LUDWIG INSTITUTE FOR CANCER RESEARCH

2007 Annual Research Highlights Report

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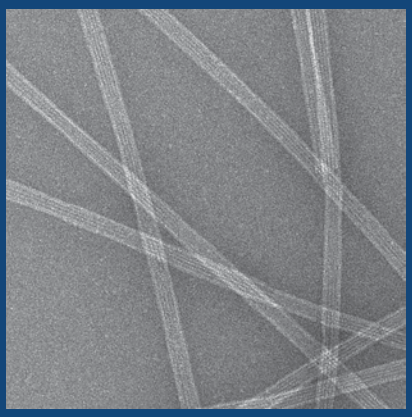


ON THE COVER:

Microtubules—the protein filaments that segregate the genome during cell division—at 50,000 times magnification. This electron microscopy image was obtained by investigators at the LICR San Diego Branch, who study how the integrity of the genome is maintained when cells divide (pp12-14).

LUDWIG INSTITUTE FOR CANCER RESEARCH

2007 Annual Research Highlights Report

Andrew J.G. Simpson, Ph.D., was appointed LICR Scientific Director in June 2007. Since 2004, he has been LICR's Executive Director for Programs & Operations. Dr. Simpson previously conducted research at the LICR São Paulo Branch in São Paulo, Brazil, the Centro de Pesquisas René Rachou in Belo Horizonte, Brazil, the National Institute for Medical Research in London (from which he received tenure in 1986) and the USA National Institutes of Health in Bethesda. For his contributions to Brazil's science, Dr. Simpson was elected a Member of the Brazilian National Academy of Sciences and awarded that country's highest civilian order, the 'Order Rio Branco.'

Since it was founded in 1973, the Ludwig Institute for Cancer Research (LICR) has made many significant advances to the understanding of human cancer. The highly desirable next step is to harness this knowledge for clinical utility. It is a core belief of the LICR that the responsibility for so doing lies not only with those who ultimately market and distribute new cancer drugs, but also with the scientists who made the discoveries possible, and the Institute itself. Accordingly, LICR has, for the last 20 years, incorporated within its scientific programs and organizational structure a number of goal oriented and developmental activities aimed at facilitating the translation of our discoveries into human benefit. While our basic discovery research remains centered in the LICR Branches around the world, the development of novel therapeutic agents has necessitated supplementing these resources with contributions from LICR Affiliates, particularly in the critical areas of clinical trials and clinical discovery.

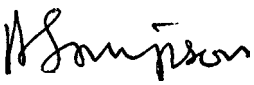
In order to reflect the changing style and focus of the work of the Institute, we have been changing the style and format of this report. In past years, this annual report was entirely structured around the work in individual Branches. We are now presenting our work in a more thematic manner, which is more representative of our programmatic collaborations between multiple Branches, and particularly our increasing focus on Cancer Initiatives, where a particular type of cancer represents the linking principle between collaborating scientists and clinicians. We hope the thematic approach to the report also more effectively communicates the integrated laboratory and clinical discovery that is a hallmark of the LICR mission. To present as complete a picture as possible of the Institute's work, however, we have also included a complete listing of the scientific output of the LICR Branches around the world as a record of our academic productivity.

The humanized monoclonal antibody G250 is illustrative of the Institute's full spectrum approach to cancer research (pp48-49). The results of early phase clinical trials, conducted and sponsored by LICR and reported herein, prompted our industrial collaborator to initiate a Phase III trial to test the diagnostic application of G250. This trial is in addition to an ongoing Phase III trial testing the antibody's therapeutic potential. This progress is the result of more than a decade of laboratory and clinical investigation by LICR investigators and Affiliates working with the staffs of the Institute's Offices of Clinical Trials Management and Intellectual Property and with industrial collaborators. Other highlights from 2007 include work conducted under the auspices of the LICR Brain Cancer Initiative to identify and exploit novel therapeutic targets in brain cancers (pp16-18), and some of the first findings from the Hilton Ludwig Cancer Metastasis Initiative, a three year partnership with the Conrad N. Hilton Foundation specifically investigating metastasis (p19).

We are proud of the advances in cancer research that we have achieved and welcome the

Dr. Andrew J.G. Simpson,
LICR Scientific Director

responsibilities brought by these achievements. The coming decade appears destined to be one of unprecedented success in translating knowledge to cancer control, and LICR intends to be an instrumental component as we progress from models and surrogates to the intended beneficiary of all our efforts, the cancer patient.



Andrew J.G. Simpson, Ph.D.
Scientific Director

BRANCHES / CENTER

The Institute's nine Branches and its Melbourne Center are each physically and functionally associated with a university or research institute and/or a non-profit hospital. This arrangement guarantees an academic environment conducive to collaborative, integrated cancer research and provides access to local institutional resources and expertise in both the laboratory and the clinic.

Brussels Branch, Belgium
Catholic University of Leuven
Saint-Luc University Clinic*

Lausanne Branch, Switzerland
Swiss Institute for Experimental Cancer Research (ISREC)
University of Lausanne (UNIL)
Federal Polytechnic School of Lausanne (EPFL)
Multidisciplinary Oncology Center (CePO) of the Central Hospital of the Vaudois University (CHUV)*

London Branch (until September, 2008), UK
University College London

Melbourne Branch, Australia
The University of Melbourne
Melbourne Health

Melbourne Center, Australia
Austin Health*

New York Branch, USA
Memorial Sloan-Kettering Cancer Center*

Oxford Branch (from October, 2007), UK
University of Oxford

San Diego Branch, USA
University of California, San Diego

São Paulo Branch, Brazil
Hospital Alemão Oswaldo Cruz

Stockholm Branch, Sweden
Karolinska Institute

Uppsala Branch, Sweden
Uppsala University

AFFILIATES

Affiliates are outstanding laboratory and clinical investigators, outside the Branch/Center structure, who are recruited to Institute-wide Programs in order to extend the knowledge and expertise required to achieve Program goals. LICR Affiliates are located in the following cities:

Auckland, New Zealand
The University of Auckland*

Beijing, China
Peking University

Belo Horizonte, Brazil
Federal University of Minas Gerais

Buffalo, NY, USA
Roswell Park Cancer Institute*

Cape Town, South Africa
University of the Western Cape

Frankfurt, Germany
Nordwest Hospital*

Heidelberg, Germany
German Cancer Research Center (DKFZ)
Heidelberg University Clinic

Helsinki, Finland
University of Helsinki

Hamburg, Germany
University Medical Center Hamburg-Eppendorf

Ithaca, NY, USA
Cornell University

Konstanz, Germany
University of Konstanz

Kuopio, Finland
University of Kuopio

Kyiv, Ukraine
Institute of Molecular Biology and Genetics

Leiden, The Netherlands
Leiden University Medical Center

London, UK
Institute of Cancer, Barts & The London School of Medicine
Imperial College
University College London

Madison, WI, USA
University of Wisconsin-Madison

Mie, Japan
Mie University School of Medicine

LICR Worldwide

Nantes, France
Regional Nantes-Atlantic Institute of Cancer*

New Haven, CT, USA
Yale University

New York, NY, USA
New York University Cancer Institute*
Weill Medical College of Cornell University

Nijmegen, The Netherlands
Radboud University Nijmegen Medical Center*

Oxford, UK
Churchill Hospital*
John Radcliffe Hospital*

Petropolis, Brazil
National Laboratory of Scientific Computing

Philadelphia, PA, USA
The Wistar Institute
Hospital of University of Pennsylvania*

Pittsburgh, PA, USA
University of Pittsburgh Cancer Institute

Ribeirao Preto, SP, Brazil
Faculty of Medicine of Ribeirao Preto, University of São Paulo

Rochester, MN, USA
Mayo Clinic*

Rockville, MD, USA
J. Craig Venter Institute

São José do Rio Preto, SP, Brazil
Faculty of Medicine of São José do Rio Preto, University of São Paulo

São Paulo, SP, Brazil
University of São Paulo

St Louis, MO, USA
Washington University in St.Louis School of Medicine

Stockholm, Sweden
Karolinska Institute

Tokyo, Japan
The University of Tokyo

Xi'an, China
The Fourth Military Medical University

Zürich, Switzerland
Zürich University Hospital*

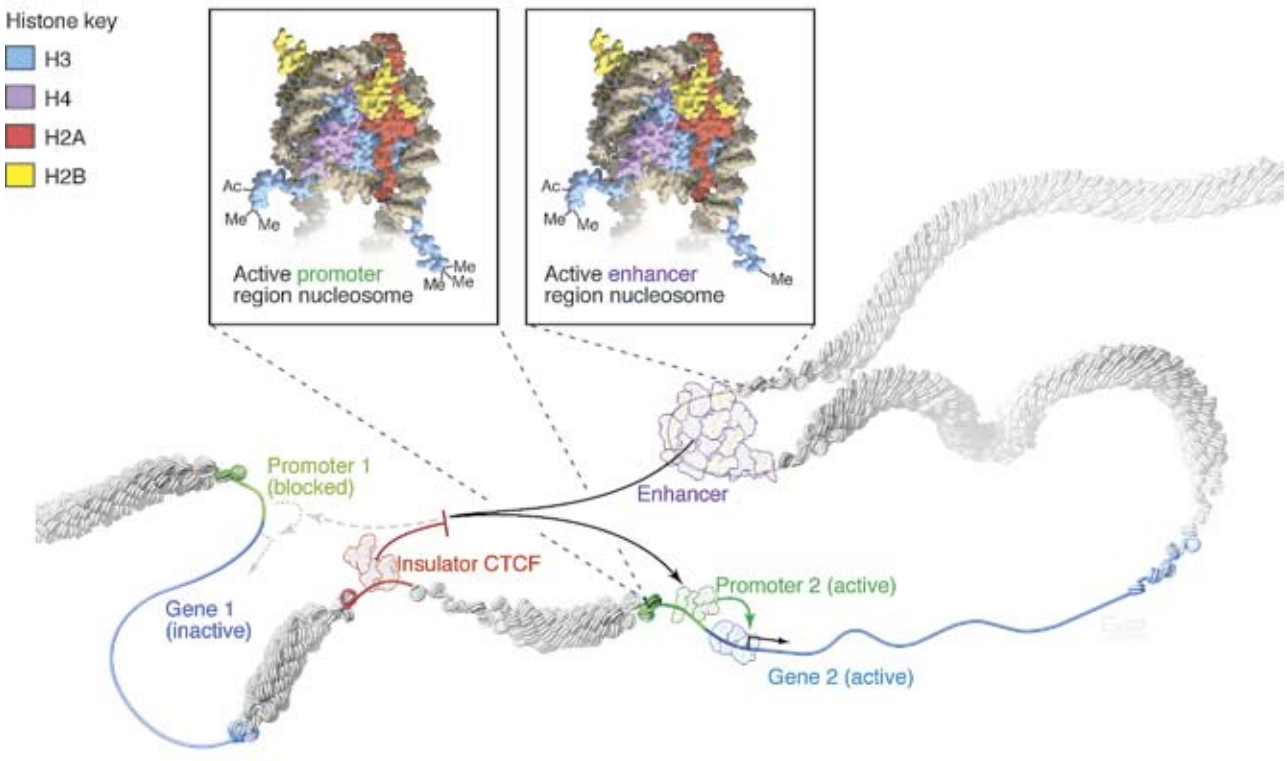
* Clinical trials site

Regulation of Gene Expression

With very few exceptions, all cells in our bodies have the same genome. However, cells can have vastly different roles in development, normal tissue function and disease. Cell diversity is mainly caused by differences in gene expression, the process through which a protein (or other molecule) encoded by a gene is produced. The most highly regulated step in this process is gene expression, the transcription of a gene's DNA sequence into RNA. This is controlled by a complex interplay of numerous proteins that bind to regulatory elements in the DNA. In recent years, a team of **LICR San Diego Branch** investigators have mapped two major types of regulatory elements in the genome: promoters, elements located next to genes upon which transcription factor proteins assemble to initiate gene transcription; and enhancers, elements that assemble proteins at positions upstream, downstream, or within the gene itself to activate transcription. Much remains to be

The genome is contained in a fiber of densely packed nucleosomes; repetitive elements of DNA (grey) wrapped around cores of histone proteins (H2A, H2B, H3 and H4). Scattered across the genome are regulatory DNA elements—promoters, enhancers, and insulators—which assemble proteins that regulate the transcription of individual genes. LICR investigators have described signatures on histone proteins that can be used to distinguish promoters and enhancers in the genome.

Figure created by Graham Johnson of www.fiVth.com.



learned about gene regulation in order to understand how normal cells become cancer cells.

CRACKING THE GENOME'S REGULATORY CODE

In 2007, the **San Diego Branch** team performed the first genome-wide analysis of insulators, a type of regulatory element to which proteins bind to prevent enhancers from activating unrelated genes. Prior to this study, only a handful of insulators had been identified. The LICR team discovered more than 13,800[1].

In a second study, the team analyzed histones, the genome's main protein components. Modifications of histone proteins can affect gene expression by altering the structure of the DNA/protein complex within gene regulatory elements. The LICR investigators mapped histone modifications within known promoter and enhancer elements, and used computational methods to identify 'signatures' that are characteristic of these elements[2]. This LICR study provides the medical research community with a large-scale method for the functional annotation of the genome. Applying the method to compare five different cell types, the team was able to identify approximately 24,000 promoters out of which nearly one fifth mediate cell-type specific regulation of gene expression[3]. This functional annotation should prove to be a powerful tool in comparing functional genome changes in normal and cancer cells.

REGULATION BY GENES ON OPPOSING DNA STRANDS

Genes are typically transcribed from only one of the two parallel DNA strands—the sense strand—in the genome. However, some genes are juxtaposed with a similar gene copy on the opposite (anti-sense) strand. In 2007, **LICR São Paulo Branch** investigators performed the largest survey of such gene pairs yet undertaken. Through computational analysis of gene expression data, the investigators identified many thousands of sense-antisense gene pairs that are transcribed from opposing DNA strands. The team also found that these gene copies may regulate each other's expression by influencing gene transcription or splicing on the opposite strand[4].

1. **Kim TH, Abdullaev ZK, Smith AD, Ching KA, Loukinov DI, Green RD, Zhang MQ, Lobanenkov VV, Ren B.** *Analysis of the vertebrate insulator protein CTCF-binding sites in the human genome.* Cell. 2007 128(6):1231-45 [PMID: 17382889]

2. **Heintzman ND, Stuart RK, Hon G, Fu Y, Ching CW, Hawkins RD, Barrera LO, Van Calcar S, Qu C, Ching KA, Wang W, Weng Z, Green RD, Crawford GE, Ren B.** *Distinct and predictive chromatin signatures of transcriptional promoters and enhancers in the human genome.* Nat Genet. 2007. 39(3):311-8 [PMID: 17277777]

3. **Barrera LO, Li Z, Smith AD, Arden KC, Cavenee WK, Zhang MQ, Green RD, Ren B.** *Genome-wide mapping and analysis of active promoters in mouse embryonic stem cells and adult organs.* Genome Res. 2007 Nov 27 [PMID: 18042645]

4. **Galante PA, Vidal DO, de Souza JE, Camargo AA, de Souza SJ.** *Sense-antisense pairs in mammals: functional and evolutionary considerations.* Genome Biol. 2007;8(3):R40 [PMID: 17371592]

DNA Damage: Detection, Response and Repair

To maintain proper function and ensure survival, cells must conserve the integrity of their genome by detecting and repairing DNA damage. Additionally, when DNA damage is detected, the cells must respond by either preventing cell division until the DNA is repaired or entering the process of apoptosis (programmed cell death). Since the mechanisms that ensure the genome's integrity are strongly conserved during evolution, **LICR San Diego Branch** investigators are able to explore them in detail using basic model organisms such as yeast and bacteria. Analyzing DNA damage detection, response and repair is critical to finding new ways to control cancer since the disease is ultimately caused by the accumulation of DNA mutations. This is illustrated by the fact that inherited defects in genes involved in genome integrity are associated with susceptibility to familial cancers, such as hereditary non-polyposis colon cancer that accounts for 5% of all cases of colon cancer.

DNA DAMAGE RESPONSE

In response to DNA damage by chemical mutagens, radiation or DNA replication errors, multiple intra-cellular signaling pathways are activated to prevent cell division, and also to initiate DNA repair or apoptosis. The DNA damage response is mediated via a cascade of multiple, interacting protein kinases that activate other proteins by phosphorylation, the addition of a phosphate group to the protein sequence. Due to the complexity of interactions between these multiple kinases and their numerous protein targets, elucidating the signaling events in the DNA damage response is difficult. However, **LICR San Diego Branch** investigators have now developed techniques to globally and quantitatively map phosphorylation events in cells using mass spectrometry, a method whereby the composition of molecules in a biological sample can be determined on a large scale. In 2007, the group published a comprehensive study of DNA damage-induced phosphorylation

events. Through analysis of a yeast strain in which the three major DNA damage response kinases were genetically inactivated, the team identified approximately 50 protein targets implicated in a variety of cellular processes[1]. Further analysis on the functional role of these targets is ongoing.

MISMATCH REPAIR

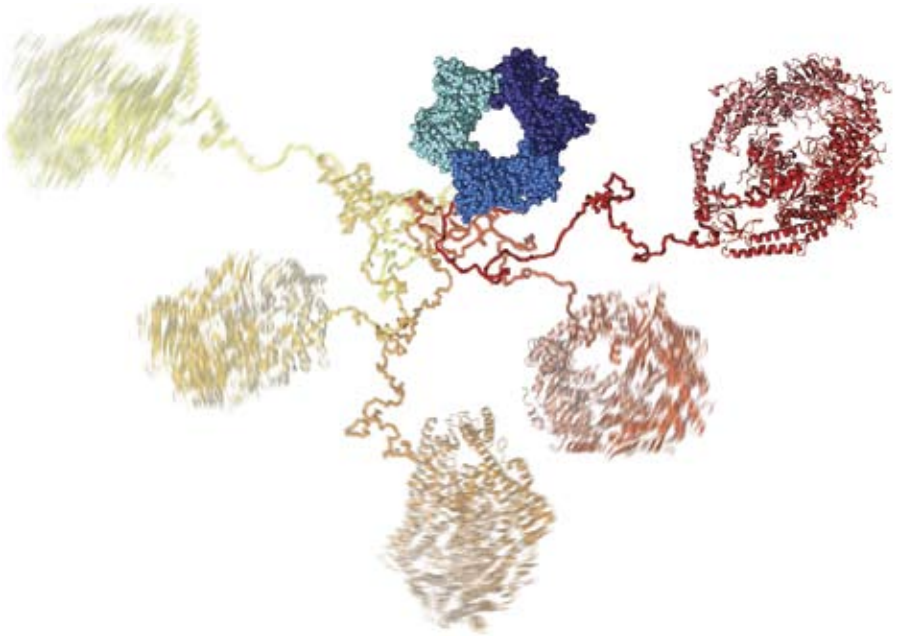
Small errors in the genomic code emerge as mismatches—wrongly paired DNA bases—that can be detected and corrected by mismatch repair (MMR), a mechanism that involves the protein complexes Msh2-Msh6 and Msh2-Msh3. A team of **LICR San Diego Branch** investigators has now clarified how the Msh2-Msh6 and Msh2-Msh3 complexes, which share similar structure and function, are able to recognize different types of mismatches caused either by insertion, deletion, or mis-incorporation of DNA bases[2,3]. Additional insights into the mechanisms of MMR were gained by the demonstration that these complexes have a remarkably flexible structure[4].

1. **Smolka MB, Albuquerque CP, Chen SH, Zhou H.** *Proteome-wide identification of in vivo targets of DNA damage checkpoint kinases*. Proc Natl Acad Sci U S A. 2007 Jun 19;104(25):10364-9 [PMID: 17563356]

2. **Harrington JM, Kolodner RD.** *Saccharomyces cerevisiae Msh2-Msh3 acts in repair of base-base mispairs*. Mol Cell Biol. 2007 Sep;27(18):6546-54 [PMID: 17636021]

3. **Shell SS, Putnam CD, Kolodner RD.** *Chimeric Saccharomyces cerevisiae Msh6 protein with an Msh3 mispair-binding domain combines properties of both proteins*. Proc Natl Acad Sci U S A. 2007 Jun 26;104(26):10956-61 [PMID: 17573527]

4. **Shell SS, Putnam CD, Kolodner RD.** *The N terminus of Saccharomyces cerevisiae Msh6 is an unstructured tether to PCNA*. Mol Cell. 2007 May 25;26(4):565-78 [PMID: 17531814]



In 2007, an LICR team analyzed the protein complexes that constitute the mismatch repair system (MMR), which identifies and corrects wrongly paired DNA bases. This three dimensional reconstruction from the group shows how one MMR molecule, Msh6, can adopt multiple, flexible conformations as it interacts with another protein, PCNA (in blue), that forms a 'sliding clamp' around replicating DNA[4]

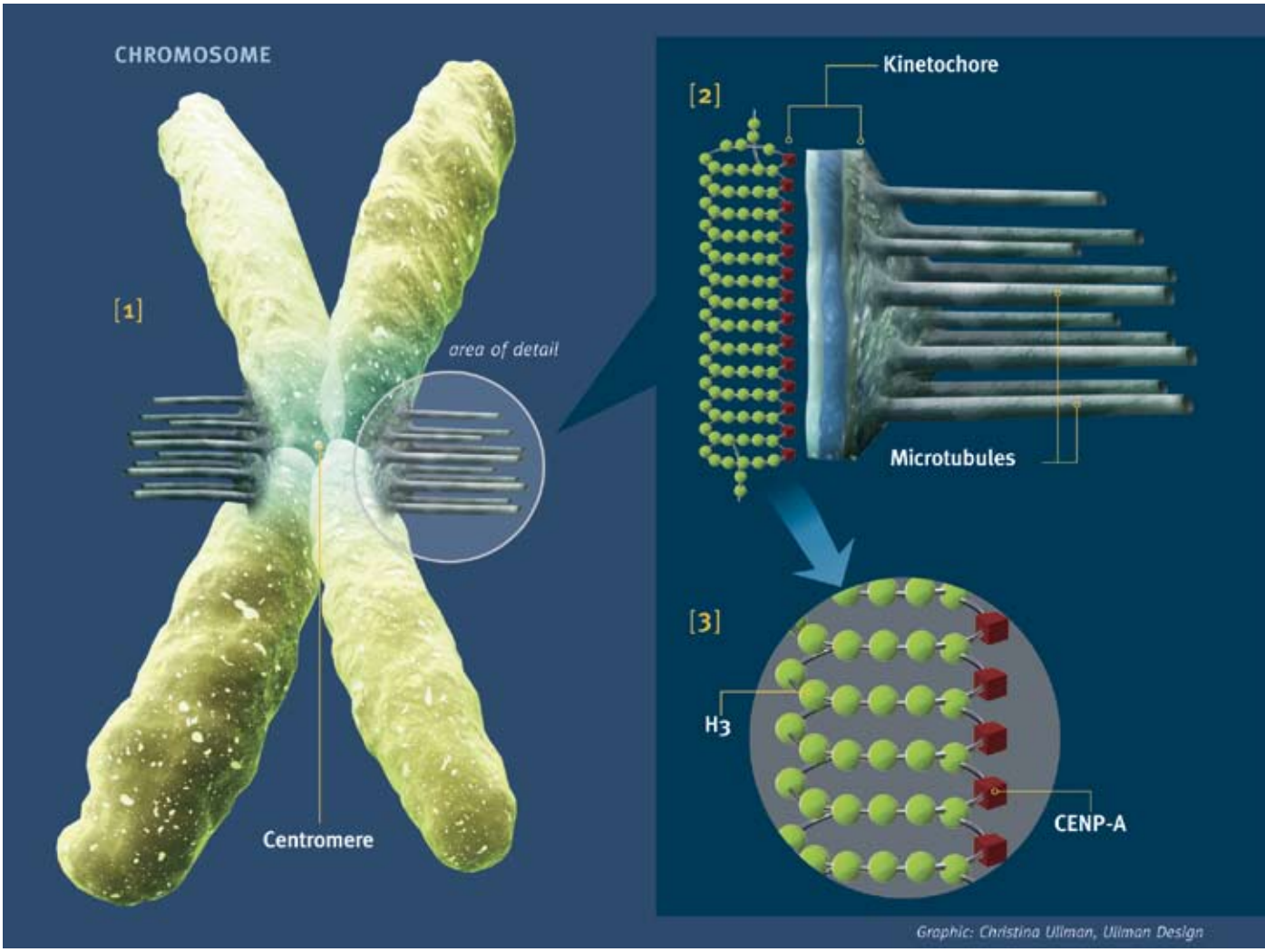
Courtesy of C. Putnam (LICR San Diego Branch).

Division of the Cell

Two major events in mitotic cell division are chromosome segregation and cytokinesis, the formation of two daughter cells. These two processes need to be tightly choreographed to ensure that the genome and cell organelles are distributed appropriately between the daughter cells. Investigators at the **LICR San Diego Branch** are methodically dissecting the molecular mechanisms of cell division to understand their relationship to cancer.

ANALYZING THE STRUCTURE OF CENTROMERES AND KINETOCHORES

Early in mitosis, pairs of newly-replicated chromosomes attach to the mitotic spindle, a bipolar cellular structure that aligns the chromosomes along a central axis and subsequently pulls each set of



The centromere region of chromosomes (1) defines the attachment site for microtubules, which connect to the chromosome via protein structures called kinetochores (2). LICR investigators have shown that the protein CENP-A, which replaces the nucleosome protein histone H3 at centromeres, exists in a disc-shaped chromosome structure that specifies the location at which kinetochores (3) are assembled.

chromosomes towards opposite ends of the dividing cell. The attachment of chromosomes to the mitotic spindle is mediated by transient structures called kinetochores, which form on a specific region of the chromosome known as the centromere. The centromere is defined epigenetically, i.e. by a mechanism that is independent of DNA sequence but nevertheless preserved from one cell generation to the next. A team of **LICR San Diego Branch** investigators found that centromeric and non-centromeric regions of the chromosome are differentiated by the composition of the protein complexes, known as nucleosomes, that package DNA into chromosomes. In 2007, they showed that a distinct region of the nucleosome protein CENP-A, which is exclusively located in centromeres, autonomously maintains the identity of the centromere region[1-2]. The investigators also identified proteins that are needed to incorporate CENP-A nucleosomes into centromeres or to assemble functional kinetochores during mitosis[3-6].

TIMING OF NUCLEAR ENVELOPE BREAKDOWN

At the onset of mitosis, protein filaments known as microtubules originate from a pair of cellular structures called centrosomes. The nuclear envelope, a double membrane that encloses the chromosomes, breaks down to allow the microtubules to bind to the duplicated chromosomes and draw one set of each toward opposite ends of the cell. Upon successful chromosome segregation, new nuclear envelopes form around the two sets of chromosomes. In 2007, **LICR San Diego Branch** investigators discovered that breakdown of the nuclear envelope is promoted by the centrosomes, the same cellular structures that nucleate microtubules. Surprisingly, though, the microtubules have no role in this process. Instead, the centrosomes signal to the nuclear envelope through Aurora A, a protein that is known to be overexpressed in many tumor types[7]. In addition, the team discovered that nuclear envelope dynamics depend on the structural integrity of the endoplasmic reticulum, a network of membrane sheets and tubules that connects to the outside of the nuclear envelope and mediates protein synthesis and other cellular functions[8]. Taken together, these findings emphasize that an extensive molecular infrastructure is involved in the regulation and timing of cell division processes.

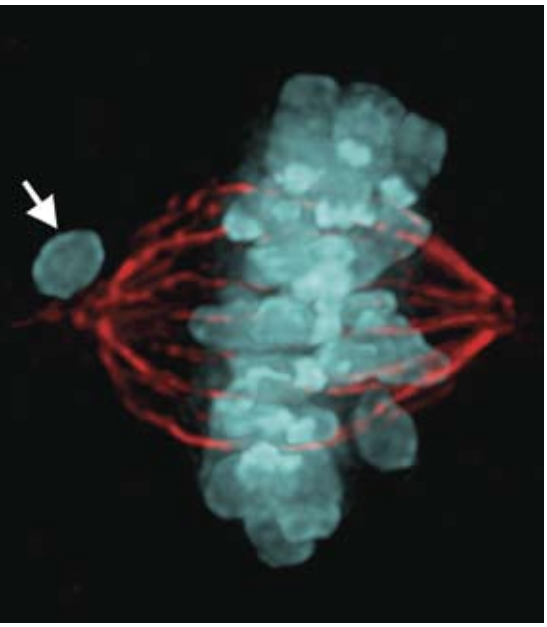
TWISTED CYTOKINESIS

After the formation of new nuclear envelopes around the two sets of chromosomes, cytokinesis begins. A cleavage furrow, an indentation of the cell surface between the segregated chromosomes, forms and then contracts, ultimately parting the cell in two. In some instances, cells can change the orientation in which they divide through a phenomenon known as asymmetric furrowing, whereby the cleavage furrow cuts the dividing cell across a lopsided plane relative to the cell's inherent axis. This mechanism may explain how cells within the epithelium, the cell layer that lines organ and tissues, are able to divide yet still maintain their contacts with neighboring cells to ensure the integrity of the epithelial layer. **LICR San Diego Branch** investigators discovered

an underlying mechanism in which the protein Anillin interferes with the intrinsic symmetry of the dividing cell by binding to septins, a group of proteins that are part of the cleavage furrow[9]. Anillin and the septins are strongly conserved through evolution, suggesting that their interaction may be fundamental in directing cell division. A role for Anillin and the septins in coupling cell division to tissue architecture may also help to explain the strong correlation between Anillin overexpression and tumor progression.

ANEUPLOIDY: A NEW PARADIGM

Aneuploidy, an incorrect number of chromosomes in the cell, was first described more than 100 years ago and for almost as long has been suggested to drive tumorigenesis. Investigators from the **LICR San Diego Branch** have now been able to analyze the relationship between aneuploidy and cancer by generating mice that express reduced levels of the CENP-E protein, a key component of the kinetochore[10]. The mice displayed aneuploidy without any other cellular defects, and were predisposed to developing spontaneous cancers late in life. Remarkably, the mice with reduced levels of CENP-E developed chemically or genetically induced tumors less readily than normal mice, indicating that aneuploidy inhibits tumorigenesis in certain contexts. The findings present a new paradigm for aneuploidy: low levels of genetic instability promote tumorigenesis, while higher levels are protective.



During mitosis, the chromosomes (blue) attach to the mitotic spindle (red) and line up on a central axis. This mouse cell, which lacks the protein CENP-E, contains a misaligned chromosome (arrow) and will thus probably produce aneuploid daughter cells.

Courtesy of B. Weaver (LICR San Diego Branch).

1. **Black BE, Jansen LE, Maddox PS, Foltz DR, Desai AB, Shah JV, Cleveland DW.** *Centromere identity maintained by nucleosomes assembled with histone H3 containing the CENP-A targeting domain.* Mol Cell. 2007 Jan 26;25(2):309-22 [PMID: 17244537]

2. **Black BE, Brock MA, Bédard S, Woods VL Jr, Cleveland DW.** *An epigenetic mark generated by the incorporation of CENP-A into centromeric nucleosomes.* Proc Natl Acad Sci U S A. 2007 Mar 20;104(12):5008-13 [PMID: 17360341]

3. **Cheeseman IM, Hori T, Fukagawa T, Desai A.** *KNL1 and the CENP-H/I/K Complex Coordinately Direct Kinetochore Assembly in Vertebrates.* Mol Biol Cell. 2007 Nov 28 [PMID: 18045986]

4. **Maddox PS, Hyndman F, Monen J, Oegema K, Desai A.** *Functional genomics identifies a Myb domain-containing protein family required for assembly of CENP-A chromatin.* J Cell Biol. 2007 Mar 12;176(6):757-63 [PMID: 17339379]

5. **Jansen LE, Black BE, Foltz DR, Cleveland DW.** *Propagation of centromeric chromatin requires exit from mitosis.* J Cell Biol. 2007 Mar 12;176(6):795-805 [PMID: 17339380]

6. **Gassmann R, Kline SL, Carvalho A, Desai A.** *Analysis of kinetochore assembly and function in Caenorhabditis elegans embryos and human cells.* Methods. 2007 Feb;41(2):177-89 [PMID: 17189860]

7. **Portier N, Audhya A, Maddox PS, Green RA, Dammermann A, Desai A, Oegema K.** *A microtubule-independent role for centrosomes and aurora a in nuclear envelope breakdown.* Dev Cell. 2007 Apr;12(4):515-29 [PMID: 17419991]

8. **Audhya A, Desai A, Oegema K.** *A role for Rab5 in structuring the endoplasmic reticulum.* J Cell Biol. 2007 Jul 2;178(1):43-56 [PMID: 17591921]

9. **Maddox AS, Lewellyn L, Desai A, Oegema K.** *Anillin and the septins promote asymmetric ingression of the cytokinetic furrow.* Dev Cell. 2007 May;12(5):827-35 [PMID: 17488632]

10. **Weaver BA, Silk AD, Montagna C, Verdier-Pinard P, Cleveland DW.** *Aneuploidy acts both oncogenically and as a tumor suppressor.* Cancer Cell. 2007 Jan;11(1):25-36 [PMID: 17189716]

LICR São Paulo Branch – New Host Institution

On December 3rd, 2007, the **LICR São Paulo Branch** celebrated the opening of its new site at the Hospital Oswaldo Alemão Cruz (HAOC) in São Paulo, Brazil. Dr. Luisa Villa, the Branch Director, hosted an inauguration in the recently completed laboratories, at which LICR President Mr. Edward A. McDermott, Jr., and Mr. Klaus Behrens, President of HAOC officially opened the new Branch site. The Branch relocated from the Hospital do Cancer in São Paulo, where it had been operating under the charge of Founding Director, Dr. Ricardo Brentani since 1983.

The HAOC environment provides LICR investigators with larger, customized laboratories and access to an expert clinical oncology community with a large patient population. The HAOC and LICR have together made a commitment to develop a world-class cancer research center that will be spear-headed by the **LICR São Paulo Branch.**

Left: The ceremonial inauguration of the new laboratories was attended by a large crowd that included the Governors of the Hospital Alemão Oswaldo Cruz, dignitaries from the State of São Paulo, and staff from the both Hospital and the LICR Branch.

Middle: Dr. Andrew J.G. Simpson, LICR Scientific Director

Right: From left, Mr. Klaus Behrens (President of the Hospital Alemão Oswaldo Cruz), Dr. Luisa L. Villa (Director, LICR São Paulo Branch) and Mr. Edward A. McDermott, Jr. (LICR President and Senior Executive Officer).

LICR Brain Cancer Initiative

Malignant brain tumors are characterized by an almost 100% tumor related mortality. Despite a multitude of technological advancements in diagnostic imaging and the development of new combination surgery/radiotherapy/chemotherapy regimens, almost all patients diagnosed with the most aggressive—and most common—form of brain cancer, glioblastoma multiforme (GBM), will die within a year of diagnosis. Changing this statistic, which has been constant for more than 30 years, is the key goal of the LICR Brain Cancer Initiative.

CANCER CELL SPECIFIC INHIBITORS OF THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

EGFR is either over produced ('over-expressed') or present in a mutated, constitutively active form in nearly 50% of all epithelial cell cancers. Clinically, these conditions are often associated with a poorer outcome for the patient, presumably because activation of the EGFR drives cell growth. EGFR inhibition has emerged as a rational drug development strategy, and agents that inhibit EGFR specifically are highly sought after in the pharmaceutical industry. LICR investigators, as well as others, have pursued the development of monoclonal antibodies (mAbs) to block EGFR function. While first generation anti-EGFR antibodies have demonstrated anti-tumor activity, they can also produce unwanted side-effects associated with targeting of EGFR on normal cells. An international collaborative effort between LICR investigators in **New York, San Diego** and **Melbourne** was the first to develop mAb806, an EGFR mAb that specifically targets over-expressed EGFR but not normal ('wildtype') EGFR. A significant population of over-expressed EGFR exists in a conformation that makes the binding site for mAb806 continually available. This binding site is not exposed in wildtype EGFRs that are expressed in lower numbers on the body's normal cells. The mAb806 also recognizes the most prevalent mutant form of EGFR present in GBM cells, which is known as de2-7 EGFR.

In 2007, investigators from the **LICR Melbourne Center** completed the first-in-man clinical trial of the 806 mAb antibody in cancer patients with a variety of epithelial or central nervous system tumors,

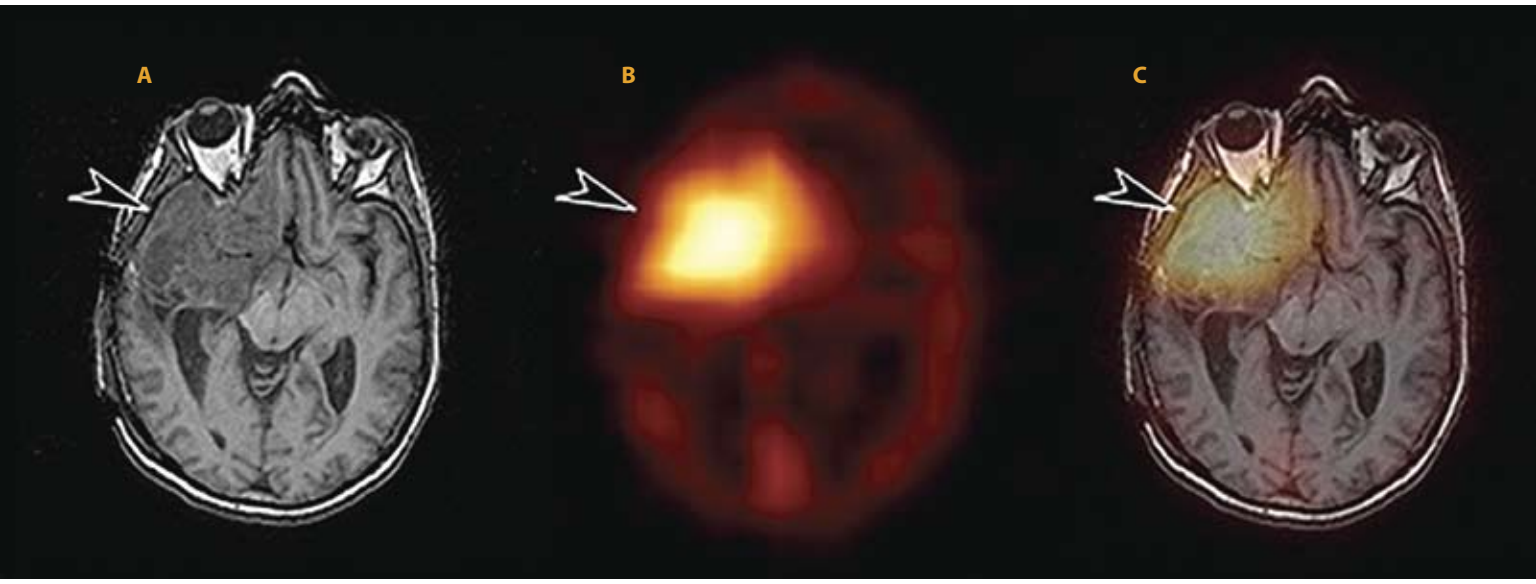
including glioma[1]. By radiolabeling the antibody, the team was able to document the pharmacokinetics, biodistribution and tumor targeting ability of mAb806. Tumor-specific localization of the antibody was observed in all patients, and none of the toxic side-effects typically associated with non-selective EGFR antibodies were noted. The **LICR Melbourne Center** team elucidated the exact cellular mechanisms by which the antibody is internalized and trafficked through intracellular compartments, and showed its specific uptake and retention within human tumor cells implanted into mice[2]. These studies indicate the potential clinical utility of mAb806 for the treatment of EGFR-positive cancers, including brain tumors.

Investigators at the **LICR Melbourne Branch**, **Melbourne Center** and **San Diego Branch** published several studies in 2007 that provide further insight into the conformation and behavior of EGFRs on the cell surface during both active (signaling) and inactive (silenced) states, and during the interaction of a small molecule inhibitor with the receptor complex[3-5]. Data from these studies are enabling the optimization of experimental anti-EGFR therapies, in particular the development of mAb806 and small molecule EGFR inhibitor combination therapies.

Unfortunately, not all cancer patients with EGFR-positive tumors respond to the current anti-EGFR antibodies that recognize the wildtype EGFR. Investigators from the **LICR Melbourne Center** and the **San Diego Branch** have been working together to identify factors that determine susceptibility or resistance to anti-EGFR therapy. Using mouse models of human glioma, the group recently discovered that tumor cells dependent on EGFR signaling for cell growth and survival respond to EGFR antibody therapy in different ways depending on receptor levels and

Specific localization of radio-labeled mAb806 in a brain tumor (in this case anaplastic astrocytoma) in the right frontal lobe of the brain is shown. A) MRI showing tumor in the right frontal lobe (arrow), B) high, specific uptake of mAb806 in the tumor, and C) combined MRI and mAb806 image, demonstrating the ability of the antibody to localize precisely to viable tumor in the brain.

Courtesy of A. Scott (LICR Melbourne Center).



the interactions between receptor forms[5]. Clinical strategies designed to detect tumors over-expressing the wildtype receptor or expressing mutant receptors (*i.e.* de2-7 EGFR) may help identify patients most likely to respond to these therapies. Further research is needed to be able to clearly distinguish between cells that are fully dependent on the EGFR signaling pathway and those that can survive when EGFR signaling is inhibited.

IDENTIFICATION OF NEW THERAPEUTIC TARGETS FOR BRAIN TUMORS

The extremely low survival of patients with aggressive GBM clearly emphasizes the need to identify new molecules for targeted therapies. A team of investigators from the **LICR São Paulo Branch** and **New York Branches**, in conjunction with **LICR Affiliates in São Paulo** (Brazil), conducted microarray analyses on multiple tumor samples to detect genes that are differentially expressed between pilocytic astrocytomas (PA), a low-grade glioma with typically favorable prognosis, and GBM, the extremely invasive and aggressive form of glioma[6]. While the behavior of these two tumors differ dramatically, only 63 genes were found to be over-expressed by a ratio of two-fold or greater in GBM compared to PA. From this list, the team identified MELK (maternal embryonic leucine zipper kinase) as one of the most highly expressed genes in GBM compared to PA. The group went on to study the role of MELK up-regulation in high grade GBM by using a siRNA approach to inhibit MELK protein expression in two malignant astrocytoma cell lines. Their experiments indicated that MELK promotes cell proliferation and anchorage-independent growth in astrocytoma cell lines, and that MELK inhibition has the potential to impact tumor growth. These studies provide evidence that the targeting of MELK may be a new therapeutic strategy for GBM.

1. **Scott AM, Lee FT, Tebbutt N, Herbertson R, Gill SS, Liu Z, Skrinos E, Murone C, Saunder TH, Chappell B, Papenfuss AT, Poon AM, Hopkins W, Smyth FE, MacGregor D, Cher LM, Jungbluth AA, Ritter G, Brechbiel MW, Murphy R, Burgess AW, Hoffman EW, Johns TG, Old LJ.** (2007) A phase I clinical trial with monoclonal antibody ch806 targeting transitional state and mutant epidermal growth factor receptors. PNAS, 104(10):4071-6.

2. **Perera RM, Zoncu R, Johns TG, Pypaert M, Lee FT, Mellman I, Old LJ, Toomre DK, Scott AM.** (2007) Internalization, intracellular trafficking, and biodistribution of monoclonal antibody 806: a novel anti-epidermal growth factor receptor antibody. Neoplasia, 9(12):1099-110.

3. **Clayton AH, Tavarnesi ML, Johns TG.** (2007) Unligated epidermal growth factor receptor forms higher order oligomers within microclusters on A431 cells that are sensitive to tyrosine kinase inhibitor binding. Biochemistry, 46(15):4589-97.

4. **Gan HK, Walker F, Burgess AW, Rigopoulos A, Scott AM, Johns TG.** (2007) The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor AG1478 increases the formation of inactive untethered EGFR dimers. Implications for combination therapy with monoclonal antibody 806. J Biol Chem., 282(5):2840-50.

5. **Johns TG, Perera RM, Vernes SC, Vitali AA, Cao DX, Cavenee WK, Scott AM, Furnari FB.** (2007) The efficacy of epidermal growth factor receptor-specific antibodies against glioma xenografts is influenced by receptor levels, activation status, and heterodimerization. Clin Cancer Res., 13(6):1911-25.

6. **Marie SK, Okamoto OK, Uno M, Hasegawa AP, Oba-Shinjo SM, Cohen T, Camargo AA, Kosoy A, Carlotti CG Jr, Toledo S, Moreira-Filho CA, Zago MA, Simpson AJ, Caballero OL.** Maternal embryonic leucine zipper kinase transcript abundance correlates with malignancy grade in human astrocytomas. Int J Cancer, Epub 10/24/07.

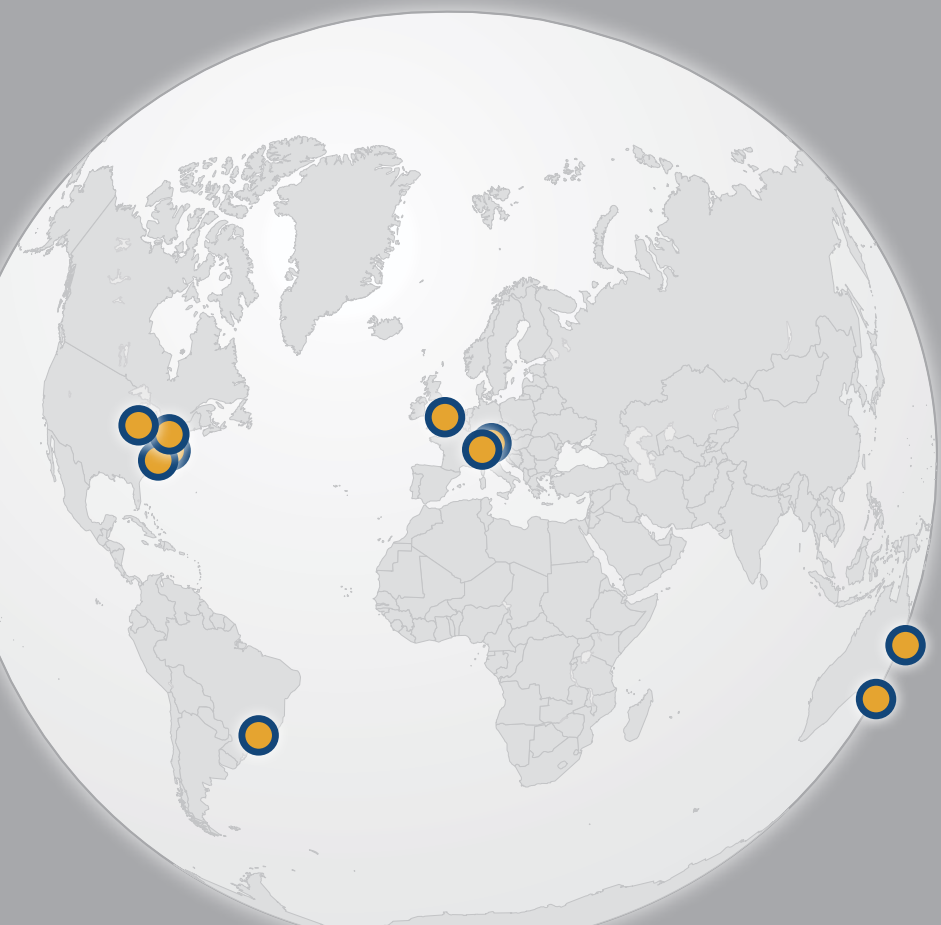
The Hilton-Ludwig Cancer Metastasis Initiative

In 2007, LICR was awarded a USD 4.5 million dollar grant from the Conrad N. Hilton Foundation (CNHF) to support a three year program investigating the process of cancer metastasis, the reason for nearly all cancer-related deaths. LICR has committed to expend the same amount on metastasis research each year. The program, named the Hilton-Ludwig Cancer Metastasis Initiative (HLCMI), has brought together investigators from LICR, the Ludwig Centers, and key external collaborators to work together to address the highly complex process of metastasis.

The HLCMI is comprised of four interrelated core efforts:

- Bio-analysis of metastasis research: an effort to create a database in which metastasis data and information from the literature can be collated and integrated.
- Establishment of metastasis tissue banks: the HLCMI is focusing its efforts on the collection of melanoma and brain (refer p19), breast, colon and ovarian cancer specimens, plus normal tissue specimens from the same patient.
- Molecular analyses of metastasis tissue banks: the provision of access to high-throughput (sequencing and transcriptomic) and specialist (immunohistochemistry) technologies to analyze tissue bank samples.
- Meetings on key research fields: in 2007, the HLCMI supported meetings on brain, breast and colon cancer research, and a combined meeting on melanoma and ovarian cancer.

HLCMI SITES WORLD WIDE



Angiogenic Growth Factors

Tumors cannot grow beyond the size of a few millimeters without blood vessels that supply nutrients and oxygen. Accordingly, tumors and their surrounding tissue—the stroma—secrete growth factors to induce angiogenesis, the formation of new blood vessels. In a similar way, tumors also induce lymphangiogenesis, the formation of new lymphatic vessels. Angiogenesis and lymphangiogenesis facilitate metastasis since cancer cells that detach from a tumor can be dispersed through the body via the bloodstream or lymphatic vessels. Metastasis is the ultimate cause of most cancer deaths. Substantial efforts in cancer research are thus aimed at developing therapeutic means to prevent metastasis by controlling tumor-induced angiogenesis and lymphangiogenesis.

TOWARD NEW ANTI-ANGIOGENIC THERAPIES

The pro-angiogenic vascular endothelial growth factor (VEGF)-D stimulates angiogenesis and lymphangiogenesis via VEGF receptors (VEGFR)-2 and VEGFR-3, which are expressed by endothelial cells lining the inner surface of blood vessels and lymphatics. In order to efficiently activate the receptors, the secreted VEGF-D protein must be processed into an active variant. Investigators at the **LICR Melbourne Branch** and **Affiliates in Helsinki** (Finland) have identified a number of proprotein convertases (PCs)—a type of protein-cleaving enzyme—that mediate VEGF-D processing. The PCs were shown to generate VEGF-D variants that bind VEGFR-2, the principal receptor involved in angiogenesis, as well as VEGFR-3[1]. As regulators of VEGF-D signaling, PCs may play an important role in angiogenesis and could be new targets for anti-angiogenic therapies.

Drugs that affect endothelial cell processes involved in angiogenesis by blocking VEGF signaling have been shown to restrict tumor growth, with some drugs already in clinical practice. Less is known

about the role of pericytes, smooth muscle-like cells that are adjacent to endothelial cells, in tumorigenesis. Pericytes are recruited to the blood vessel wall in response to the growth factor PDGF-BB, which is secreted during angiogenesis by endothelial cells. A team of **LICR Uppsala Branch** investigators have described a mutation that causes the receptor for PDGF-BB to be constantly active and that allows tumors to produce larger blood vessels that are extensively covered with pericytes[2]. In a separate pre-clinical study, the team explored the utility of anti-angiogenic cancer treatments that target both VEGF and PDGF receptors. A subpopulation of pericytes was identified that respond to PDGF receptor kinase inhibitors, and simultaneous treatment with inhibitors of VEGF and PDGF receptors resulted in efficient reduction of tumor growth[3]. Extensive pericyte coverage of blood vessels—which is typically observed in advanced tumors—may obstruct the administration of anti-angiogenic drugs in patients and could be overcome by new therapies that combine VEGF- and PDGF receptor targeting.

PDGF SIGNALING AND HYALURONAN

Hyaluronan is a molecule present in stroma that promotes tumor progression when bound to the receptor CD44. **LICR Uppsala Branch** investigators discovered that the binding of hyaluronan to CD44 is necessary for PDGF-BB-induced growth of fibroblasts, the main cells of the stroma. Moreover, they observed that PDGF-BB signaling stimulates the production of hyaluronan by inducing the expression of HAS2, a hyaluronan-synthesizing enzyme. In contrast, signaling by TGF-ß (refer pp22-23) stimulates the expression of hyaluronan-degrading enzymes that prevent hyaluronan accumulation[4]. In a second study, the team showed that expression of HAS2 is elevated in cells isolated from aggressive breast tumors and that this may confer breast cancer malignancy[5].

1 **McColl BK, Paavonen K, Karnezis T, Harris NC, Davydova N, Rothacker J, Nice EC, Harder KW, Roufail S, Hibbs ML, Rogers PA, Alitalo K, Stacker SA, Achen MG.** Proprotein convertases promote processing of VEGF-D, a critical step for binding the angiogenic receptor VEGFR-2. FASEB J. 2007 Apr;21(4):1088-98. Epub 2007 Jan 22 [PMID: 17242158]

2 **Suzuki S, Heldin CH, Heuchel RL.** Platelet-derived growth factor receptor-beta, carrying the activating mutation D849N, accelerates the establishment of B16 melanoma. BMC Cancer. 2007 Dec 12;7:224 [PMID: 18076756]

3 **Hasumi Y, Kłosowska-Wardega A, Furuhashi M, Ostman A, Heldin CH, Hellberg C.** Identification of a subset of pericytes that respond to combination therapy targeting PDGF and VEGF signaling. Int J Cancer. 2007 Dec 15;121(12):2606-14 [PMID: 17691110]

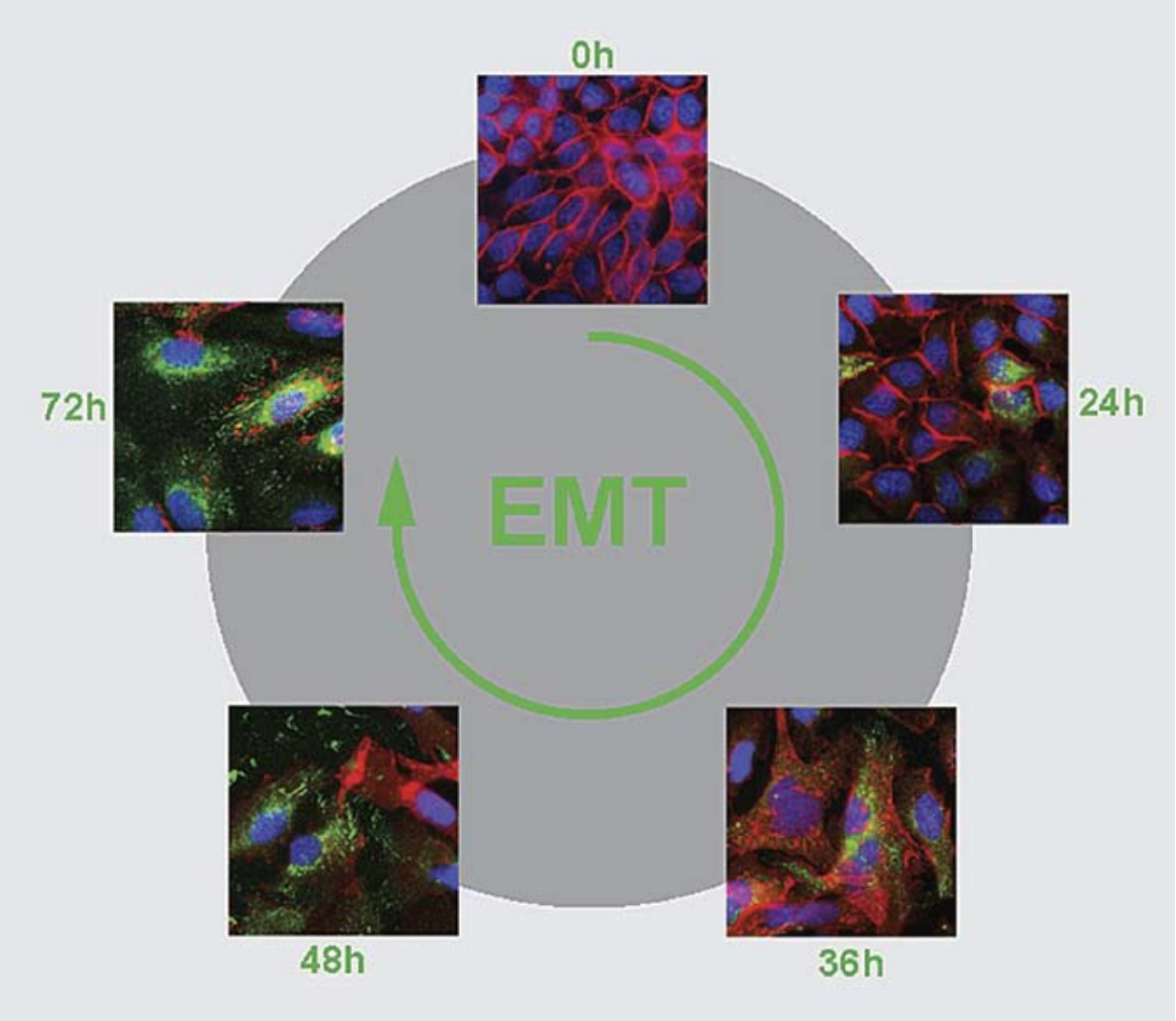
4 **Li L, Asteriou T, Bernert B, Heldin CH, Heldin P.** Growth factor regulation of hyaluronan synthesis and degradation in human dermal fibroblasts: importance of hyaluronan for the mitogenic response of PDGF-BB. Biochem J. 2007 Jun 1;404(2):327-36 [PMID: 17324121]

5 **Li Y, Li L, Brown TJ, Heldin P.** Silencing of hyaluronan synthase 2 suppresses the malignant phenotype of invasive breast cancer cells. Int J Cancer. 2007 Jun 15;120(12):2557-67 [PMID: 17315194]

Exploring the Dual Role of TGFβ in Cancer

The transforming growth factor (TGF) β family of proteins regulates cell growth, differentiation, and apoptosis. The TGFβ proteins transduce signals from activated TGFβ receptors (TGFβR) on the cell surface via the Smad family of intracellular signaling proteins to ultimately regulate the expression of numerous genes.

The TGFβ signaling pathway is often deregulated in cancer, thus the inhibition of TGFβ signaling has long been considered a promising approach for new cancer therapies. However, the prospect of designing therapies that target TGFβ signaling is complicated by the fact that the pathway influences tumorigenesis both negatively



and positively: TGFβ signaling generally suppresses the growth of early stage tumors, but can also promote the invasiveness and the metastatic spread of cancer cells.

Investigators at the **LICR Uppsala Branch** are studying the cellular processes mediated by TGFβ in tumors that originate in the epithelium, the cell layer that lines many organs and tissues. TGFβ signaling is known to suppress the growth of these tumors either by triggering apoptosis or by inducing cytostasis, a condition that prevents cells from dividing. In 2007, the team discovered that TGFβ–induced cytostasis is mediated by a combination of Smad proteins and components of an additional signaling pathway activated by the cell surface protein Notch[1]. This occurs in part via the regulation of *p21*, a gene that controls the rate of cell division. The team discovered a new transcription factor, named Meox-2, which acts with the Smad proteins to increase the expression of the *p21* gene[2].

LICR Uppsala Branch investigators also found that when the signaling events that normally cause apoptosis and cytostasis are suppressed, TGFβ signaling triggers a process known as epithelial-mesenchymal transition (EMT)[3]. EMT confers upon epithelial cancer cells the ability to migrate and to invade surrounding tissues. Since these capabilities are required for cancer metastasis, the prevention of EMT might constitute an important therapeutic approach to controlling cancer. The LICR investigators found that TGFβ signaling in epithelial cells changes over time: in the short term, TGFβ signaling inhibits cell growth, but sustained signaling induces EMT[3].

These findings suggest that the TGFβ signaling pathway harbors an intrinsic switch between tumor suppression and metastasis.

1. **Niimi H, Pardali K, Vanlandewijck M, Heldin CH, Moustakas A.** *Notch signaling is necessary for epithelial growth arrest by TGF-beta.* J Cell Biol. 2007 Feb 26;176(5):695-707 [PMID: 17325209]

2. **Valcourt U, Thuault S, Pardali K, Heldin CH, Moustakas A.** *Functional role of Meox2 during the epithelial cytostatic response to TGF-β.* Mol. Oncol. 2007 1:55-71

3. **Gal A, Sjöblom T, Fedorova L, Imreh S, Beug H, Moustakas A.** *Sustained TGFbeta exposure suppresses Smad and non-Smad signalling in mammary epithelial cells, leading to EMT and inhibition of growth arrest and apoptosis.* Oncogene. 2007 Aug 27 [PMID: 17724470]

These images from the Uppsala Branch show epithelial cells undergoing EMT in response to TGFβ at time intervals of 0, 24, 36, 48 and 72 hours (green arrow). As EMT proceeds, the cells lose the adhesion protein E-cadherin (stained red) and accumulate and secrete the protein fibronectin (stained green). Cell nuclei are stained blue to demarcate individual cells.

Courtesy of M. Vanlandewijck (LICR Uppsala Branch).

PI3K Research Enters the Clinic

In 2003, LICR spun off its first company, PIramed Limited, to develop new cancer therapies based on selective inhibitors of PI3Ks. These inhibitors resulted from research conducted by investigators at the LICR London Branch and collaborators at Cancer Research UK and the Institute of Cancer Research (both in London, UK). A first candidate drug designed to inhibit PI3K signaling is expected to enter clinical development in 2008 through a collaboration between PIramed and Genentech Inc. The advancement of PI3K research into product development affirms the value of LICR's commitment to taking responsibility for the translation of its laboratory discoveries into applications for human benefit.

PI3K Regulation: Towards Clinical Application

PI3Ks are intracellular enzymes that transduce signals from cell surface receptors to other intracellular proteins in order to mediate processes such as cell growth, differentiation and migration. Deregulation of these processes is required for tumorigenesis, and PI3K signaling has been shown to be disrupted in most types of cancer. The PI3Ks comprise a heterogeneous group of enzymes divided into three classes based on their structure and function. A further understanding of how these complex enzymes are regulated may guide the development of new therapies that by targeting PI3K-mediated processes can restore signaling regulation in cancer cells.

NEW INSIGHTS INTO PI3K REGULATION

The Class 1A PI3Ks contain one of three catalytic subunits—p110α, p110β, or p110δ—bound to one of five regulatory subunits: p85α, p85β, p55γ, p55α, or p50α. The regulatory subunit is thought to stabilize the catalytic subunit and control PI3K activation. The ratio of catalytic and regulatory subunits in the cell has been held to be an important determinant of PI3K activity, with 'free' regulatory subunits, i.e., those that are not bound to catalytic subunits, thought to act as negative regulators of the signaling pathway. However, this hypothesis has now been refuted by a series of analyses conducted at the **LICR London Branch**. These analyses showed that the amounts of catalytic and regulatory PI3K subunits are equal in a range of different cells and tissues, indicating that no regulatory subunits exist in a free form. This suggests that factors other than the ratio of the catalytic and regulatory subunits account for the inhibition of PI3K signaling[1].

The tumor suppressor protein PTEN has a well-established role in controlling PI3K signaling, but the regulation of PTEN itself is not well understood. Recently, a study carried out at the **LICR London Branch** revealed that the signaling protein RhoA, which activates PTEN, is inhibited by the catalytic PI3K subunit p110δ[2]. This finding indicates that PI3Ks can regulate their own signaling by modulating the activity by PTEN.

1 **Geering B, Cutillas PR, Nock G, Gharbi SI, Vanhaesebroeck B.** *Class IA phosphoinositide 3-kinases are obligate p85-p110 heterodimers.* Proc Natl Acad Sci U S A. 2007 May 8;104(19):7809-14 [PMID: 17470792]

2 **Papakonstanti EA, Ridley AJ, Vanhaesebroeck B.** *The p110delta isoform of PI 3-kinase negatively controls RhoA and PTEN.* EMBO J. 2007 Jul 11;26(13):3050-61 [PMID: 17581634]

Characterizing the Roles of Interleukins in Cancer

During the process of hematopoiesis, a variety of critical signaling molecules stimulate progenitor cells to differentiate into specific blood cell types. Cytokines are one such group of signaling molecules. Different cytokines act to regulate cell differentiation by binding to cell surface receptors that transduce messages through an intracellular signaling cascade mediated by enzymes known as JAKs. The JAKs in turn activate STAT transcription factors, which mediate the expression of genes required for hematopoiesis. Faulty regulation of JAK-STAT signaling can lead to the development of a variety of blood cancers, i.e. leukemia, lymphoma and myeloma, and other blood cell diseases, such as polycythemia vera (PV) and thrombocytosis.
One area of research within LICR is the elucidation of the roles of the interleukin (IL) family of cytokines in blood cancers and disease.

In 2007, investigators from the **LICR Melbourne Branch** published new data defining distinct roles for the IL-6 and IL-11 cytokines in the development of pathologies caused by STAT3 hyperactivity via signaling from the gp130 transmembrane receptor[1]. Using a genetically engineered mouse model, the team determined that IL-6 is the predominant regulator of STAT3 activation for the formation of blood cells and also of B cells and T cells of the immune system. IL-11 was found to be involved in regulating the maturation of the lymphoid precursors into B and T cells (refer p29), and also provides some functional redundancy

for IL-6 signaling. The STAT3-dependent phenotype in the mouse model is reminiscent of increased activation of STAT3 associated with human diseases, such as multiple myeloma, non-Hodgkin lymphoma and acute myeloid leukemia, suggesting deregulation of gp130-STAT3 signaling might also play a role in the development of these diseases in humans. The **LICR Melbourne Branch** team is now utilizing this mouse model to test whether therapeutic inhibition of STAT3 may ultimately provide potential clinical benefit in the treatment of diseases associated with persistent STAT3 activation.

The frequently observed connection between constitutive STAT activation and tumorigenesis is also being studied by a team of investigators from the **LICR Brussels Branch**. The Brussels team generated a cell line that produces elevated levels of JAK and showed JAK overexpression led to continual activation of the JAK-STAT signaling pathway, a phenomenon commonly observed in a variety of tumors[2]. JAK overexpression alone was not sufficient to induce oncogenic transformation of normal cells, but it did increase cell sensitivity to the IL-9 cytokine, which may provide a growth advantage to the cells under certain conditions. **LICR Brussels Branch** investigators had previously shown that JAK2 mutations cause PV, but these new data suggest that overexpressed, non-mutated JAK kinases might also contribute to the constitutive STAT activation observed in blood cancers and diseases.

1. **Jenkins BJ, Roberts AW, Greenhill CJ, Najdovska M, Lundgren-May T, Robb L, Grail D, Ernst M.** (2007) Pathologic consequences of STAT3 hyperactivation by IL-6 and IL-11 during hematopoiesis and lymphopoiesis. Blood, 109(6):2380-8.

2. **Knoops L, Hornakova T, Royer Y, Constantinescu SN, Renauld JC.** (2008) JAK kinases overexpression promotes in vitro cell transformation. Oncogene, 27(11):1511-9. Epub Sept. 17, 2007.

Colony Stimulating Factors: From Bench to Bedside and Back

The innate immune system provides the first line of defense against infectious organisms. Central to both the innate immune and inflammatory responses are the white blood cells, or leukocytes, a group of specialized cells that includes neutrophils, eosinophils, monocytes and macrophages. Leukocytes are produced when hematopoietic stem cells (HSCs) in the bone marrow differentiate into the specialized cell types in response to regulators, such as the colony-stimulating factors (CSFs). Many chemotherapeutic regimens destroy leukocytes, often leaving oncology patients susceptible to infection and unable to undergo further chemotherapy treatments.

In 1984, **LICR Melbourne Branch** investigators were the first to clone GM-CSF (granulocyte/macrophage-CSF). The first-in-man clinical trial of GM-CSF, also conducted by the **LICR Melbourne Branch**, assessed the ability of GM-CSF to stimulate leukocyte production in cancer patients. Furthermore, LICR investigators were involved in the discovery of a second CSF, namely granulocyte-CSF (G-CSF), and a first-in-man trial of this neutrophil-specific stimulator was also organized by clinical staff at the **LICR Melbourne Branch**. The GM-CSF discovery was licensed to industrial partners to move its clinical development forward, and GM-CSF is now part of treatments to support bone marrow transplantation and some chemotherapies.

Investigators at the **LICR Melbourne Branch** have maintained a leading role in the area of CSF research. Some years ago, the team showed that the production of neutrophils was possible in mice lacking G-CSF, a cytokine thought to be an absolute requirement for the generation of this type of leukocyte, in response to stimulation by exposure to yeast

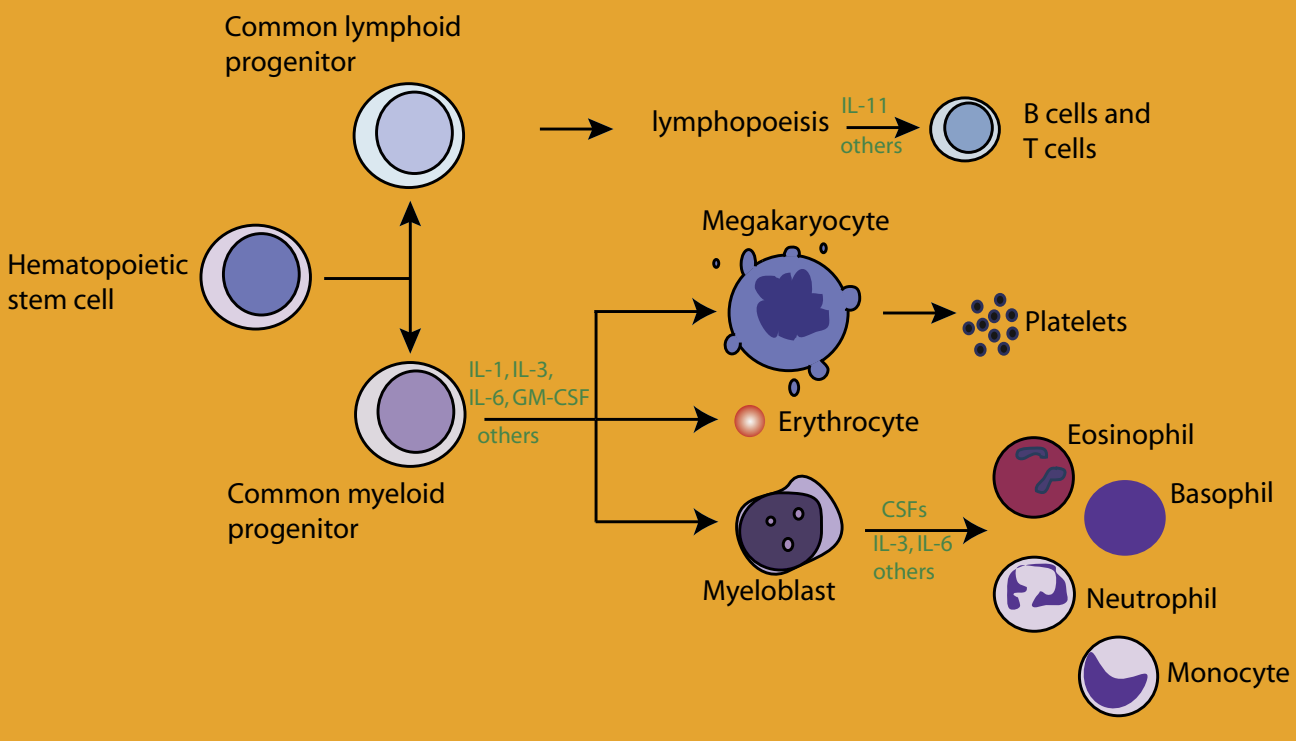
or lipopolysaccharide, a lipid-carbohydrate made by bacterial cells. In 2007, the LICR team discovered that mice lacking all three CSFs, G-CSF, GM-CSF and M-CSF (macrophage-CSF), were still able to produce low levels of leukocyte cells, and were also still able to mount an inflammatory response[1]. These and subsequent studies from the LICR team have revealed that the IL-6:sIL-6R complex (Interleukin 6 and a soluble form of its receptor) is able to stimulate neutrophil production in response to external challenges to the immune system[2,3].

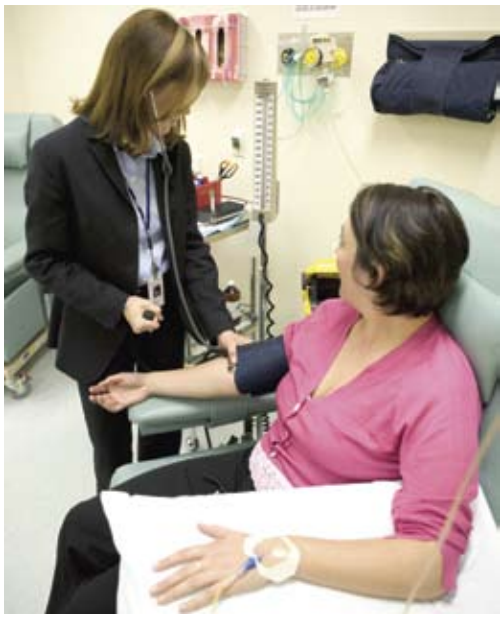
1. **Hibbs ML, Quilici C, Kountouri N, Seymour JF, Armes JE, Burgess AW, Dunn AR.** (2007) Mice lacking three myeloid colony-stimulating factors (G-CSF, GM-CSF, and M-CSF) still produce macrophages and granulocytes and mount an inflammatory response in a sterile model of peritonitis. J Immunol. 178(10):6435-43.

2. **Zhang HH, Basu S, Wu F, Begley CG, Saris CJ, Dunn AR, Burgess AW, Walker F.** (2007) Macrophage-colony stimulating factor is required for the production of neutrophil-promoting activity by mouse embryo fibroblasts deficient in G-CSF and GM-CSF. J Leukoc Biol., 82(4):915-25.

3. **Walker F, Zhang HH, Matthews V, Weinstock J, Nice EC, Ernst M, Rose-John S, Burgess AW.** (2007) IL6/sIL6R complex contributes to emergency granulopoietic response in G-CSF and GM-CSF deficient mice. Blood, Epub 12/21/07.

A simplified diagram of blood cell differentiation. Specific growth factors (only some of which are depicted in green below) control the differentiation of blood cell types from hematopoietic stem cells.



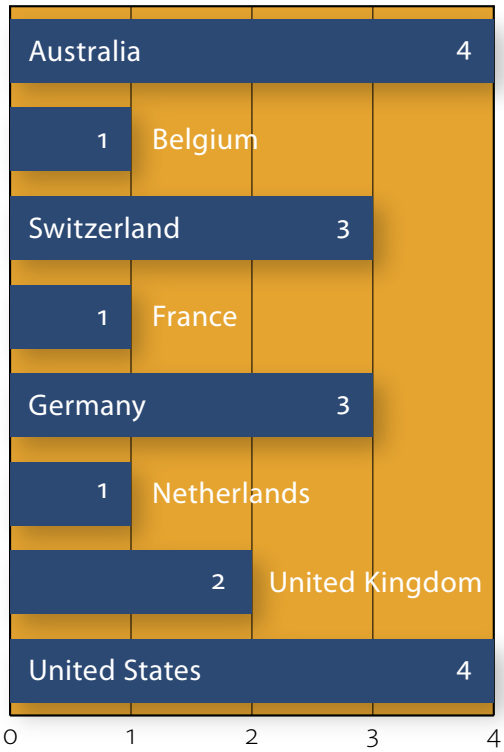


LICR Clinical Trials

A core philosophy of the Ludwig Institute for Cancer Research is to fully explore the therapeutic potential of its research findings for the benefit of cancer patients. To achieve this, the entire discovery process from laboratory research through early phase clinical trials is undertaken by the Institute. LICR believes that research should be carried through the clinic door, and that much can be learned from the integration of laboratory and clinical research. Clinical discovery at the LICR focuses on exhaustive investigation of the biological and biochemical effects of a potential therapy or therapeutic modality in the clinical setting. Results from this clinical research are critical for designing trials that will evaluate the therapeutic benefit of an investigational agent. The LICR clinical discovery strategy offers the opportunity to explore new treatments with maximum efficiency and innovation, while ensuring patient safety and adherence to regulatory guidelines.

In 2007, LICR initiated three clinical trials, bringing the number of open LICR sponsored studies to 18 at the end of 2007. The physical structure of the Institute, in which sites are located around the globe (pp6-7), creates a worldwide network that enables the Institute to conduct its trials where experts in patient care and clinical and laboratory research, plus the appropriate patient populations, are located.

LICR SPONSORED CLINICAL TRIALS WITH PATIENTS ON STUDY IN 2007.



18 Studies with Active Patients in 2007

3 Studies Initiated in 2007

LICR and GlaxoSmithKline Partner to Develop a Vaccine Against Lung Cancer

To ensure that the therapeutic potential of its research findings are fully explored, LICR focuses on the discovery phase, including pre-clinical laboratory studies through early stage clinical trials, and then, when opportunities arise, aligns with industry or other academic partners for later stage clinical development. An example of this model is the partnership between LICR and the pharmaceutical company GlaxoSmithKline (GSK) to develop therapeutic cancer vaccines—the first being MAGE-A3 antigen, discovered by the **LICR Brussels Branch**, in combination with a proprietary GSK adjuvant—for patients with non-small cell lung cancer (NSCLC).

The **LICR Brussels and New York Branches** conducted early phase clinical trials to demonstrate safety of the vaccine and provide evidence that it induced an antigen-specific immune response in patients with NSCLC. GSK used the results from the LICR trials as the rationale for exercising their option to license the MAGE-A3 antigen and commit to the clinical development of the vaccine.

A subsequent phase II trial conducted by GSK, the results of which were reported in 2007, demonstrated that the vaccine reduced the relative risk of cancer recurrence by 27% in NSCLC patients. Based on these encouraging data, GSK initiated a phase III clinical trial to test the ability of the MAGE-A3 vaccine (which GSK calls an antigen-specific cancer immunotherapy, or 'ASCI') to reduce recurrence of lung cancer following surgery. This ongoing trial, involving some 2270 patients, is the largest ever phase III trial for lung cancer.

Cancer Antigen Characterization

Cancer antigens are molecules that are present in cancer cells and that can be recognized and targeted by cells of the immune system. Cancer antigens that are frequently expressed in cancer cells, but have limited expression in normal adult tissues, are promising targets for the development of cancer immunotherapies, in particular monoclonal antibodies (pp46-49) and therapeutic cancer vaccines (pp42-45). Traditionally, cancer antigens were discovered by identifying the targets of antibodies or T cells detected in the blood of cancer patients. Now, LICR investigators are utilizing computational methods to identify novel cancer antigens based on their gene and/or protein expression profiles in normal tissues and different types of cancers.

The cancer/testis (CT) (or cancer/germline) antigens are a family of cancer antigens that, in addition to being present in various cancer cells, are known to be expressed in germ cells of the testes, but not other normal adult tissues. Because of their selective expression and immunogenicity, LICR has invested considerable efforts conducting laboratory, pre-clinical and clinical research on CT antigens, in particular, to assess their potential as immunotherapy targets. Comprehensive studies of the gene families that encode CT proteins, as well as the function and role of CT proteins in the cancer cell, are now being undertaken.

A POTENTIAL NEW ADJUVANT THERAPY FOR BREAST CANCER

In recent years, approaches for new breast cancer treatments have focused on the development of adjuvant therapies. Adjuvant therapies are designed to prevent the recurrence of cancer following surgery or treatment by killing not yet detectable cancer cells that may have spread (metastasized) from the primary tumor mass. Therapeutic cancer vaccines are some of the most promising adjuvant therapies

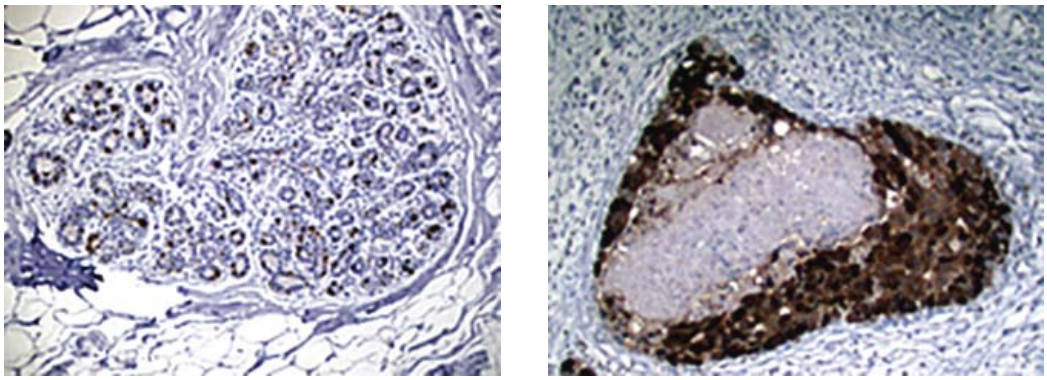
in development today. In 2007, investigators from the **LICR New York Branch** and **Affiliates in Heidelberg** (Germany), **Kyiv** (Ukraine), **London** (UK), **New York** (USA) and **Zurich** (Switzerland) assessed the therapeutic potential of the putative breast cancer antigen NY-BR-1[1]. Using newly developed monoclonal antibodies, the team was able to characterize NY-BR-1 protein expression in normal tissues and in cancer. They determined that the NY-BR-1 protein is present in normal and neoplastic breast tissue, but that it is not detectable in large variety of healthy tissues. NY-BR-1 protein was found to be most highly expressed in a particular and quite common type of breast carcinoma, the so-called ductal carcinoma in situ (DCIS). In DCIS, tumor cells are still confined to preformed anatomical structures of the breast gland without invading the surrounding tissue. Interestingly, lower NY-BR-1 levels were found in invasive carcinomas. These data indicate that NY-BR-1 may have clinical utility as a valuable diagnostic marker to determine disease progression or as a therapeutic drug target for adjuvant therapies.

CT GENE EXPRESSION AND CORRELATION WITH CANCER PROGRESSION

While several clinical studies in cancer patients have demonstrated CT antigens to be immunogenic, little is known about the relationship between their gene expression and disease progression. In 2007, investigators from the **LICR Brussels, Lausanne** and **New York Branches**, and their collaborators, investigated CT antigen expression in primary and metastatic tumor samples from patients with melanoma or colorectal cancers (CRC). In the melanoma study, conducted by the New York team, in collaboration with **Affiliates in New York** (USA), an increased prevalence of NY-ESO-1 expression was detected in metastases compared to primary melanomas[2]. Positive associations were also observed between NY-ESO-1 expression and both tumor thickness and clinical stage at initial diagnosis. Additionally, investigators from the **LICR Brussels Branch** characterized the expression of the CT antigen, BORIS, in samples from melanoma patients[3]. The Brussels team found BORIS to be expressed in 16% of primary melanomas and 34% of metastatic melanomas analyzed. Although the etiological relevance of these observations is unknown, the use of therapeutic cancer vaccines based on CT

These images show NY-BR-1 staining (brown) in normal breast tissue (left) and increased staining in intraductal carcinoma (right).

Courtesy of A. Jungbluth (LICR New York Branch).



antigens as adjuvant therapies becomes more promising in light of the evidence of increased CT antigen expression in metastasis. Furthermore, both NY-ESO-1 and BORIS may have clinical utility as markers for disease prognosis.

In contrast to the findings in melanoma, the **LICR Lausanne Branch** reported that expression frequencies of the CT antigens MAGE-A3, MAGE-A4, MAGE-A10, NY-ESO-1 and SSX2 were not related to disease stage in CRC[4]. CRC metastases did not have increased expression of these antigens compared to primary CRC tumors. However, the team did observe that a small subset of CRC cancer patients with tumors expressing CT antigens had antigen-specific T cell responses.

UNDERSTANDING THE ROLE OF CT PROTEINS IN THE PLACENTA AND FETAL OVARY

Scientists from the **LICR New York Branch** and their collaborators demonstrated, for the first time, that CT proteins are expressed in the placenta[5] and germ cells of the fetal ovary[6], in addition to germ cells of the normal adult testis. The team showed the presence of CT proteins MAGE-A1, MAGE-A3, MAGE-A4, MAGE-C1 and NY-ESO-1 in fetal ovary, with expression peaking during weeks 16 to 23 of embryological development. The study indicates that CT proteins may play an important role in male and female germ cell development. While placental expression of the CT proteins varied widely, MAGE-A3 and MAGE-A4 were expressed predominantly and were mainly localized to the trophoblast cells in the placenta. Trophoblasts are often referred to as 'pseudo-tumorigenic' cells because they share some of the characteristics of cancer cells, such as their potential to grow invasively and/or to give rise to spread comparable to the process of metastasis. These results provide further circumstantial evidence that CT genes, which are frequently over-expressed in metastatic cells, may play a role in facilitating or driving cancer spread.

A NEW FORM OF CANCER ANTIGEN?

In search of additional genes with expression profiles similar to CT antigens, investigators at the **LICR New York Branch** mined publicly available data sets containing gene expression profiles from placenta. This led the team to identify a new CT gene that encodes a putative cell surface protein termed PLAC1[7]. Immunohistochemistry data suggest that PLAC1 protein is expressed in the placenta and in low levels in the testes, but not any other normal adult tissues. Unlike most other CT proteins, PLAC1 expression appears to occur in a particular cell layer of the testis, and not the spermatogonia. Because of its predominant expression in the placenta and its testicular staining pattern, PLAC1 has been proposed to represent the first member of a new type of antigen, the cancer/placenta (CP) antigens[8]. The LICR team, with **Affiliates in New York** (USA), is now investigating PLAC1 expression in various types of cancers, including non-

small cell lung cancer (NSCLC), and developing new reagents to more accurately define its tissue distribution. Spontaneous immunogenic responses to this antigen have been detected in a number of lung cancer patients. The putative cell surface location of PLAC1, its immunogenicity, and unique expression patterns identify PLAC1 as a promising target for NSCLC cancer immunotherapies.

CT GENES AND EVOLUTIONARY PRESSURE

Approximately half of the nearly 100 CT genes identified thus far map to the X chromosome, and are termed 'CT-X' genes. The remaining, 'non-X CT,' genes are located on autosomes (non-sex chromosomes). Over the course of evolution, the overall DNA sequence of the X chromosome has changed less than that of autosomes, despite evidence suggesting that many protein-coding genes on the X chromosome are under higher evolutionary pressure as they show sequence diversification between species. Recently, the draft genome of the chimpanzee, the closest evolutionary neighbor to man, was made publicly available. Having the chimpanzee genome allowed investigators from the **LICR Lausanne** and **New York Branches**, together with **Affiliates in Cape Town** (South Africa)**,** to study CT gene conservation[9]. The analyses showed that chimpanzees have an equivalent of nearly all human CT genes, and that the genes are at the same chromosomal location in both species. Moreover, CT genes are under higher evolutionary pressure to undergo sequence diversification than other genes. Additionally, CT-X genes are evolving more rapidly than non-X CT genes. The team concluded that the CT-X genes are, on average, amongst the fastest evolving genes in the human genome.

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Developing Adjuvants for Cancer Vaccines

LICR is analyzing vaccine compositions and delivery methods that might increase the antigen-specific immune response induced by therapeutic cancer vaccines. One critical element is the incorporation of an immunostimulatory adjuvant into the vaccine composition. Typically, these compounds activate the innate immune system that defends against infection by bacteria or viruses. In addition, adjuvants can indirectly stimulate the adaptive immune system by promoting the maturation of dendritic cells (DCs), resulting in specific and long lasting immune responses. DCs are immune cells that process and present antigens in order to induce the production of antigen-specific T cells that recognize and destroy cancer cells.

CHARACTERIZING THE EFFECTS OF TLR AGONISTS

Immature DCs express a number of different Toll-like receptors (TLRs). These receptors recognize specific, pathogen-derived molecules and, upon activation, mediate the maturation of antigen-presenting DCs. Therefore, agonists (receptor-activating molecules) of TLRs are good candidates for cancer vaccine adjuvants. In 2007, the TLR9 agonist CpG was assessed with recombinant NY-ESO-1 protein in a phase I study of patients with different cancer types. The study—conducted by investigators at the **LICR New York Branch** and **Affiliates in New York** (USA)—showed that this vaccine was well-tolerated and elicited specific, integrated immune responses in several patients[1].

Further research focused on other TLR agonists, where investigators at the **LICR Lausanne Branch** discovered that TLR3 is expressed by tumor cells isolated from patients with melanoma. When exposed to a TLR3 agonist, these tumor cells ceased to divide and underwent apoptosis[2]. The results of this and previous studies by the group suggest that a TLR3 agonist could strengthen the effect of a cancer vaccine via increased presentation of cancer antigens by DCs to T cells, increased elimination of cancer cells mediated by cytotoxic T lymphocytes, and also by the apoptosis of TLR3-expressing cancer cells.

OVERCOMING IMMUNE SUPPRESSION FOR CANCER THERAPY

LICR investigators are exploring the clinical potential of using a non-pathogenic strain of the bacterium *Salmonella typhimurium* that produces and secretes the cancer/testis (CT) antigen NY-ESO-1. A pre-clinical study, performed by investigators from the **LICR New York Branch** and **Affiliates in Frankfurt** (Germany), **Mie** (Japan) and **New York** (USA), showed that *Salmonella* is not only a delivery system for the cancer vaccine—it also acts as an adjuvant to enhance the immune response to NY-ESO-1. Antigen-specific T cells elicited by *in vitro* exposure to *Salmonella* were, surprisingly, found to be resistant to the effect of regulatory T cells (Tregs)[3]. Tregs play a role in preventing auto-immunity (immune system attack on normal cells) by suppressing the activity of other T cell populations. However, LICR and other investigators have now shown that Tregs might also suppress anti-tumor immune responses. For cancer vaccines to realize their clinical potential, Tregs must be prevented from counteracting the immune response induced by cancer vaccines. The findings from this study identify a prospective method of vaccine delivery that can overcome Treg-mediated suppression of anti-tumor immunity.

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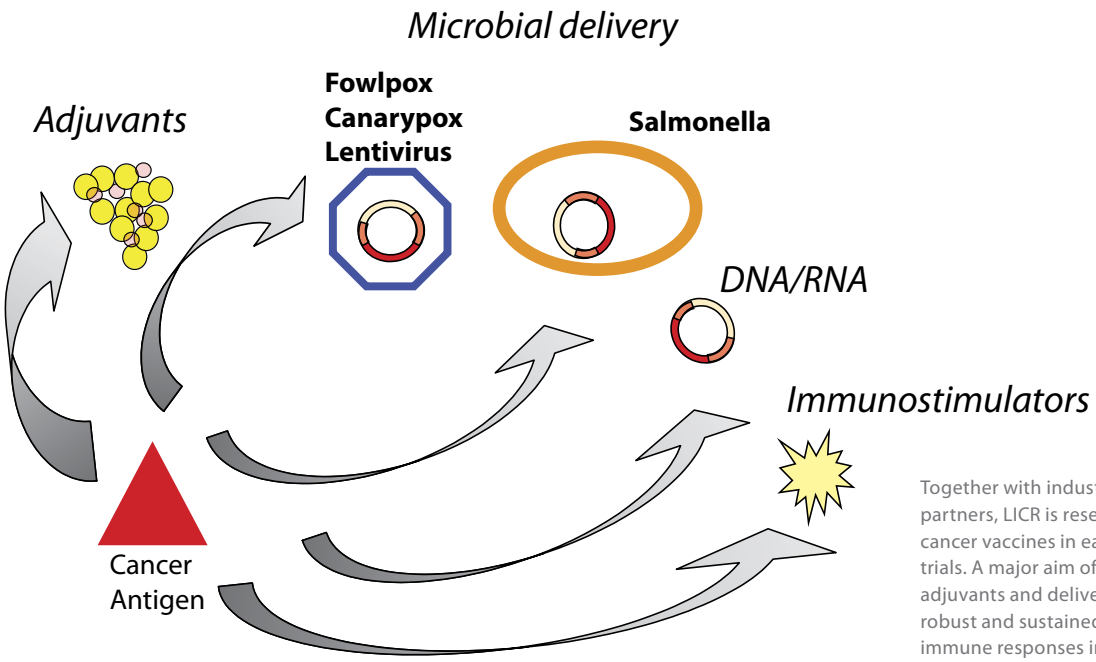


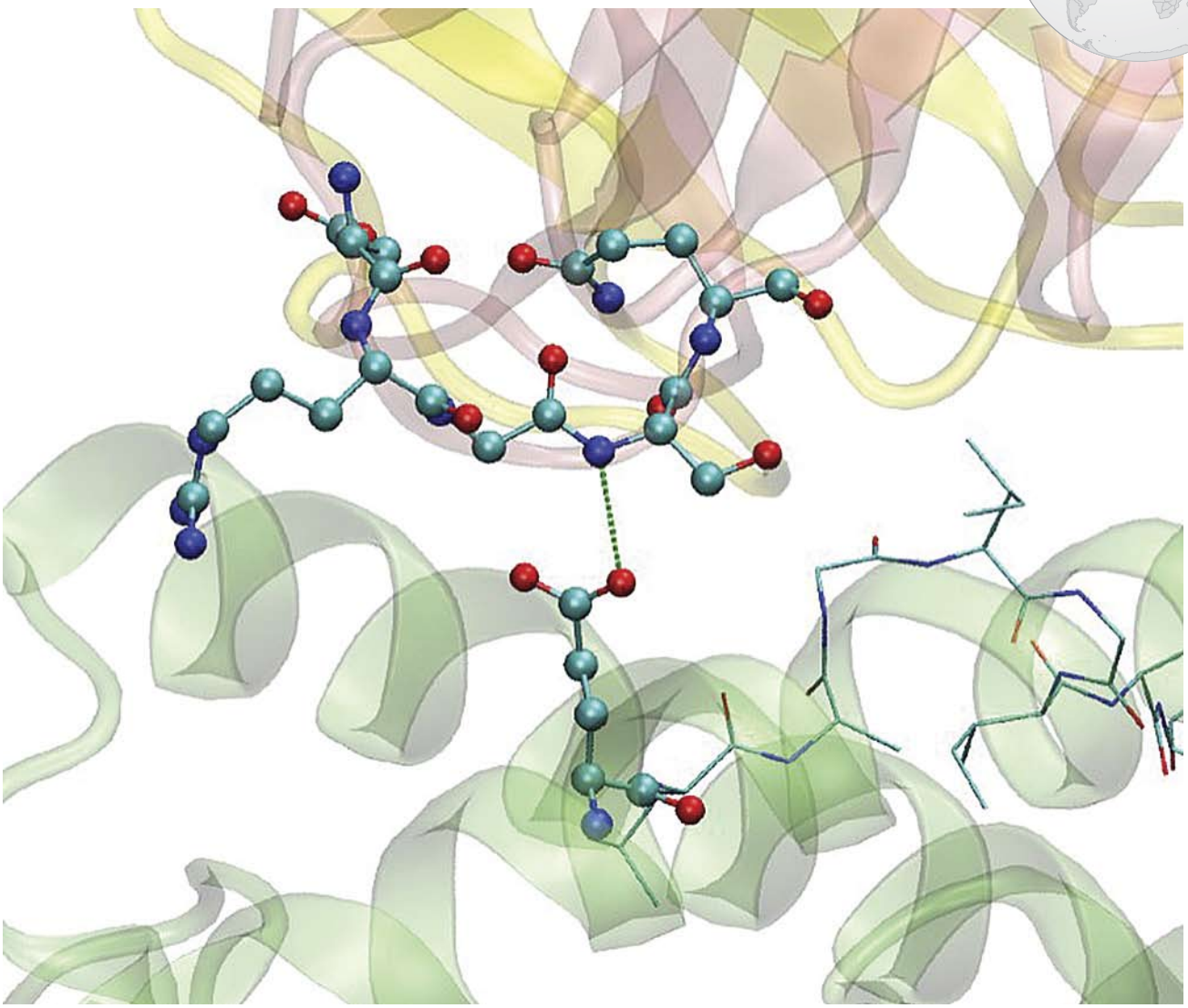
Together with industry and academic partners, LICR is researching therapeutic cancer vaccines in early-phase clinical trials. A major aim of the work is to identify adjuvants and delivery systems that induce robust and sustained antigen-specific immune responses in cancer patients.

Understanding the Immune Response to Cancer

The rationale of therapeutic cancer vaccines is to employ and strengthen the immune system to fight cancer. White blood cells known as T cells identify cancer cells or cells infected with pathogens as 'foreign' by virtue of certain molecules, known as antigens, that are displayed on the surface of the cancer or infected cell, but not present on the surface of normal (uninfected) cells. Cancer antigens are typically peptides (protein fragments) that are, like other antigens, recognized by specific T cell receptors (TCRs). Of particular importance in the immunological response to cancer are the cytolytic T lymphocytes (CTLs), a subgroup of T cells that destroy foreign cells. Upon their first encounter with an antigen, CTLs are selected and propagated to form a heterogeneous immunological repertoire that varies over time and between individuals. A more detailed understanding of how anti-cancer immune responses are generated and maintained will guide the development of effective therapeutic cancer vaccines.

T CELL DEVELOPMENT

All T cells originate from the bone marrow but develop in the thymus. During T cell development, complex rearrangements occurring within four TCR-coding genes (α, β, γ and δ) allow each T cell to produce a distinct TCR with unique antigen specificity. The rearrangement of TCR genes also results in the divergence of T cells carrying either the α and β or the γ and δ genes into two separate lineages, from which different T cell types are subsequently developed. In 2007, a team of **LICR Lausanne Branch** investigators discovered that specific interactions between the cell surface receptor Notch1 and one of its ligands (Delta-like 4) preferentially induced differentiation of T cell precursors along the αβ lineage[1]. Moreover, pre-Tα (an invariant component of the pre-TCR complex expressed by early T



In this diagrammatical representation, T cells bind to a Melan-A peptide (represented in the lower part of the ball-and-stick model) via their T cell receptor (upper part). A hydrogen bond (dotted line) contributes significantly to the binding force and explains why the T cells recognize cancer cells with extraordinary high specificity.

Courtesy of Mathias Ferber (LICR Lausanne Branch).

cell precursors) was found to play a critical role in T cell development. Prior to lineage commitment, pre-Tα mediates allelic exclusion, a mechanism by which the cell prevents the expression of two functionally rearranged TCRβ genes[2].

CHARACTERIZING T CELL RESPONSES TO CANCER ANTIGENS

Upon their first encounter with an antigen, CTLs proliferate and acquire specialized functions. 'Effector' CTLs have the ability to destroy foreign cells, mainly by inducing apoptosis, while 'memory' CTLs mediate rapid and strong immune responses to previously encountered antigens.

A team of investigators at the **LICR Lausanne Branch** has carried out the first detailed investigation of a cancer-specific CTL response in a patient over time. The patient was vaccinated with a peptide against the cancer antigen NY-ESO-1, and a number of distinct CTL clonotypes (groups of identical cells) were examined over the course of several years. This study has provided new insights into how antigen-specific T cells are maintained in the immune system to generate a long-lasting anti-cancer response[3]. Another study revealed the existence of conditional CTLs in cancer patients, the effector function of which is activated by the cytokine signaling molecule IL-12[4]. The investigators also described four distinct subtypes of memory CTLs with different degrees of effector function[5]. The knowledge of antigen-induced CTLs gained in these studies should provide new perspectives for future development of vaccine-based immunotherapies.

REGULATION OF NATURAL KILLER CELL RESPONSES

Natural killer (NK) cells have effector functions similar to those of CTLs and contribute to the immune system's defense against tumors. However, NK cells do not, like CTLs, recognize specific cancer antigens on tumor cells but act on cells that overexpress or fail to express certain antigens. The major histocompatibility complex class I (MHC-I) antigens are expressed on the surface of most normal cells but often lost in cancer or infected cells. The attack of NK cells on normal cells is prevented as these MHC-I molecules bind to inhibitory Ly49 receptors on NK cells. In 2007, a team of **LICR Lausanne Branch** investigators discovered that NK cells can modulate the accessibility of their Ly49 receptors by binding to the NK cells' own MHC-I[6-7]. This mechanism appears to improve the effector activity of NK cells and could potentially be exploited to improve anti-cancer immunity.

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LICR Spin-Off Company is Brazil's First Oncology Biotech

Brazil's first oncology biotechnology company, Recepta was launched this past year by LICR and PR&D, a Brazilian venture capital company. Recepta was formed to further the development and commercialization of four of LICR's targeted antibodies—A34, Le^b, MX35 and hu3S193—for the treatment and/or diagnosis of a variety of cancers.

Not only is Recepta leading the way as Brazil's first oncology biotechnology company, it is also on track to initiate the first oncology phase II trial sponsored by a Brazilian company. The trial, which is expected to initiate in May, 2008, will test the hu3S193 antibody (refer pp46-47) for the treatment of women with chemotherapy-resistant ovarian, primary peritoneal, or fallopian tube cancers. If hu3S193 is found to block disease progression, this monoclonal antibody-based therapy could be a major advance in the treatment options for patients with these aggressive tumors.

LICR is committed to translating its discoveries into applications for human benefit, and the creation of spin-off companies with the capacity to conduct late-stage clinical development and commercialization activities enables the Institute to effectively pursue this goal. Recepta is the fifth LICR spin-off company.

Top: National press conference announcing the launch of Recepta.

Below: Recepta's laboratories are opened by federal and state dignitaries.

Cancer Vaccines

In addition to protecting the body against invading pathogens, the immune system can also recognize cancer cells and mount an attack against them. Alone, this response is often not robust enough to elucidate the escape tactics employed by cancer cells to evade the immune response or to prevent tumor growth and/or disease progression. LICR investigators have been committed to the development of antigen-specific therapeutic cancer vaccines that induce sustained anti-cancer responses, specifically to eliminate minimal or recurrent disease. Critical considerations for cancer vaccine design include: the selection of a cancer antigen appropriate to the patient population; the form of the antigen used in the vaccine: the choice of adjuvant to augment the immune response to the antigen; the delivery method for the vaccine; and the ability of the vaccine to induce an antigen-specific, integrated (T cell plus antibody) response in the patient. LICR is conducting both preclinical and clinical studies to evaluate each of these considerations.

AN ANTIGEN RECOGNIZED IN TWO DIFFERENT FORMS AT THE CANCER CELL SURFACE

To selectively target and destroy cells that have become malignant or infected with foreign pathogens, specific cytotoxic T lymphocytes (CTLs) of the immune system identify peptides presented on the surface of compromised cells by the major histocompatibility complex (MHC). In the case of targets for cancer vaccines, the antigenic peptides should be derived from proteins produced by malignant, but not normal, cells to ensure the specificity of the therapeutic modality.

Investigators at the **LICR Lausanne Branch** have made significant advances towards the characterization of these antigenic peptides. A paper recently published by this group analyzed antigenic peptides derived from Melan-A, an antigen expressed by cancer cells from greater than 95% of patients with malignant melanoma[1]. The LICR team assessed the ability of Melan-A-specific CTLs to identify peptides composed of nine amino acids, a nonamer, or 10 amino acids, a decamer. Previously, several

The therapeutic cancer vaccine is composed of a cancer-specific antigen plus adjuvant (a compound that stimulates the immune system) [1]. The vaccine antigen is taken up by antigen presenting cells (APC) and displayed as a peptide MHC on the surface of those cells [2]. This in turn induces the generation of antigen-specific CD4+ and CD8+ T cells [3 and 4], which target cells presenting the cancer antigen on their surface.

investigators reported that one population of CTLs exhibited a high degree of cross-reactivity to the two peptides. However, the LICR team discovered CTLs that exclusively recognize the nonamer. Using molecular modeling, the team was able to show that the nonamer and decamer have distinct conformations that affect their binding by the CTLs. These data indicate that CTLs can differentially recognize two different forms of one cancer antigen on the surface of melanoma cells. This extraordinarily high level of specificity will clearly be important in the future design of cancer vaccines.

A NEW TUMOR-SPECIFIC ANTIGEN IDENTIFIED BY CLINICAL DISCOVERY

Of critical importance in the design of a cancer vaccine is the identification of antigens appropriate for a specific cancer. In 2007, a team of investigators from the **LICR Brussels Branch** identified a new antigen encoded by the cancer/testis (CT) gene, MAGE-C2, MAGE-C2.B44[2]. The MAGE-C2.B44 antigen was discovered by analyzing CTLs isolated from tumor and blood samples from a melanoma patient who received a cancer vaccine targeting a different CT antigen, MAGE-3.A1, in an LICR clinical trial. A comprehensive analyses of the resulting CTLs showed that the vaccine induced only a minor fraction of CTLs against MAGE-3.A1, and yet the patient's melanoma started to regress. This observation strongly suggests that the few anti-vaccine T cells elicited by the vaccine may prime or re-stimulate additional anti-tumor T-cell clones that eventually cause tumor regression.

This particular study illustrates the importance and potential of LICR's clinical discovery model. Clinical discovery is the concept that the same systematic, investigative rigor that yielded the laboratory discovery in the first place should be applied in early-phase clinic trials to assess fully a discovery's therapeutic potential. A traditional approach to clinical trial analysis—assessing only clinical endpoints of patient survival and/or disease recurrence—would not have identified this new antigen, nor would it have indicated that the putative tumor effect might largely be due to a secondary immune response and not the primary response induced by the vaccine target.

VACCINATION PROTOCOLS SHOW PROMISE

In 2007, results were published from two LICR-sponsored phase I clinical trials of cancer vaccines based on peptides from the CT antigen NY-ESO-1. These trials assessed the effect of more intensive (more frequent) immunization protocols on the induction of antigen-specific immune responses in multiple cancers.

The first trial, published by a team from the **LICR New York Branch** and **Affiliates in Buffalo** (USA), tested vaccination with the NY-ESO-1 DP4 peptide, $ESO_{157-170}$, in patients with ovarian cancer[3]. The team determined that the vaccination protocol did, in fact, induce NY-ESO-1-specific $CD4^+$ T cell, $CD8^+$ T cell and humoral (antibody)

responses in several of the patients. Furthermore, the vaccine-induced T cells were observed in some patients for at least one year after immunization. The team showed that increasing the number of vaccinations resulted in increasingly detectable $CD4^+$ T cells that specifically recognize the $ESO_{157-170}$ peptide in a cell line (SK-Mel 26) that expressed the NY-ESO-1 antigen.

In the second trial, investigators from the **LICR New York Branch** and **Affiliates in Zurich** (Switzerland), and **Frankfurt** and **Heidelberg** (Germany) evaluated intensive vaccination (daily for five days every three weeks) with NY-ESO-1 peptides in patients with various cancers expressing NY-ESO-1, including esophageal, breast, ovarian, prostate and non-small cell lung cancers, as well as sarcoma and melanoma[4]. Importantly, intense vaccination induced $CD8^+$ T cells in one-third of the seronegative patients, i.e. those patients with no pre-existing antigen-specific $CD8^+$ T-cells. The number of $CD8^+$ T-cells in seropositive patients, i.e. those with pre-existing antigen-specific $CD8^+$ T cells increased or remained stable. This indicates the vaccine was able to enhance the apparent spontaneous immunity against the cancer cells. The team also demonstrated that intensive vaccination resulted in a NY-ESO-1 peptide-specific immune response of higher magnitude and earlier onset when compared to less intensive immunization regimes.

Both studies showed that vaccination with NY-ESO-1 peptides enhanced immune responses without causing significant toxicity in cancer patients with NY-ESO-1-positive tumors. Intensive immunization courses appear to be beneficial in inducing earlier and more robust immune responses. These clinical discovery efforts are enabling LICR investigators to make significant progress towards proving the therapeutic capacity of cancer vaccines.

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3. **Odunsi K, Qian F, Matsuzaki J, Mhawech-Fauceglia P, Andrews C, Hoffman EW, Pan L, Ritter G, Villella J, Thomas B, Rodabaugh K, Lele S, Shrikant P, Old LJ, Gnjatic S.** (2007) Vaccination with an NY-ESO-1 peptide of HLA class I/II specificities induces integrated humoral and T cell responses in ovarian cancer. Proc Natl Acad Sci U S A. 104(31):12837-42.

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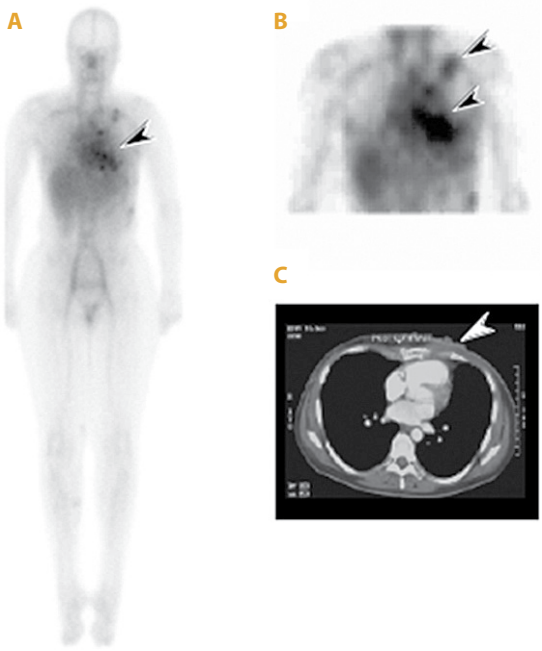
Characterizing the Hu3S193 Targeted Antibody

The Lewis Y (Le^y) antigen is an attractive target for antibody therapy because it is over-expressed on nearly 90% of epithelial cell tumors and associated metastases. Normal expression of the Le^y antigen in adults is limited to certain white blood cells (granulocytes) and regions of epithelial cell surfaces that are less accessible to circulating antibodies. A monoclonal antibody that specifically binds to the Le^y antigen, hu3S193, has been developed by the **LICR New York Branch** and **Melbourne Center**, and shown to induce a potent anti-tumor immune response *in vitro* and *in vivo* and tumor regression in mouse models.

In 2007, LICR investigators published promising results from two clinical studies using hu3S193. The first-in-human clinical trial of this antibody, conducted by a team at the **LICR Melbourne Center**, analyzed the safety, specificity and pharmacokinetics of hu3S193 in patients with advanced epithelial cell cancers expressing the Le^y antigen[1]. Hu3S193 was reported to selectively target tumor tissue and have a long serum half-life, without causing significant toxicity or stimulating immune responses against the antibody. Based on this favorable therapeutic profile, a team of investigators from the **LICR New York Branch** and **Affiliates**



Biodistribution of ^{111}In-hu3S193 in a patient with metastatic breast cancer. A) anterior whole body image demonstrates no normal tissue uptake, and localization of hu3S193 in metastatic lesions on the chest wall (arrow) B) Tomographic 3D image showing specific localization of hu3S193 antibody in chest wall and lymph node metastases (arrows). C) CT scan of the chest showing metastatic chest wall lesion (arrow), targeted by hu3S193

Courtesy of A. Scott (LICR Melbourne Center)..

in New York (USA) conducted an LICR-sponsored clinical trial in patients with Le^{y}-positive small cell lung cancer (SCLC)[2]. This was the first study testing such an antibody for SCLC, a disease for which therapeutic advancements are desperately needed. By using a radiolabeled version of the antibody (^{111}indium-hu3S193), the team was able to readily visualize Le^{y}-positive lung tumor tissue, particularly in lesions larger than 2 cm in diameter. Again, the antibody was shown to have a favorable toxicity profile.

A team from the **LICR Melbourne Center** published results from their pre-clinical investigation of the suitability of hu3S193 for the delivery of toxic radioactive payloads directly to tumor cells[3]. The antibody was labeled with the radioisotope bismuth-213 (^{213}Bi), which has properties suitable for small tumors and metastases and reduces the danger of toxicity to healthy cells near the tumor. The team tested ^{213}Bi-hu3S193 in cultured Le^{y}-positive breast cancer cells, and observed it to be highly specific and rapidly internalized into the cells. Furthermore, the radiolabeled antibody induced apoptosis in greater than 90% of the cell population. The ^{213}Bi-hu3S193 antibody was also found to significantly reduce growth of new and established tumors that were generated from human breast cancer cells implanted into mice. This tumor suppressive effect was magnified when ^{213}Bi-hu3S193 was combined with the chemotherapeutic agent paclitaxel, providing the first reported evidence of enhanced radioimmunotherapy with paclitaxel *in vivo*. These pre-clinical and clinical investigations illustrate the great potential of hu3S193 for use as an immunotherapeutic either alone or to deliver cytotoxic molecules directly to cancer cells expressing the Le^{y} antigen.

In 2007, LICR licensed the intellectual property relating to hu3S193 to its spin-off company Recepta to enable and guide its further development into a therapeutic agent for use in the treatment of Le^{y}-positive cancers (refer pp46-47).

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A Potential New Tool for the Diagnosis and Therapy of Kidney Cancer

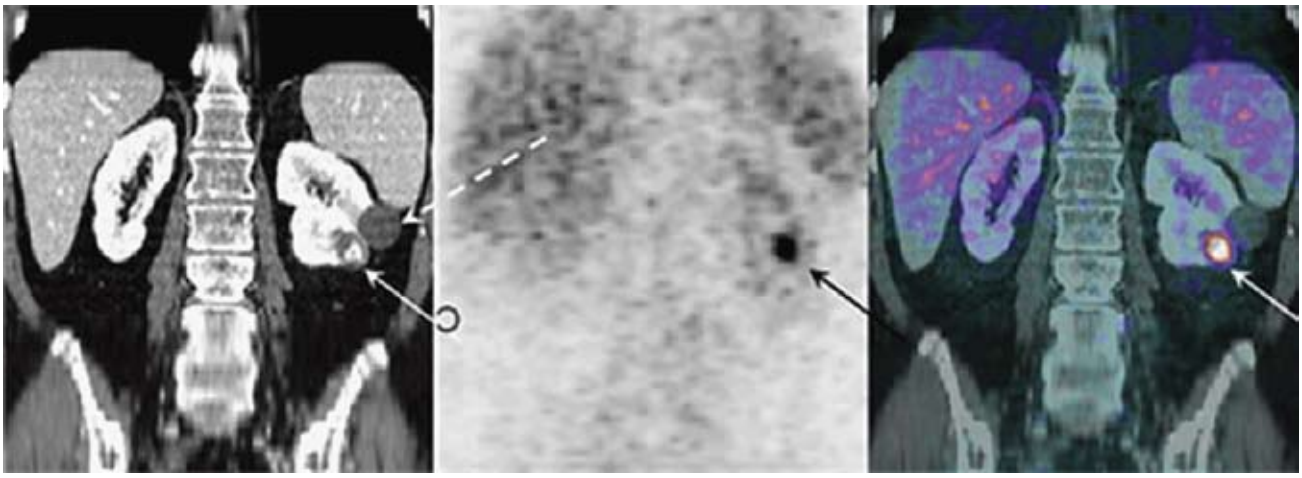
Currently, patients with metastatic renal cell carcinoma (RCC) have a five year survival rate of approximately 30%. While new RCC chemotherapeutics are showing benefit in the clinic, significant therapeutic advances are still critically needed.

LICR has been conducting laboratory and clinical research on an antibody, cG250, to assess its potential as a targeted therapy for RCC. The cG250 antibody binds to the CAIX molecule, which is present on the surface of more than 85% of RCC cells and several normal cell-types in the stomach, bile ducts and pancreas, but is not present on normal kidney cells. In 2007, the results of three LICR clinical trials focused on the development of the cG250 antibody for the treatment and detection of clear cell RCC were published by LICR scientists and Affiliates.

Investigators at the **LICR Melbourne Center** reported on the results of two phase I trials studying the safety, pharmacokinetics and distribution of cG250. The first study was a dose escalation trial of cG250 antibody as a monotherapy[1], which demonstrated that doses of up to 50 mg/m^2 cG250 are safe, that the antibody has a long half-life and that it effectively targets clear cell RCC. The investigators reported that a complete response was

Specific targeting of clear cell renal cancer by I-124 cG250 immunoPET. The left image shows two lesions (solid and broken arrow) in the left kidney, evident on a CT scan. ImmunoPET (middle image) shows radioactivity in only one of those lesions (solid arrow). The right image is a superimposition ("fusion") image, confirming radioactivity in the inferior lesion, which was the only one of the two to be of clear cell histology.

Courtesy of C. Divgi (LICR Affiliate, Philadelphia, USA).



observed in one patient, while nine stabilized and three had disease progression. The team at the **LICR Melbourne Center** also completed a pilot study demonstrating the feasibility and safety of a weekly treatment regimen of cG250 plus IL-2, a current chemotherapeutic agent used to treat RCC, in nine patients with inoperable metastatic or locally advanced clear cell RCC[2]. The investigators reported that radiolabeled doses of the antibody showed excellent targeting to the tumor cells, and that IL-2 did not influence the biodistribution of the cG250 antibody. This result paves the way for future studies to assess the potential clinical benefit of any synergy between cG250 and IL-2. The biopharmaceutical company Wilex AG (Munich, Germany), with whom LICR has had a long-standing research and development collaboration, is now exploring the commercial development of cG250. Wilex is pursuing the development of the cG250 antibody as an adjuvant therapy (Rencarex®) in patients who have non-metastatic RCC in a Phase III randomized clinical trial.

The third LICR-sponsored clinical trial assessed the use of cG250 as a diagnostic tool for clear cell RCC, the most aggressive subtype of RCC, and produced extraordinary results[3]. A team comprised of **LICR New York Branch** investigators and **Affiliates in New York** showed that iodine-124 (^{124}I)-labeled cG250 antibody accurately identified 15 out of 16 clear cell RCC's using positron emission tomography (PET) imaging, while all nine non-clear cell RCC's were negative for the labeled antibody. The ^{124}I-labeled cG250 antibody had a sensitivity of 94% for the clear cell RCC subtype, and the specificity and positive predictive accuracy were both 100%. The use of ^{124}I-labeled cG250 and PET imaging as a diagnostic tool in patients suspected of having RCC obviates the need for surgery to determine if the patient has clear cell or non-clear cell RCC. The development of a non-invasive diagnostic tool for clear cell RCC would make a substantial difference to the care and welfare of people suspected of having renal cell cancers. Wilex AG is conducting a pivotal Phase III trial to confirm radiolabeled cG250 antibody's ability to diagnose clear cell RCC with PET imaging. Wilex has named the compound, CA9-SCAN®.

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Notable Events

Anamaria Camargo Ph.D. an Assistant Member at the LICR São Paulo Branch was named as one of four investigators to receive the 2007 TWAS ROLAC Young Scientist Prize at the Brazilian Academy of Sciences annual welcoming ceremony on May 30, 2007 in Rio de Janeiro.

Webster K. Cavenee Ph.D., Director of the LICR San Diego Branch, was awarded the American Association for Cancer Research (AACR) Princess Takamatsu Memorial Award Lectureship and the 2nd Annual Albert Szent-Györgyi Prize for Progress in Cancer Research by the National Foundation for Cancer Research. Dr. Cavenee was also elected as a Member of the Institute of Medicine (IOM).

Andrew Clayton Ph.D., an Assistant Member at the Melbourne Branch, was awarded the 2007 Young Fluorescence Investigator Award by the American Biophysical Society.

Richard D. Kolodner Ph.D., Executive Director for Laboratory Sciences & Technology and Member at the LICR San Diego Branch, was awarded the 2007 Kirk A. Landon - AACR Prize for Basic Cancer Research.

H. Robson MacDonald Ph.D. was appointed Director of the LICR Lausanne Branch.

Thomas Perlmann Ph.D. was appointed Director of the LICR Stockholm Branch.

Pierre Languetin, who retired from the LICR Board of Directors at the end of 2007, received the D.K. Ludwig Award.

Lloyd J. Old M.D., Chairman of the LICR Board of Directors and Director of the LICR New York Branch, was awarded the 2007 Charles Rodolphe Brupbacher Cancer Research Award.

Benoît Van den Eynde Ph.D., a Member at the LICR Brussels Branch, was awarded the GlaxoSmithKline Prize for Medical Sciences.

Ricardo R. Brentani, M.D., Ph.D. (left) Founding and former Director of the LICR Sao Paulo Branch, was presented with the D.K. Ludwig Award by LICR President, Mr. Edward A. McDermott, Jr. (right).

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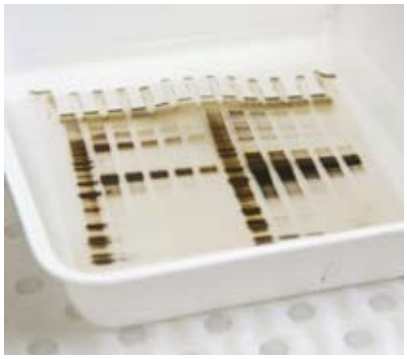

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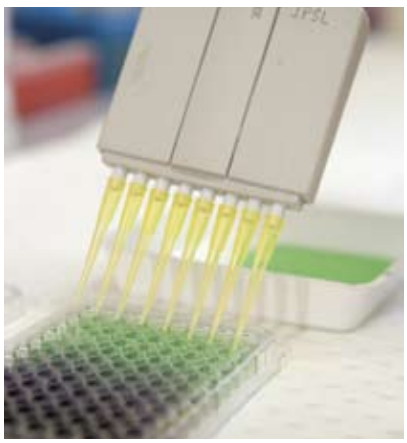

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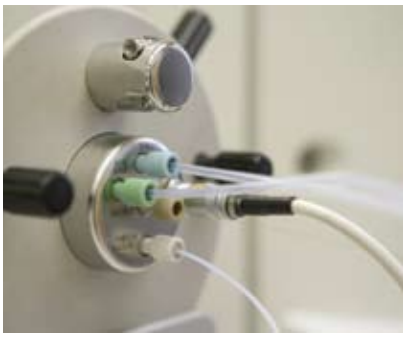

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