Centre for Cancer Research

ADVANCING BASIC, TRANSLATIONAL, AND CLINICAL RESEARCH:

A Strategic Plan for the Centre for Cancer Research 2013-2015

IMU IRDI
INSTITUTE FOR RESEARCH, DEVELOPMENT & INNOVATION

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The Centre for Cancer Research (CCR) conducts and supports research on cancer and across an integrated continuum of discovery, development, and delivery.

At the CCR, we leverage our scientific expertise and technological forces with key partners to achieve our vision of reducing the burden and eliminate the adverse outcomes of cancer by leading an integrated effort to advance fundamental knowledge about cancer across a dynamic continuum of discovery, development, and delivery.

Fulfilling our vision requires ingenuity and collaborations across:

- CCR research groups and laboratories
- Government and funding agencies
- Extramural laboratories at universities and research institutes
- Technology companies
- Pharmaceutical companies
- National and international biomedical consortia
- Combinations of the above

Advancing Basic, Translational, and Clinical Research: A Strategic Plan for the Centre for Cancer Research is a dynamic document intended to inform, lead, and fuel discovery among CCR investigators and trainees, our colleagues throughout IMU, and the wider biomedical research community.

Advancing Basic, Translational, and Clinical Research:

A Strategic Plan for the Centre for Cancer Research

For Internal Use Only

International Medical University (IMU), Malaysia

Content

Director's Message

Identifying High-Impact Priorities

Advances in the prevention and treatment of cancer are the result of hard work, patience, ingenuity, careful planning, and significant investments of time and resources. Capitalizing on these investments requires looking back at how far we've come and looking forward to identify the areas in which we can do our best work. Cancer research in IMU has made, and continues to make, critical advances in the understanding of cancer. As part of the IMU Institute of Research, Development and Innovation (IRDI), the Centre for Cancer Research (CCR) will conduct basic, translational, and clinical research — from fundamental research on the origins of cancer, to clinical trials that test promising discoveries, to development of novel therapies and prevention approaches to cancer. Our goal is to work in tandem with our academic and industry colleagues to share discoveries made here as broadly as possible.

By maintaining a clear focus on our purpose, we will build synergy around a seamless, integrated, and continuous discovery, development, and delivery process. Our research will be targeted to those areas of pursuit that show greatest promise. New development will promote the most compelling interventions based on evidence emerging from that discovery. The delivery of evidence-based interventions will be universal. What we learn in public health and medical practice will foster our understanding of the biology of cancer and make possible increasingly more effective interventions.

The CCR Strategic Plan, *Advancing Basic, Translational, and Clinical Research,* contains the most compelling initiatives that the CCR will pursue over the next several years to make the new era in cancer care a reality. Developed by teams of CCR investigators, the plan sets forth four distinct yet highly interrelated objectives that fit squarely within the framework of the current *Institute of Research, Development, and Innovation (IRDI) Strategic Plan* and the *IMU ASPIRE Strategic Plan,* both of which chart far-reaching initiatives to reshape the way medical research is conducted. Like these plans, the CCR Strategic Plan articulates our commitment to deepen our understanding of cancer and deliver effective therapies to improve public health. It is our hope that each and every scientist, physician, and trainee at the CCR will be inspired to take on the challenges set forth in this plan. Doing so will lead us all toward new insights and research paths that unravel the complexities of cancer and take us in unanticipated and exciting new directions.

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IMU, Vice President (Research)
Institute for Research, Development, and Innovation (IRDI), Director
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The Centre for Cancer Research

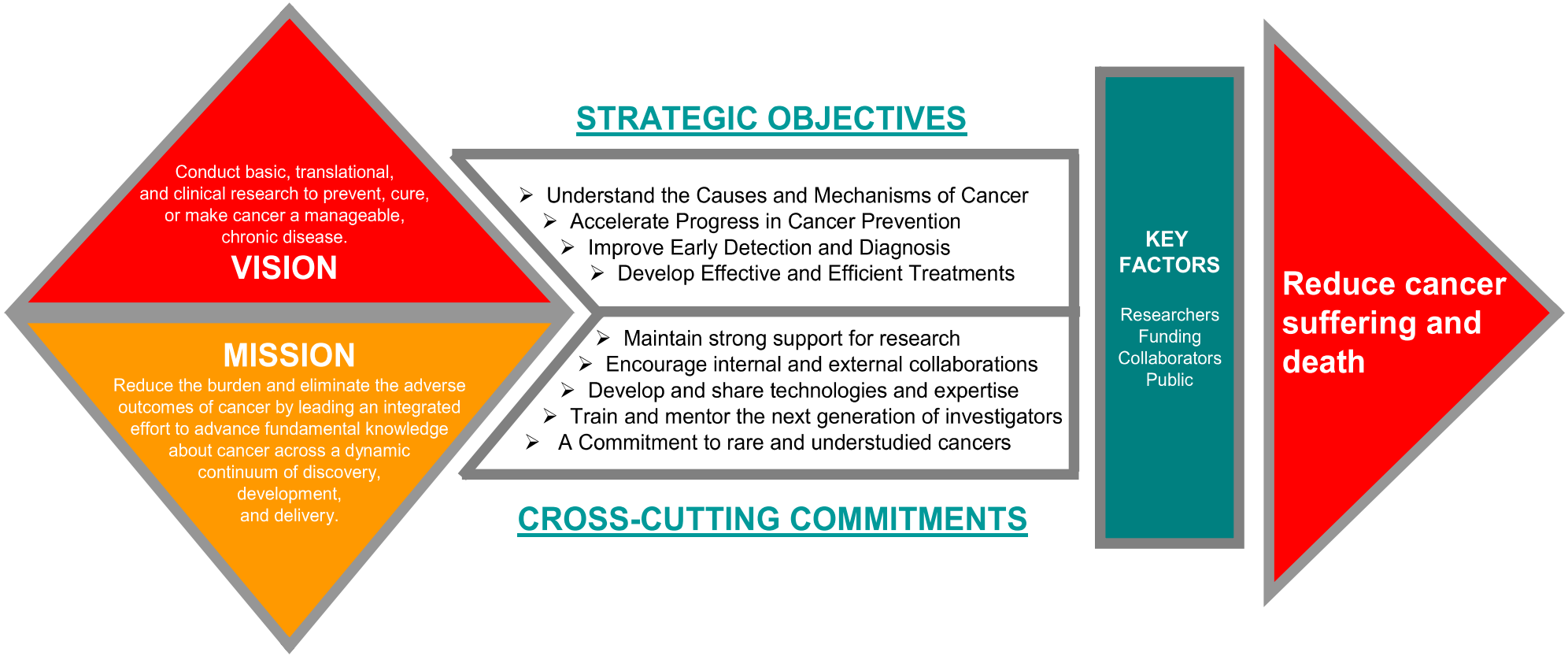
Our Vision

Conduct basic, translational, and clinical research to prevent, cure, or make cancer a manageable, chronic disease.

Our Mission

Reduce the burden and eliminate the adverse outcomes of cancer by leading an integrated effort to advance fundamental knowledge about cancer across a dynamic continuum of discovery, development, and delivery.

THE FRAMEWORK TO ENHANCE CANCER RESEARCH IN IMU



Executive Summary

Overview of the CCR Strategic Plan

Advancing Basic, Clinical, and Translational Research is a series of four distinct yet highly interrelated objectives that the CCR will pursue over the next several years to reduce the burden of cancer. As the research arm of the IMU's Intramural Research Program, the CCR is the centre within the IMU Institute of Research, Development and Innovation (IRDI) that conducts long-term, high-priority basic laboratory research in cancer and translates promising findings into novel therapies through its in-house clinical research program and collaborations with external partners. In this capacity, the CCR aims to play an integral role in the development of many of the prevention and treatment approaches used in the near future and continues to stimulate discovery in cancer research worldwide. In this important role, it is imperative that the CCR identify and share its top priority objectives through its Strategic Plan.

A Basis for Priority-Setting

The CCR Strategic Plan sets the stage for the future by building on current cancer research as well as several core beliefs and understandings. Among those beliefs is that a greater understanding of how cancers arise and behave will lead to improved or more effective prevention, detection, diagnosis, and treatment approaches. Another is that to understand the cancer process, we first need to understand the processes of normal cell growth and differentiation in order to compare disease initiation and progression. In addition, the sequencing of the human genome presents enormous opportunities for improved understanding and predicting cancer risk, prognosis, and responses to treatment. Likewise, the emerging fields of nanotechnology, genomics, advanced imaging, and proteomics will empower the research community to develop less invasive interventions at the molecular level, identify and characterize human proteins and their biological functions, and create new technologies to deliver precise treatments and predict therapeutic effectiveness.

Emerging Themes to Guide Research

The CCR Strategic Plan reflects the current state of cancer research and is based on several core beliefs and understandings that have general acceptance in the research community. In addition to the four strategic objectives, the plan presents several overarching themes meant to guide the work of every CCR investigator, regardless of his or her expertise, and to stimulate dialogue among colleagues.

- To fully unravel the complexities of the cancer process, normal cell growth and differentiation must be studied and understood.

- Greater understanding of how cancers originate, progress, and behave will lead to improved or more effective prevention, detection, diagnosis, and treatment approaches.

- Prevention and early detection are key to disease control; adapting discoveries to prevent or intervene early in the disease process will help to make the greatest strides in reducing cancer incidence and mortality.

- Combining effective agents, including both conventional and molecularly targeted therapies, has led to greater efficacy against several types of cancer and should be encouraged to develop less toxic and more effective treatments.

- An emphasis on individualized medicine, enabled through the mapping of the human genome and other research advances, will allow us to predict a patient's susceptibility to cancer and to use this knowledge to treat the disease on a personalized level.

- Advanced biomedical technologies, such as nanotechnology, genomics, imaging, and proteomics, are essential to developing interventions at the molecular level, identifying human proteins and their biological functions, and creating instruments that deliver highly targeted treatments and predict therapeutic effectiveness.

Our Strategic Objectives

Understand the Causes and Mechanisms of Cancer

We will conduct and support basic, translational, and clinical research to gain a more complete understanding of the genetic, epigenetic, environmental, behavioural, and the biological mechanisms underlying cancer resistance, susceptibility, initiation, regression, progression, metastasis, and recurrence.

Accelerate Progress in Cancer Prevention

We will accelerate the discovery, development, and delivery of cancer prevention interventions by investing in research focused on systems biology, behaviour modifications, environmental, medical and nutritional approaches.

Improve Early Detection and Diagnosis

We will support the development and dissemination of interventions to detect and diagnose early-stage malignancy.

Develop Effective and Efficient Treatments

We will support the development and dissemination of interventions to treat malignancy by either destroying all cancer cells or modulating and controlling metastasis, both with minimal harm to healthy tissue.

Strategic Objective 1

Understand the Causes and Mechanisms of Cancer

Cancer is a complex, multistep process that can be interrupted at many stages, from initiation to disease progression to metastasis. While basic science exploration into the many factors that influence the cancer process has always been a major component of cancer research, it takes on increased importance today as accumulated knowledge and groundbreaking technologies such as imaging, nanotechnology, and metabolomics are enabling us to interrogate in precise detail the tumour microenvironment and the larger biologic system in which it exists. Within this area of basic research, the CCR will focus intently on the critical steps of cancer development to lay the foundation for intervening in the carcinogenic process.

Strategy 1.1 — Understand genetic susceptibility and the biology of cancer development

Changes in an individual's genes, including gene mutations, genetic modifiers, and polymorphisms, can alter his or her lifetime risk for cancer. To continue to elucidate the genetic factors that influence a person's risk for cancer, CCR scientists will:

- define the role of inherited or acquired genetic alterations, in combination with lifestyle factors and environmental exposures such as radiation and chemical elements, as important determinants of an individual's cancer susceptibility;

- identify new tumour suppressor genes and oncogenes and elucidate their mechanisms of action;

- identify gene expression patterns that enable early cancer detection and diagnosis, and selection of drug targets; and

- define genetic mechanisms that govern patient response or resistance to individualized treatments.

Strategy 1.2 — Understand the impact of the microenvironment and the surrounding biologic system on tumour development, metastasis, and recurrence

Significant progress has been made in dissecting the molecular pathways and mechanisms that have gone awry within malignant tumours. Capitalizing on these gains, the CCR will further explore the contributions of the biological system in which tumours reside — the microenvironment — and the larger system of which they are a part in order to determine the best points of intervention. The CCR will:

- elucidate mechanisms that influence tumour initiation, promotion, and progression, including those associated with lifestyle, the environment, inflammation, the immune system, host-tumour interaction in metastasis, wound healing, and angiogenesis;

- identify the distinguishing features within the microenvironment among dormant cancers, progressing tumours, and metastatic disease; and

- using animal models, examine how changes in the microenvironment and larger biologic system influence genetic susceptibility and resistance.

Strategy 1.3 — Accelerate cancer stem cell research

The CCR will establish a program in cancer stem cell and tissue stem cell biology research to test the theory that some tumours contain small populations of self-renewing cells that give rise to all of the cells in tumours but are themselves resistant to conventional treatment. The CCR will:

- identify cancer stem cells and tissue stem cells and their distinguishing molecular characteristics in various organ systems;

- explore cancer stem cells and their progenitors as targets for cancer initiation, promotion, metastasis, and phenotypic heterogeneity;

- determine the impact of the micro- and macroenvironment on cancer stem cells and their role in cancer aetiology, progression, and resistance to treatment; and

- use knowledge of cancer stem cells and tissue stem cells to develop better cancer interventions and therapies.

Strategy 1.4 — Understand epigenetics and chromosome biology
Increased understanding of epigenetics — the study of heritable changes in gene function that occur without change in DNA sequence — and the intricacies of gene regulation and expression will provide new opportunities to develop novel intervention strategies. The CCR will conduct research to:

- understand epigenetic inheritance both at the cellular and organism level;

- identify genetic and environmental factors that influence cancer epigenetics and the cancer epigenome;

- use experimental model systems to further investigate the effects of chromatin structure, dynamics, and gene regulation on tumour development; and

- advance scientific understanding and impact of RNAi and microRNA on the cancer processes.

Strategy 1.5 — Understand the pathogenesis of inflammatory and infection-associated malignancies
We will stimulate research to improve understanding of the causes and mechanisms of inflammatory and infection-associated malignancies to identify new viral and host factors as targets for improved antivirals and enhancing prevention, detection, diagnosis, and treatment options for cancer patients. The CCR will:

- conduct basic research into virus structure, genetics, and interaction with cellular factors;

- understand virus-host interaction in the pathogenesis of virus-induced malignancies, and mechanisms by which malignancies develop as a result of microbial infection;

- continue to identify mechanisms by which cancer causes immune dysregulation and immune deficiency; and

- identify susceptibility and resistance genes as well as genetic modifiers in patients using cutting-edge tools and approaches.

Impact

Discoveries in the basic science of cancer development and progression will provide new information about the many processes that contribute to these events in the cell and in the patient with cancer. A more comprehensive understanding of the abnormalities involved in the conversion of normal cells to malignant cells and how they progress will give rise to myriad discoveries, including the development of more accurate diagnostic tests. These tests will have the precision to assess the state of the microenvironment and identify the targets to help us develop personalized, informed prevention and treatment interventions for people with cancer.

Interleukins, laminin and Epstein - Barr virus latent membrane protein 1 (EBV LMP1) promote metastatic phenotype in nasopharyngeal carcinoma.

Chew MM, Gan SY, Khoo AS, Tan EL.

BACKGROUND: Nasopharyngeal carcinoma (NPC) is a type of neoplasm that is highly prevalent in East Asia and Africa with Epstein-Barr virus (EBV), genetic, and dietary factors implicated as possible aetiologic factors. Previous studies suggested the association of certain cytokines with the invasion and metastatic properties of NPC. The present study examined the roles of EBV latent membrane protein-1 (LMP1), interleukin-6 (IL-6), interleukin-10 (IL-10), transforming growth factor-beta 1 (TGF-β1) and laminin in the regulation of matrix-metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) in NPC. The effects of these factors on bmi-1, an oncogene, and ngx6, a tumour suppressor gene, were also investigated.

METHODS: TW01 cells expressing LMP1 (TW01-LMP1) were established via transfection with the B95.8 EBV LMP1 gene. Both TW01 and TW01-LMP1 cells were treated with 100 pg/ml IL-6, 1000 pg/ml IL-10 and 100 pg/ml TGF-β1, separately and also in combination at their respective concentration for 48 hours. Treated cells were subjected to laminin adherence assay. The cells were also cultured with and without laminin and assayed for MMP-3, MMP-9 and VEGF production using enzyme-linked immunosorbent assay (ELISA). The cellular apoptotic property was analysed using caspase-3 apoptosis assay. The expression of bmi-1 and ngx6 gene was investigated using real time reverse transcriptase polymerase chain reaction.

RESULTS: LMP1 was found to reduce the adherence of NPC cells towards laminin ($p < 0.05$) as compared to control. Treatment with IL-6 at 100 pg/ml enhanced the production of MMP-9 in both TW01 and TW01-LMP1 cells ($p < 0.05$). When cultured on laminin, the levels of MMP-3 and VEGF were significantly increased ($p < 0.05$) in TW01-LMP1 cells. TW01-LMP1 cells had relatively greater resistance to apoptosis as compared to TW01 cells ($p < 0.05$). Laminin, IL-6 and LMP1 were found to up-regulate the expression of bmi-1 and suppressed the expression of ngx6.

CONCLUSIONS: We conclude that IL-6 reduced cell adherence towards laminin and increased MMP-9 production in NPC cells. Our data suggested that EBV LMP1 was able to confer resistance of apoptosis and increased MMP-9 production in NPC cells. When cultured on laminin, TW01 cells expressing the EBV LMP1 (TW0-LMP1) that were treated with IL-6 at 100 pg/ml displayed increased MMP-9 production, up-regulation of bmi-1 oncogene expression and down-regulation of ngx6 tumour suppressor gene expression. These findings implicate the roles of EBV LMP1, laminin and IL-6 in the promotion of invasion and metastasis in NPC.

BMC Cancer. 2010 Oct 22;10:574.

Mutant p53 mediates survival of breast cancer cells.

Lim LY, Vidnovic N, Ellisen LW, Leong CO.

BACKGROUND: p53 is the most commonly mutated tumour-suppressor gene in human cancers. Unlike other tumour-suppressor genes, most p53 cancer mutations are missense mutations within the core domain, leading to the expression of a full-length mutant p53 protein. Accumulating evidence has indicated that p53 cancer mutants not only lose tumour suppression activity but also gain new oncogenic activities to promote tumourigenesis.

METHODS: The endogenous mutant p53 function in human breast cancer cells was studied using RNA interference (RNAi). Gene knockdown was confirmed by quantitative PCR and western blotting. Apoptosis was evaluated by morphological changes of cells, their PARP cleavage and annexin V staining.

RESULTS: We show that cancer-associated p53 missense mutants are required for the survival of breast cancer cells. Inhibition of endogenous mutant p53 by RNAi led to massive apoptosis in two mutant p53-expressing cell lines, T47D and MDA-MB-468, but not in the wild-type p53-expressing cells, MCF-7 and MCF-10A. Reconstitution of an RNAi-insensitive mutant p53 in MDA-MB-468 cells completely abolished the apoptotic effects after silencing of endogenous mutant p53, suggesting the specific survival effects of mutant p53. The apoptotic effect induced by mutant p53 ablation, however, is independent of p63 or p73 function.

CONCLUSION: These findings provide clear evidence of a pro-survival 'gain-of-function' property of a subset of p53 cancer mutants in breast cancer cells.

Br J Cancer. 2009 Nov 3;101(9):1606-12

Strategic Objective 2

Accelerate Progress in Cancer Prevention

Prevention is our first line of defence against cancer. Preventing cancer focuses on understanding and modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting carcinogenesis through early medical intervention. Dramatic developments in technology and a more complete understanding of the causes and mechanisms of cancer will enable us to provide more effective ways to prevent the disease. Identifying critical molecular pathways of pre-cancers will provide new drug targets for preempting cancer. Transdisciplinary research will provide a more complete understanding of the interplay of molecular, behavioural, genetic, and other factors contributing to cancer susceptibility. We must systematically identify the most promising advances, harness their application for new prevention approaches, and encourage and monitor the adoption of prevention interventions in public health and clinical settings. It is imperative that evidence-based advances shown to inform and motivate people are disseminated and made accessible.

Strategy 2.1 — Develop new cancer prevention strategies

Identifying the multiple steps in cancer development will enable us to target numerous points along the cancer continuum where we can prevent or interrupt the cancer process. New approaches using novel agents separately, in combination with one another, and in combination with standard interventions will be critical to preventing cancer. CCR scientists will:

- advance understanding of the effects of lifestyle (including physical activity and diet) and genetics on cancer prevention, initiation, and progression;
- uncover and compare the characteristics of precancers that are indolent (do not grow) with the cancers that progress; and
- identify and validate promising molecular targets for cancer prevention and reduce the toxicity of standard of care approaches, including chemotherapy and radiation, by exploring various combination strategies;

Strategy 2.2 — Develop medical interventions that suppress cancer initiation and progression.
Scientific advances are providing new evidence for the potential use of drugs, vitamins and minerals, vaccines, food constituents, and other substances to slow, halt, or reverse precancerous conditions in people at risk for cancer. The CCR will:

- support a robust cancer prevention agent development program to identify the most promising synthetic and natural agents to prevent or delay cancer onset;

- advance studies to identify agents that interfere with carcinogenesis by affecting cellular targets; and

- continue to support a consortium of research centres for conducting clinical trials to assess the potential of new agents and other approaches to inhibit the cancer process.

Impact

There are significant barriers to getting people to change their behaviours. A greater understanding and dissemination of research and best practices on how to motivate people to adopt healthy behaviours will help reduce cancer risk for individuals and communities and ultimately decrease cancer incidence. Medical interventions, in combination with lifestyle and environmental changes, hold great promise to dramatically reduce cancer incidence in future generations.

Inhibitory activities of microalgal extracts against Epstein-Barr virus DNA release from lymphoblastoid cells.

Kok YY, Chu WL, Phang SM, Mohamed SM, Naidu R, Lai PJ, Ling SN, Mak JW, Lim PK, Balraj P, Khoo AS.

This study aimed to assess the inhibitory activities of methanol extracts from the microalgae Ankistrodesmus convolutus, Synechococcus elongatus, and Spirulina platensis against Epstein-Barr virus (EBV) in three Burkitt's lymphoma (BL) cell lines, namely Akata, B95-8, and P3HR-1. The antiviral activity was assessed by quantifying the cell-free EBV DNA using real-time polymerase chain reaction (PCR) technique. The methanol extracts from Ankistrodesmus convolutus and Synechococcus elongatus displayed low cytotoxicity and potent effect in reducing cell-free EBV DNA (EC(50)<0.01 μg/ml) with a high therapeutic index (>28000). After fractionation by column chromatography, the fraction from Synechococcus elongatus (SEF1) reduced the cell-free EBV DNA most effectively (EC(50)=2.9 μg/ml, therapeutic index>69). Upon further fractionation by high performance liquid chromatography (HPLC), the sub-fraction SEF1'a was most active in reducing the cell-free EBV DNA (EC(50)=1.38 μg/ml, therapeutic index>14.5). This study suggests that microalgae could be a potential source of antiviral compounds that can be used against EBV.

J Zhejiang Univ Sci B. 2011 May;12(5):335-45.

Antiproliferative activity and induction of apoptosis in estrogen receptor-positive and negative human breast carcinoma cell lines by *Gmelina asiatica* roots.

Balijepalli MK, Tandra S, Pichika MR.

Low risk of breast cancer has been proposed to be associated with high intake of lignans. We have reported the presence of lignans in Gmelina asiatica roots. There are no scientific reports on the antiproliferative activity of G. asiatica roots. The objective of the present study was to evaluate the effect of ethyl acetate extract from G. asiatica roots (EGAR) on estrogen receptor-positive (MCF-7) and negative (MDA-MB-231) human breast cancer cell lines. The effects of 50% inhibitory concentrations (IC(50)) of EGAR on MCF-7 and MDA-MB-231 cells were determined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay kit. The mode of cell death caused by EGAR was determined using dual apoptosis assay kit by observing the cells under fluorescent microscope. The quantification of apoptosis and necrosis in cells caused by EGAR was determined using cell death detection kit through ELISA. Down-regulation of the proliferative activity occurred in a clear dose-dependent response with IC(50) values of 32.9 ± 3.8 μg/mL in MCF-7 and 19.9 ± 2.3 μg/mL in MDA-MB-231 cell lines. Treatment of breast cancer cells with EGAR resulted in significant apoptosis. The EGAR contain lignans and flavonoids. The antiproliferative activity of the extract is attributed to the presence of these secondary metabolites. The results suggest the efficacy of G. asiatica roots as antiproliferative agents on human breast cancer cells, supporting the hypothesis that plants containing lignans have beneficial effects on human breast cancer.

Pharmacognosy Res. 2010 Mar;2(2):113-9.

Tocotrienol-treated MCF-7 human breast cancer cells show down-regulation of API5 and up-regulation of MIG6 genes.

Ramdas P, Rajihuzzaman M, Veerasenan SD, Selvaduray KR, Nesaretnam K, Radhakrishnan AK.

BACKGROUND: Tocotrienols belong to the vitamin E family and have multiple anticancer effects, such as antiproliferative, antioxidant, pro-apoptosis and antimetastatic. This study aimed to identify the genes that are regulated in human breast cancer cells following exposure to various isomers of vitamin E as these may be potential targets for the treatment of breast cancer.

MATERIALS AND METHODS: Gene expression profiling was performed with MCF-7 cells at inhibitory conditions of IC(50) using Illumina's Sentrix Array Human-6 BeadChips. The expression levels of selected differentially expressed genes were verified by quantitative real-time-PCR (qRT-PCR).

RESULTS: The treatment with tocotrienol-rich palm oil fraction (TRF), α-tocopherol and isomers of tocotrienols (α, γ, and δ) altered the expression of several genes that code for proteins involved in the regulation of immune response, tumour growth and metastatic suppression, apoptotic signalling, transcription, protein biosynthesis regulation and many others.

CONCLUSION: Treatment of human MCF-7 cells with tocotrienol isomers causes the down-regulation of the API5 gene and up-regulation of the MIG6 gene and the differential expression of other genes reported to play a key role in breast cancer biology.

Cancer Genomics Proteomics. 2011 Jan-Feb;8(1):19-31

***Bacillus thuringiensis* parasporal proteins induce cell-cycle arrest and caspase-dependant apoptotic cell death in leukemic cells.**

Chan KK, Wong RS, Mohamed SM, Ibrahim TA, Abdullah M, Nadarajah VD.

Bacillus thuringiensis (Bt) parasporal proteins with selective anticancer activity have recently garnered interest. This study determines the efficacy and mode of cell death of Bt 18 parasporal proteins against 3 leukemic cell lines (CEM-SS, CCRF-SB and CCRF-HSB-2).Cell-based biochemical analysis aimed to determine cell viability and the percentage of apoptotic cell death in treated cell lines; ultrastructural analysis to study apoptotic changes and Western blot to identify the parasporal proteins' binding site were performed. Bt 18 parasporal proteins moderately decreased viability of leukemic cells but not that of normal human T lymphocytes. Further purification of the proteins showed changes in inhibition selectivity. Phosphatidylserine externalization, active caspase-3, cell cycle, and ultrastructural analysis confirmed apoptotic activity and S-phase cell-cycle arrest. Western blot analysis demonstrated glyceraldehyde 3-phosphate dehydrogenase as a binding protein. We suggest that Bt 18 parasporal proteins inhibit leukemic cell viability by cell-cycle arrest and apoptosis and that glyceraldehyde 3-phosphate dehydrogenase binding initiates apoptosis.

J Environ Pathol Toxicol Oncol. 2012;31(1):75-86.

Anti-proliferative and mutagenic activities of aqueous and methanol extracts of leaves from *Pereskia bleo* (Kunth) DC (Cactaceae).

Er HM, Cheng EH, Radhakrishnan AK.

The anti-proliferative effects of the aqueous and methanol extracts of leaves of Pereskia bleo (Kunth) DC (Cactaceae) against a mouse mammary cancer cell line (4T1) and a normal mouse fibroblast cell line (NIH/3T3) were evaluated under an optimal (in culture medium containing 10% foetal bovine serum (FBS)) and a sub-optimal (in culture medium containing 0.5% FBS) conditions. Under the optimal condition, the aqueous extract showed a significant ($p<0.05$) anti-proliferative effect at 200 microg/mL and 300 microg/mL in 4T1 cells and 300 microg/mL in NIH/3T3 cells, whereas the methanol extract did not show any notable anti-proliferative effect in these cell lines, at any of the concentrations tested. Under the sub-optimal condition, the aqueous extract showed a significant ($p<0.05$) anti-proliferative effect at 200 microg/mL and 300 microg/mL in NIH/3T3 cells, whilst the methanol extract showed a significant ($p<0.05$) anti-proliferative effect at 200 microg/mL and 300 microg/mL in both cell lines. An upward trend of apoptosis was observed in both 4T1 and NIH/3T3 cells treated with increasing concentrations of the aqueous extract. The level of apoptosis observed at all the concentrations of the aqueous extract tested was consistently higher than necrosis. There was a significant ($p<0.05$) increase in the level of necrosis observed in the 4T1 cells treated with 300 microg/mL of the methanol extract. Generally, the level of necrosis was noted to be higher than that of apoptosis in the methanol extract-treated cells. The mutagenicity assay performed showed that in the absence of S-9 liver metabolic activation, the extract was not mutagenic up to the concentration of 165 microg/mL . However, in the presence of S-9 liver metabolic activation, the aqueous extract was mutagenic at all the concentrations tested. This study shows that both the aqueous and methanol extracts of the leaves from Pereskia bleo (Kunth) DC (Cactaceae) do not have appreciable anti-proliferative effect on the 4T1 and NIH/3T3 cells as the EC(50) values obtained are greater than 50 microg/mL when tested under optimal culture condition. Moreover, the aqueous extract may form mutagenic compound(s) upon the metabolisation by liver enzymes.

J Ethnopharmacol. 2007 Sep 25;113(3):448-56

Strategic Objective 3

Improve Early Detection and Diagnosis

Detecting and diagnosing tumours early in the disease process, before the tumour becomes invasive and metastatic, can dramatically improve the patient's odds for successful treatment and survival and eliminate a large proportion of cancer deaths. For example, evidence suggests that 90 percent or more of colorectal cancer deaths could be prevented if precancerous polyps were detected with routine screening and removed at an early stage. However, the screening rate for colorectal cancer lags far behind that of other cancers, and the disease remains the second leading cause of cancer death in our Nation. For many other cancers— e.g., ovarian and pancreatic — there are no reliable early-stage screening tests to offer patients. For still others, such as lung cancer, screening tests are available but have not been proven to reduce mortality. Furthermore, although investigators continue to make promising discoveries that apply diverse technologies to early cancer detection, few of these advances have reached the patient.

By implementing the focused strategies described below, we will speed the translation of effective early detection and diagnostic approaches to the clinic. Healthcare providers and their patients will have access to sophisticated, minimally invasive procedures that harness imaging, proteomics, nanotechnology, and other advanced early detection and diagnostic techniques as well as improved access to and understanding of follow-up procedures.

Strategy 3.1 — Promote collaborative multidisciplinary research for validating biomarkers.
Rapidly emerging discoveries in the laboratory promise better ways to distinguish cancer and early cancerous changes from normal tissue. To generate more effective markers for diagnosing cancer and predicting risk or treatment response, it is critical that we accelerate the movement of research findings into validation studies and clinical research where their true potential can be determined. The CCR will:

- promote collaborative, multidisciplinary research to validate biomarkers for early detection and diagnosis;

- support research to determine whether a biomarker test predicts the true presence or absence of disease for all individuals;

- promote research that tests the biomarker in an adequate spectrum of patients with and without cancer and accurately summarizes the sensitivity, specificity, and other performance characteristics of the test; and

- encourage public-private partnerships to provide researchers with access to necessary technologies and other resources.

Strategy 3.2 — Develop better diagnostic and screening tools for early detection, risk assessment, and recurrence.
Increasing accuracy in the characterization of cancers at the time of diagnosis will allow physicians to develop the most appropriate treatment plan for individual patients. The CCR will:

- support the development and evaluation of high-throughput, cost-effective technologies that permit rapid and accurate patient diagnoses;

- encourage the movement of new research areas such as micro-RNA expression and epigenetics/epigenomics to development and clinical translation; and

- strengthen the development process with the expertise of interdisciplinary teams, including clinicians, pathologists, laboratory researchers, and statisticians.

Strategy 3.3 — Encourage and provide investigator training to facilitate the development and application of diagnostic tests.
The CCR will support training opportunities that will lead to collaborations among basic bench scientists, clinicians, population scientists, medical educators, and experts from other disciplines such as imaging and informatics. The CCR will:

- sustain training activities that encourage exploratory and developmental research, promote collaborations that bring together ideas and approaches from diverse scientific disciplines, and support businesses in conducting innovative research;

- support training related to technology development, including high risk, early-stage research, and increase support for developing and validating technologies for early detection and diagnosis; and

- place greater training emphasis on innovative research activities that have high translation impact and go beyond strictly mechanistic studies.

Impact

Dramatic developments in technology and a more complete understanding of the causes and mechanisms of cancer will enable us to provide more effective ways to prevent the disease. Advances in biomarkers and the promise of new approaches such as nanotechnology will make early detection and diagnosis of cancer and prediction of patient response to treatment even more precise. Approaches currently used in early detection and diagnosis may be applied to new prevention strategies and to interventions to treat localized cancers before they spread.

Gastric cancer in Malaysia: the need for early diagnosis.

Kandasami P, Tan WJ, Norain K.

Gastric cancer is an important cause of death among patients with malignancies in Malaysia. Survival of patients with gastric cancer is dependent on the stage at which diagnosis is made. We report our experience in dealing with gastric cancer in a major Ministry of Health Hospitals in Malaysia. A retrospective review of two hundred and fifty consecutive histologically proven gastric adenocarcinoma at Hospital Ipoh for the period January 1988 to 1998 was performed. The study confirms that gastric cancer is a disease of the elderly and has a male preponderance. It is also identifies the Chinese and Indians to be at increased risk of gastric cancer when compared to the Malays. The most striking finding in this study was the very late stage of disease at time of presentation. Eighty-two percent of the patients presented with stage IV disease and curative surgery was offered only to a 16% of them. In a substantial number of patients not even a palliative procedure was offered. Early detection is the key to improving survival in gastric cancer patients. There is an urgent need for clinicians to change their approach to the management of the disease. Patients with dyspeptic symptoms should be investigated early rather then wait for classical symptoms of gastric cancer.

Med J Malaysia. 2003 Dec;58(5):758-62.

Clinical usefulness of tumour markers.

Lai LC, Cheong SK, Goh KL, Leong CF, Loh CS, Lopez JB, Nawawi H, Sivanesaratnam V, Subramaniam R; Clinical Practice Guidelines Committee on Tumour Markers of the Academy of Medicine of Malaysia.

Tumour markers are substances related to the presence or progress of a tumour. An ideal tumour marker is (1) detectable only when malignancy is present, (2) specific for the type and site of malignancy, (3) correlates with the amount of malignant tissue present and (4) responds rapidly to a change in tumour size. At present, no tumour marker fulfills all of the above criteria. The first part of the review discusses the clinical usefulness of the commonly requested serum tumour markers, namely, prostate-specific antigen (PSA), CA 19-9, carcinoembryonic antigen (CEA), CA 125, CA 15-3, human chorionic gonadotrophin (hCG) and alpha-foetoprotein (AFP). It is hoped that this review article will decrease the abuse and misuse of these commonly requested serum tumour markers. The second part of the review discusses the clinical usefulness of catecholamines and their metabolites, calcitonin, thyroglobulin, parathyroid hormone, prolactin, adrenocorticotrophic hormone, oestrogen and progesterone receptors, p53, HER-2/c-erbB2, BRCA1 and BRCA2.

Malays J Pathol. 2003 Dec;25(2):83-105.

Strategic Objective 4

Develop Effective and Efficient Treatments

Developing more efficient and effective cancer treatments that leave surrounding healthy tissue unharmed is at the heart of CCR's research agenda. These efforts build on our accelerated progress in preventing cancer and complement our increasing ability to thwart the progression of cancer to a metastatic state. Individualized therapies tailored to the specific characteristics of a patient's cancer provide hope that some cancers can be cured and many others managed as chronic diseases with little or no adverse effect on the daily lives or life expectancy of patients.

A strong understanding of the fundamental mechanisms leading to cancer progression and metastasis will dramatically improve our ability to identify key biochemical events in the disease process as targets for treatment. Accelerating target validation and the development of new treatment modalities will be possible through recent advances in biomedical technologies such as genomics, proteomics, metabolomics, nanotechnology, and imaging. Rapid translation from development to delivery will ensure that promising therapeutics move safely and efficiently from preclinical development through late-stage clinical trials and into clinical practice.

Strategy 4.1 — Support the discovery and development of novel molecular targets

We will develop and validate novel molecularly targeted agents and search for new targets important in the cancer process. These steps are critical for improving diagnostics and generating effective therapeutics. CCR scientists will:

- facilitate the drug discovery and development process by leveraging the CCR's strength in cancer biology with expertise in chemistry and structural biology; and

- partner with academia, industry, and the extramural communities to discover and develop molecularly targeted drugs.

Strategy 4.2 — Develop new therapeutics
The CCR will support basic science efforts to develop new molecular targets and move them more efficiently through the development pipeline to deliver novel agents to the clinical setting. CCR scientists will:

- closely align the exploration and discovery phases of agent development with the performance of early-stage lead compounds development by utilizing the resources and expertise of the Centre of Bioactive Molecules;

- develop biomarkers to monitor the success of molecularly targeted agents and response to interventions;

- conduct pre-clinical studies on molecularly based interventions to validate their effectiveness and move successful agents into clinical trials; and

- encourage partnerships with pharmaceutical companies to validate targets and advance the development process.

Strategy 4.3 — Identify and validate rationally based combination therapies and multimodality approaches
Guided by evidence that the rational combination of treatments is often more effective and less toxic than individual interventions, CCR will cultivate a leadership role in identifying combinations of agents and/or modalities that work through complementary mechanisms to interrupt cancer development and progression. The CCR will:

- support translational research focused on developing novel agents for use alone or in combination with other agents, or in combination with chemotherapy, radiation, surgery, and/or immunotherapy;

- facilitate the testing of combinations of agents in the in vitro and preclinical settings with a clear path to early-phase clinical trial design and implementation; and

- partner with the Clinical Research Centre (CRC) to facilitate the translation of successful preclinical studies into clinical trials.

Impact

Molecularly targeted therapies will provide effective ways to personalize cancer treatment, reduce treatment side effects, and improve the quality of life of people living with cancer. The CCR's focus on developing a more coordinated approach to the chemistry aspect of drug development will be essential to achieving this goal.

Reversing multidrug resistance in breast cancer cells by silencing ABC transporter genes with nanoparticle-facilitated delivery of target siRNAs.

Li YT, Chua MJ, Kunnath AP, Chowdhury EH.

BACKGROUND: Multidrug resistance, a major impediment to successful cancer chemotherapy, is the result of overexpression of ATP-binding cassette (ABC) transporters extruding internalized drugs. Silencing of ABC transporter gene expression with small interfering RNA (siRNA) could be an attractive approach to overcome multidrug resistance of cancer, although delivery of siRNA remains a major hurdle to fully exploit the potential of siRNA-based therapeutics. Recently, we have developed pH-sensitive carbonate apatite nanoparticles to efficiently carry and transport siRNA across the cell membrane, enabling knockdown of the cyclin B1 gene and consequential induction of apoptosis in synergy with anti-cancer drugs.

METHODS AND RESULTS: We report that carbonate apatite-mediated delivery of the siRNAs targeting ABCG2 and ABCB1 gene transcripts in human breast cancer cells which constitutively express both of the transporter genes dose-dependently enhanced chemosensitivity to doxorubicin, paclitaxel and cisplatin, the traditionally used chemotherapeutic agents. Moreover, codelivery of two specific siRNAs targeting ABCB1 and ABCG2 transcripts resulted in a more robust increase of chemosensitivity in the cancer cells, indicating the reversal of ABC transporter-mediated multidrug resistance.

CONCLUSION: The delivery concept of multiple siRNAs against ABC transporter genes is highly promising for preclinical and clinical investigation in reversing the multidrug resistance phenotype of breast cancer.

Int J Nanomedicine. 2012;7:2473-81

Suppression of BCL-2 synergizes cisplatin sensitivity in nasopharyngeal carcinoma cells.
Low SY, Tan BS, Choo HL, Tiong KH, Khoo AS, Leong CO.

The efficacy of cisplatin for treating nasopharyngeal carcinoma (NPC) is limited by the dose-related toxicities and the development of resistance to cisplatin. Recent studies have shown that B cell lymphoma-2 (BCL-2) is overexpressed and confers chemoresistance in NPC. Thus, targeted therapy against BCL-2 may enhance the antitumour effects of chemotherapy by sensitizing the tumor cells to undergo apoptosis. This study evaluated the combined effects of BCL-2 inhibition and cisplatin in NPC cells. Our results demonstrate that inhibition of BCL-2 by small-hairpin RNA (shRNA) or the BCL-2 inhibitor YC137, synergizes cisplatin sensitivity in NPC cells that overexpress BCL-2. We also show that YC137 enhance cisplatin-induced apoptosis in HK1 and CNE1 cells through suppression of BCL-2 protein expression, induction of mitochondrial depolarization and activation of caspase 9 and caspase 3/7. These findings suggest that the combination of BCL-2 inhibition and cisplatin represents a promising strategy for treating NPC.

Cancer Lett. 2012 Jan 28;314(2):166-75

CYP2S1 and CYP2W1 mediate 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (GW-610, NSC 721648) sensitivity in breast and colorectal cancer cells.

Tan BS, Tiong KH, Muruhadas A, Randhawa N, Choo HL, Bradshaw TD, Stevens MF, Leong CO.

Both 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F-203; NSC 703786) and 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (GW-610; NSC 721648) are antitumor agents with novel mechanism(s). Previous studies have indicated that cytochrome (CYP) P450 1A1 is crucial for 5F-203 activity. In the present study, we investigated the functional role of 2 newly identified CYP P450 enzymes, CYP2S1 and CYP2W1, in mediating antitumor activity of benzothiazole compounds. We generated isogenic breast cancer (MDA-MB-468, MCF-7) and colorectal cancer (CRC; KM12 and HCC2998) cell lines depleted for CYP1A1, CYP2S1, or CYP2W1. The sensitivity of these cells to 5F-203 and GW-610 was then compared with vector control cells. 5F-203 exhibited potent activity against breast cancer cells, whereas GW-610 was effective against both breast and colorectal cancer cells. CYP1A1 was induced in both breast cancer and CRC cells, while CYP2S1 and CYP2W1 were selectively induced in breast cancer cells only following treatment with 5F-203 or GW-610. Depletion of CYP1A1 abrogated the sensitivity of breast cancer and CRC cells to 5F-203 and GW-610. Although depletion of CYP2S1 sensitized both breast cancer and CRC cells toward 5F-203 and GW-610, CYP2W1 knockdown caused marked resistance to GW-610 in CRC cells. Our results indicate that CYP-P450 isoforms, with the exception of CYP1A1, play an important role in mediating benzothiazole activity. CYP2S1 appears to be involved in deactivation of benzothiazoles, whereas CYP2W1 is important for bioactivation of GW-610 in CRC cells. Because CYP2W1 is highly expressed in colorectal tumors, GW-610 represents a promising agent for CRC therapy.

Mol Cancer Ther. 2011 Oct;10(10):1982-92

Rapamycin synergizes cisplatin sensitivity in basal-like breast cancer cells through up-regulation of p73.

Wong SW, Tiong KH, Kong WY, Yue YC, Chua CH, Lim JY, Lee CY, Quah SI, Fow C, Chung C, So I, Tan BS, Choo HL, Rosli R, Cheong SK, Leong CO.

Recent gene expression profiling studies have identified five breast cancer subtypes, of which the basal-like subtype is the most aggressive. Basal-like breast cancer poses serious clinical challenges as there are currently no targeted therapies available to treat it. Although there is increasing evidence that these tumors possess specific sensitivity to cisplatin, its success is often compromised due to its dose-limiting nephrotoxicity and the development of drug resistance. To overcome this limitation, our goal was to maximize the benefits associated with cisplatin therapy through drug combination strategies. Using a validated kinase inhibitor library, we showed that inhibition of the mTOR, TGFβRI, NFκB, PI3K/AKT, and MAPK pathways sensitized basal-like MDA-MB-468 cells to cisplatin treatment. Further analysis demonstrated that the combination of the mTOR inhibitor rapamycin and cisplatin generated significant drug synergism in basal-like MDA-MB-468, MDA-MB-231, and HCC1937 cells but not in luminal-like T47D or MCF-7 cells. We further showed that the synergistic effect of rapamycin plus cisplatin on basal-like breast cancer cells was mediated through the induction of p73. Depletion of endogenous p73 in basal-like cells abolished these synergistic effects. In conclusion, combination therapy with mTOR inhibitors and cisplatin may be a useful therapeutic strategy in the treatment of basal-like breast cancers.

Breast Cancer Res Treat. 2011 Jul;128(2):301-13

Cross-Cutting Commitments

Maintaining a Foundation for Long-Term Success

Success of the four objectives in the CCR Strategic Plan is dependent on the commitment of CCR and IRDI leadership to foster an innovative and creative research environment. By its charter, the CCR supports both investigator-initiated research and multidisciplinary translational research teams that pursue high-risk, high-impact research. Several critical components contribute to this distinctive culture and underpin the plan's strategic objectives:

Maintain strong support for basic, translational, and clinical research. One of the CCR's objectives is to move discoveries made in the lab into the clinical setting as rapidly as possible so that interventions quickly reach patients. To make this translational research process as seamless as possible, the CCR will:

- strongly support basic science exploration and discovery which provides the foundation for translational and clinical research;
- more closely align the exploration and discovery phases of novel agent development with the initiation of preclinical development on promising approaches to validate their effectiveness;
- advance successful agents into early stage clinical trials by partnering with the CRC, other institutes, industry, academic researchers, pharmaceutical companies, and patient volunteers; and
- maintain a focus on research into rare and underserved patient populations to develop novel therapies for understudied cancers.

Encourage internal and external collaborations
Solving the complexities of cancer requires scientists to move beyond their own disciplines and explore new ways to conduct team science. The CCR's partnerships with scientists at universities, medical schools, hospitals, government agencies, and other non-profit and for-profit research facilities in the Malaysia and abroad, and its Centres of Excellence, faculties, and working groups will cut across organizational boundaries to foster collaborative research. To further support these relationships and develop new partnerships, CCR will:

- recognize and review team science to encourage talented independent investigators to join multidisciplinary initiatives;

- improve exchange and sharing of patient biospecimens and data by promoting collaborative interactions between basic scientists and clinicians; and

- serve as a model of multidisciplinary research for the extramural research community and explore approaches to working more seamlessly with this community

Develop and share technologies and expertise
CCR investigators have access to the latest technologies, specialized expertise, and technical support in genetics and genomics, proteomics, metabolomics, bioinformatics and, and other areas. The CCR encourages its investigators to take full advantage of the technologies and research support available to them and is committed to sharing its expertise through training and consultation and encouraging new uses for core facilities as our research priorities evolve. The CCR will:

- support the development, evaluation, and sharing of novel, cost-effective technologies that enable basic research discovery and permit rapid, accurate patient diagnosis;

- enhance the range of technologies available to researchers,

- create an accessible, systematic, secure, and centralized biospecimen procurement and processing centre to coordinate the analysis of human samples collected during clinical studies; and

- ensure that bioinformatics support is available to CCR investigators through expansion and sharing of resources, increased training and integration of computers, and the provision of software and personnel to assist in the mining of data.

Train and mentor the next generation of investigators
The CCR will maintain a robust core of scientists and physician-scientists through active recruitment, training, and mentorship to ensure the next generation of laboratory and clinical leaders. To continue to provide top scientists the opportunity to develop and refine skills, CCR will:

- support recruitment, training, and mentoring of postgraduate students, postdoctoral fellows, junior investigators, and physician-scientists into existing and emerging areas of research;

- provide extramural researchers opportunities to train at CCR labs and encourage CCR staff to continue their education through course work within and outside of IMU; and

A Commitment to Rare and Understudied Cancers

A significant portion of the CCR's research portfolio is devoted to the study of rare cancers including cancer of the children, pancreas, and others, some of which have rising rates. Cutting across all areas of research, the CCR is committed to studying rare and understudied cancer for several reasons, both practical and ethical. Among them, many rare cancers are highly lethal, their study may be informative about the aetiology of more common tumours, and some have disproportionately high incidence in certain medically underserved populations. Altogether, the total incidence of all rare tumours is substantial and places a heavy burden on public health.

Acknowledgements:
CCR Strategic Planning Participants

Strategic Objective 1

Understand the Causes and Mechanisms of Cancer

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Strategic Objective 2

Accelerate Progress in Cancer Prevention

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Strategic Objective 3

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Develop Effective and Efficient Treatments

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