithelial Mesenchymal Transition (EMT) Spectrum with EMT Transcriptional Drivers
Supervisor: Prof. Wee Joo CHNG
Co-Supervispor: Dr Ruby Yun Ju HUANG

Xiao Jinfen
Functional Analysis and Mechanistic Study of SETDB1 in Breast Cancer
Supervisor: Prof Phillip KOEFFLER

You Jia
Hypoxia-Dependent Alteration of 5-Hydroxymethylation Levels in Liver Cancer Progression
Supervisor: Prof. H. Phillip KOEFFLER

Zhang Yanzhou
Mechanism and Implications of Destabilizing TIP60, A Tumor Suppresor
Supervisor: Dr. Sudhakar JHA

Chong Qing Yun
Trefoil Factor 3 (TFF3) is HER2-Regulated and Substitutes for HER Signalling in Trastuzumab Resistant HER2+/ER+ Breast Cancer
Supervisor: Prof Peter LOBIE

Daniel Tan Shao Weng
Targeting the Phosphotidylinositol-3-Kinase Pathway in Non-Small Cell Lung Cancer
Supervisor: Prof. Daniel G. TENEN
Co-Supervisor: Prof. Patrick TAN

Huang Kie Kyon
Clinical Application of Cancer Exome Sequencing
Supervisor: Prof. Patrick TAN

Lim Kee Siang
Implication of Highly Cytotoxic Natural Killer Cells for Esophageal Cancer Treatment
Supervisor: Dr. Wei Peng YONG

5.3

NEW IN 2017...

RNA BIOLOGY SCHOLARSHIP

JANUARY 2017

CSI is excited to offer the RNA Biology Scholarship and the applications for January 2017 intake has ended on 31 August 2016.

The PhD projects are RNA biology-focused and students will be supervised by Principal Investigators of the RNA Biology Program who are CSI faculty.

5.4

STUDENT PUBLICATIONS

1. Bhat AV, Hora S, Pal A, Jha S, Taneja R. Stressing the (Epi)Genome: Dealing with Reactive Oxygen Species in Cancer. Antioxid Redox Signal. 2017:doi: 10.1089/ars.2017.7158.

2. Cao F, Fang Y, Goh Y, Choy JYH, Koh BTH, Tan JH, Bertin N, Ramadass A, Hunter E, Green J, Salter M, Akoulitchev A, Wang W, Chng WJ, Tenen DG, Fullwood MJ. Super-enhancers and broad H3K4me3 domains form complex gene regulatory circuits involving chromatin interactions. Scientific Reports. 2017;7(1):2186.

3. Cho SSL, Han J, James SJ, Png CW, Weerasooriya M, Alonso S, Zhang Y. Dual-specificity phosphatase 12 targets p38 MAP kinase to regulate macrophage response to intracellular bacterial infection. Frontiers in Immunology. 2017;8:1259.

4. Chong Q-Y, You M-L, Pandey V, Banerjee A, Chen Y-J, Poh H-M, Zhang M, Ma L, Zhu T, Basappa S, Liu L, Lobie PE. Release of HER2 repression of trefoil factor 3 (TFF3) expression mediates trastuzumab resistance in HER2+/ER+ mammary carcinoma. Oncotarget. 2017;8:74188-208.

5. Ding K, Yuan Y, Chong Q-Y, Yang Y, Li R, Li X, Kong X, Qian P, Xiong Z, Pandey V, Ma L, Wu Z, Lobie PE, Zhu T. Autocrine prolactin stimulates endometrial carcinoma growth and metastasis and reduces sensitivity to chemotherapy. Endocrinology. 2017;158(6):1595-611.

6. Goh JY, Feng M, Wang W, Oguz G, Yatim SMJM, Lee PL, Bao Y, Lim TH, Wang P, Tam WL, Kodahl AR, Lyng MB, Sarma S, Lin SY, Lezhava A, Yap YS, Lim AS, Hoon DSB, Ditzel HJ, Lee SC, Tan EY, Yu Q. Chromosome 1q21.3 amplification is a trackable biomarker and actionable target for breast cancer recurrence. Nature Medicine. 2017;23(11):1319-30.

7. Han J, Li J, Ho JC, Chia GS, Kato H, Jha S, Yang H, Poellinger L, Lee KL. Hypoxia is a key driver of alternative splicing in human breast cancer cells. Scientific Reports. 2017;7(1):4108.

8. Ng SB, Chung TH, Kato S, Nakamura S, Takahashi E, Ko YH, Khoury JD, Yin CC, Soong R, Jeyasekharan AD, Hoppe MM, Selvarajan V, Tan SY, Lim ST, Ong CK, Nairismagi ML, Maheshwari P, Choo SN, Fan S, Lee CK, Chuang SS, Chng WJ. EBV-associated primary nodal T/NK-cell lymphoma shows distinct molecular signature and copy number changes. Haematologica. 2017:doi: 10.3324/haematol.2017.180430.

9. Pandey V, Zhang M, Chong Q-Y, You M-L, Raquib AR, Pandey AK, Liu D-X, Liu L, Ma L, Jha S, Wu Z-S, Zhu T, Lobie PE. Hypomethylation associated enhanced transcription of trefoil factor-3 mediates tamoxifen-stimulated oncogenicity of ER+ endometrial carcinoma cells. Oncotarget. 2017;8:77268-91.

10. Qi L, Song Y, Chang THM, Yang H, Lin CH, Tay DJT, Hong H, Tang SJ, Tan KT, Huang XX, Lin JS, Ng VHE, Maury JJP, Tenen DG, Chen L. An RNA editing/dsRNA binding-independent gene regulatory mechanism of ADARs and its clinical implication in cancer. Nucleic Acids Research. 2017;45(18):10436-51.

11. Rajagopalan D, Pandey AK, Xiuzhen MC, Lee KK, Hora S, Zhang Y, Chua BH, Kwok HS, Bhatia SS, Deng LW, Tenen DG, Kappei D, Jha S. TIP60 represses telomerase expression by inhibiting Sp1 binding to the TERT promoter. PLOS Pathogens. 2017;13(10):e1006681.

12. Tan DQ, Suda T. Reactive oxygen species and mitochondrial homeostasis as regulators of stem cell fate and function. Antioxid Redox Signal. 2017:doi: 10.1089/ars.2017.7273.

13. Tan S, Ding K, Chong Q-Y, Zhao J, Liu Y, Shao Y, Zhang Y, Yu Q, Xiong Z, Zhang W, Zhang M, Li G, Li X, Kong X, Ahmad A, Wu Z-S, Wu Q, Zhao X, Lobie PE, Zhu T. Decreased miR26a/b and increased HuR expression post-transcriptionally upregulates ERBB2 to mediate acquired tamoxifen resistance in ER+ breast cancer cells Journal of Biological Chemistry. 2017;10.1074/jbc.M117.780973.

14. Tirado-Magallanes R, Rebbani K, Lim R, Pradhan S, Benoukraf T. Whole genome DNA methylation: beyond genes silencing. Oncotarget. 2017;8(3):5629-37.

15. Wang X, Gu M, Toh TB, Abdullah NLB, Chow EK. Stimuli-responsive nanodiamond-based biosensor for enhanced metastatic tumor site detection. SLAS Technology. 2017:doi: 10.1177/2472630317735497.

16. Wong RWJ, Ngoc PCT, Leong WZ, Yam AWY, Zhang T, Asamitsu K, Iida S, Okamoto T, Ueda R, Gray NS, Ishida T, Sanda T. Enhancer profiling identifies critical cancer genes and characterizes cell identity in adult T-cell leukemia. Blood. 2017;130(21):2326-38.

17. You M-L, Chen Y-J, Chong Q-Y, Wu M-M, Pandey V, Chen R-M, Liu L, Ma L, Wu Z-S, Zhu T, Lobie PE. Trefoil factor 3 mediation of oncogenicity and chemoresistance in hepatocellular carcinoma is AKT-BCL-2 dependent. Oncotarget. 2017;8(24):39323-44.

18. Zhang Y, CHia GS, Tham CY, Jha S. Live-imaging of breast epithelial cell migration after the transient depletion of TIP60. Journal of Visualized Experiments. 2017;130:e56248.

06

AWARDS & HONORS

Being at the forefront of cancer research, the relentless pursue of ground-breaking discoveries is the way of life in CSI. The CSI team is passionate and committed to advance research and discover novel therapies for cancer. In this section, we honor our award recipients and celebrate their achievements.

6.1 FACULTY

Dr. Anand JEYASEKHARAN
Transition Award
National Medical Research Council (NMRC) Awards 2017

Dr. David TAN
Clinician Scientist Award
National Medical Research Council (NMRC) Awards 2017

Prof. Wee Joo CHNG
STaR Investigator Award
National Medical Research Council (NMRC)

PROVOST Chair Researcher of the Year
National Medicine (NUSMed) Awards 2017

Dr. Polly CHEN
Young Researcher of the Year
NUS Medicine (NUSMed) Awards 2017

Dr. Alan Prem KUMAR
Graduate Student Mentor of the Year
NUS Medicine (NUSMed) Awards 2017

6.2 RESEARCH STAFF

Dr. Tan Boon TOH
Best Short Talk Award
EMBO Travel Award

Basic Science Best Oral Presentation (Runner-Up)
NCAM 2017

Dr. Shi Hao TAN
Outstanding Poster Award
RNA Biology Symposium 2017

Mr. Daryl Jin Tai TAY
Outstanding Poster Award
RNA Biology Symposium 2017

Dr. Takayoshi MATSUMURA
Best Oral Presentation Award (Runner-Up)
Frontiers in Cancer Science (FCS) 2017

Dr. Zhigang XIE
2017 ASH Abstract Achievement Award
American Society of Hematology (ASH)

Dr. Liang XU
Basic Science Best Poster Award
NCAM 2017

Dr. Avinash BAHIRVANI
Basic Science Best Poster Award (Runner-Up)
NCAM 2017

Ms. Michelle MOK
Translational Science Best Poster Award (Runner-Up)
NCAM 2017

Dr. Li Ren KONG
Translational Science Best Oral Presentation
NCAM 2017

Dr. Jianbiao ZHOU
Translational Science Best Oral Presentation (Runner-Up)
NCAM 2017

6.3 STUDENTS

Eve Chao WANG
Korean Breast Cancer Foundation Scholarship for Outstanding Oral Presentation
Global Breast Cancer Conference 2017

Best Oral Scientific Presentation Award
International Conference on Scientific Frontiers in Natural Product Based Drugs (SFNPBD) 2017

Shreya KAR
Good Poster Award
Global Breast Cancer Conference 2017

Cheng Yong THAM
Selected for Oral Presentation
12th Great Lakes Bioinformatics Conference (GLBIO)

Masturah binte Mohd Abdul RASHID
Best Poster Presentation
NUS Medicine 7th Annual Graduate Scientific Congress (AGSC) 2017

Best Poster Award & AACR Travel Award
Frontiers in Cancer Science (FCS) 2017

Darren Qiancheng TAN
Best Poster Presentation
NUS Medicine 7th annual Graduate Scientitfic Congress (AGSC) 2017

Huiqi HONG
Travel Award, Selected for Oral Presentation
Heidelberg Forum for Young Life Scientists (HFYLS)

Deepa RAJAGOPALAN
Basic Science Best Oral Presentation
NCAM 2017

Regina WONG
Basic Science Best Oral Presentation (Runner-Up)
NCAM 2017

Nish KUMARI
Translational Science Best Poster Award
NCAM 2017

Jing Yuan CHOOI
Translational Science Best Oral Presentation (Runner-Up)
NCAM 2017

Madhu Mathi KANCHI
Best Poster Scientific Presentation Award
International Conference on Scientific Frontiers in Natural Product Based Drugs (SFNPBD) 2017

Shreya KAR
Best Poster Scientific Presentation Award
International Conference on Scientific Frontiers in Natural Product Based Drugs (SFNPBD) 2017

Yanjing LIU
Selected for SRBA Oral Presentation
RNA Biology Symposium 2017

07

SCIENTIFIC EVENTS

7.1

RESEARCH MEETINGS

The CSI Research Meetings provide a platform for dynamic exchange of scientific ideas and updates among the researchers and students within the institute.

JANUARY

13 JANUARY

Investigating the role of ZBTB33 as a pioneer factor
- ***Lin Xiaoxuan***

Role of renal cell carcinoma-related FLCN-TFE3 pathway for regulation of cellular metabolism and phagocytosis
- **Mitsuhiro Endoh**

The development of nanodiamond-based drug-delivery complexes for treatment and diagnosis of oncogene-specific hepatocellular carcinoma
- ***Wang Xin***

FEBRUARY

17 FEBRUARY

CSI web portal: an online platform for automated NGS analysis and data sharing
- ***Omer An***

Epigenomic profiling of primary gastric adenocarcinoma reveals super-enhancer heterogeneity
- ***Ooi Wen Fong***

Runx1 enhancer element marks stem cell in multiple organs
- ***Akihiro Yamamura***

MARCH

10 MARCH

Interplay between mevalonate & hippo pathways regulates DDX20 transcription via YAP-TEAD complex in triple negative breast cancer
- ***Eve Wang***

Environmental colitic signals suppress common lymphoid progenitors and B-lymphogenesis
- ***Lufei Chengchen***

Implication of highly cytotoxic natural killer cells for ESCC treatment
- ***Akihiro Yamamura***

24 MARCH

Role of PPP2R2B in resistance to targeted therapies in breast cancer
- ***Bao Yi***

APRIL

7 APRIL

MMSET I acts as an oncoprotein and regulates GLO1 expression in t(4;14) multiple myeloma cells
- ***Xie Zhigang***

Symmetric dimethylation as a potential marker of replication stress
- ***Hoang Mai Phuong***

21 APRIL

Mechanisms governing epithelial-mesenchymal transition in bladder carcinoma
- ***Prasanna Vasudevan***

Understanding 3D genome organisation in cancer
- ***Lim Mei Chee***

Identifying pathways regulated by TIP60
- ***Deepa Rajagopalan***

MAY

5 MAY

The interplay between GRHL2 and epigenetics in the regulation of EMT in ovarian cancer
- ***Chung Vin Yee***

Identification of a novel long non-coding RNA regulated by the TAL1 transcriptional complex in T-cell acute lymphoblastic leukemia
- ***Tan Shi Hao***

BCL6 promotes glioma and serves as a novel therapeutic target
- ***Xu Liang***

19 MAY

TFF3 reduces doxorubicin and docetaxel sensitivity by inhibiting the drug-induced apoptosis in breast cancer
- ***Poh Han Ming***

RNA approach for gene specific demethylation & activation
- ***Liu Yanjing***

Understanding tumor-associated retinoic acid receptor alpha mutations in breast fibroepithelial tumors
- ***Liu Yanjing***

JUNE

2 JUNE

Characterization of MET-N3755 as an activating mutation in squamous cell carcinoma
- **Kong Li Ren**

Targeting defective RNA damage response in diffuse gastric cancer
- **Lau Wen Min**

p53 mediated cell cycle arrest causes male subfertility and sex-ratio distortion in Msy3 knockout mice
- **Md. Zakir Hossain**

16 JUNE

PPARγ-annexin A1 axis in the dynamics of macrophage polarization in breast cancer
- **Shreya Kar**

The impact of antisense RNAs on hepatocellular cancer development
- **Fernando Bellido Molias**

The role of G9a in Myc-driven liver cancer
- **Toh Tan Boon**

JULY

7 JULY

Enhancer for Runx1, eR1: a powerful tool in stem cell & cancer biology
- **Avinash Govind Bahirvani**

Oncogenic roles of maternal exbryonic leucine zipper kinase (MELK) in gastric cancer and its therapeutic targetting using small molecule inhibitor OTS 167
- **Vinod Vijay Subhash**

21 JULY

A distinct role of RhoB in simvastatin-induced cytotoxicity in breast cancer cells
- **Serene Seah**

Post-transcriptional regulation of the proto-oncogene c-Myc by RNA binding proteins in colon cancer
- ***Desi***

Role of tumor-microenvironmental interactions in pancreatic cancer
- ***Lee Puay Ling***

AUGUST

11 AUGUST

Computational identification of RNA modifications
- **Tan Kar Tong**

scRNA-seq reveals highly-defined hepatic development from embryonic endoderm to fetal liver stage
- **Mu Tianhao**

A biochemical analysis of RUNX function in the Fanconi anemia pathway of DNA repair
- **Vaidehi Krishnan**

25 AUGUST

Characterizing structural variants in acute myeloid leukemia cells using hybrid sequencing
- **Tham Cheng Yong**

Epigenomic promoter alterations amplify isoform and immunogenic diversity in gastric adenocarcinoma
- **Aditi Qamara**

ESCAPE RNA sequencing: moving toward combining protein and gene expression analysis in single cells
- **Jonathan Scolnick**

SEPTEMBER

15 SEPTEMBER

ZBTB48 is both a telomere-binding protein & a transcriptional activator
- **Grishma Rane**

Functional analysis of a novel mutation identified in familial platelet disorder with myeloid malignancy
- **Takayoshi Matsumura**

Polo-like kinase inhibitors synergize with ARID1A depletion
- **Upadhyayula Sai Srinivas**

OCTOBER

27 OCTOBER

The relationship between ADAR1 and STAT3 and its relevance in multiple myeloma
- **Teoh Phaik Ju**

Identifying the oncogenic role of USP10 as the regulator of PTEN function in breast cancer.
- **Nishi Kumari**

ASXL2 is recurrently mutated in t(8;21) and regulates hemapoietic development
- **Vikas Madan**

NOVEMBER

27 OCTOBER

The oncogenic role of Trefoil Factor 3 (TFF3) in non-small cell lung cancer.
- **Zhang Mengyi**

Predicting chromatin interactions from DNA sequence
- **Cao Fan**

Application if novel synthetic methodology & mechanism-informed phenotypic screening for the identification of drug candidates against drug-resistant cancers
- **Chow Mun Juinn**

7.2 SEMINARS

CSI hosts regular seminars in recognition of the scientific contribution of the global cancer research community. In addition to conducive interactions with CSI researchers, the invited speakers present their latest findings in various aspects of cancer research.

JANUARY

3 JANUARY

RNA-binding activity of Suv39h1 chromodomain is coupled with its H3K9 methylation recognition in assembling heterochromatin

Yoichi Shinkai, *RIKEN, Japan*

9 JANUARY

Biophysics in the cell - CETSA to guide preclinical drug development

Par Nordlund, *Visiting Professor, Karolinska Institute*

16 JANUARY

Genetics and therapy of myeloid malignancies

Ross Levine, *Laurence Joseph Dineen Chair in Leukemia Research; Director, Memorial Sloan Kettering Center for Hematologic Malignancies*

FEBRUARY

20 FEBRUARY

Signalling to chromatin from transcription and metabolism

Jerry Workman, *Principal Investigator, Stowers Institute for Medical Research*

21 FEBRUARY

CTFC mediates allele-specific sub-TAD organization at paternally imprinted gene loci

Daan Noordermeer, *Group Leader, Chromatin Dynamics Group, Institute for Intergrative Biology of the Cell (I2BC) - CNRS*

MARCH

21 JANUARY

InfoSigMap: Google maps for informative gene signatures visualizes their compositional and functional redundancies in transcriptomic studies

Andrei Zinovyev, *Researcher, Institut Curie, Paris*

APRIL

20 APRIL

Targeting a new class of oncofetal proterin SALL4 in cancer

Li Chai, *Associate Professor, Harvard Medical School; Associate Director, Joint Program of Adult Transfusion Medicine, Pathology Department, Brigham and Women's Hospital*

MAY

2 MAY

A new circulatory system for bone marrow myeloid progenitors in inflammation

Jose Cancelas, *Professor of Pediatrics, University of Cincinnati College of Medicine*

JUNE

19 JUNE

Mechanism and function of Tet/Tdg-mediated DNA demethylation

Zhang Yi, *Fred Rosen Chair Professor, Department of Genetics, Harvard Medical School & Boston Children's Hospital; Investigator, Howard Hughes Medical Institute*

JULY

18 JULY

Biology of actively cycling & reserve intestinal stem cells

Calvin Kuo, *Professor of Medicine (Hematology); Professor of Chemical & Systems Biology, Standard University*

AUGUST

1 AUGUST

Epstein Barr virus drives cancer through transcriptional regulation and chromatin dynamics

Jiang Sizun, *Postdoctoral Fellow, Garry Nolan Lab, Stanford University*

23 AUGUST

Noncoding RNA regulation in B cell immunity and cancer

Uttiya Basu, *Associate Professor, Department of Microbiology and Immunology, Columbia University, New York*

SEPTEMBER

12 SEPTEMBER

InfoSigMap: Google maps for informative gene signatures visualizes their compositional and functional redundancies in transcriptomic studies

Tobias Langenhan, *Chair and Professor of Biochemistry, Rudolf Schonheimer Institute of Biochemistry, Division of General Biochemistry, Leipzig University*

14 SEPTEMBER

Actin retrograde flow actively aligns and orients ligand-engaged intergrins in focal adhesions

Clare Waterman, *Distinguished Investigator, National Heart, Lung and Blood Institute, National Institutes of Health (NIH)*

OCTOBER

2 OCTOBER

Insights into the function of Setd2 and H3K36 trimethylation in leukemia, chemo-resistance and hematopoietic stem cells

Gang Huang, *Associate Professor of Pathology and Laboratory Medicine, Divisions of Pathology and Experimental Hematology and Cancer Biology, Cincinnati Children's Hospital Medical Center*

20 OCTOBER

Cancer cells undergo DNA damage while migrating through small constrictions

Matthew Raab, *Senior Research, Scientist, BIGHEART*

NOVEMBER

16 NOVEMBER

G9a histone methyltransferase: a link between epigenetic regulation and tumour hypoxia

Jason Lee, *Associate Professor & QIMR Berghofer International Research Fellow, QIMR Berghofer Medical Research Institute*

28 NOVEMBER

Actin dynamics regulate differentiation of cancer cells

Hideyuki Saya, *Professor, Division of Gene Regulation, Institute for Advanced Medical Research (IAMR), Keio University School of Medicine*

7.3
DISTINGHUISHED SPEAKERS' SERIES

The invited speakers for our Distinguished Speaker's Series are outstanding and internationally-renowned scientists who address various topics of interest to the CSI faculty.

Each series is also a unique opportunity for the exchange and debate of scientific ideas while the invited speakers give a seminar and meet with researchers at the institute.

23 May 2017

Ashok Ventikaraman

Director, Medical Research Council (MRC) Cancer Unit, University Of Cambridge

Genome instability and carcinogenesis: insights from the breast cancer gene, BRCA2

25 September 2017

Anindya Dutta

Harry F. Byrd Professor and Chair, Biochemistry and Molecular Genetics, University of Virginia School of Medicine

ORC, MCM9 and microDNAs: questioning paradigms

7.4
CONFERENCES AND SYMPOSIA

CSI-ENS BIOINFORMATICS WORKSHOP

10 February - 27 March 2017

The workshop series in Bioinformatics was organized in conjunction to our partnership with the *Ecole Normale Superieure de Paris* (ENS) under the Merlion Program.

The series of 8 sessions covered a wide range of topics, including RNAseq and ChIPseq dataset analysis as well as an introduction to system biology and genes network modelling.

The sessions were delivered by bioinformatician experts in the field of NGS analysis and genes network modelling, and was well-received by a total of 122 participants.

CSI-CMU Joint Symposium
22 September 2017

The CSI-CMU Joint Symposium was a partnership between CSI and the China Medical University (CMU) in Taiwan.

The joint symposium sought to enhance collaboration between both institutes and to allow exchange and communication of new scientific knowledge in the field of cancer.

The symposium was well-received by a total 136 participants who had valuable opportunities to gain new insights into the latest development in cancer research.

RNA BIOLOGY SYMPOSIUM
5-6 October 2017

The 3rd RNA Biology Symposium is part of an ongoing effort of the RNA Biology Center at the institute to bring together internationally renowned experts with common interest in understanding RNA biology.

Over the course of 2 days, more than 204 participants gained insights and updates in various aspects of RNA Biology. The symposium featured 2 keynote talks by Lynne Maquat (University of Rochester, USA) and John Mattick (Garvan Institute, Australia), both known for their work in RNA decay pathways and non-protein coding RNAs, respectively.

Prior to the symposium, a satellite RNA Analysis Mini-Workshop was held and imparted a great deal of knowledge and practical skills to a total of 42 participants on RNA-sequencing data analysis.

Frontiers in Cancer Science 2017

6-8 November 2017

The annual international flagship conference featured an impressive program with 16 international speakers and 16 local speakers covering a broad range of topics in novel cancer discoveries.

The highlight of the conference was the new Pigeonhole Live component which featured live Q&A with question voting to allow the 696 members of the audience to ask questions, vote on them and provide their feedback.

In addition to a poster presentation contended by 119 abstracts selected from a highly competitive pool of submissions, 6 excellent abstracts were chosen to deliver a 10-minute oral presentation.

We were proud to collaborate with the American Association for Cancer Research (AACR) this year in the sponsorship of two commendable Poster Presenters to travel to the prestigious 2018 AACR Meeting in Chicago, USA. All delegates were also given free online access to AACR journals for one week following FCS 2017.

We were also honored to award four selected abstract submitters (1 from Italy and 3 from India) with the Oncotarget Travel Awards worth S$2,000.

08

BENEFACTIONS

CSI appreciates the philanthropic support it received over the years. Benefactors listed here reflect generous contributions made to CSI between 1st April 2013 & 31st March 2017

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09

PUBLICATIONS

PUBLICATIONS

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