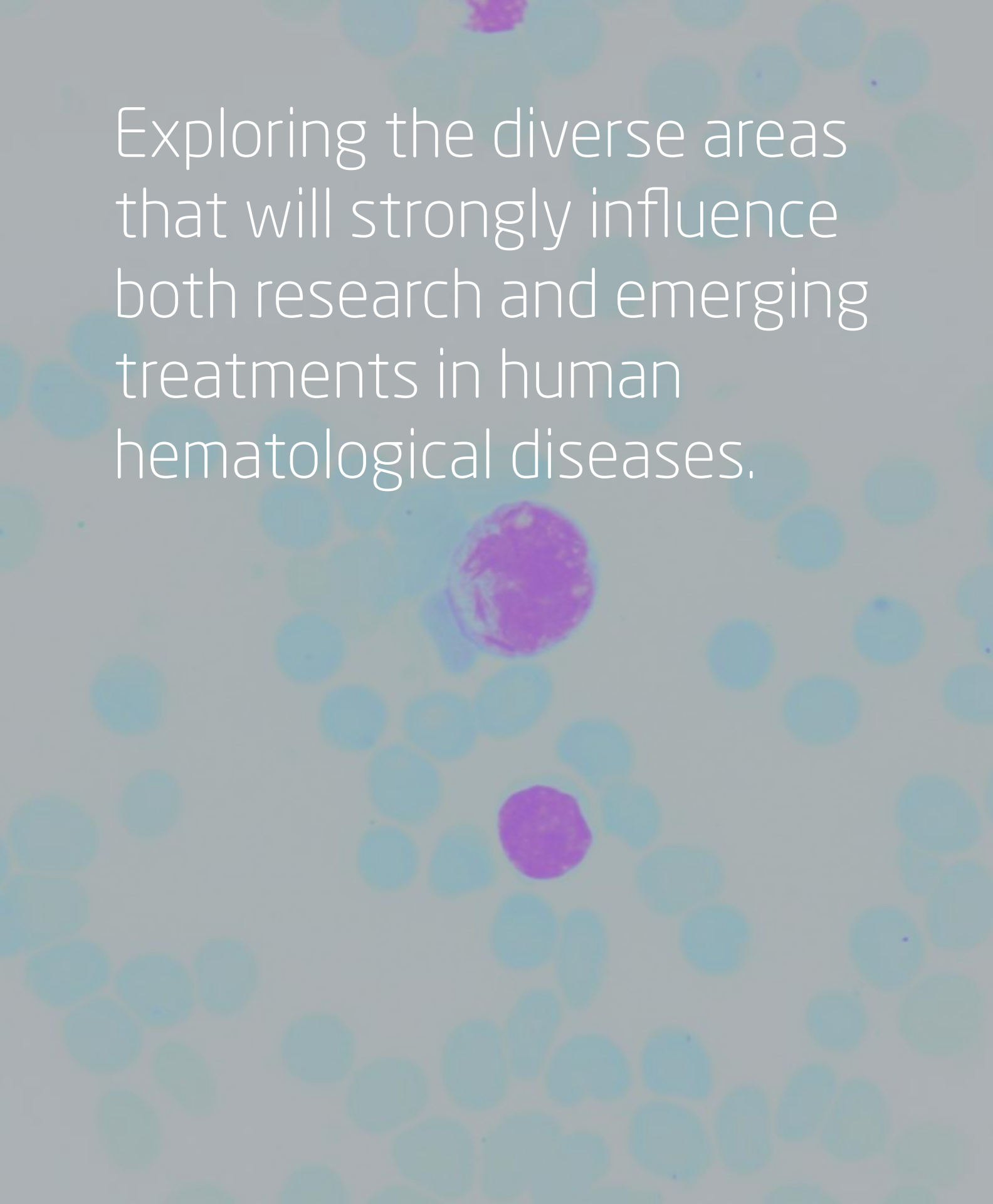
HEMATOLOGICAL MALIGNANCIES

Synergies: Basic Science and Medicine

AN NCBS & ST. JOHN'S NATIONAL ACADEMY OF HEALTH SCIENCES COLLABORATIVE INITIATIVE


Exploring the diverse areas
that will strongly influence
both research and emerging
treatments in human
hematological diseases.

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The National Centre for Biological Sciences (NCBS), Bangalore is part of the Tata Institute of Fundamental Research. Research at NCBS uses experimental and computational approaches to the study of molecules, cells and organisms. We aim to understand biology at each of these levels to advance an integrated view of life processes. While the mandate of NCBS is the study of biology, we realize that success requires research problems to be approached from a variety of directions. We therefore have on campus researchers with a variety of backgrounds in the natural sciences, mathematics and computer science, among others. Collaboration at every level – within NCBS, within the country and internationally – is strongly encouraged.

Published in conjunction with a seminar series on 'Hematological Malignancies' held on August 02 and 03 2010 in Bangalore. The ICTS program 'Hematological Malignancies: A basic science-clinical interphase meeting' is the first in a series of activities in this cross-disciplinary effort to study hematological diseases.

Design: Trapeze (www.trapeze.in)
Photography for NCBS: Manoj Sudhakaran
Photography for St.John's Medical Academy: Sandeep Sangaru
Catalogue printed at: Pragati Offset Pvt. Ltd.

National Centre for Biological Sciences | Tata Institute of Fundamental Research
GKVK, Bellary Road, Bangalore 560065, India

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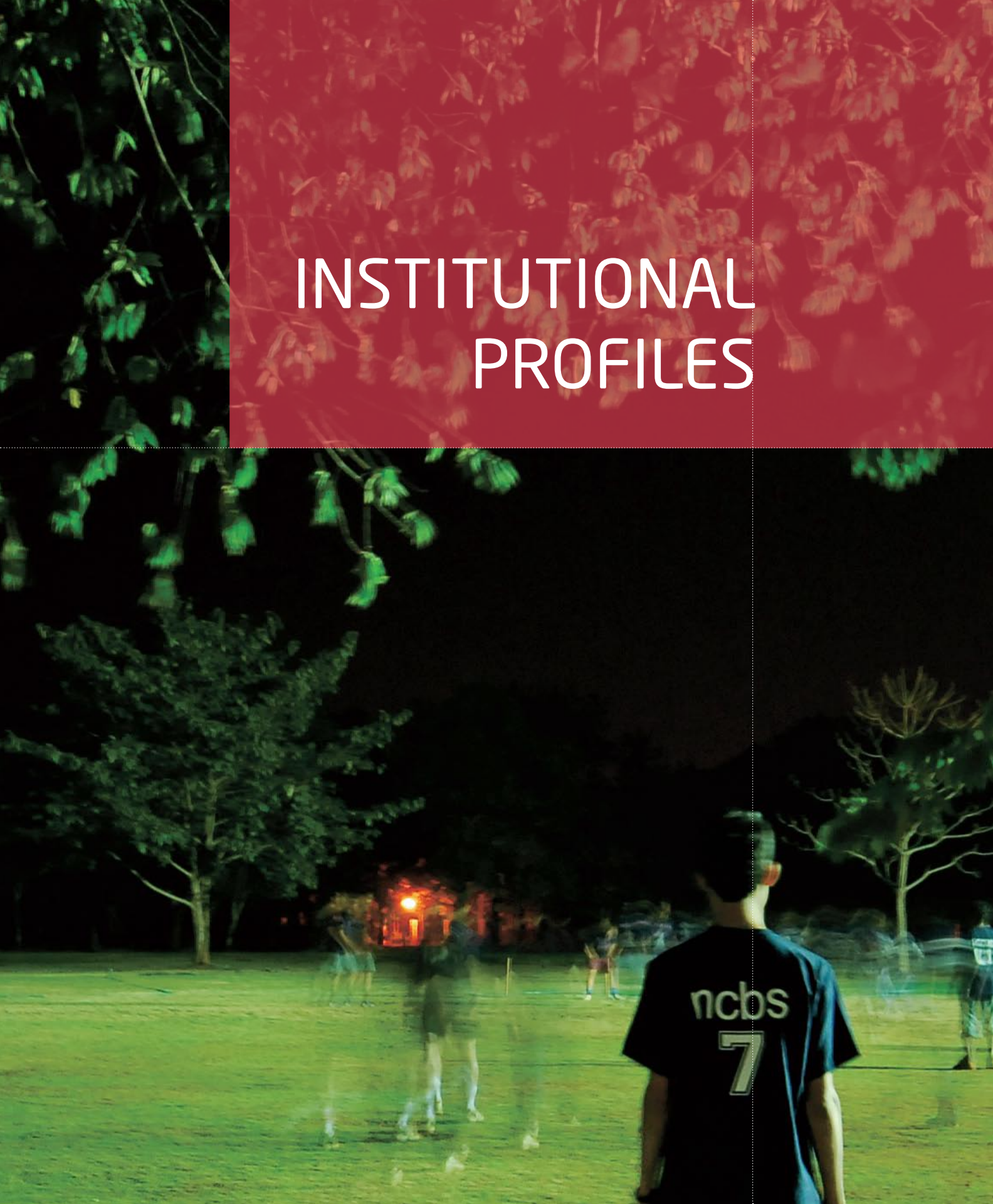
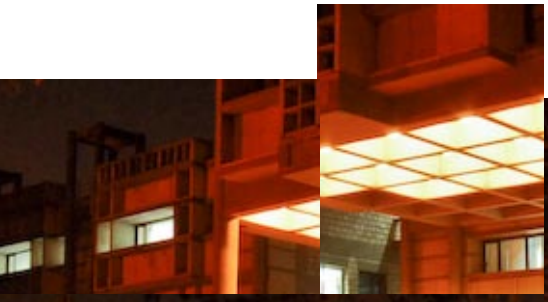


01

> NATIONAL CENTRE FOR BIOLOGICAL SCIENCES, TIFR
> ST. JOHN'S NATIONAL ACADEMY OF HEALTH SCIENCES



NATIONAL CENTRE FOR BIOLOGICAL SCIENCES,

Tata Institute of Fundamental Research

The National Centre for Biological Sciences (NCBS), located in Bangalore, is a part of Tata Institute of Fundamental Research. The mandate of NCBS is fundamental research in frontier areas of biology, right from single molecules to ecology and evolution. NCBS was started officially in the year 1992 as an autonomous unit under the aegis of TIFR and was intended to be a broad-based institution, dealing with all levels of biology: cell biology, development of animals and plants, brain research, behavior, ecology and theoretical biology. Over 18 years of existence and functioning, today NCBS stands out a lively and vibrant institution with about 35 research groups carrying out quality research.

NCBS facilities and equipment are accessible, well managed, used optimally and allow most kinds of modern research in modern biology to be conducted in-house. Where large- scale facilities are required for specific projects we encourage the use of national and international resources and collaborative arrangements. Well-qualified and trained staff manages the facilities and equipments.

Students, research fellows, and post- doctoral fellows are the strength of NCBS research community and keep the environment vibrant and young as do a range of laboratory and lecture courses, seminars, symposia and meetings, with speakers, teachers and participants from all over the world. Academic programmes can lead to a Ph.D. or other degrees, awarded by the Tata Institute of Fundamental Research.

While NCBS is a fundamental research institute that is engaged in studying biology, it also encourages applications and recruits people from variety of backgrounds in natural sciences, mathematics and computer science. Biological problems not only require multiple approaches for their solution, but also need researchers of varied expertise to collaborate. Collaboration at every level—within NCBS, within the country and internationally—is strongly encouraged. Research groups in NCBS are small and with specific strengths that make interactions with complementary groups fruitful.

ST. JOHN'S NATIONAL ACADEMY OF HEALTH SCIENCES

St John's National Academy of Health Sciences is located in Bangalore on a 135 acre campus. It is an integrated health care campus with outreach programs in rural areas. It is owned by the Catholic Bishops Conference of India, and is an academy that has five Institutes placed under it:

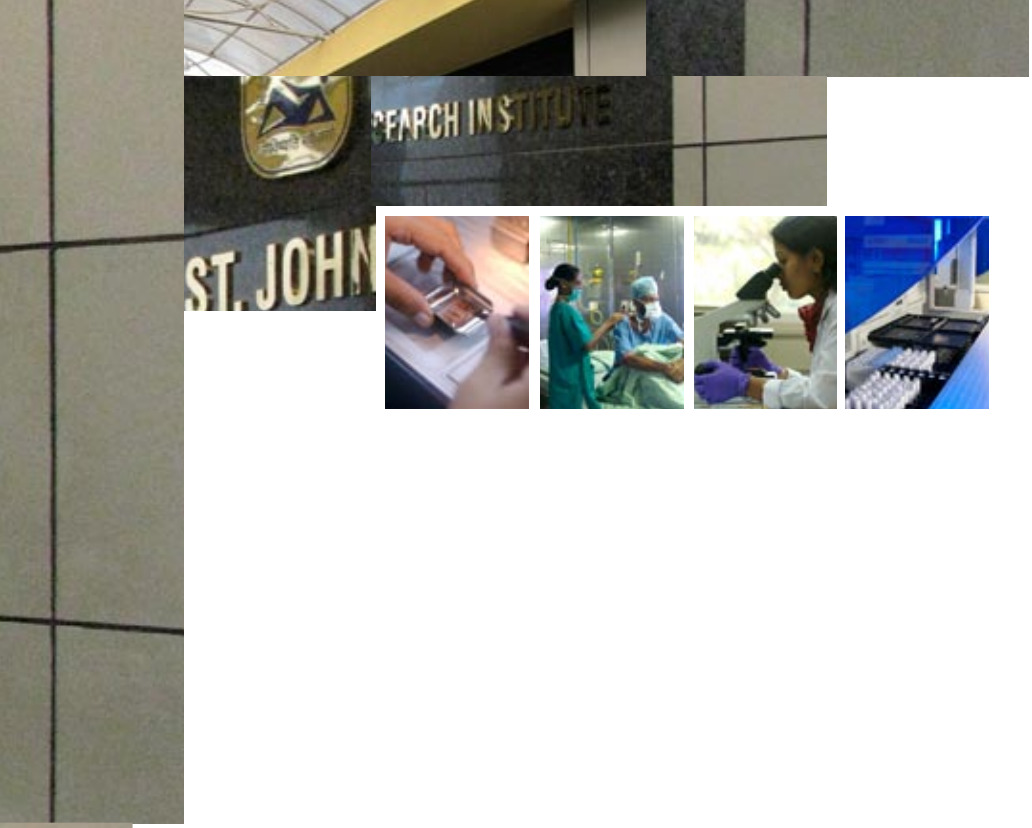
1. St. John's Medical College;
2. St. John's College of Nursing;
3. St. John's Institute of Health Management and Para Medical Studies;
4. St. John's Hospital;
5. St. John's Research Institute.

St. John's Hospital and Medical College

St. John's Hospital is a super-specialty hospital, and one of the largest in Bangalore. St.John's Medical College Hospital is a tertiary medical service centre with 1200 beds. It offers specialty and super specialty services, including state-of-the-art diagnostic facilities to ensure the delivery of holistic patient care. The hospital is staffed with dedicated and highly competent members of the medical fraternity along with trained personnel who work with sophisticated state-of-the-art equipment.

St. Johns Medical College was started in 1963 by the Catholic Bishop Conference of India. It offers graduate, postgraduate, diploma and super specialty degrees recognized by the Rajiv Gandhi University of Health Sciences (RGUHS), Bangalore, Karnataka. The mission orientation of the institution is to train healthcare professionals, especially to serve in the medically underserved areas of the country.


IAEA Collaborating Centre
ST. JOHN'S
RESEARCH INSTITUTE



St. John's Research Institute

In 2000, the Academy decided that its commitment to excellence in research required the setting up of an Institute that was dedicated to the pursuit of research and capacity development in St John's. This vision encompassed the improvement of the health of the community and patients through research, and the development of a centre of excellence in medical research in India. From this vision was developed the St John's Research Institute. This Institute is now in its 6th year of existence, but has cross appointed staff with the Medical College and Hospital. The total number of scientists who work at the Institute is about 40, but there are 500 mid level and junior level staff including field workers.

The St. John's Research Institute comprises of groups with a wide range of research interests spanning the gamut from population health and epidemiology to molecular mechanisms of disease. The divisions include Clinical Trials, Nutrition, Epidemiology and Statistics, Data management and Informatics, Infectious Diseases and Molecular Medicine. The laboratories are equipped to use the approaches and tools of whole animal physiology, biochemistry including mass spectrometry based proteomics, microbiology and molecular and cellular biology.
There are two aspects of the Research Institute that deserve attention. The first is its location. Being situated alongside a medical college and tertiary care teaching hospital provides the opportunity for practicing clinicians to be true collaborators with scientific interests in much of the research efforts.

The second is a conscious choice to build many of research programs around the establishment of long term patient/subject cohorts. This permits the systematic study of phenotypes of interest spread over the natural history of the condition.

INTER-DISCIPLINARY TEACHING PROGRAMMES

02

> COURSES, MEETINGS, SEMINARS ETC.

Overview

There is considerable global interest in models that can further the interactions between the basic sciences and medicine. The evolving initiative of NCBS/TIFR and St. John's Medical College in 'hematological malignancies' has its genesis in a course that was organized during January - March, 2009. This was a "leukemia as a disease paradigm" course and aimed at the basic sciences community in India. There were three distinctive components to this course:

1. A mix of physicians and scientists as teachers
2. A mix of experimental and theoretically inclined scientists with a strong component of mathematical modeling
3. Varied locations of the classes inclusive of hematology wards

This course has served as a template and drawn together a nucleus of people who together are interested in growing this initiative, while being rooted in their institutions and their core expertise. The present brochure for a meeting on hematological malignancies in early August, 2010, showcases the theme of expanding interactions between the clinicians and basic scientists with Leukemia as the focus and as an exclusive mechanism.

In addition to courses and workshops around this theme, the NCBS/TIFR-St. John's Medical College initiative will build a strong research component that parallels the teaching programmes. There are three critical components to building a vigorous programme in this domain.

FIRST, the location where the research is undertaken must facilitate the close interactions of physicians and scientists and allow easy access to material that would aid the research process.

SECOND, the nature of the problems chosen should reflect the mix of both basic science driven curiosity and the need for translation to the community, both in the hospital and in an "outreach manner".

THIRD, the programme must be inclusive in it's approach and must build on the existing multiple anchoring institutions and at the same time give a contemporary flavour to research in the hematological malignancies.

Leukemia as a disease paradigm course: 2009

Core organizers: Sudhir Krishna, Cecil Ross, Seema Nanda

The leukemia course conducted from Feb-April 2009 was meant to be the first in a series planned on a regular basis that is attempting to use "leukemia" as a system to familiarize basis scientists with research issues in the context of disease biology. Leukemia serves as a useful template given the extensive research over several decades of study of genetics and molecular biology, cytogenetics, hematological lineage analysis, drug discovery and related structural biology. The course involved teachers who were either basic scientists or clinicians. The topics covered and the teachers were as follows:

FEBRUARY '09 Clinical introduction

1. Introduction to hematological pathology inclusive of bone marrow.
2. Chronic Myeloid Leukemia
3. Pro-erythrocytic leukemia and hematological ward round
4. Hematopoietic stem cells and bone marrow niche
5. Bone Marrow transplantation

MARCH '09 Biology of leukemias

6. Hematopoietic stem cells: old and new concepts
7. Leukemic stem cells: Chronic Myeloid leukemia
8. Research seminar on cancer stem cells
9. Mathematical modeling of leukemias-Introduction
10. Mathematical modeling of leukemias

APRIL '09 Molecular mechanisms/structural biology of leukemias

11. FiSH and chromosomal translocations in leukemias
12. Mechanisms of rearrangements in leukemias
13. Epigenetics of leukemias
14. Structural basis of c-kit activation
15. Structural biology of BCR-Abl
16. miRNA in leukemia

TEACHERS:

1. Dr. R. Madhumati, Pathology Department, Kidwai Memorial Institute of Oncology
2 and 3. Dr. Cecil Ross, Professor of Medicine and Hematology, St. John's Medical College, Bangalore
4. Dr. Prithi Rajan, Stem Cell Institute, Christian Medical College, Vellore
5. Dr. Vikram Mathew, Department of Hematology, Christian Medical College, Vellore
6, 7 and 8. Dr. Connie Eaves, Director, Terry Fox Laboratory, VP of Research, Professor of Genetics, University of British Columbia, Canada
9 and 10. Dr. Lisette DePillis, Professor of Mathematics and the Norman F. Sprague, Professor of Life Sciences, California, USA and Dr. Seema Nanda, TIFR, Centre for Applicable Mathematics, Bangalore
11 and 12. Dr. Jayarama, Centre for Human Genetics, Bangalore and Dr. Sathees Raghavan, Department of Biochemistry, Indian Institute of Science, Bangalore.
13. Dr. Fredrerique Madignier, Lyon, France
14. Dr. Sandhya (from Dr. R. Sowdhamini's laboratory, NCBS)
15. Dr. Deepak Nair, NCBS
16. Dr. Yamuna Krishnan, NCBS

Meeting on hematological malignancies: basic and clinical interphase

AUGUST 02 - 03 2010

LIST OF SPEAKERS :

1. Dr. B. Poonkuzhali (Christian Medical College, Vellore)
2. Dr. Rajan Badwe, (TMH, Mumbai)
3. Dr. Freddy Radtke (EPFL Lausanne)
4. Dr. Ernesto Guccione (IMCB Singapore)
5. Col. Ajay Sharma (Army R&R Hospital, Delhi)
6. Dr. Sathees Raghavan (IISc. Bangalore)
7. Dr. Vikram Mathews (CMC Vellore)
8. Dr. Soniya Nityanand (Hematology Dept, SGPGI, Lucknow)
9. Dr. Sumeet Gujral (TMH, Mumbai)
10. Dr. Soumen Chakraborty (ILS, Bhubaneswar)
11. Dr. Chitra Mandal (IICB, Kolkata)
12. Dr. Swaminathan Padmanabhan (San Antonio, Texas)
13. Dr. John Powers (Harvard Medical School)
14. Dr. Cecil Ross (St John's Medical College and Hospital, Bangalore)
15. Dr. Seema Nanda (TIFR Centre for Applicable Mathematics, Bangalore)
16. Dr. Vishva Dixit (Genentech Inc.)

Exploring NOTCH and TAL1 pathways in human normal hematopoiesis and in T cell acute leukemias

VISIT OF FRANCOISE PFLUMIO, UNIVERSITY OF PARIS, DIDEROT, 3RD WEEK OF AUGUST, 2010
SPONSORED BY THE FRENCH GOVERNMENT, AS PART OF A FRENCH SCIENTISTS SEMINAR SERIES IN INDIA

DR. FRANCOISE PFLUMIO *is Research Director at INSERM, France and Group Leader, IRCM /CEA, "Hematopoietic and Leukemic Stem Cells". He obtained a PhD in immunology from University Louis Pasteur, Strasbourg, France and pursued post-doctoral studies at the Genetics department, Sick Children Hospital, Toronto, Canada and the Institut Gustave Roussy, Villejuif, France.*

Our work has been focused for several years on defining the role of molecular pathways, such as pathways regulated by the transcription factor SCL/TAL1, in human hematopoiesis and in particular in hematopoietic stem cells (HSC). In this context we have shown that enhanced TAL1 expression in human CD34+ cord blood cells increases HSC properties while decreasing TAL1 expression abolishes human hematopoietic development (Brunet et al. 2006, 2008 and Reynauld et al. 2005). As TAL1 is also implicated in human T-ALL development, we wished to investigate its role in human T cell leukemogenesis.

Several mouse transgenic models have been previously published that provided interesting findings on the biology of TAL1 induced T cell leukemia. In humans, except for large-scale gene expression analysis or studies on T-ALL derived cell lines, very few functional studies were previously performed using newly diagnosed patient samples, as they are difficult to manipulate. Our recent experiments thus focused on setting up conditions that allow reproducible in vitro growths, in vivo leukemia development and gene transfer of human newly diagnosed T-ALL samples. We have shown that activation of NOTCH pathway allows blast proliferation and preserves the leukemia initiating cell (LIC) activity (Armstrong et al. 2009). We have found that T-ALL cell populations are heterogeneous in terms of their response to NOTCH activation and drug sensitivity and that combination of CD34 and CD7 surface expression can enrich for T-LIC but can also define normal HSC/progenitor populations (Submitted paper). In parallel, we have defined gene transfer conditions that allow successful culture and xeno-grafting of T-ALL (Gerby et al. 2009). Under these conditions, we have shown that decreasing TAL1 expression in T-ALL dramatically interferes with proliferation and leukemia development in immune-deficient mice and we have defined NKX3.1, a tumor suppressor in prostate, as a direct target gene of TAL1 that can partly mediate TAL1 effects in human but not mouse leukemia development (Submitted paper). Our current experiments focus on the role of other oncogenic pathways for T-ALL development and studying the role of TAL1 in normal human HSC.

Workshop on clinical cytometry

3RD ANNUAL MEETING OF THE CYTOMETRY SOCIETY – INDIA & 11TH INDO-US CYTOMETRY WORKSHOP (OCTOBER 19TH – 24TH, 2010), NCBS, BANGALORE

PNH and lymphocyte subset analysis

OCTOBER 20TH (POST LUNCH) TILL OCTOBER 22ND (PRE-LUNCH)

VENUE: ST JOHN'S MEDICAL COLLEGE

This 2 day workshop will be focussed on Paroxysmal nocturnal hemoglobinuria and lymphocyte subset analysis Paroxysmal nocturnal hemoglobinuria (PNH): PNH is a rare disorder characterized by nocturnal hemoglobinuria (red urine), chronic intravascular hemolysis (complement mediated anemia), thrombosis, pancytopenia. Rarely it may be associated with myeloid malignancies. It is an acquired and intrinsic defect of cell membrane and affects erythroid, granulocytic, and megakaryocytic cell lines. These cells lack glycosylphosphatidylinositol (GPI)-linked proteins. Flow cytometry is an important tool for the diagnosis of this disease and helps detect the presence or absence of these GPI-linked proteins in granulocytes, monocytes, erythrocytes, and/or lymphocytes using monoclonal antibodies directed against CD14, CD55, CD59 and FLAER.

Lymphocyte subset analysis: The analysis of peripheral blood for lymphocyte subsets is used to assess immunological status in a wide variety of clinical conditions. Lymphocyte subset analysis is important in the diagnosis and management of autoimmune diseases, viral infections, leukemia, renal transplant and acquired immune deficiency syndrome. Participants will be taught how to process, acquire and analyse such cases.

Leukemia/lymphoma immunophenotyping

OCTOBER 22ND (POST LUNCH) TILL OCTOBER 24TH (PRE-LUNCH)

VENUE: KIDWAI CANCER HOSPITAL, BANGALORE

In this 2 days hands on workshop, participants will be taught processing, acquiring and analysis of samples of hematolymphoid neoplasms. Troubleshooting and common issues related to immunophenotyping will be discussed.

CLINICAL HEMATOLOGY

03

> HEMATOLOGY CENTRE AT ST. JOHN'S MEDICAL COLLEGE HOSPITAL
> ALLOGENEIC STEM CELL TRANSPLANTATION ~ VIKRAM MATHEWS, CMC, VELLORE
> PRINCIPLES AND CLINICAL APPLICATION OF FLOW CYTOMETRY IN HEMATOLYMPHOID NEOPLASMS ~ SUMEET GUJARAL, TMH, MUMBAI

HEMATOLOGY CENTRE
AT ST. JOHN'S MEDICAL COLLEGE HOSPITAL

The Hematology Services was started in 1990 from the department of Medicine. The clinical services began with the starting of Hemophilia care and blood component therapy with the support, training and encouragement of the Christian Medical College Hospital Vellore and further training at the royal free Hospital London and the St. Louis University MO USA. The blood bank became a blood component therapy unit in 1992 and the transfusion services provides red blood cells, platelets, plasma and other blood products. The Apheresis Programme was started 1997. Today the apheresis programme includes the collection of stem cells, white cells, platelets and plasma. It is a part of the Haematopoietic Stem Cell Transplant Programme and coordinates all activities of transplants including allogeneic stem cell transplant, non-myeloablative allogeneic stem cell transplant and autologous stem cell transplant providing the logistic support. The hematology unit is now able to provide comprehensive care and specialist consultation for the treatment of blood disorders and blood cancers. These include the various types of anemia, marrow aplasia, coagulation disorders, acute and chronic leukemia, myeloma, lymphoma and lymphoproliferative disorders. In addition to hematopoietic stem cell transplants, we also provide Biological and Cellular Therapies like administration of monoclonal antibody, interferons, growth factors and other specific agents. A supportive care programme is available to help patients who are convalescing from chemotherapy and stem cell transplant. This includes a Day Care facility for patients to receive outpatient chemotherapy, teaching class on care of central venous catheter, outpatient antibiotic and infusional therapy.

The blood bank at St.Johns Medical hospital

Allogeneic stem cell transplantation

VIKRAM MATHEWS, CMC, VELLORE

DR. VIKRAM MATHEWS *is a Professor at the Department of Clinical Hematology, Christian Medical College, Vellore.*

An allogeneic stem cell transplant (SCT) remains the only curative option for a number of benign and malignant hematological conditions. The central concept revolves around the ability to replace the haematopoietic stem cells (HSC) from a donor to a recipient resulting in a new donor derived haematopoietic system in the recipient. As a result, any disorder in which there is a HSC defect, either inherited or acquired, could potentially be treated by a haematopoietic SCT. Recognition of the key role played by human leucocyte antigens (HLA) in rejection of donor cells by the recipient and prevention of graft versus host disease (GVHD) mediated by donor derived lymphocytes resulted in the ability to consistently carry out this procedure between HLA identical recipients and donors. Prior to doing such a transplant it was essential to ablate the existing marrow and immuno-suppress the recipient to accept the donor derived stem cells. This was done by a various combinations of chemotherapeautic agents with or without irradiation and was called the conditioning regimen. In the early days, it was believed that this was the most important aspect of curing malignant hematological conditions. However, subsequent clinical observations noted a much higher relapse risk in transplants between identical twins vs. those from non-identical siblings paving the way for the notion of the donor derived immune system exerting a graft versus tumor (GVT) effect. Subsequent animal experiments and clinical experience established that this GVT effect was the most important factor that contributed to cure of patients with malignant disorders and that this effect could also be seen in non-haematopoietic tumors. Recognition of this resulted in changes in conditioning regimens which were less intensive with less treatment related mortality and relied mainly on the GVT effect to cure the malignant conditions. The ability to change the immune system also resulted in this therapy being tried with varying success in a number of auto-immune disorders. There continue to be significant advances made in optimizing conditioning regimens, GVHD prophylaxis, manipulation of grafts and supportive care that is steadily improving the clinical outcomes for patients undergoing this procedure.

Principles and clinical application of flow cytometry in hematolymphoid neoplasms

SUMEET GUJARAL, TMH, MUMBAI

DR. SUMEET GUJRAL *is an Associate Professor at the department of Pathology and an assistant officer-in-charge of Hemato-Oncology laboratory at the Tata Memorial Hospital, Mumbai. He completed his MBBS from PGIMS, Rohtak, India and obtained a MD in Pathology from All India Institute of Medical Sciences, New Delhi, India.*

FLOW cytometry (FCM) is a technology that simultaneously measures and analyzes multiple physical as well as chemical properties of cells, as they flow in a fluid stream through a beam of light (LASER). The properties measured include a particle's relative size, relative granularity or internal complexity, and relative fluorescence intensity. The blood sample (or the tissue sample broken into single cells) is held in a test tube, which is run in the FCM. These cells are tagged with fluorescent coated antibodies. The data thus generated is analyzed with the help of computer software.

Common clinical applications of FCM include CD4/CD8 counts (monitor sero-positive patients), immunophenotyping and CD34 hematopoietic stem cell counts. Lymph node biopsies may also be flowed for diagnosis and sub-typing of lymphomas, after making a single cell suspension. FCM helps in quantitation of antigens and provides an absolute value for the light intensity it measures (with the help of commercially available beads).

FCM is an integral part of any laboratory doing management of hematolymphoid neoplasms (leukemia/lymphoma). Common hematolymphoid neoplasms in children are acute lymphoblastic leukemias, while acute myeloid leukemias, chronic myeloid leukemias and chronic lymphoid leukemias are common in adults. Hematolymphoid neoplasms diagnosis involves integration of results of several modalities of investigation – morphology, immunohistochemistry (IHC), flow cytometry (FCM), cytogenetics and molecular diagnostics, in the context of clinical presentation and imaging investigations.

FCM is essential in diagnosis, sub-typing and follow-up of acute leukemias (in their lineage assignment), since treatment, prognosis and risk stratification are based on subtype of leukemia. It is also essential in diagnosis of lymphomas, especially in leukemia phase (chronic lymphoproliferative disorders). FCM analysis is usually performed on blood, bone marrow specimens and other body fluids or tissues (lymph nodes).

Laboratories generally design their own antibody panels for diagnosis of hematolymphoid neoplasms. Indian Guidelines (published, IJPM 2008) for panel selection are based on minimal panels based on morphology. Bethesda Consensus Guidelines define panels based on clinical indications. It is important to have a stringent internal quality control program and also participate in a proficiency testing program.

RESEARCH ABSTRACTS

04

> HEAT SHOCK PROTEIN 90 REGULATES THE EXPRESSION OF WILMS' TUMOR 1 PROTEIN IN MYELOID LEUKEMIAS ~ SWAMINATHAN PADMANABHAN, SAN ANTONIO
> IDENTIFICATION OF CRITICAL GENES THAT REGULATE DISEASE PROGRESSION IN ACUTE MYELOID LEUKEMIA ~ SOUMEN CHAKRABORTY, ILS, BHUBANESWAR
> NOVEL BIOMARKERS IN ACUTE LYMPHOBLASTIC LEUKEMIA ~ CHITRA MANDAL, INDIAN INSTITUTE OF CHEMICAL BIOLOGY, KOLKATA

Heat shock protein 90 regulates the expression of Wilms' tumor 1 protein in myeloid leukemias

SWAMINATHAN PADMANABHAN, SAN ANTONIO

DR. SWAMINATHAN PADMANABHAN *is the Director of Hematological Malignancies at the Institute for Drug Development, and the Cancer Therapy & Research Center, of the University of Texas Health Science Center at San Antonio, Texas. The IDD is internationally recognized for conducting the largest oncology phase I clinical drug studies program in the world. His research interests include elucidating the biology of Wilm's Tumor 1 protein and Heat shock proteins in acute leukemias, along with development of a translational drug development program in hematological malignancies.*

THE aberrant overexpression of Wilms' tumor 1 (WT1) in myeloid leukemia plays an important role in blast cell survival and resistance to chemotherapy. High expression of WT1 is also associated with relapse and shortened disease-free survival in patients. However, the mechanisms by which WT1 expression is regulated in leukemia remain unclear. Here, we report that heat shock protein 90 (Hsp90), which plays a critical role in the folding and maturation of several oncogenic proteins, associates with WT1 protein and stabilizes its expression. Pharmacological inhibition of Hsp90 resulted in ubiquitination and subsequent proteasome- dependant degradation of WT1. RNAi-mediated silencing of WT1 reduced the survival of leukemia cells and increased the sensitivity of these cells to chemotherapy and Hsp90 inhibition. Furthermore, Hsp90 inhibitors 17-AAG and STA-9090 significantly reduced the growth of myeloid leukemia xenografts *in vivo* and effectively downregulated the xpression of WT1 and its downstream target proteins c-Myc and Bcl-2. Collectively, our studies identify WT1 as a novel Hsp90 client and support the crucial role for the WT1- Hsp90 interaction in maintaining leukemia cell survival. These findings have significant implications for developing effective therapies for myeloid leukemias and offer a strategy to inhibit the oncogenic functions of WT1 by clinically available Hsp90 inhibitors.

Identification of critical genes that regulate disease progression in Acute Myeloid Leukemia

SOUMEN CHAKRABORTY, ILS, BHUBANESWAR

DR. SOUMEN CHAKRABORTY *is a Research Scientist at the Institute of Life Sciences, Bhubaneshwar. He obtained his PhD in microbiology from the National Institute of Cholera and Enteric Diseases, Kolkata. He has been a Research Associate at the Loyola University Medical Centre, Chicago and held the positions of Research Associate and Assistant Professor at the University of Illinois, Chicago. His research interests include the molecular and biological characterization of oncogenes involved in leukemias and solid tumors.*

OF the heterogeneous human leukemia, CML characterized by BCR-ABL gene rearrangement has been studied extensively. The main characteristics of CML include blocked differentiation, enhanced proliferation, growth factor independence and resistance to apoptosis. In patients with CML who do not reach a (near) complete cytogenetic response, the disease progresses over several years from an indolent, chronic phase into a rapidly growing fatal blast crisis phase. Disease progression and blast crisis CML are associated with characteristic non-random cytogenetic events like increased oncogenic activity or loss of tumor suppressor activity. However, what causes transformation and disease progression to blast crisis is poorly understood. To identify novel genes and changes in gene expression profile that occur during the course of the disease, microarray analysis on sequentially collected blood mononuclear cell pellets from leukemic patients are carried out in the laboratory. Differential expression of identified genes is validated in other patient samples by qPCR. Identification of new genes will help us understand the contribution of molecular events and/or secondary mutations (other than BCR-ABL) to disease progression and to improve therapeutic approaches for CML. Although we are a long way from discovering all the players involved in CML and CML-BC, we have made a beginning.

EVI1 (ecotropic viral integration site 1) is one of the genes associated with murine and human myeloid leukemia. It is inappropriately expressed by chromosomal rearrangements that disrupt the 3q26.2 chromosomal region. The proto-oncogene EVI1 synergizes with pre-existing oncogenes (such as BCR/ABL) to give a highly proliferating and aggressive leukemic clone in a subgroup of CML patients that progresses to blast crisis. EVI1 upregulates cell cycle, causes loss of hematopoiesis and is unresponsive to cytokines that control hematopoietic growth or differentiation. EVI1 belongs to a family of nuclear proteins that are post-translationally modified i.e. it is both acetylated and phosphorylated. Multiple post translational modifications lead to a complex regulatory program that transduces molecular information to and from signaling pathways. Whether similar cascade of events occur in the context of EVI1 and whether the cellular mechanisms for coordination of EVI1 phosphorylation and acetylation support leukemogenesis remains to be determined.

Novel biomarkers in Acute Lymphoblastic Leukemia

CHITRA MANDAL, INDIAN INSTITUTE OF CHEMICAL BIOLOGY, KOLKATA

DR. CHITRA MANDAL *is a Director Grade Scientist at the Indian Institute of Chemical Biology, Kolkata. She has worked in the field of glyco immunology and its application in both applied and basic medical research. The main theme of her research group is to understand the mystery of glycosylation of biomolecules in health and disease. She has established novel decisive-biomarkers specifically induced in lymphoblasts of children with acute lymphoblastic leukemia (ALL) this is helpful for both the diagnosis and monitoring of the disease. She has established an antigen based diagnostic technology for patients with visceral leishmaniasis. She has demonstrated for the first time glycosylated human C-reactive protein (CRP) in different pathological conditions and their role in innate immunity. All these works have lead to the transfer of three technologies to the industry.*

ACUTE lymphoblastic leukemia (ALL) is the single commonest type of cancer in pediatric population and may be defined as a clonal haematopoietic disorder, characterized by cell maturation arrest, aberrant proliferation and accumulation of malignant lymphoblasts in the bone marrow (BM), which migrate to the peripheral blood (PB) in due course.

With current treatment protocols, the threat of relapse remains, and about 20% patients in remission may harbor residual leukemic blasts defined as minimal residual disease (MRD). The sophisticated technical expertise required to detect MRD constrains its overall clinical acceptance. Therefore, identification of new biochemical markers is still in demand, whose varied expression could be utilized for monitoring individual chemotherapeutic response and predicting impending relapse.

Sialic acids generally found as the terminal sugar of glycan chain attached to cell surface glycoproteins and glycolipids as well as secreted glycoconjugates. Frequent O-acetylations of sialic acids generate a family of O-acetylated sialoglycoconjugates and play an important role in modulating various biological and pathological processes including adhesion, signaling, differentiation, apoptosis and malignancy.

Based on hard clinical data, we have firmly established a few ALL-associated 9-O-acetylated sialoglycoproteins and glycolipids as decisive novel biomarkers induced on lymphoblasts of childhood ALL (Sinha et al., 1999, Mandal et al., 2000, Pal et al., 2004). We have further demonstrated a link between induction of this sialoglycotope and their role in regulating viability of lymphoblasts suggesting that O-acetylation of sialic acids on lymphoblasts may be an additional mechanism that promotes the survival of these cells by escaping apoptosis (Gosh et al., 2005, Bandyopadhyay et al., 2005). Proteomics approaches to understand these clinically important molecules might help to find out suitable drug target.

Recently, we have demonstrated an increased sialate-O-acetyltransferase activity (Mandal et al., 2009) responsible for O-acetylation of sialic acids, enhanced expression of sialyltransferases and decreased membrane associated sialiadase activity in ALL (Mandal et al., 2010). More importantly, expression of these enzymes changes with the disease progression (Mandal et al., 2009, Mandal et al., 2010). Thus these enzymes responsible for the specific sialylation will help us to find some specific inhibitors and may be used as molecular targets.

These sialoglycoconjugates are highly immunogenic as high levels of disease-associated antibodies were found in the serum of these patients (Bandyopadhyay et al, 2005). Therefore, sialoglycoconjugates, their antibodies and enzymes involved in their metabolism could reasonably be used as suitable markers in ALL and to identify MRD. Additionally, we are in a process of identifying anti-leukemic pure herbal agents as well as potential target molecule for future improved chemotherapy exploring through systems biology approache (Bhattacharya et al., 2010).

Normal haematopoiesis occurs in BM microenvironment where haematopoietic progenitor cells (HSCs) adhere selectively to stromal cells and extracellular matrix. In order to understand the defect in maturation of HSCs in ALL, currently, we are in a process of investigating the role of differential sialylation in maturation and mobilization of HSCs from BM and their signaling process. Investigation of normal HSCs for autologous transplantation and identification of leukemic stem cells are ongoing.

Building a strong research component with a mix of both basic science driven curiosity and the need for translation to the community, both in the hospital and in an "outreach" manner.

COMMENTARIES

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The hematopoietic system and the Notch pathway

FREDDY RADTKE, EPFL, LAUSANNE

THE hematopoietic system is mesoderm derived, originates from different sites during embryonic development and is generally closely associated with vasculogenesis. The most primitive hematopoietic cells are found within the extra-embryonic yolk sac before hematopoiesis shifts to intra-embryonic sites including the para-aortic splanchnopleiura and aorta-gonad mesonephros (P-sP and AGM). Later hematopoiesis occurs in the fetal liver before it is finally established in the bone marrow (Godin and Cumano, 2002). The first hematopoietic stem cells (HSCs) capable of long-term repopulation of all blood lineages upon transplantation are found within the AGM region. These cells are generated from a bipotent hemangioblast by budding off from the dorsal aorta of midgestation embryos (de Bruijn et al., 2002). In the adult, HSCs localize near bone surfaces and the sinusoidal epithelium, which supposedly function as stem cell niches. The cross talk between HSCs and niche molecules are thought to control self-renewal and differentiation (Wilson and Trumpp, 2006). HSC have the unique capacity to self-renew and to differentiate thereby giving rise to all mature blood cell types. Flow cytometric analysis combined with transplantation experiments have allowed to establish a cellular hematopoietic hierarchy characterized by HSCs giving rise to lineage restricted oligo-potent progenitor cells for lymphoid, myeloid and megakaryocyte-erythrocyte lineages that then differentiate into terminally differentiated blood cells (Kondo et al., 2003). Generation of stem cells, its maintenance and differentiation are controlled by many factors and signaling pathways. One of these signaling pathways that play an important role within the hematopoietic system at different levels is the evolutionarily conserved Notch cascade. The Notch pathway mediates cell-to-cell signaling and thereby influences many cell fate decisions and differentiation process. In hematopoiesis, Notch is required for the generation of hematopoietic cells to establish definite hematopoiesis in the developing embryo. In the adult Notch function is important in particular for the lymphoid arm of the hematopoietic hierarchy. Notch specifies the generation of a subset of B-lymphocytes called marginal zone B cells, which are an important line of defense against blood borne pathogens against which they produce a first wave of antibodies. Another well-known and characterized function of Notch is its essential role for the specification of T lymphocytes as well as its ability to influence T cell specific responses against different pathogens. Thus Notch is a master regulator for T cells. This is also reflected by the fact that aberrant Notch signaling causes T- cell acute lymphoblastic leukemia (T-ALL), in mouse and man. In fact more then 50% of all T-ALL patients harbor activating mutations within the NOTCH1 gene, which represents the most frequent genetic alteration found in T-ALL (reviewed in Radtke et al. 2010).

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Cancer stem cell paradigm in leukemia

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CANCER stem cells (CSCs) are defined as a small population of cells in a tumor that retain the ability to re-initiate the cancer with a much higher efficiency than the bulk tumor cell population. CSCs share many properties with normal stem cells like the ability to grow indefinitely, self-renew and differentiate. CSCs may also show high membrane ATP-binding Cassette (ABC) transporter activity which confers multi-drug resistance (Woodward et al., 2007). They additionally have the ability to form tumors in immuno-compromised mice, to migrate and metastasize (Wicha et al. 2006). In many cases, cancer stem cells share markers of the normal stem cells of the tissue of origin of the cancer. Since cancer stem cells share many features of the adult stem cells, it is important to understand the differences in signaling operating between the two populations. Such studies will help design therapies uniquely targeting the cancerous population.

The existence of CSC was first reported by John Dick's group in Acute Myeloid Leukemia (AML) (Lapidot et al., 1994 and Bonnet et al., 1997). In a series of elegant experiments they proved that the cells that initiate AML were phenotypically similar to the normal adult hematopoietic stem cells and were CD34+ CD38-. Additionally, once leukemia developed it could be serially transplanted to secondary recipients showing self-renewal of these cells. This discovery raised the possibility that the mutations resulting in cancer actually occur in primitive tissue stem cells which then divide uncontrollably. Alternatively, the mutations could occur in early progenitors which gain the ability of self-renewal (Tan et al., 2006). Since then, cancer stem cells have been reported from various hematological malignancies like CML (Holyoake et al., 2002), Multiple Myeloma (Matsui et al., 2008) etc. The identification of stem cells in AML in the mid-90s sparked similar research in solid cancers. But it was only nearly after a decade that a similar population could be isolated from solid tumors. Peter Dirks' group identified a small subset of cells from brain cancers that expressed CD133 (which also marks normal neuronal stem cells) and preferentially gave rise to tumors in mice (Singh et al., 2003 and Singh et al., 2004). Cancer stem cells have since been reported from cancers of the breast, prostate, colon etc (Al-Hajj et al., 2003, Collins et al., 2005, O'Brien et al., 2007 and Ricci-Vitiani et al. 2007).

Cancer genomes: Implications for hematological malignancies

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CANCER is a disease of genome and each patient's genome is different with different unique combination of single nucleotide polymorphisms, germline and somatic mutations. Although the identification of specific genetic lesions occurring within tumour genomes has been a goal of many molecular oncologists, using conventional cytogenetics techniques, they have primarily focused on a candidate set of genes and have thus provided a constrained view of the mutational spectrum.

Currently, a lot of work is undergoing to identify genetic variations underlying the risks and pathogenesis of several cancers and to develop diagnostic tests to predict patient's responses to targeted therapy. Most strikingly, with the latest next generation sequencing facility, we will be able to get a catalogue of cancer genome mutations/alterations from hundreds of cancer patients in a very short span of time. With all these enormous amounts of new information from unbiased and comprehensive Cancer Genome Project, we will be able unravel the DNA and RNA level somatic alterations that are specific for tumor development and progression. These discoveries will not only enhance our understanding about the pathobiology of cancer but will also lead to development of new strategies for treating patients. One can begin mapping these mutations/alterations on the signaling pathways and if one or two signaling pathway is dysregulated by these mutations in a patient. Clinicians can then develop new strategies to treat them by using the best combination of drugs targeting those pathways.

With the advent of new sequencing technology, scientists from Washington University unraveled the genetic basis of first cancer genome from an AML patient and discovered 8 novel mutations present in virtually all the tumour cells at presentation and relapse suggesting its important functional role in the progression of the disease (Ley T.J. et al., 2008). Later several unbiased whole genome sequencing of matched tumor and normal samples, or matched primary and metastatic cancer genomes from the same patient has lead to discovery of the most interesting and unexpected genomic alterations like several point mutations, inter and intra chromosomal translocations, inversion and large deletions in the cancer genome. For example, using transcriptome sequencing, Maher et al., 2009 discovered a novel fusion transcript in prostate tumor which would have been missed by conventional techniques and was a starting point to further investigate the functional role of these novel fusion transcripts in prostate cancer development. All this information from the cancer genome will allow researchers to create better molecular diagnostic tools, determine which patients will benefit most from certain treatments, and identify candidate genes for new or improved targeted therapeutics in near future.

Epigenetics in leukemia

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IDENTITIES of cells in multicellular organisms are defined by the individual gene expression programmes of different cell types. Since all cell types contain the same DNA, epigenetic regulation of gene expression is necessary for such differential gene expression. Similarly, gene expression in hematopoeisis is influenced by factors like DNA methyltransferases (DNMTs), Histone acetyltransferases (HATs), Histone methyltransferases (HMTs), and Chromatin remodelers. Epigenetic phenomena and aberrant gene regulation play a major role in carcinogenesis. Such mechanisms are also implicated in manifestation of leukemia, which notably include translocations, leading to the expression of fused gene-regulatory proteins; aberrant gene silencing by imposing inactive histone marks on promoters; aberrant methylation of DNA at CpG islands; aberrant expression of microRNAs and the active repression of promoters by oncoproteins. Translocations could fuse the DNA-binding domain of a transcription factor with a novel interaction domain of another, thereby inactivating the latter or recruiting chromatin modifying agents that are not desired for normal function as seen in case of RUNX1(a factor vital for hematopoetic lineage specificity) fusions, which inactivate it. Translocations could also lead to chromatin modifying complexes being recruited to ectopic sites by fusion of a chromatin modifier to a DNA-binding moiety or an interaction surface recognizing other transcription factors. For e.g., fusions involving MLL1 methyltransferase interfere with the proper regulation of histone H3 Lys4 tri-methylation at promoters, which is necessary for activation of transcription, leading to either loss or deregulated transcriptional state and thus deregulated gene expression. Fusions of a phospoprotein nucleophosmin (NPM1) with many partners like NPM-ALK, NPM-RAR NPM-MLF1 is well known in leukemia. NPM1 being a recently discovered histone chaperone that activates chromatin transcription in an acetylation dependent manner, its role in pathogenesis of leukemia need to be relooked. NPM1 has roles in ribosome biogenesis. NPM1 is acetylated by p300 acetyltransferase and further activates expression of genes responsible for oral cancer manifestation. It is unsure if such a mechanism operates in Leukemia. Further studies are required to understand the role of NPM1 in Leukemia from an epigenetic point of view.

MicroRNAs (miRNAs) are non-coding small RNAs that bind to mRNAs and form duplex molecules that are either degraded or are unable to be translated. miRNA targets include mRNA for transcription factors and signaling proteins that are required for proper haematopoiesis. Genes encoding miRNAs are also deregulated or mutated in leukemia. The deletion of a miRNA cluster in the 13q14.3 region is associated with loss of miR-15a/16-1,

which targets the anti-apoptotic protein Bcl-2. Thus loss of this miRNA leads to overexpression of this protein, thus contributing to the pathogenesis of chronic lymphocytic leukemia. Leukemic oncoprotein RUNX1–ETO (RUNX1T1) downregulates miR223 expression and this contributes to the differentiation block in myeloid precursors.

Yet another mode of epigenetic regulation is methylation of DNA. It has now been proved to be a suppressor of transcription in vivo. Establishment of correct DNA methylation patterns is intricately linked to differential gene expression as the basis of all cell differentiation processes including hematopoesis. Aberrant methylation of DNA on the promoters of tumor suppressor genes is reported to be a cause for malignancy. This could be true in leukemia as well. Considering the fact that in normal cells, there is a negative cross talk between MLL1 mediated active epigenetic mark H3K4 trimethylation and DNMT3L mediated inhibitory mark i.e., DNA methylation at the same promoter, any disruption of this mechanism could potentially inhibit expression of tumor suppressors leading to leukemia. Considering the wealth of information available on epigenetic mechanisms that could cause leukemia there has been an active search for agents that target the particular epigenetic phenomena in question. siRNAs targeted to RUNX1-ETO in leukemia patients inhibited the expression of the abnormal fusion protein and resulted in improved differentiation of precursor cells. Peptides and Small molecules that target protein-protein interaction and thus abolish oligomerization of abnormal fusion proteins are the need of the hour. Hypomethylating agents like 5-Azacytidine have been used to rescue cells from aberrant hypermethylation of promoters of important cell cycle genes and tumor suppressors. Global hypomethylation has been demonstrated in following treatment of patients with DNMT inhibitors, demonstrating the proof of principle. They have also added to overall survival of patients. Histone acetylation is necessary for active transcription. Histone deacetylation and the promoters of tumor suppressor genes is known for many forms of cancer including leukemia. Theoretically, use of histone deacetylase inhibitors could hyperacetylate promoters of tumor suppressors thus reversing the pathology. This has warranted the use of inhibitors of histone deacetylases like Sodium Valproate. It could be possible that combination of hypomethylating agents with histone deacetylase inhibitors could prove to be more useful than any one agent since their effects are additive in nature. So elucidating the right combination of drugs and the right category of responders is vital. One impediment to such therapeutics is the existence of multiple forms of leukemia afflicting different hematopoetic cell lineage, with varied molecular and cellular pathology. Hence, to resolve this issue systematic profiling of each of the leukemic forms, for epigenetic signatures, is necessary.

Mathematical modeling of leukemias

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THE last 10 years has seen a tremendous growth in the use of mathematical modeling in cancer research. Earlier models in cancer gave qualitative information. As the efforts in mathematical modeling of cancers increases, there is a shift to useful quantitative results which may help to make predictions. In 1972, Lincoln suggested that by 2001 mathematical models and simulations would become a major part of clinical practise. We have moved slowly in this direction though it has not happened in its entirety for most cancers including leukemias.

One of the earliest mathematical models of leukemia, (Fokas et al 1991) studied granulocytopoiesis in normal and CML patients. This paper along with several others (Moore & Li 2003, Adimy 2005, Colijn & Mackey 2005, Lee et al 2005 to name a few) that were published in the subsequent two decades continued to be theoretical in nature, in the sense that while an understanding of the biological processes was incorporated in the model development process, these models continued to be separate from clinical practise. Most of these models have used Ordnary Differential Equations (ODEs) which are somewhat simpler to handle mathematically, as opposed to Partial Differential Equations (PDEs) used to model cancer tumors. A simplifying assumption that peripheral blood is well mixed and hence spatial effects can be ignored allows us to use ODEs for leukemias.

ODEs are population level models and useful to study longer term disease progression and generally provide good qualitative information such as important parameter values that could play a part in curbing disease progression. Recently with the introduction of molecular targeted therapies, mathematicians and clinicians have been interested in questions such as ' What would be an optimal dosing strategy for an individual patient?' Optimal control techniques have been used with ODEs to try and answer this question (Nanda et al., 2007). While using parameter values from medical literature, most of these models continue to be separate from clinical practise though motivated by relevant questions for clinicians.

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Leukemias offer a tractable disease paradigm for mathematical modeling as clinical measurements are easily quantifiable with a blood draw. The disease lends itself to well organized therapy regimens. Cell kinetics can be quantified through the course of the treatment allowing us to verify models. Thus many discovery opportunities await clinicians and mathematicians willing to partner in research efforts. Michor et al, 2005 was one of the first models that used clinical patient data. They quantified the hitherto unknown, turn over rates of leukemic cells in different stages of cell differentiation process. While these conclusions would have to be conclusively verified by experiments, this is a significant step forward.

The mathematical techniques that could be used in studying leukemias vary depending upon the biology being studied. Models at the gene level are generally probability models or algorithmic in nature. Almost all of mathematical modeling of cancers today uses computations for solutions. Thus while the tools needed in mathematical modeling are vast, it is essential for the biologist today to have some familiarity with them for collaborative research with non-biologists.

TECHNIQUES

06

Proteomics in leukemia

AKHILESH PANDEY, IOB, BANGALORE AND JOHNS HOPKINS, USA

MUTATIONS and other genome level alterations including translocations, copy number variations (CNVs), mRNA expression and miRNAs have been extensively studied in leukemia. Although targeted therapies have been developed in some cases where the molecular mechanisms are well understood, the pathogenesis of many subsets of leukemias is still not understood. It is beginning to be appreciated that cancers are often driven by activation of signaling pathways involved in cell growth and proliferation. Global analysis of aberrantly regulated signaling pathways in cancers is now underway to determine the pathways affected in cancers. This will not only aid in determining the underlying mechanisms that govern cancers, but will also provide options for therapeutic intervention. While genomic and transcriptomic methods can reveal the underlying alterations, the functional implication of these alterations is more apparent at the proteome level. Mass spectrometry is a generic technology that allows researchers to study protein level changes in a high-throughput fashion. The most commonly used quantitative proteomics strategies are SILAC and iTRAQ, which are now routinely used to study various diseases including cancers. These techniques can be utilized to study differences in protein abundance and post-translational modifications such as phosphorylation on a global scale. A recent study by Cynthia et al in the journal Cancer Cell exemplifies the utility of proteomic approaches to identify potential therapeutic targets in leukemia. This study carried out phosphoproteomic analysis using mass spectrometry to identify SYK as a therapeutic target in acute myeloid leukemia.

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miRNAs are already well documented to play an important role in the biology of leukemias and leukemic stem cells. It is understood that miRNAs often regulate gene expression through translational repression rather than mRNA degradation. Thus technologies such as gene expression microarrays that measure changes at the mRNA level are quite limited in identifying miRNA targets. Quantitative proteomics enables researchers to identify targets of miRNA in a direct and efficient manner.

Cancer stem cells are known to possess high tumorigenic potential and resistance to chemotherapeutic agents. Identification of cancer stem cells in leukemia has generated a lot of curiosity among researchers and opened up several avenues to interrogate their role in cancer initiation and progression. Although some of the surface markers have now made it possible to enrich this sub-population for further characterization, efforts are underway to identify additional surface markers for more specific enrichment of the stem cell population. Proteomics can be used to identify cell surface molecules in this scenario.

Induced pluripotent stem cells hold great promise as a therapeutic strategy in wide range of disorders. Several approaches have been used to induce pluripotency in somatic cells. Most of these approaches rely on expression of a combination of transcription factors. The complex signaling events that lead to induced pluripotency in these somatic cells remain ill understood. Further, molecular differences and similarities across various types of iPS cells and between ES cells and iPS cells remain largely uncharacaterized. Proteomic strategies can facilitate systematic studies on iPS cells to determine underlying signaling pathways that dictate pluripotency and also to develop markers that can track differentiation along various lineages.

EMERGING PERSPECTIVES

We are planning to take the courses, meetings and workshops that we have been organizing around the theme of hematological malignancies further by building a vigorous research programme. One of the themes that has emerged as a likely focus is the “biology of relapses in hematological malignancies”. With the emergence of therapies that have had some success in these diseases, a focus on resistance and relapses would offer an opportunity for basic scientists to work closely with clinicians in an area of both clinical and and basic science importance. In addition, to understanding the molecular mechanisms of relapse and resistance, this process is likely to generate immediate benefits in terms of better techniques of early detection, optimization of therapeutic protocols etc. This brochure has attempted to provide a snapshot of the diversity of areas that are likely to strongly influence both research and emerging treatments in human hematological diseases. There is already an ecosystem to support and nurture an initiative in hematological malignancies with the established basic science and medical centres in North and South Bangalore respectively. We also hope to engage closely with newer initiatives such as the Institute for stem cell biology and regenerative medicine, International Centre for Theoretical Sciences, Institute of Bioinformatics etc. In addition to core institutional funding, we will continue to engage governmental agencies such as the Department of biotechnology in this research and teaching programme in hematological malignancies.


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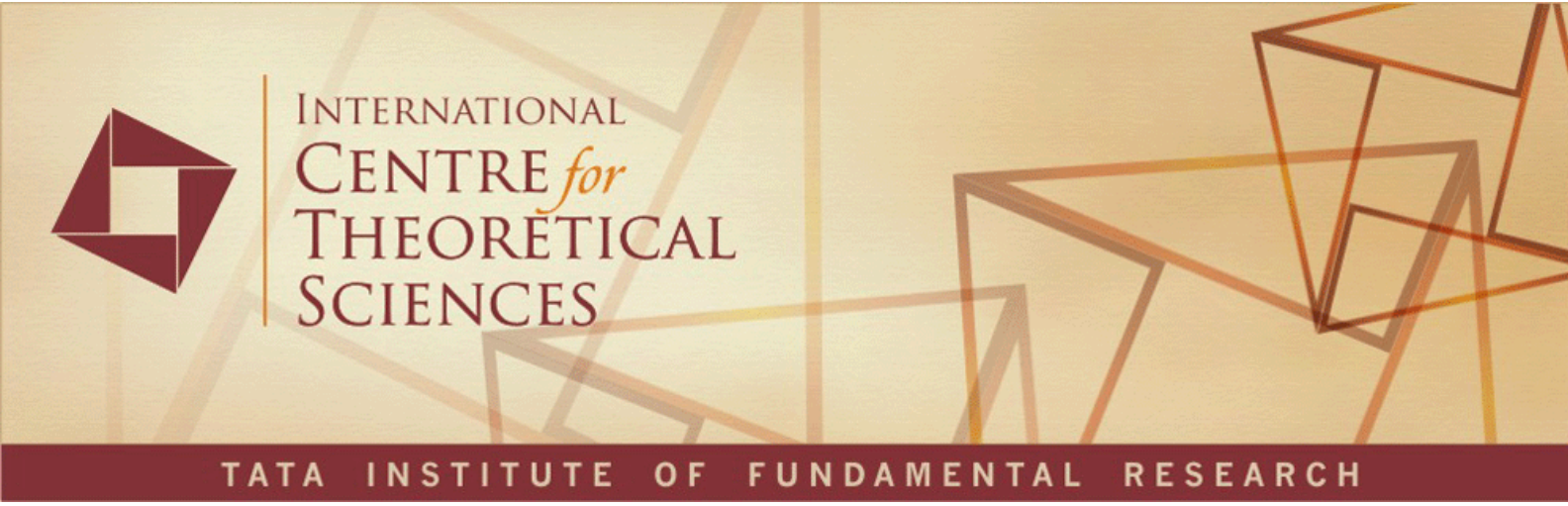
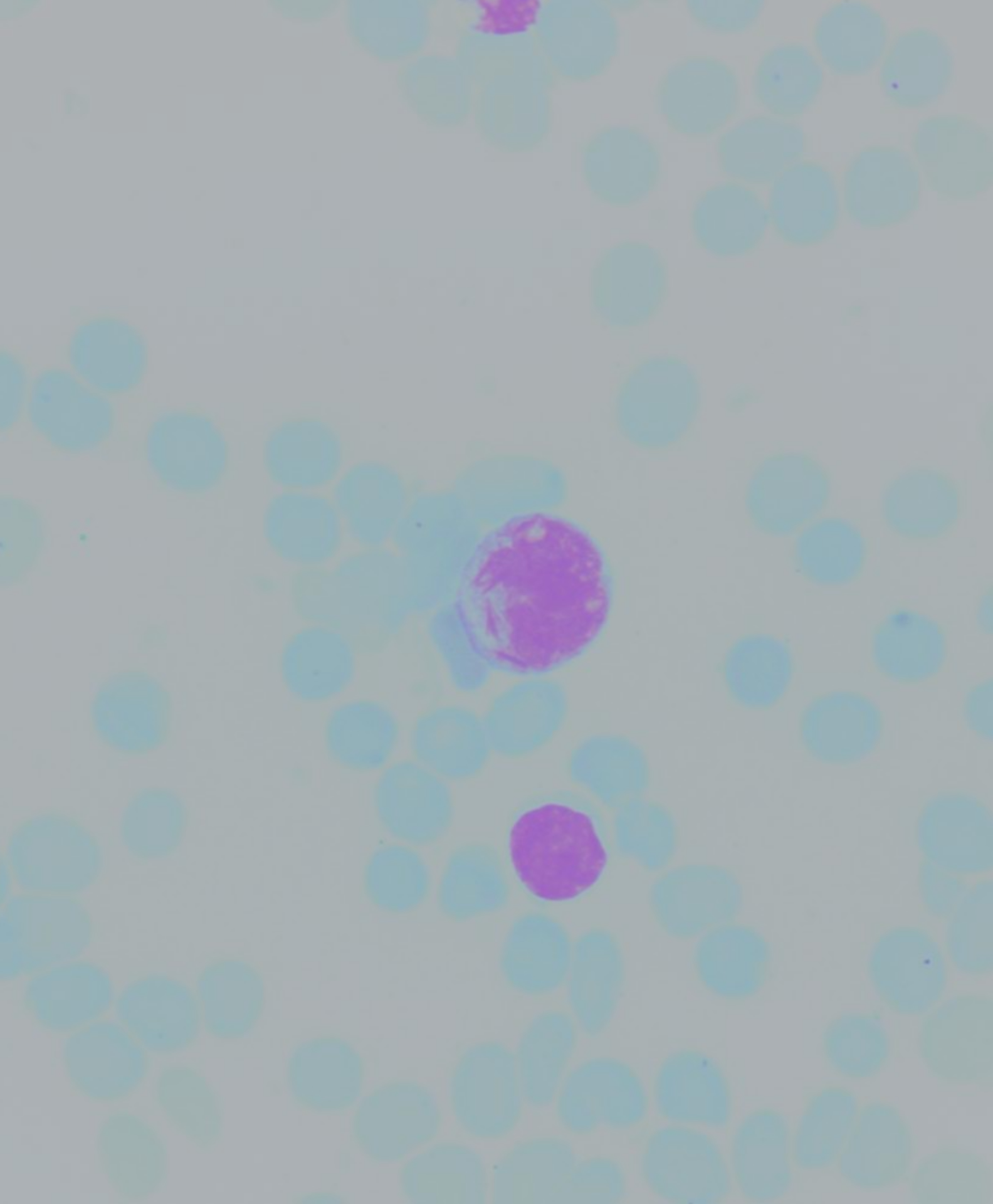


Leukemia Program 2010-2011

This program consisting of the meeting *Hematological Malignancies: a basic science and clinical initiative* Aug 2-3, 2010 and the year long Leukemia Course during the academic year 2010-2011 is an ICTS program. The goal of this program is to bring together medical practitioners, basic scientists and mathematicians to pursue fundamental research in the Hematology. For program details visit http://www.icts.res.in

This program is the first in a long term effort to organize an interdisciplinary research community in Hematology in the Bangalore and surrounding areas, and would not have been possible without the encouragement and support of ICTS.

The International Centre for Theoretical Sciences (ICTS), located in Bangalore, is a newly established centre of TIFR, Mumbai. Its primary mandate is to provide a platform and infrastructure to organize various activities in theoretical and mathematical sciences, at the forefront of knowledge, with an emphasis on activities in areas overlapping traditional fields of science. The aim is to contribute critically to research excellence and build strength in theoretical sciences through a well thought out, responsive, program of research activities and necessary education/training. For further details about the Centre and how to apply for organizing a program, please visit the website http://www.icts.res.in/



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