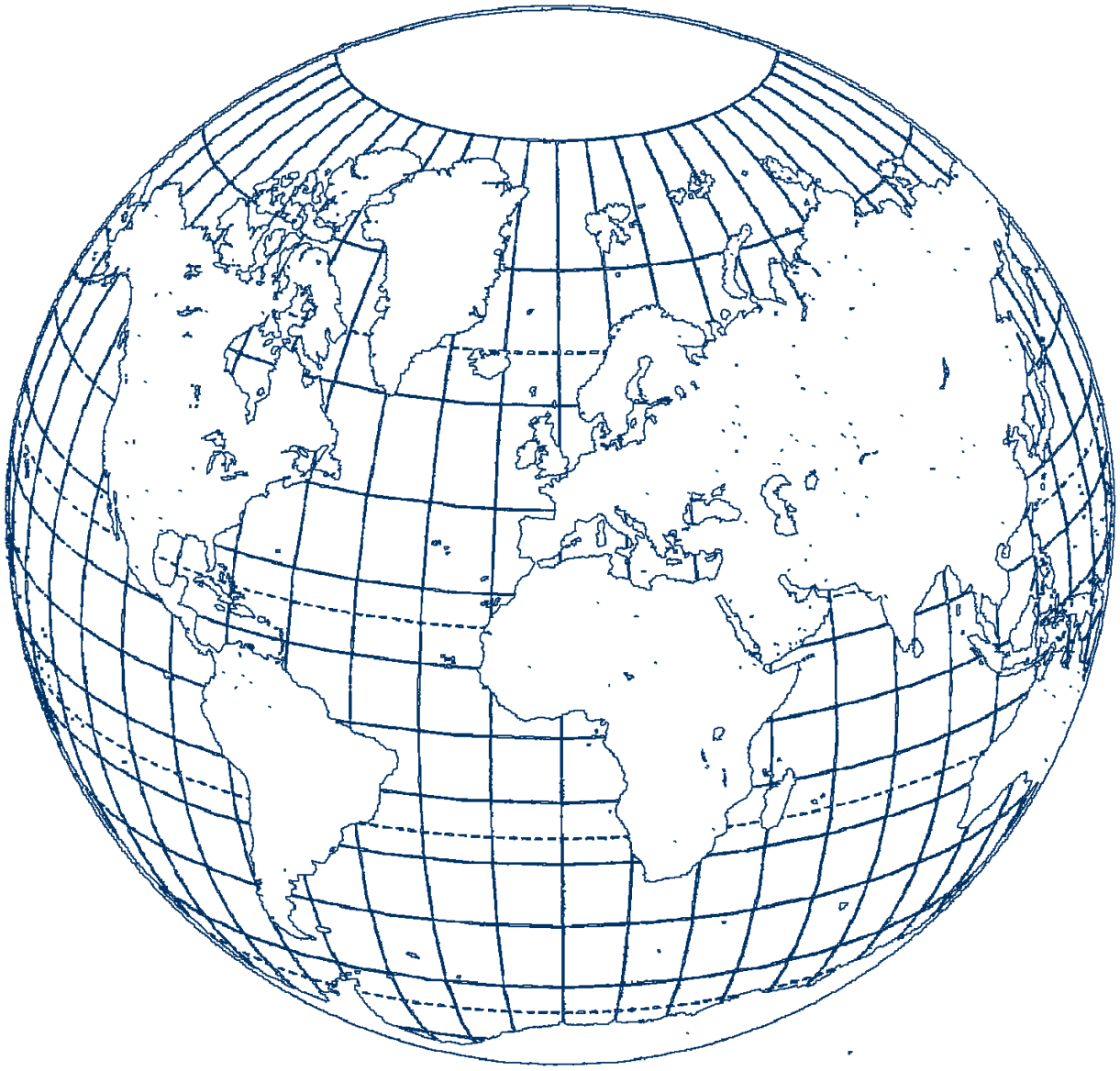
LUDWIG INSTITUTE FOR CANCER RESEARCH

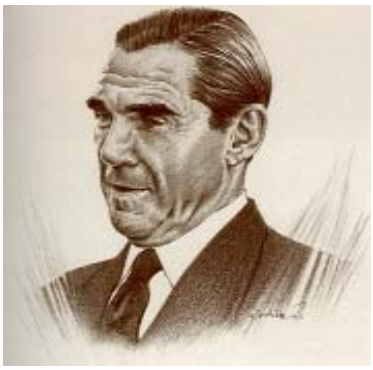
ANNUAL REPORT

FOR THE YEAR 2005



A Statement by the Founder

In creating this organization I have been guided by certain principles which throughout my life I have found to be highly effective. Success in any complex enterprise consists in bringing the best minds to bear on each problem, in providing the best resources possible, and in putting each concept into practice whenever and wherever the opportunities are most favorable. I believe firmly in the value of applying these principles in grappling with tasks as momentous as finding ways to relieve the human suffering caused by cancer.



Why should this undertaking be international? The rare vision and ability needed in the battle against cancer are not limited by frontiers, and the scientists who possess these gifts must be sought wherever they are to be found. Nor does cancer reveal itself in the same guise in every nation, but strikes different populations in different forms. Yet despite the growing necessity for concerted worldwide effort, I find no agency, which has both the truly international scope and the substantial resources, which I deem essential for a comprehensive attack on human cancer.

In my judgment the ultimate conquest of this frightful disease is not yet in sight, and the same view is held by most informed physicians and scientists in bio-medical research. In contrast to those who would yield to undue optimism, and who hope for too much from present programs,

I am persuaded that eventual mastery of cancer will come only from intense and unremitting scientific exploration over many decades. This should not be hindered by the changing policies of governments and the vagaries of public interest. Accordingly it is my intention that the Institute shall be so structured as to ensure secure and continuing support for the attainment of its aims.

The elimination of cancer will surely rank as one of man's greatest and uncontroversial achievements. That day may be long delayed. How long we cannot tell. But I do not doubt that it will surely come.

D. K. Ludwig

December 17, 1974

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(as of 31 December 2005)

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Custodian Bank	Boston Safe Deposit & Trust Co., Boston
Company registration numbers	
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Belgium	BE 0418.853.522
United Kingdom	FC007198
United States of America	EIN 23-712 1131

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Aims and Principles

The purpose of the Institute is to originate and conduct incisive long-range research programs, to be carried out on a continuing basis in conjunction with hospitals in established medical centers, directed to the ultimate goal of eradicating cancer. It is neither the province nor the intention of the Institute to award grants for the conduct of research by others, - in fact its charter precludes this. Rather, substantially all research financed by the Institute is carried out by the Institute itself through its own appointed research staff or through laboratory and clinical collaborations involving Institute research staff and outside academic investigators. The research staff of the Institute are organized in Branches. Nine are in operation - one in Australia; one in Belgium; one in Brazil; one in Switzerland; two in Sweden; one in the United Kingdom and two in the United States of America. Each Branch is focused on a program of research defined by the Branch Director in relation to the overall objectives of the Institute. The Branches are established in association with University Hospitals to facilitate close collaboration between laboratory and clinical scientists and to provide the clinical resources required for Ludwig Institute programs. The Branches are staffed so that Branch Directors can address complex biological problems related to cancer with a critical mass of interactive scientists having expertise in several scientific disciplines. Branch staffs vary in size from 20 to 155. The Institute employs around 900 scientists, clinicians and support personnel worldwide. Support of the Branches' research is principally provided by the Institute and supplemented with governmental and other grants. Since its inception the Ludwig Institute has expended over CHF 1.9 billion on medical research and for 2005 had a total annual budget, financed by Institute funds, of CHF 87.4 million.

Legal status

The Institute was incorporated in 1971 in Zurich, Switzerland as a not-for-profit corporation. Based on its present activities, the Institute is exempt from direct taxes on income and capital gains in all territories in which it operates.

Statutes

The activities of the Institute are governed by its Statutes. The exclusively charitable purpose contained therein is for the Institute to engage itself directly in continuous active conduct of medical research, especially in the field of cancer. This research is to be for the benefit of the public and carried out in conjunction with hospitals which provide medical care and are organized and operated exclusively for charitable purposes.

Organization and Investments

The Institute's Endowment is held for its benefit by a separate legal entity, LICR Fund, Inc. ("the Fund"), a not-for-profit Delaware, USA corporation. The Fund was established exclusively to further the charitable and scientific purposes of the Ludwig Institute by receiving, holding and investing funds on behalf of, and remitting funds to the Institute. The Fund is a membership corporation with no authority to issue capital stock. The Board of Directors of the Institute are the Members of the Fund and constitute the Board of Directors of the Fund.

The Endowment held by the Fund is invested on its behalf by investment managers appointed by the Board of Directors and Fund management. Substantially all of the investment instruments are held by the Custodian Bank in the name of the Fund. Income and principal of funds of the Fund can only be applied to the Ludwig Institute.

Scientific Report

In the 34 years since the Ludwig Institute for Cancer Research (LICR) was founded, it has grown to become the largest international non-profit institute dedicated to the fight against cancer. The research of the Institute is carried out at research Branches in seven countries around the world, and also in cooperation with an international network of affiliated scientists and clinicians. This organizational structure maximizes the Institute's opportunities to interact with a broad range of different laboratory and clinical environments, and facilitates the worldwide engagement of outstanding scientists.

The research orientation of each LICR Branch is defined by the Branch Director in the context of the overall objectives of the Institute. Each Branch is staffed to enable it to address complex biological problems related to cancer, and provide a critical mass of scientists with expertise in relevant scientific disciplines. Branches have formal associations with University Hospitals, which allows not only a close interaction between laboratory and clinical scientists, but also the provision of clinical resources required for basic research and LICR's early-phase clinical trials.

The quality of research conducted by LICR scientists is monitored on an ongoing basis by the LICR Scientific Directorate and Scientific Advisory Committee, and is independently assessed through external peer-review processes. A commitment to programmatic-based research has resulted in the establishment of numerous collaborations between Branches and Affiliates, individual investigators who are experts in fields that complement LICR's research objectives. LICR also benefits from affiliations, through The James R. Kerr Program, with investigators in Brazil, China, Russia, South Africa, Turkey, and Ukraine; countries that are scientifically talented but have fewer opportunities for international collaboration in advanced cancer research. All of these activities extend the Institute's global opportunities for cancer research, in accordance with the wishes of its founder, Mr. Daniel K. Ludwig.

The following scientific progress report summarizes examples of LICR's research, based on studies published in 2005 by LICR Branch staff members and Affiliates.

Genetics Discipline

Carcinogenesis disrupts important cell processes, for example migration, growth or apoptosis (programmed cell death). These processes control, and are controlled by, the 'expression' of genes - the 'transcription' of DNA into RNA, which is in turn 'translated' into a protein. The regulation of transcription is a critical first step in the control of gene expression necessary for all cellular processes. Examining how transcription is regulated is important to elucidate fundamental cell biology, and also to understand how cell processes are corrupted by and/or contribute to cancer. Research areas in the discipline of Genetics include: Cancer Genetics (Gene Discovery & Characterization and Transcription Regulation), Cancer Genomics (Genome Annotation and Gene Expression Profiling) and Cancer Epidemiology (Human Papillomavirus & Cancer).

Transcription Regulation

Transcription is regulated by complex interactions between 'transcription factors', which bind to the 'promoter' sequence at the beginning of each gene, and proteins that bind to regulatory 'enhancer', 'repressor' and/or 'insulator' sequences in the genome. These regulatory sequences define the combinatorial codes that direct and specify gene expression patterns. Identification and characterization of these regulatory sequences are vital to understanding the complex patterns or 'profiles' of gene expression and elucidating the molecular basis of cancer. The following several studies illustrate some of the work published by LICR investigators in 2005 in the area of Transcription Regulation.

A team from the San Diego Branch reported the development of an efficient, new method to identify thousands of regulatory sequences. This whole genome promoter mapping approach marks a major advance in decoding regulatory networks in the human genome. The study was conducted with a commercial partner and is part of a competitive National Human Genome Research Institute (USA) initiative, 'The ENCODE Project: ENCyclopedia of DNA Elements.

The Sterol Regulatory Element Binding Proteins (SREBP) family of transcription factors regulates genes involved in the synthesis of lipids, which are required for, amongst other things, the formation of cell membranes. LICR scientists from the Uppsala Branch analyzed the expression of key genes involved in lipid metabolism, and found that SREBP-mediated transcription was regulated during the cell cycle as a result of specific modifications of the SREBP proteins. The team also showed that the SREBP family is itself regulated by the SCFFbw7 protein, which has been shown to control several other proteins vital for cell cycle control, and also to be inactivated in cancers of the breast, endometrium, ovary and colon. The evidence supports the hypothesis that deregulation of lipid synthesis facilitates the growth and proliferation of cancer cells. The research also suggested that SCFFbw7 and its interaction with SREBPs may be an attractive target for developing new cholesterol-lowering therapies for the fight against cardiovascular disease.

Research from the Stockholm Branch was featured on the cover of *Nature Neuroscience* in August, 2005. The stunning image showed fluorescent-labeled transcription factors in the spinal cord of an embryonic chick. The team discovered that Sox21 inhibits the Sox1-3 transcription factors that prevent the differentiation of neural cells. The balance of Sox21/Sox1-3 determines whether neural cells remain as precursors or differentiate into neurons. It is highly plausible that the mechanism governing neural stem cell differentiation has parallels in cancer stem cell differentiation.

Biochemistry Discipline

Cells interact with their environment by sending and receiving signals that initiate and terminate cellular processes such as cell division, growth, differentiation, migration and survival. External signals activate receptors on the cell surface, which in turn activate intracellular signal transduction cascades that regulate cellular processes. Cancer cells have abnormal signal generation and reception, which allow them to grow out of control, escape apoptosis, and invade other tissues. Research areas in the discipline of Biochemistry center largely on Signal Transduction and include: Receptor Kinases and Phosphatases, Non-Receptor Kinases and Phosphatases, Receptor Transcription Factors, and Cytokines.

Signal Transduction - Myeloproliferative Diseases

Hematopoiesis is the formation of blood cells, and disruptions to this process can result in myeloproliferative disesases such as leukemia (abnormal proliferation of white blood cells), polycythemia vera (PV, excessive production of red blood cells), and thrombocytosis (excessive production of platelets). A group of signaling factors critical in hematopoiesis are the cytokines, which regulate cell growth and differentiation by binding to cell surface receptors that signal through the Janus kinases (JAKs) to activate the STAT family of transcription factors. The receptor transcription factor, Notch, has also been implicated previously in disturbances in hematopoiesis. The following studies illustrate briefly LICR publications on biochemistry research in the context of myeloproliferative diseases.

The interleukin-6 (IL-6) cytokine family binds to the gp130 receptor to regulate cellular responses during hematopoiesis. Investigators from the Melbourne Branch found, in a mouse model, that mutated gp130 resulted in hyperactivation of STAT1 and STAT3 and caused a broad spectrum of hematopoietic abnormalities. The team showed that gp130-dependent STAT3, but not STAT1,

hyperactivity is responsible for thrombocytosis, and enlargement of the spleen and lymph nodes in mice.

Scientists from the Brussels Branch were part of a collaborative study that identified a Janus Kinase 2 (JAK2) mutation as being the principal cause of PV. JAK2 was originally discovered at the Melbourne Branch in 1992. It has subsequently been shown to play crucial roles in signal transduction, via cytokine, G protein-coupled and tyrosine kinase growth factor receptors, in mammalian development, physiology and disease. The mutation discovered by the Brussels team and their collaborators constitutively activated JAK2, and is found in other myeloproliferative disorders. Subsequently, the LICR investigators showed that the homologous mutations in two other JAKs, JAK1 and Tyk2, led to constitutive activation of STAT3, STAT5 and several other signaling pathways implicated in cancer. These results suggest that JAK1 and Tyk2 are potential oncogenes, and should be investigated in various human cancers.

Finally, conventional thinking has been that Jagged1, a ligand for Notch receptors, was critical for renewal of the hematopoietic stem cells (HSC) from which blood and immune cells are formed. However a team from the Lausanne Branch showed that inactivating the *jagged1* gene in bone marrow does not impair HSC self-renewal. These data have thus confounded the paradigm that Jagged1-dependent Notch signaling is essential for hematopoiesis.

Cell Biology Discipline

Research in Cell Biology examines how the function and structure of the cell is affected by the disruption of cellular processes by cancer. Research areas in the discipline of Cell Biology include: Angiogenesis and Lymphangiogenesis; Cell Migration and Metastasis (Rho GTPases and Cell Polarity); Cell Cycle and Apoptosis (Cell Cycle and Apoptosis, and Genome Integrity).

Cell Cycle Checkpoints and Cancer

Genome integrity and cell growth and division are tightly regulated by cell cycle checkpoints that must be disrupted for tumor development and progression to occur. Many of the known oncogenes, such as p53, the function of which is lost in >50% of cancers, are part of checkpoint protein complexes. Many current cancer therapies, particularly chemotherapies, act by blocking the division of cells that are rapidly cycling, cancerous or not, which frequently result in side effects. Understanding the cell cycle may give clues for the design of new, cancer-specific therapies.

The p53 family of transcription factors (p53, p63 and p73), detects DNA damage during G1 and responds by halting the cell cycle and initiating apoptosis (programmed cell death). Investigators at the University College London Branch found that E2F1, a member of the transcription factor family regulating the expression of multiple cell cycle control proteins, stimulates the apoptotic function of p53, but not p63 and p73. This is the first demonstration of p53 activity being regulated during the cell cycle by E2F/p53 interactions. The University College London team is also characterizing the ASPP protein family, which was discovered at the Branch and activates p53-mediated apoptosis. The team showed that both ASPP1 and ASPP2 are transcriptional targets of the E2F family, providing a mechanism by which E2F cooperates with p53 to induce apoptosis. The aim of this research is to explore the therapeutic potential of re-activating p53 function to cause apoptosis of cancer cells.

Cell cycle progression in the G1 and S phases is controlled by cyclin-dependent kinases (cdk) that are positively regulated by cyclins and negatively regulated by two families of cdk inhibitors, cip/kip and ink4. The expression levels of cdks are fairly constant, but they must be complexed with cyclins, the expression levels of which rise and fall as the cell cycle progresses, to be active. For example, cylin E/cdk2 kinase activity is important in G1, while the ‘S phase promoting factor’ includes the cyclin

A/cdk2 complex. In 2005, a team from the Uppsala Branch found that all members of the TGFβ super-family (see p8-9, 'TGFβ Program') can inhibit epithelial cell growth by inducing the expression of $p21^{cip1}$ to inhibit cyclin E/cdk2 kinase activity. Meanwhile, a team of investigators from the University College London Branch and the James R. Kerr Program in Xi'an, China, showed that the binding of different cyclins and cdks to $p27^{kip1}$, which also inhibits cyclin E/cdk2 kinase activity, is dependent on the posttranslational modification of $p27^{kip1}$. Understanding the regulation of $p21^{cip1}$ and $p27^{kip1}$ may provide new strategies to inhibit cancer cell growth through reactivation of the growth inhibitory activities of these proteins.

The 'mitotic spindle' is a network of microtubules that connect the kinetochore, at the centromere of the chromosome, to the centrosome, which separates chromosome pairs. The mitotic checkpoint halts cell cycle progression when even one chromosome has not properly attached to the mitotic spindle, thus ensuring that all chromosomes are divided equally between daughter cells. Scientists at the San Diego Branch have been investigating the mitotic checkpoint and the disruptions that cause aneuploidy, an abnormal number of chromosomes, which is a characteristic of cancer cells. The team identified the protein complex, ZW10-Rod, as the bridge between the kinetochore and the Mad1-Mad-2 heterodimer that forms the checkpoint's actual 'wait' signal. ZW10 recruits the Mad1-Mad2 complex to unattached kinetochores and then removes the complex after kinetochore attachment to the centromere. ZW10, Mad1 and Mad2 have all been shown to be mutated in colorectal cancers with gross aneuploidy.

The centromeric protein CENP-A is the foundation for the assembly of kinetochores, and its misregulation has been reported in colorectal cancers. Research by investigators at the San Diego Branch have found a surprising CENP-A independent mechanism that is responsible for segregating holocentric chromosomes in C. elegans meiosis. Further studies of this adaptation should provide insight into the mechanisms by which chromosomes are connected to the spindle apparatus and segregated during cell division. The San Diego Branch teams also focused on the characterization of the kinetochore proteins, CENP-E and CENP-F, finding that CENP-E is responsible for appropriately silencing the mitotic checkpoint 'wait' signal and that CENP-F is essential for efficient assembly of a stable microtubule-kinetochore interface.

Mitotic checkpoint breakdown results in a phenotype of chromosomal instability (CIN), which involves changes in chromosome number (aneuploidy) or structure, and is seen in several hereditary cancer predisposition syndromes. However understanding the CIN phenotype has been complicated by the complexity of systematically organizing and characterizing the multiplicity of different genome rearrangements. Investigators from the San Diego Branch analyzed the phenotypes of different yeast mutations to correlate particular classes of genome rearrangements with disruptions in mechanistic pathways such as DNA recombination, telomerase activity or cell cycle checkpoints. Parallels revealed by the comparison of the yeast genome rearrangement classes with 47800 human cancer karyotypes suggests that genome rearrangements in human cancers might provide information about human carcinogenesis and which genes are best candidates for mutation screening in cancer.

Immunology Discipline

The immune system has a remarkable capacity for fending off infectious diseases, and it has become clear that these same defenses can recognize and destroy cancer cells. LICR is working on treatment strategies, such as targeted antibodies and cancer vaccines, which harness the body's immune system to more effectively and specifically fight cancer cells. An understanding of the role of the immune system in cancer development and the development of cancer therapies based on immunologic principles continue to be major objectives of LICR, which is, arguably, the largest academic center in the world for cancer immunology studies. Programs in the discipline of Immunology include: Cancer

Vaccine (Characterization of Human Immune Response, and Vaccine Constitution and Development); Cellular and Molecular Immunology (Adaptive Immune Response, and Innate Immune Response); Cancer Antigen Discovery (Cancer Antigen Identification, and Cancer Antigen Characterization); and Antibody Targeting (Antibody Characterization, and Antibody Engineering).

Antibody Targeting Program - The 806 Antibody

Antibody-based therapies have long been an interest at LICR. Antibodies that target signaling molecules promoting cancer cell growth currently represent one of the most promising areas in the development of new treatments for cancer. Pharmaceutical companies have recently brought to market several antibody therapies that effectively benefit patients by targeting the epidermal growth factor receptor (EGFR) (cetuximab), vascular endothelial growth factor (bevacizumab) or hematopoietic differentiation antigens (rituximab). Mutations or overexpression of EGFR are linked to over 50% of all cancers of epithelial cell origin, which makes this a very promising target for novel cancer therapies.

Some ten years ago, a collaboration between the San Diego and New York Branches was formed specifically to generate antibodies that target a mutant variant of EGFR, de2-7 EGFR (ΔEGFR, or EGFR variant III). The de2-7 EGFR mutant is found mostly in glioblastoma, a cancer that is intractable to virtually all conventional treatments, and is an excellent candidate for antibody targeting given that the variant is on the cell surface and is structurally distinct from normal, or 'wild-type', EGFR (wtEGFR). In the characterization process, one of those anti- de2-7 EGFR antibodies, 806, was found to also bind a subset of wtEGFR molecules, but only when the molecule was over-expressed, as in the case on many forms of carcinoma. The distinct affinity of 806 for de2-7 EGFR and overexpressed wtEGFR, but not wtEGFR on normal tissue, makes this antibody unique, with less likelihood to cause toxic side-effects when used clinically and with the potential to have a far greater therapeutic index than other available agents that attach less selectively to all forms of EGFR. LICR's Antibody Targeting Program has been investigating the 806 antibody in preclinical and clinical studies to assess its potential as a highly-specific anti-EGFR therapy. The original 806 was generated as a mouse antibody that may be immunogenic, *i.e.* cause the human immune system to react against the antibody therapy and clear it from the blood. Thus the mouse antibody was re-engineered by a team from the Melbourne Branch and Affiliates in Homburg (Germany) to enable production of a chimeric antibody, ch806, appropriate for early-phase clinical trials.

LICR investigators have taken advantage of the unique binding specificity of 806 to further unravel the complexities of EGFR activation and its hyper-activity in cancer. In back-to-back *Journal of Biological Chemistry* papers, a team from the Melbourne and New York Branches discovered that EGFR exposes the epitope (binding site) for 806 as it transits from an inactive, tethered form to an active, ligand-bound form. This was a major advance in our understanding of conformational epitopes in growth factors and revealed the structural basis for the specificity of 806. The team also demonstrated that although EGFR can be untethered on the cell surface, ligand binding is still required for the receptor to become active. Also, a team from the Melbourne and New York Branches and Affiliates from New Haven (USA) demonstrated that over-expression of EGFR leads to the accumulation of under-glycosylated EGFR in the cell's endoplasmic reticulum. Unexpectedly, this immature form of the receptor was also detected at the cell surface. Since under-glycosylated EGFR is primed for activation, it may contribute to spontaneous receptor activity and cancer cell growth. This body of work furthers our understanding of the activation and conformation of EGFR and also presents two new approaches to generating potential anti-tumor antibodies with reduced targeting of normal tissues; the generation of antibodies specific to receptors in their transitional state or specific to immature receptors.

The treatment of human tumor xenografts in mice by research teams from the Melbourne, New York and San Diego Branches have shown that 806 has anti-tumor activity against glioma and against tumors with overexpressed EGFR. Further preclinical studies showed that combining 806 with a second form of anti-EGFR antibody or with a tyrosine kinase inhibitor specific to the EGFR results in additive and, in some cases, synergistic anti-tumor activity.

The first clinical trial of ch806 was initiated in 2005 at the LICR Melbourne Branch. The trial is testing the safety of ch806 in patients with carcinomas that express de2-7 EGFR or overexpress wtEGFR.

The James R Kerr Program

The James R. Kerr Program was established to honor the memory of Mr. James R. Kerr, a trusted friend and colleague of Mr. Daniel K. Ludwig. Through the wisdom of Mr. Kerr who served as Chairman of the Board of LICR from 1984 until 1995, LICR has the administrative structure and financial-base required to fulfill its obligation as a global cancer research organization. The James R. Kerr Program, led by Dr. Andrew J.G. Simpson, continues to establish international collaborations with leading scientific investigators throughout the world in order to develop and strengthen the global network of cancer research conducted by LICR. Currently, the James R. Kerr Program consists of collaborative research projects at leading academic centers in Brazil, China, Russia, South Africa, Turkey and Ukraine.

In 2005, the James R. Kerr Program focused on its strength in bioinformatics in order to further develop a cancer/testis (CT) database originally created by LICR investigators and located via the Cancer Immunity online journal (www.cancerimmunity.org). In July 2005, leading bioinformaticians from the James R. Kerr Program from Russia, Brazil and South Africa met with experts from the CT field at the Moscow Conference on Computational Molecular Biology at Moscow State University to create a more comprehensive tool for investigating CT antigens.

Monoclonal antibody development continues to be a focus of the James R. Kerr Program. Resources from the Program have been used to produce recombinant proteins corresponding to some of the cancer target antigens newly identified at LICR. These recombinant proteins were subsequently used to produce monoclonal antibodies against those cancer target antigens. Researchers at the LICR Monoclonal Antibody Core Facility located in Xi'an, China, have worked on collaborative projects to develop novel reagents for potential therapeutic use. Additionally, James R. Kerr investigators from Ukraine have collaborated with LICR researchers to develop monoclonal antibodies as part of the collaborative research of the LICR TGF-β Program.

Clinical Trials

LICR believes that human benefit from laboratory research is derived most efficiently when early clinical studies are conducted to verify and explore these discoveries in the human setting. Based on this principle, LICR assesses the therapeutic utility of its research discoveries by sponsoring and conducting its own early phase proof-of-concept clinical trials. The global LICR Phase I and II clinical trials are coordinated centrally by the Office of Clinical Trials Management in New York.

LICR initiated 10 early-phase clinical trials in 2005, bringing the total number of active LICR sponsored trials to 33. The clinical trials used expertise and reagents generated primarily through the Antibody Targeting and Cancer Vaccine Programs.

Ludwig Institute for Cancer Research

Clinical Trial Sites

The following LICR Clinical Trial Centers had active trials in 2005:

Asia

- Mie University School of Medicine, Mie, Japan
- Okayama University Medical School, Okayama, Japan
- Osaka University Graduate School of Medicine, Osaka, Japan

Australasia

- Austin Health (LICR Melbourne Branch), Melbourne, Australia

Europe

- Centre Hospitalier Universitaire Vaudois (LICR Lausanne Branch), Lausanne, Switzerland
- Clinique Universitaires Saint-Luc (LICR Brussels Branch), Brussels, Belgium
- Krankenhaus Nordwest, Frankfurt, Germany
- University Hospital Nijmegen, Nijmegen, Netherlands
- University Hospital Zürich, Zürich, Switzerland
- University of Saarland Medical School, Homburg, Germany

North America

- M.D. Anderson Cancer Center, Houston, USA
- Memorial Sloan-Kettering Cancer Center (LICR New York Branch), New York, USA
- Roswell Park Cancer Institute, Buffalo, USA
- Weill Medical College of Cornell University, New York, USA
- New York University Clinical Cancer Center, New York, USA

Biological Production Facilities

Investigational agents for use in human clinical trials must meet extensive standardization and quality control criteria. These "current Good Manufacturing Practices" (cGMP), extensive testing, and secure and monitored storage conditions ensure the safety of investigational agents and compliance with regulatory and licensing requirements. To translate discoveries rapidly and effectively into investigational agents for clinical trials, facilities that perform these functions must be able to meet these high standards.

The Cornell University/LICR BPF at Ithaca, New York utilizes bacterial and yeast expression systems to produce proteins, including NY-ESO-1, SSX2, MAGE-3 and Melan A, all of which are required for LICR's clinical vaccine program.

These proteins are then transferred to the LICR facility in Melbourne which serves as the testing, storage, documentation and distribution center for all LICR investigational agents.

Intellectual Property Program

To ensure that the Institute is able to capitalize on its discoveries, a vigorous patent protection policy has been pursued. In 2005, 14 patents were issued, 17 patents published and 25 new patent applications filed in the United States of America Patent and Trademark Office (PTO). A further 9 patents were issued and 22 patents published by the European patent Office (EPO) and a further 31 new international patent (PCT) applications were published by the World Intellectual Property Organization (WIPO). Most of these patents are related to growth factors, cytokines, signaling molecules, antibodies and human tumor antigens.

The research efforts of the LICR have resulted in a series of unique scientific discoveries, leading to the establishment of a significant intellectual property portfolio. As an example, the Institute's Antigen Discovery Program underlies several other LICR Programs, including the Antibody Targeting, Bioinformatics, Genomics, and Cancer Vaccine Programs. Intense endeavors are now underway to bring these discoveries to the attention of the pharmaceutical and biotechnology industries as new candidates for licensing and to further the development of these potential cancer therapies.

Academic Matters

During 2005, LICR investigators published in excess of 360 papers in peer-reviewed journals.

The quality of the Institute's science continued to be internationally recognized. In the last year, the following distinctions and awards were received:

- Dr. Thomas Perlmann (Stockholm Branch) was elected to the 50-member Nobel Assembly responsible for electing the Nobel Prize laureates in Physiology or Medicine;
- Dr. Benoît Van den Eynde (Brussels Branch) was awarded the honor of presenting a cycle of conferences for the Francqui Chair, Louvain University, Brussels;
- Dr. Antony Burgess (Melbourne Branch) was awarded the Leach Lecture Medal;
- Dr. Serhiy Souchelnytskyi (Uppsala Branch) was awarded a Roche Award by the Human Proteome Organization (HuPO) Conference.

Formal academic review to assess the quality and impact of the research performed by LICR staff members was conducted in 2005 by the Scientific Advisory Committee and Scientific Directorate.

Three staff members underwent external review for Associate Member rank and were promoted:- Dr. Stefan Constantinescu (Brussels Branch), Dr. Weisan Chen (Melbourne Branch) and Dr. Ian Davis (Melbourne Branch).

One staff member, Dr. Andrew Clayton (Melbourne Branch) underwent review for Assistant Member rank and was appointed.

One staff member, Dr. Karen Arden (San Diego Branch) underwent review for Senior Investigator rank and was appointed.

Ludwig Institute for Cancer Research

One staff member, Dr. Brian Stevenson (Office of Information Technology Lausanne) underwent view for Associate Investigator rank and was appointed.

Three staff members underwent review for Assistant Investigator rank and were appointed:-
Dr. Christian Iseli (Office of Information Technology Lausanne), Dr. Zhanqi Liu (Melbourne Branch) and Dr. Carina Hellberg (Uppsala Branch).

Ludwig Institute for Cancer Research, Zurich

Report of the Statutory Auditors to the General Meeting

Financial Statements 2005

KPMG Fides Peat
Zurich, April 7, 2006
Ref. M. Herzog

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Report of the Statutory Auditors to the General Meeting of the

Ludwig Institute for Cancer Research, Zurich

As statutory auditors, we have audited the accounting records and the financial statements presented on pages 17 to 24 (balance sheet, income statement and notes) of the Ludwig Institute for Cancer Research for the year ended December 31, 2005.

These financial statements are the responsibility of the board of directors. Our responsibility is to express an opinion on these financial statements based on our audit. We confirm that we meet the legal requirements concerning professional qualification and independence.

Our audit was conducted in accordance with Swiss Auditing Standards, which require that an audit be planned and performed to obtain reasonable assurance about whether the financial statements are free of material misstatement. We have examined on a test basis evidence supporting the amounts and disclosures in the financial statements. We have also assessed the accounting principles used, significant estimates made and the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the accounting records and financial statements comply with Swiss law and the company's articles of incorporation.

We recommend that the financial statements submitted to you be approved.

KPMG Fides Peat

Martin Schaad
Swiss Certified Accountant
Auditor in Charge

Michael Herzog
Swiss Certified Accountant

Zurich, April 7, 2006

Balance sheet
as at December 31, 2005

	USD		*CHF*	
	2005	*2004*	*2005*	*2004*
Assets				
Current assets				
Liquid funds (Note 1.b)	9,609,169	7,799,507	12,663,919	8,868,847
Fixed term deposits (Note 1.b)	9,071,954	8,215,670	11,955,941	9,342,203
Other receivables -				
third parties	2,211,928	1,386,224	2,915,098	1,576,292
external funding	3,755,254	4,059,294	4,949,061	4,615,859
Prepayments and accrued income	1,802,751	2,503,926	2,375,847	2,847,226
Total current assets	26,451,056	23,964,621	34,859,866	27,250,427
Fixed assets				
Financial fixed assets -				
Investments (Note 4)	5,108,060	5,103,853	6,731,912	5,803,590
Other financial fixed assets	912,505	984,304	1,202,593	1,119,250
Total fixed assets	6,020,565	6,088,157	7,934,505	6,922,840
Total assets	32,471,621	30,052,778	42,794,371	34,173,267
Liabilities and net worth				
Current liabilities				
Accounts payable - third parties	7,142,739	8,952,117	9,413,427	10,179,504
Accruals	8,748,897	6,855,022	11,530,181	7,794,911
Deferred Income	4,681,344	4,432,136	6,169,523	5,039,865
Total current liabilities	20,572,980	20,239,275	27,113,131	23,014,280
Total liabilities	20,572,980	20,239,275	27,113,131	23,014,280
Net worth				
Share capital (Note 1e)	33,722	33,722	50,000	50,000
Legal reserve (Note 1e)	6,744	6,744	10,000	10,000
Cumulative exchange adjustment (Note 1e)	5,061	12,300	0	0
Excess of income over expenditure (Note 3)	11,853,114	9,760,737	15,621,240	11,098,987
Net worth	11,898,641	9,813,503	15,681,240	11,158,987
Total liabilities and net worth	32,471,621	30,052,778	42,794,371	34,173,267

Statement of income and expenditure for the year ended December 31, 2005

	USD		CHF	
	2005	*2004*	*2005*	*2004*
Income (Note 1.c)				
Contributions and dividends	72,496,825	67,471,451	88,325,215	86,128,845
Interest	660,091	487,124	817,180	616,462
External funding (Note 9)	26,562,490	23,806,364	32,883,927	30,127,117
License fees and patent royalties (Note 2)	4,925,492	4,975,633	6,097,686	6,296,639
Other Income	182,290	112,596	225,669	142,492
Total Income	104,827,188	96,853,168	128,349,677	123,311,555
Medical research and related expenditure				
Salaries & social benefits	54,622,134	52,871,733	67,621,580	66,909,383
Laboratory	13,788,990	13,974,647	17,070,600	17,684,995
Equipment & other assets (Note 1.f)	4,388,642	4,420,699	5,433,082	5,594,426
Leasehold improvements (Note 1.f)	316,824	494,639	392,214	625,969
Clinical trials	2,421,774	2,628,706	2,998,113	3,326,637
Collaborative research programs	5,642,717	5,238,889	6,985,649	6,629,795
Occupancy	7,466,751	7,217,607	9,243,822	9,133,879
Travel	842,962	806,096	1,043,583	1,020,114
Scientific conferences, seminars etc.	1,110,235	1,037,155	1,374,456	1,312,531
Consultants	2,151,193	2,280,469	2,663,173	2,885,932
Patent costs	2,769,989	3,452,880	3,429,231	4,369,609
Other operating expenses	5,955,397	4,215,708	7,372,756	5,334,991
Total expenditure	101,477,608	98,639,228	125,628,259	124,828,261
Excess of income over expenditure / (expenditure over income) before other items	3,349,580	(1,786,060)	2,721,418	(1,516,706)
Other items				
Net gain / (loss) on foreign exchange (Note 1.e)	(1,257,203)	663,209	1,800,835	(845,178)
Excess of income over expenditure / (expenditure over income) for the year	2,092,377	(1,122,851)	4,522,253	(2,361,884)
Excess of income over expenditure at beginning of year	9,760,737	10,883,588	11,098,987	13,460,871
Excess of income over expenditure at end of year	11,853,114	9,760,737	15,621,240	11,098,987

Notes to Financial Statements – December 31, 2005

1 Accounting policies

1.a Basis of preparation

These financial statements have been prepared in accordance with the provisions of the Swiss Code of Obligations.

1.b Liquid funds and fixed term deposits

Cash on hand and at banks and funds on call available within 48 hours are classified as liquid funds. Cash deposits fixed for periods of longer than 48 hours are classified as fixed term deposits.

1.c Income

Contributions and dividends are accounted for on the cash basis.

Interest is accounted for on the accruals basis.

External funding received from any outside source, whether of cash or a non-cash nature, is recorded in the Institute's books of account upon receipt. External funding received is taken to income when the corresponding expenditure is incurred. Any unspent income is deferred to future accounting periods. External funding pledged, but not received where expenditure has been incurred, is taken to account as income and is accounted for as receivable pending receipt.

License fees and royalties are accounted for on the modified cash basis.

1.d Joint ventures

The Institute has entered into joint ventures to carry out research projects on a joint basis with affiliated hospitals and research institutions. Income received and expenditure incurred under joint ventures is accounted for by the method of proportional consolidation.

1.e Translation of foreign exchange transactions

The Institute's Zurich and Lausanne offices' Swiss franc transactions and the Lausanne Branch's operations are recorded in Swiss francs. Those of the Brussels, London St. Mary's, London University College, Melbourne, New York, San Diego, Sao Paulo, Stockholm and Uppsala Branches are recorded in the currencies of their respective countries. The foreign branch accounts and the Zurich, New York, London and Lausanne offices' transactions in currencies other than Swiss francs are translated for the purpose of preparing statutory financial statements of the Institute as a whole into Swiss francs in accordance with the following principles: -

i. Income – contributions and dividends at the monthly rates as published by the Swiss VAT authorities. All other income is translated at the yearly average of the monthly rates as published by the Swiss VAT authorities.

ii. Expenditure – at the yearly average of the monthly rates as published by the Swiss VAT authorities.

iii. Assets and liabilities – at the rates ruling at the end of the respective year.

Where foreign exchange contracts are entered into for the purpose of hedging future commitments, any net gains are deferred whilst provision is made for any net losses arising thereon.

The USD equivalents of the statutory financial statements in CHF are presented in accordance with the same principles as stated above and in addition share capital, legal reserve and the balance of income at the beginning of the year are translated at historical rates.

The resulting translation adjustments are included in the excess of income over expenditure for the year.

1.f Tangible fixed assets

Expenditure on equipment and other assets and leasehold improvements is charged in full against revenue in the year it is incurred.

2 License fees and royalties

License fees and royalties are shown net of co-owners' share of income.

	USD		*CHF*	
Description	***2005***	***2004***	***2005***	***2004***
Gross license fees and royalties	7,634,190	7,650,994	9,451,054	9,682,308
Co-owners' shares distributed	2,708,698	2,675,361	3,353,368	3,385,669
Net license fee and royalties income	4,925,492	4,975,633	6,097,686	6,296,639

3 Excess of income over expenditure

The Statutes of the Institute stipulate that the excess of income over expenditure shall not be distributed to shareholders and accordingly the Board of Directors proposes that the available excess of income over expenditure of CHF 15,621,240 (USD 11,853,114) at December 31, 2005 be carried forward.

4 Investments

Description	*USD* 2005	*USD* 2004	*CHF* 2005	*CHF* 2004
Universe Tankships, Inc.				
Investment	5,103,000	5,103,000	6,725,244	5,802,621
Interest in capital	100%	100%	100%	100%
Dividends paid to Institute	0	0	0	0
PIramed Ltd				
Investment	756	845	996	960
Interest in capital	8%	8%	8%	8%
Dividends paid to Institute	0	0	0	0
XCellSyz Ltd				
Investment	7	8	9	9
Interest in capital	1%	1%	1%	1%
Dividends paid to Institute	0	0	0	0
Lymphatix Ltd				
Investment	4,297	0	5,663	0
Interest in capital	36%	0%	36%	0%
Dividends paid to Institute	0	0	0	0
Total Investments	5,108,060	5,103,853	6,731,912	5,803,590

As part of a licensing arrangement, in 2005 the Institute acquired a 36.43% interest in the company Lymphatix Ltd, a Finnish corporation. The relevant shares are valued at the acquisition costs of EUR 3,643 (CHF 5,663, USD 4,297).

5 Fire insurance values

Description	*USD* 2005	*USD* 2004	*CHF* 2005	*CHF* 2004
Equipment and other assets	80,534,065	78,078,418	106,135,844	88,782,969
Leasehold improvements	34,792,202	31,500,226	45,852,643	35,818,907
Tangible fixed assets	115,326,267	109,578,644	151,988,487	124,601,876

6 Liabilities to pension funds

	USD		CHF	
Description	*2005*	*2004*	*2005*	*2004*
Current liabilities	32,093	167,323	42,295	190,263

Branches and offices with defined contribution schemes are located in Belgium, Brazil, Sweden, Switzerland and the United States of America. The branches in Australia and the United Kingdom are registered employers with the local university pension schemes, which set the level of contributions based on the advice of the schemes' actuaries. In view of the size of the schemes and the Institute's limited participation in the management of the schemes, the two university schemes are treated as defined contribution schemes. The contributions are calculated as a percentage of the insured salary.

Institute wide, the annual cost of the employer's contributions in 2005 and 2004 for all plans amounted to CHF 5,782,791 (USD 4,671,075) and CHF 6,096,280 (USD 4,817,290) respectively.

From 2002, a second pension scheme in the United Kingdom, the Federated Pension Scheme (FPS), has been accounted for as a defined benefit scheme in accordance with Swiss GAAP FER 16. The scheme's pension liabilities are set out in the following table: -

	USD		CHF	
Description	*2005*	*2004*	*2005*	*2004*
Value of funded obligations	9,025,218	8,443,720	11,894,334	9,601,354
Market value of the scheme's assets	8,942,811	8,148,056	11,785,731	9,265,154
Shortfall	82,407	295,664	108,603	336,200
(Excess provision)	(343,359)	(99,835)	(452,522)	(113,519)
Provision for funded obligations	425,766	395,499	561,125	449,719

This provision of CHF 561,125 (USD 425,766) has been accounted for in the balance sheet under "Accruals".

The total cost for the FPS defined benefit plan in 2005 amounted to CHF 412,102 (USD 332,877), being the cost of contributions 2005 of CHF 316,476 (USD 255,635) and the amortization cost of the shortfall 2005 of CHF 95,626 (USD 77,242).

In 2004 total costs for the FPS defined benefit plan were CHF 429,280 (USD 339,218), being the cost of contributions 2004 of 365,003 (USD 288,426) and the amortization cost of the shortfall 2004 of CHF 64,277 (USD 50,792).

The underlying actuarial assumptions, used in the calculation are based on current economic circumstances and tax exemption status, are as follows: -

Description	*2005*	*2004*
Discount rate	4.90%	5.35%
Expected rate of return	7.00%	6.60%
Annual increase of future salaries	3.50%	3.60%

An actuarial valuation is carried out triennially and in addition a valuation in accordance with Swiss GAAP FER 16 is carried out annually.

No surplus of scheme assets has been capitalized in the balance sheet.

7 Lease commitments

	USD		*CHF*	
Description	*2005*	*2004*	*2005*	*2004*
Lease commitments not recorded in the balance sheet	24,457,957	24,967,361	32,233,132	28,390,437

8 Value added tax

The Institute is registered for value added tax in Switzerland.

In September 2004, the Federal Tax Administration carried out an audit at the Institute's Zurich office. In an informal report, the Federal Tax Administration questioned the method used by the Institute in calculating the reduction of the input tax for the years 2000 to 2004.

The report set out three different methods to calculate the input tax reduction with claims ranging for 2003 - the year audited in detail - between CHF 889,937 (USD 782,637) and CHF 929,802 (USD 817,696).

In May 2005 the Federal Tax Administration revised their initial position and invoiced the Institute for a total amount of CHF 1,739,606 (USD 1,319,983) with amounts ranging between CHF 301,866 (USD 229,051) and CHF 374,404 (USD 284,091) for the years 2000 to 2004.

The Institute's management continues to be not in agreement with these calculations and its tax advisors wrote to the Federal Tax Administration in June 2005 setting out again the Institute's position. The Federal Tax Administration has not, as yet, responded to this letter.

In the opinion of management, based on professional advice received, the Institute expects a further substantial reduction in the claim by the Federal Tax Administration. However, taking account of the developments that took place in 2005, for the sake of prudence, an accrual of CHF 1,205,000 (USD 914,333) has been included in the financial statements 2005, whereas no accrual was made in 2004.

9 External funding

The Institute receives external funding from third parties including government agencies, in return for which the Institute may be obliged to comply with specific conditions. In certain cases, the right and / or obligation exists to confirm compliance by means of audit. The Board of Directors does not expect that these arrangements will result in any significant adverse financial consequences for the Institute.

10 Related party transactions

The Institute effectively controls LICR Fund Inc. (the "Fund"), a non-profit membership corporation incorporated in Delaware, USA, which was established to receive, hold and invest funds on behalf of the Institute.

During 2005 and 2004 the Fund was a material source of funding and made grants of CHF 84,982,672 (USD 69,796,825) and CHF 82,999,429 (USD 64,996,451) respectively.

Effective January 1, 1996, the Institute entered into an administrative service agreement with The Ludwig Group Inc. (LGI), a wholly owned subsidiary of Universe Tankships Inc., Delaware, USA.

Fees paid by the Institute New York office under the service agreement including occupancy related costs amounted to CHF 1.8 Mio (USD 1.4 Mio) in 2005 and CHF 1.9 Mio (USD 1.5 Mio) in 2004.

Payables in favor of LGI by the Institute New York office as at December 31, 2005 and December 31, 2004 amounted to CHF 472,673 (USD 358,656) and CHF 429,143 (USD 377,401).

Ludwig Institute for Cancer Research, Zurich

Report of the Group Auditors to the General Meeting

Consolidated Financial Statements 2005

KPMG Fides Peat
Zurich, April 7, 2006
Ref. M. Herzog

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Report of the Group Auditors to the General Meeting of the

Ludwig Institute for Cancer Research, Zurich

As group auditors, we have audited the consolidated financial statements presented on pages 27 to 39 (balance sheet, income statement cash flow statement and notes) of the Ludwig Institute for Cancer Research for the year ended December 31, 2005.

These consolidated financial statements are the responsibility of the board of directors. Our responsibility is to express an opinion on these consolidated financial statements based on our audit. We confirm that we meet the legal requirements concerning professional qualification and independence.

Our audit was conducted in accordance with Swiss Auditing standards, which require that an audit be planned and performed to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement. We have examined on a test basis evidence supporting the amounts and disclosures in the consolidated financial statements. We have also assessed the accounting principles used, significant estimates made and the overall consolidated financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the consolidated financial statements give a true and fair view of the financial position, the results of operations and the cash flows in accordance with Swiss GAAP FER and comply with Swiss law.

We recommend that the consolidated financial statements submitted to you be approved.

KPMG Fides Peat

Martin Schaad
Swiss Certified Accountant
Auditor in Charge

Michael Herzog
Swiss Certified Accountant

Zurich, April 7, 2006

Consolidated Balance Sheet
as at December 31, 2005

	USD		CHF	
	2005	*2004*	*2005*	*2004*
Assets				
Current assets				
Liquid funds (Note 2)	9,686,221	7,821,731	12,765,466	8,894,118
Short-term cash deposits (Note 2)	9,071,954	8,215,670	11,955,941	9,342,203
Investments (Notes 2 & 3)	1,180,306,389	1,170,212,327	1,555,525,790	1,330,648,437
Collateral under securities loan agreement (Note 4)	91,580,608	58,731,799	120,694,083	66,783,929
Interest & dividends receivable	2,989,338	3,085,354	3,939,649	3,508,357
Research external funding receivables (Note 2)	3,755,254	4,059,294	4,949,061	4,615,859
Other receivables - third parties	2,387,772	1,509,616	3,146,843	1,716,601
Prepayments	1,789,703	2,482,247	2,358,651	2,822,574
Total current assets	1,301,567,239	1,256,118,038	1,715,335,484	1,428,332,078
Fixed assets				
Financial fixed assets -				
Investments (Notes 1 & 5)	28,871,060	28,122,853	38,049,170	31,978,495
Other financial fixed assets	912,505	984,304	1,202,593	1,119,250
Total fixed assets	29,783,565	29,107,157	39,251,763	33,097,745
Total assets	1,331,350,804	1,285,225,195	1,754,587,247	1,461,429,823
Liabilities and net worth				
Current liabilities				
Creditors - third parties	8,900,808	10,791,272	11,730,386	12,270,807
Payables under securities loan agreement (Note 4)	91,580,608	58,731,799	120,694,083	66,783,929
Accruals (Note 13)	8,323,131	6,855,022	10,969,056	7,794,911
Deferred income (Notes 2 & 6)	4,681,344	4,432,136	6,169,523	5,039,865
Total current liabilities	113,485,891	80,810,229	149,563,048	91,889,512
Total liabilities	113,485,891	80,810,229	149,563,048	91,889,512
Net worth				
Share capital (Note 6)	33,722	33,722	50,000	50,000
Legal reserve (Note 6)	6,744	6,744	10,000	10,000
Endowments (Notes 1 & 6)	572,000,000	572,000,000	773,352,000	773,352,000
Cumulative excess of income over expenditure per statement attached (Note 6)	645,819,191	632,362,005	840,599,999	820,548,288
Cumulative translation adjustment (Notes 1 & 6)	5,256	12,495	(8,987,800)	(224,419,977)
Net worth	1,217,864,913	1,204,414,966	1,605,024,199	1,369,540,311
Total liabilities and net worth	1,331,350,804	1,285,225,195	1,754,587,247	1,461,429,823

Consolidated Statement of Income and Expenditure for the year ended December 31, 2005

	USD		CHF	
	2005	*2004*	*2005*	*2004*
Investment income				
Interest	8,883,601	9,704,600	10,997,885	12,281,178
Dividends	7,863,299	5,953,879	9,734,764	7,534,634
Earnings from short term investments and other investment income	118,574	158,316	146,795	200,349
Income from securities lending (Note 4)	300,327	173,045	371,805	218,988
Total investment income	17,165,801	15,989,840	21,251,249	20,235,149
Other gains from investment activities				
Net realised gains on investment transactions (Notes 2 & 3)	86,192,693	64,174,820	106,706,554	81,213,235
Net unrealised (depreciation) / appreciation of investments (Notes 2 & 3)	(14,299,542)	72,875,187	(17,702,833)	92,223,549
Unrealised foreign exchange (losses) / gains (Note 2)	(1,386,205)	667,068	1,923,639	(856,759)
Net gain of unconsolidated subsidiary (Note 5)	744,000	99,000	921,072	125,285
Total other gains from investment activities	71,250,946	137,816,075	91,848,432	172,705,310
Expenditure related to investment activities				
Management, custodian & other fees	7,751,170	7,333,878	9,595,948	9,281,023
Administration expenses	655,823	589,091	811,909	745,495
Total expenditure related to investment activities	8,406,993	7,922,969	10,407,857	10,026,518
Net gain from investment activities	80,009,754	145,882,946	102,691,824	182,913,941
Medical research related income				
Research external funding (Notes 2 & 6)	26,910,371	24,317,880	33,887,258	30,334,390
License fees and royalties	4,925,492	4,975,633	6,097,686	6,296,639
Contributions	2,700,000	2,475,000	3,342,543	3,129,416
Other	182,290	112,596	225,669	142,492
Total medical research related income	34,718,153	31,881,109	43,553,156	39,902,937
Medical research related expenditure				
Salaries & social benefits	54,622,134	52,871,733	67,621,580	66,909,383
Laboratory expenditure	13,788,990	13,974,647	17,070,600	17,684,995
Equipment & other assets (Note 2)	4,388,642	4,420,699	5,433,082	5,594,426
Leasehold improvements (Note 2)	316,824	494,639	392,214	625,969
Other	27,904,922	26,877,510	34,546,135	34,013,488
Total medical research related expenditure	101,021,512	98,639,228	125,063,611	124,828,261
Excess of income over expenditure				
Excess of income over expenditure for year	13,706,394	79,124,827	21,181,369	97,988,617
Excess of income over expenditure at beginning of year	632,362,005	553,752,553	820,548,288	722,755,363
Net increase in restricted funds (Note 6)	(249,208)	(515,375)	(1,129,658)	(195,692)
Excess of income over expenditure at end of year	645,819,191	632,362,005	840,599,999	820,548,288

Consolidated Statement of Cash Flows
for the year ended December 31, 2005

	USD		CHF	
	2005	*2004*	*2005*	*2004*
Operating activities				
Medical research related income	34,718,153	31,881,109	43,553,156	39,902,937
Medical research related expenditure	(101,021,512)	(98,639,228)	(125,063,611)	(124,828,261)
Excess of operating expenditure over income	(66,303,359)	(66,758,119)	(81,510,455)	(84,925,324)
Net change in receivables and payables relating to operations	(89,960)	(243,216)	(111,370)	(307,790)
Net cash used by operating activities	(66,393,319)	(67,001,335)	(81,621,825)	(85,233,114)
Investing activities				
Net gain from investment activities	80,009,754	145,882,946	102,691,824	182,913,941
Net realised gain on investment transactions	(86,192,693)	(64,174,820)	(106,706,554)	(81,213,235)
Net unrealised depreciation / (appreciation) of investments	14,299,542	(72,875,187)	17,702,833	(92,223,549)
Net unrealised loss / (gain) on forward foreign currency contracts	1,196,594	(79,939)	1,481,383	(101,163)
Net gain of unconsolidated subsidiary (Note 5)	(744,000)	(99,000)	(921,072)	(125,285)
Net change in receivables and payables relating to investing activities	(46,153)	1,967,468	(57,137)	2,489,831
Purchase / acquisition of securities	(1,101,333,737)	(1,273,649,693)	(1,363,451,166)	(1,611,803,686)
Proceeds from sale / disposal of securities	1,163,128,619	1,328,942,227	1,439,953,230	1,681,776,388
Effects of exchange movements	(1,203,833)	84,193	(2,586,430)	680,542
Net cash generated by investing activities	69,114,093	65,998,195	88,106,911	82,393,784
Net increase / (decline) in liquid funds and cash deposits	2,720,774	(1,003,140)	6,485,086	(2,839,330)
Liquid funds and cash deposits at beginning of year	16,037,401	17,040,541	18,236,321	21,075,651
Liquid funds and cash deposits at end of year	18,758,175	16,037,401	24,721,407	18,236,321

Notes to the Consolidated Financial Statements

as at December 31, 2005

1 Accounting principles and scope of consolidation

Basis of presentation
The accompanying consolidated financial statements of the Ludwig Institute for Cancer Research are presented in accordance with generally accepted accounting principles in Switzerland (Financial Reporting Standards – Swiss GAAP FER). As from the year 2003 the accounting standard FER 21 has been adopted.

Scope of consolidation
These consolidated financial statements include the Ludwig Institute for Cancer Research (the "Institute"), a non-profit organization incorporated in Switzerland and LICR Fund Inc. (the "Fund"), a non-profit membership corporation incorporated in Delaware, U.S.A. which was established to receive, hold and invest funds on behalf of the Institute and which is effectively controlled by the Institute. The consolidation is based on the audited financial statements of the Institute and the Fund. All inter-company transactions and balances have been eliminated and no minority interests exist.

Universe Tankships Inc. (UTI), a wholly owned subsidiary of the Institute, which is not managed by the Institute on a unified basis, has been accounted for using the equity method.

Nature of operations
The Institute carries out its scientific and clinical activities at its branches in conjunction with hospitals in university medical centers. The Institute's research branches are situated in Brussels, Lausanne, London (St. Mary's [closed Aug 2005] and University College), Melbourne, New York, San Diego, Sao Paulo, Stockholm and Uppsala. In addition, administrative offices are maintained in Lausanne, London, New York and Zurich. The Institute has a broadly based research program that addresses the challenge of cancer using the disciplines of biochemistry, cell biology, genetics, immunology, molecular biology and virology.

Foreign currency translation
CHF financial statements
The consolidated accounts presented in CHF include the Institute's financial statements denominated in CHF and the Fund's financial statements denominated in USD. Translation of the Fund's Balance Sheet into CHF is achieved by using the exchange rate prevailing at year-end with the exception of endowments and accumulated earnings, which are translated at historical rates. The Fund's income and expenditure are translated at the average rate existing during the year. The resulting translation difference is shown as a separate component of equity. The currency translation adjustment, which arises on the translation of the Fund's USD based financial statements into CHF is being accumulated with effect from January 1, 1994 and has not been calculated retrospectively.

USD financial statements
The consolidated accounts presented in USD include the Institute's financial statements denominated in USD and the Fund's financial statements denominated in USD. As the Institute has historically maintained USD accounts in addition to its CHF accounts, there is no need to perform a translation for the purposes of preparing a consolidation in USD. Accordingly, there is no translation effect in the consolidated USD accounts apart from share capital and legal reserve. The share capital and legal reserve are translated into USD at the rate ruling on January 1, 1994, being the initial year in which consolidated financial statements were prepared. The resulting translation difference is shown as a separate component of net worth.

Foreign exchange differences, which arise from foreign exchange in preparing the Institute's USD accounts, are included on a yearly basis in the excess of income over expenditure for the year.

2 Accounting policies

Liquid funds and short-term cash investments
Cash at banks and funds on call available within 48 hours are classified as liquid funds. Cash deposits fixed for periods of longer than 48 hours are classified as short-term cash investments.

Investments and related income
Investments are valued at the last reported sales price for the year, as quoted on major securities exchanges. Securities that are not traded on major securities exchanges are valued based on quotations received from leading brokers. Forward foreign currency contracts are valued based on the average of closing bid and asked quotations from banks and brokers. Investments in limited partnerships are valued based on the Fund's underlying holding in these partnerships, which represent market values as determined by the general partners of the partnership. Unrealized appreciation and depreciation on investments as at the year-end are included in the excess of income over expenditure for the year.

Securities transactions are recorded on the trade date. Realized gains and losses from security transactions are calculated on the average cost basis.

Foreign exchange transactions
Assets and liabilities denominated in foreign currencies are translated into the reporting currencies at the closing rate of exchange at year-end. Income and expenditure denominated in foreign currencies are translated into the reporting currencies on the following basis: -

i) Dividend income and contributions are translated at the average monthly rates as published by the Swiss tax authorities of the month in which the dividends and contributions have been received.

ii) Research expenditure and research external funding income are translated at the yearly average rates of the monthly rates as published by the Swiss tax authorities.

iii) Purchases and sales of investments securities are translated at the rates of exchange prevailing on the respective dates of such transactions.

iv) All other income and expenditure are translated at the yearly average rates of the monthly rates as published by the Swiss VAT authorities.

Net realized and unrealized foreign exchange differences include gains and losses on foreign currency positions and changes in the value of other assets and liabilities arising as a result of changes in exchange rates.

Research external funding
External funding received from any outside source, whether of a cash or a non-cash nature, is recorded in the Institute's books of account upon receipt. External funding received (in terms of restricted funds) is taken to income when the corresponding expenditure is incurred. Any unspent restricted funds are deferred to future accounting periods. Unrestricted funds received are taken to income in the year of receipt. External funding pledged, but not received where expenditure has been incurred, is taken to account as income and is accounted for as receivable pending receipt.

Joint ventures
The Institute has entered into joint ventures with affiliated hospitals and research institutions to primarily fund research expenditures on a joint basis. Income received and expenditure incurred under such joint ventures is accounted for by the method of proportional consolidation.

Tangible and intangible assets
Expenditure on equipment & other assets and leasehold improvements is charged in full against revenue in the year it is incurred in accordance with accepted practice for cancer research organizations. The resale value of research equipment is minimal and no significant income is generated there from.

The value of intangible assets is not recorded in the balance sheet. All research expenditure, including the cost of patenting and licensing intellectual property, is charged in full against revenue in the year it is incurred.

Taxes
The Institute and the Fund are tax-exempt organizations and accordingly are not subject to income taxes.

Withholding taxes on foreign dividends and interest have been provided for in accordance with the applicable countries' tax rates.

3 Current assets - investments

Investments, at fair value, held at December 31, 2005 and 2004 were as follows: -

	USD		*CHF*	
Description	***2005***	***2004***	***2005***	***2004***
Invested cash and cash equivalents				
- USD	35,782,346	38,228,632	47,157,554	43,469,777
- Non-USD currencies	19,971,338	3,374,204	26,320,226	3,836,807
Equity investments	597,232,018	573,166,217	787,092,077	651,747,305
Fixed income investments				
- Government	160,825,613	133,310,879	211,952,075	151,587,801
- Other	10,239,657	60,886,360	13,494,844	69,233,880
Alternative investments (limited partnerships)	357,535,195	329,835,404	471,195,633	375,055,838
Due from brokers	24,821	31,518,636	32,712	35,839,841
Net unrealized loss on foreign currency contracts	(1,304,599)	(108,005)	(1,719,331)	(122,812)
Investments, at fair value	1,180,306,389	1,170,212,327	1,555,525,790	1,330,648,437
Investments, at cost	949,583,571	925,189,968	1,251,456,188	1,052,033,513

4 Collateral under securities loan agreement

By agreement, the custodian, acting on behalf of the Fund, may lend Fund securities to broker-dealers. The Fund receives as compensation a portion of the interest earned on the investment of the cash received as collateral. The Fund continues to earn dividends and interest on the securities loaned. The loans are secured by cash collateral at least equal, at all times, to the market value of the securities loaned plus accrued dividends and interest, if any. If the borrower defaults and the value of the collateral is inadequate, or if bankruptcy proceedings are commenced with respect to the borrower of the security, the custodian will assume such risk and indemnify the Fund.

	USD		*CHF*	
Description	***2005***	***2004***	***2005***	***2004***
Market value of securities loaned	88,426,368	56,107,801	116,537,110	63,800,181
Value of collateral	91,580,608	58,731,799	120,694,083	66,783,929

5 Fixed assets - investments

	USD		*CHF*	
Description	***2005***	***2004***	***2005***	***2004***
Universe Tankships, Inc.				
Share capital	5,103,000	5,103,000	6,725,244	5,802,621
Percentage owned	100%	100%	100%	100%
Net assets at January 1	28,122,000	28,023,000	31,977,526	34,658,847
Dividends paid to the Institute	0	0	0	0
Net income for the year	744,000	99,000	921,072	125,285
Rounding / translation adjustment	0	0	5,143,904	(2,806,606)
Net investment at December 31	28,866,000	28,122,000	38,042,502	31,977,526
PIramed Ltd				
Percentage owned	8%	8%	8%	8%
Net investment	756	845	996	960
XCellSyz Ltd				
Percentage owned	1%	1%	1%	1%
Net investment	7	8	9	9
Lymphatix Ltd				
Percentage owned	36%	0%	36%	0%
Net investment	4,297	0	5,663	0
Total net investments	28,871,060	28,122,853	38,049,170	31,978,495

Universe Tankships, Inc.'s primary business function is to oversee the management of its remaining investments and to provide administrative services to related parties.

Universe Tankships, Inc. has been accounted for using the equity method.

All other assets were acquired as part of licensing arrangements and are valued at acquisition costs. In 2005, the Institute acquired 36,430 shares of the company Lymphatix Ltd, a Finnish corporation, at a nominal value of EUR 0.10 each.

6 Capital changes

Net worth
The share capital consists of 50 fully paid shares of nominal value CHF 1,000 each. The shareholders do not have any interest in the assets or income of the Institute. Their sole power is to vote the shares in accordance with the exclusively charitable and scientific purpose of the Institute.

USD	Share capital	Legal reserve	Endowments	Cumulative excess of income	Cumulative translation adjustment	Total net worth
Balance at January 1, 2005	33,722	6,744	572,000,000	632,362,005	12,495	1,204,414,966
Excess of income over expenditure	0	0	0	13,706,394	(7,239)	13,699,155
Net increase in restricted funds	0	0	0	(249,208)	0	(249,208)
Balance at December 31, 2005	33,722	6,744	572,000,000	645,819,191	5,256	1,217,864,913

CHF	Share capital	Legal reserve	Endowments	Cumulative excess of income	Cumulative translation adjustment	Total net worth
Balance at January 1, 2005	50,000	10,000	773,352,000	820,548,288	(224,419,977)	1,369,540,311
Excess of income over expenditure	0	0	0	21,181,369	215,432,177	236,613,546
Net increase in restricted funds	0	0	0	(1,129,658)	0	(1,129,658)
Balance at December 31, 2005	50,000	10,000	773,352,000	840,599,999	(8,987,800)	1,605,024,199

Included in the Current year movements is an increase of USD 425,766 (CHF 561,125), which is due to the dissolution of a provision in respect of the Federated Pension Scheme, which was previously set up in accordance with IAS19. This has been reversed to follow the provisions of the revision of FER16.

Endowments
Universe Tankships Inc. made the endowments to the Fund in the following years: -

Description	Year		Amount		Amount
Initial Endowment	1990	USD	500,000,000	CHF	673,500,000
Second Endowment	1991	USD	24,000,000	CHF	36,588,000
Third Endowment	1992	USD	48,000,000	CHF	63,264,000
Total		USD	572,000,000	CHF	773,352,000

Cumulative excess of income over expenditure
The Statutes of the Institute stipulate that the balance of income shall not be distributed to shareholders and accordingly the available balance of income is carried forward.

Changes in deferred income (restricted funds)

	USD		*CHF*	
Description	***2005***	***2004***	***2005***	***2004***
Fund balances at January 1	4,432,136	3,916,761	5,039,865	4,844,173
Usage of funds	(3,014,340)	(3,755,840)	(3,427,721)	(4,645,223)
New funds	3,362,221	4,267,356	4,431,052	4,852,496
Exchange rate adjustments	(98,672)	3,859	126,327	(11,581)
Fund balances at December 31	04,681,345	4,432,136	6,169,523	5,039,865
Net change of fund balances	249,208	515,375	1,129,658	195,692

In accordance with Swiss GAAP FER 21 as from January 1, 2003 all changes in restricted funds balances are shown gross as part of the Consolidated Statement of Income and Expenditure (see Note 2, Accounting policies, Research external funding).

7 Cash flow statement

Tangible fixed assets
During the years ended December 31, 2005 and December 31, 2004 the purchase of equipment & other assets and expenditure on leasehold improvements, amounting to CHF 5,825,296 (USD 4,705,466) and CHF 6,220,395 (USD 4,915,338) respectively, was charged in full against revenue in the years in which it was incurred. Receipts arising from the disposal of equipment & other assets amounting to CHF 121,983 (USD 98,533) and CHF 645 (USD 510) respectively were credited in full to revenue in the years in which the proceeds were received.

8 Forward currency contracts

The Institute enters into forward currency contracts in order to hedge its exposure to fluctuations in foreign currency exchange rates in respect of anticipated expenditure in these currencies for periods of up to one year. The Fund enters into forward contracts in order to hedge its exposure to changes in foreign currency rates on its assets and liabilities denoted in foreign currencies. In 2005 and 2004 unrealized gains of CHF 2,141,695 (USD 1,625,081) and CHF 3,186,167 (USD 2,417,609) and unrealized losses of CHF 3,861,026 (USD 2,929,680) and CHF 3,328,507 (USD 2,525,614) respectively, arising from contracts open at year end are included in the statement of income and expenditure.

The values of the forward foreign currency contracts held by the Institute and the Fund translated at the relevant year-end exchange rates were as follows in units of thousand: -

	USD		*CHF*	
Description	***2005***	***2004***	***2005***	***2004***
Forward currency sales	191,262	175,228	252,064	199,250
Forward currency purchases	192,567	175,336	253,784	199,374

9 Lease commitments

	USD		CHF	
Year	***2005***	***2004***	***2005***	***2004***
2005	0	4,562,700	0	5,188,241
2006	4,292,188	3,517,880	5,656,675	4,000,184
2007	3,379,284	3,218,399	4,453,564	3,659,646
2008	3,002,869	2,775,963	3,957,481	3,156,557
2009	2,621,678	2,587,610	3,455,112	2,942,379
2010	2,523,965	2,476,718	3,326,326	2,816,281
2011-2015	8,375,713	5,546,859	11,038,349	6,307,357
2016-2020	262,260	281,232	345,626	319,791
Lease commitments not recorded in the balance sheet	24,457,957	24,967,361	32,233,133	28,390,436

10 Fire insurance values

	USD		CHF	
Description	***2005***	***2004***	***2005***	***2004***
Equipment and other assets	80,534,065	78,078,418	106,135,844	88,782,969
Leasehold improvements	34,792,202	31,500,226	45,852,643	35,818,907
Total insurance values	115,326,267	109,578,644	151,988,487	124,601,876

11 Liabilities to pension funds

	USD		CHF	
Description	***2005***	***2004***	***2005***	***2004***
Current liabilities	32,093	167,323	42,295	190,263

Institute-wide, the annual cost of the employer's contributions in 2005 and 2004 amounted to CHF 5,782,791 (USD 4,671,075) and CHF 6,096,280 (USD 4,817,290) respectively.

Listed below are all the pension schemes for which information is required under the early application of the revision of FER 16, which will be effective as from January 1, 2006. All amounts are in units of thousand: -

Name / Country	Surplus / (Shortfall) 31.12.05 USD	Share of Surplus / (Shortfall) 31.12.05 USD	Share of Surplus / (Shortfall) 31.12.04 USD	Change of Surplus / (Shortfall) 2005 USD	Contribu-tions 2005 incl change surplus / (shortfall) USD	Contribu-tions 2005 USD	Contribu-tions 2004 USD
Federated Pension Scheme (UK)	(82)	0	0	0	256	256	288
Vita Collective Insurance (CH)	N/A	0	0	0	376	376	461
Winterthur Collective Insurance (CH)	N/A	0	0	0	292	292	332

Name / Country	Surplus / (Shortfall) 31.12.05 CHF	Share of Surplus / (Shortfall) 31.12.05 CHF	Share of Surplus / (Shortfall) 31.12.04 CHF	Change of Surplus / (Shortfall) 2005 CHF	Contribu-tions 2005 incl change surplus / (shortfall) CHF	Contribu-tions 2005 CHF	Contribu-tions 2004 CHF
Federated Pension Scheme (UK)	(109)	0	0	0	316	316	365
Vita Collective Insurance (CH)	N/A	0	0	0	465	465	583
Winterthur Collective Insurance (CH)	N/A	0	0	0	362	362	420

The Federated Pension Scheme as described above has been accounted for as a defined benefit scheme in accordance with Swiss GAAP FER16 as from 2002. Employer contributions are fixed on an annual basis. It is the employer's responsibility to finance any potential shortfall of the scheme. However, there is no requirement to provide shortfall financing at the current time.

The underlying actuarial assumptions, used in the calculation are based on current economic circumstances and tax exemption status, are as follows: -

Description	***2005***	***2004***
Discount rate	4.90%	5.35%
Expected rate of return	7.00%	6.60%
Annual increase of future salaries	3.50%	3.60%

An actuarial valuation is carried out triennially and in addition, valuations in accordance with IAS19 are carried out annually.

Vita Collective Insurance discloses a cover ratio of approx 104%; detailed amounts however are not yet available. The total surplus is attributed to the scheme and not to the employer.

The Winterthur Collective Insurance does not disclose any figures on surplus or shortfall. All risks (old age, disability, death benefits) are insured with Winterthur Life, which also invests the respective assets independently. As at December 31, 2005, the scheme does not have a shortfall and there is therefore no requirement to provide shortfall financing.

Branches and offices with defined contribution schemes are located in Belgium, Brazil, Sweden and the United States of America. The branches in Australia and the United Kingdom are registered employers with the local university pension schemes, which set the level of contributions based on the advice of the schemes' actuaries. In view of the size of the schemes and the Institute's limited participation in the management of the schemes, the two university schemes are treated as defined contribution schemes. The contributions are calculated as a percentage of the insured salary. No obligations or benefits exist versus these schemes.

12 Directors' emoluments

The members of the Institute's Board of Directors constitute all of the Board of Directors of the Fund.

Emoluments, consisting of (i) Directors' Fees and (ii) Salary, pension and other benefits, were paid by (a) the Institute and Ludwig Group Inc, a subsidiary company, and (b) the Fund to the members of the two respective Boards as follows: -

	USD		*CHF*	
Description	***2005***	***2004***	***2005***	***2004***
Directors' Fees	304,621	303,216	377,120	383,720
Salary, pension and other benefits	1,416,041	1,357,996	1,753,059	1,718,543
Total emoluments	1,720,662	1,661,212	2,130,179	2,102,263

The Chairman of the two Boards, the Chief Executive Officer and the President of the Institute received Salary, pension and other benefits but did not receive Directors' Fees.

The remaining members of the two Boards received Directors' Fees but did not receive Salary, pension and other benefits.

The remuneration of the two Boards of Directors, the Chairman of the two Boards, the Chief Executive Officer and the President of the Institute are subject to review by both the Institute Shareholders' Compensation Committee and the Institute Board Compensation Committee, which were established in 1998. Recommendations made by the Shareholders' Compensation Committee set the outside limits of compensation which the Boards of Directors establish for the Chairman of the Boards, the Chief Executive Officer, the President of the Institute and for the members of the Boards.

At December 31, 2005 and 2004, there were eleven members respectively of both the Board of Directors of the Institute and the Fund.

13 Value added tax

The Institute is registered for value added tax in Switzerland.

In September 2004, the Federal Tax Administration carried out an audit at the Institute's Zurich office. In an informal report, the Federal Tax Administration questioned the method used by the Institute in calculating the reduction of the input tax for the years 2000 to 2004.

The report set out three different methods to calculate the input tax reduction with claims ranging for 2003 - the year audited in detail - between CHF 889,937 (USD 782,637) and CHF 929,802 (USD 817,696).

In May 2005 the Federal Tax Administration revised their initial position and invoiced the Institute for a total amount of CHF 1,739,606 (USD 1,319,983) with amounts ranging between CHF 301,866 (USD 229,051) and CHF 374,404 (USD 284,091) for the years 2000 to 2004.

The Institute's management continues to be not in agreement with these calculations and its tax advisors wrote to the Federal Tax Administration in June 2005 setting out again the Institute's position. The Federal Tax Administration has not, as yet, responded to this letter.

In the opinion of management, based on professional advice received, the Institute expects a further substantial reduction in the claim by the Federal Tax Administration. However, taking account of the developments that took place in 2005, for the sake of prudence, a provision of CHF 1,205,000 (USD 914,333) has been included in the financial statements 2005, whereas no accrual was made in 2004.

14 Related party transactions

Effective January 1, 1996, the Institute and the Fund entered into administrative service agreements with The Ludwig Group Inc. (LGI), a wholly owned subsidiary of UTI.

Fees paid by the Institute and the Fund under the service agreements including occupancy related costs amounted to CHF 3.8 Mio (USD 3.1 Mio) in 2005 and CHF 3.7 Mio (USD 2.9 Mio) in 2004.

Payables in favor of LGI by the Institute and the Fund as at December 31, 2005 and December 31, 2004 amounted to CHF 996,000 (USD 756,000) and CHF 882,000 (USD 776,000) respectively.

Future minimum rental payments in favor of LGI as at December 31, 2005 and December 31, 2004 amounted to CHF 3.6 Mio (USD 2.7 Mio) and CHF 3.5 Mio (USD 3.1 Mio) respectively.

15 Expenditure analysis

For fiscal reporting purposes, expenditure is analyzed between programme service expenditure, management and general expenditure and fundraising expenditure. For the year 2004 (the latest year where analysis data is currently available), CHF 112,116,273 (USD 88,594,447) were reported as programme service expenditure, CHF 21,502,286 (USD 16,991,139) as management and general expenditure, and CHF 1,289,781 (USD 1,019,187) as fundraising expenditure on a consolidated basis.

In 2003 CHF 110,406,110 (USD 80,424,031) were reported as programme service expenditure, CHF 20,465,577 (USD 14,907,909) as management and general expenditure, and CHF 1,562,175 (USD 1,137,948) as fundraising expenditure on a consolidated basis.

16 Reclassifications

Certain reclassifications have been made to prior year amounts to conform to the current year presentation.

Performance Report

Purposes of the organization

The purpose of the Ludwig Institute for Cancer Research is to originate and conduct incisive long-range research programs to be carried out on a continuing basis in conjunction with hospitals in established medical centres, directed to the ultimate goal of controlling and eradicating cancer.

The Institute is a Swiss not-for-profit organization with around 900 scientists, clinicians, students and support staff in various countries who are focused on multiple aspects of basic and clinical cancer research, including cancer genetics and genomics, tumor immunology, and cell growth and differentiation.

The Institute's research activities are organized through 9 Branches located in 7 different countries.

Each Branch leases space, has its own Ludwig Institute staff and functions in close association with a local university and a not-for-profit hospital. A number of affiliated individual investigators and laboratories complement the Institute's Branch network and extend its global reach.

The Institute does not make grants and contributions to others. Instead, it applies its resources to its own cancer research activities.

The Institute continued to be very successful in attracting external funding to support its core research programs. In 2005, the Institute received CHF 19.4 million (USD 15.4 million) from industrial, philanthropic and government sources. In addition, external funding for fellowships and studentships amounting to CHF 14.5 million (USD 11.5 million) was taken to income in 2005. The total amount received of CHF 33.9 million (USD 26.9 million) was 11.7 % (CHF) and 10.7 % (USD) higher than the 2004 amount received of CHF 30.3 million (USD 24.3 million), primarily due to higher government and fellowship grants. Research external funding income represented 27.1% of the total medical research related expenditure during 2005.

The Institute is committed to translating its basic research discoveries into therapeutic practices and is an active sponsor of its own clinical trials.

Managing bodies and Senior staff

The Statutes and By-laws of the Institute determine the responsibilities and the authority of the following organs of the company:

- the Board of Directors
- the Management, comprising the Executive Officers, and
- the Branch Directors.

The Board is elected at the General Meeting of Shareholders held each year in June for a one-year term of office. The members of the Institute Board of Directors are automatically members of the Board of Directors of LICR Fund Inc.

The individuals who served as members of the Board of Directors of both the Institute and the Fund in 2005 were as follows: - Mr R Palmer Baker Jnr. (Chairman); Mr Alfred Berger; Mr Georges-André Cuendet; Mr Olivier Dunant; Mr John D. Gordan III; Dr Adolf E. Kammerer; Mr Pierre Languetin; Mr Edward A. McDermott Jnr.; Dr Lloyd J. Old; Sir Derek Roberts and Prof Jane Royston.

The Executive Officers of the Institute comprised its management and consisted of the President; the Institute Director; the Associate Directors; the Chief Financial Officer and the Secretary to the Board of Directors. These posts were held as of December 31, 2005 by the following individuals: -

President	Mr Edward A. McDermott Jnr.
Institute Director	Dr Lloyd J. Old
Associate Director of Clinical Investigations	Dr George D. Demetri
Associate Director of Intellectual Property and Licensing	Dr Jonathan Skipper
Associate Director of Laboratory Investigations	Dr Richard Kolodner
Associate Director of Programs	Dr Andrew Simpson
Chief Financial Officer and Secretary to the Board	Mr Richard D. J. Walker

The Executive Officers were supported by the Directors of the following Administration Offices: -

Office of Academic Review	Dr Ellen Puré
Office of Clinical Trials Management	Dr Eric Hoffman
Office of Communications	Dr Sarah White
Office of Information Technology	Dr Victor Jongeneel
Office of Intellectual Property	Dr Jonathan Skipper

The Executive Officers and Directors of the Offices are all employed on open and rolling contracts with varying notice periods.

The Institute's By-Laws were revised in December 2005.

The Institute has a Scientific Advisory Committee that provides advice to the President and the Executive Officers on scientific matters as well as on the scientific staff review process. The secretary to the Scientific Advisory Committee in 2005 was Dr. A. Munro Neville.

The Institute effects its research activities primarily through its Branches. These are long-term arrangements and all of the Branches were founded between 1972 and 1991. Branches are managed by a Branch Director, who is responsible for the Branches' scientific program and for all Branch administrative arrangements.

The Branch Directors who were in post during 2005 were: -

Brussels Branch	Dr Thierry Boon
Lausanne Branch	Dr Jean-Charles Cerottini
London Imperial College Branch (to August 2005)	Dr Paul J. Farrell
London University College Branch	Dr. Xin Lu
Melbourne Branch	Dr Antony W. Burgess
New York Branch	Dr Lloyd J. Old
San Diego Branch	Dr Webster K. Cavenee
Sao Paulo Branch	Dr Ricardo R. Brentani
Stockholm Branch	Dr Ralf F. Pettersson
Uppsala Branch	Dr Carl-Henrik Heldin

All Branch Directors hold Member appointments with the Ludwig Institute and as such have five-year rolling contracts.

Various Executive Officers and Branch Directors hold academic and senior executive positions within the host university and hospital organizations and other scientific institutions with which the Ludwig Institute is associated.

Ludwig Institute for Cancer Research

Results of work on Institute research programs in 2005

Scientific results and publications

During the past year, an LICR-sponsored Phase I clinical trial of a monoclonal antibody, mAb 806, was initiated to examine its tumor targeting ability and safety profile. The mAb 806 antibody targets the epidermal growth factor receptor (EGFR), which promotes cancer cell growth and is linked to over 50% of all cancers of epithelial cell origin. A pharmaceutical company has recently brought to market an antibody therapy (cetuximab) that effectively benefits patients by targeting EGFR, but this therapy has side-effects from targeting normal liver and skin cells. LICR has shown, in preclinical investigation, that mAb 806 does not target normal liver and skin cells and thus would not be expected to induce side-effects. Additionally, several small molecule inhibitors of EGFR have been developed or are in clinical testing from other biopharma firms. However, resistance to these inhibitors remains a major clinical problem limiting their efficacy.

Three publications from LICR investigators were featured on the front covers of prestigious science journals during 2005. A micro array analysis identifying early changes in the intestine and esophagus, which could be used to diagnose Barrett's disease (a risk factor for adenocarcinoma of the esophagus), was featured on the front cover of the American Association for Cancer Research's journal, *Cancer Research*. Two publications were featured on the front covers of journals from the Nature group, one characterizing the details behind the regulation of neural stem cell differentiation, which is likely to have parallels in cancer stem cell differentiation, was featured in *Nature Neuroscience*, while the other, discovering a new mechanism for segregating chromosomes, was featured in *Nature Cell Biology*. Additionally, findings from the discovery of the primary mutation causing polycythemia vera, a myeloproliferative disease characterized by the excessive production of red blood cells, were featured on the front cover of *The American Society of Hematology Education Program Book, 2005*.

The Ludwig Institute for Cancer Research is committed to prompt and active dissemination of its research results. In the year 2005, LICR investigators published 366 scientific papers in recognized peer-reviewed journals.

The publication record by Branch is as follows: -

Brussels	37
Lausanne	46
London Imperial College	3
London University College	35
Melbourne	56
New York	41
San Diego	57
Sao Paulo	33
Stockholm	17
Uppsala	41
Total	366

Clinical Trials

As part of its program of clinical discovery in 2005, 33 trials were open to patient accrual and a total of 150 patients were enrolled. Ethics Committee approval was received for ten trials. The Institute had 17 active Investigational New Drug (IND) applications (USA) and two Investigational Medicinal Product Dossiers (EU).

Patents

The Institute and co-owners filed approximately 45 new priority, continuation, continuation-in-part or divisional patent applications during 2005. On a cumulative basis, about 1,000 different patent applications and a further 2,500 regional and national patent filings have been made since 1990.

About 50 patents including national patents were issued to the Institute and co-owners during 2005. On a cumulative basis, more than 1,100 patents have been issued to the Institute and co-owners. About ¾ of these patents are currently considered active, i.e. the patents have not expired and will continue to be maintained by the Institute at the next renewal.

The analysis of active patents by branch is as follows:

	Priority		Total including national patents	
	2005	**2004**	**2005**	**2004**
Brussels	34	34	451	418
Lausanne	4	4	18	18
London Imperial College	1	1	2	1
London University College	5	5	60	56
Melbourne	11	11	67	52
New York	23	20	108	88
San Diego	0	0	0	0
Sao Paulo	2	1	12	10
Stockholm	1	2	25	8
Uppsala	4	4	48	46
Affiliates/inventors from several Branches	18	17	138	110
Total	103	99	929	807

Material Transfer Agreements

The Institute entered into 571 material transfer agreements during 2005. These were mainly with academic institutions (549 agreements) whereby the Institute supplied reagents free of charge to the academic community while 22 material transfer agreements were entered into with commercial organizations. One agreement may cover several reagents.

The material originated from the following locations: -

	2005	**2004**
Brussels	28	70
Lausanne	17	34
London Imperial College	5	11
London University College	74	67
Melbourne	59	56
New York	23	16
San Diego	128	32
Sao Paulo	4	3
Stockholm	3	1
Uppsala	122	161
Affiliates/inventors from several Branches	108	121
Total	571	572

Licensing / Royalties

In accordance with the objective of making scientific discoveries available to the general public, the Institute enters into agreements with commercial organizations having the substantial financial and management resources necessary and/or which may own key complementary technologies necessary to develop Institute discoveries for therapeutic purposes.

The Institute was party to 121 license, sublicense, option and evaluation agreements with commercial organizations at the beginning of 2005. A further 15 agreements were signed during the year while 17 agreements expired or were terminated with the result that at year end the portfolio comprised 119 agreements.

A large number of these agreements are with companies selling Institute reagents for laboratory research purposes or with companies using Institute developed reagents for in-house research purposes only. A total of 31 of these agreements relate to the development of therapeutic products. Two agreements relate to a therapeutic product presently on the market, GM-CSF (granulocyte macrophage colony stimulating factor), while the rest relate to products at various stages of development from pre-clinical testing to Phases I, II and III clinical trials of the products.

GM-CSF is a broad stimulator of haematologic progenitor cells for patients with low white blood cell counts and has been licensed to Schering-Plough Corp. and Immunex, Inc. and subsequently to Schering AG by Research Corporation Technologies Inc. (RCT), Tucson, Arizona under an Invention Administration Agreement with the Institute. GM-CSF was co-invented with The Walter and Eliza Hall Institute for Medical Research, Melbourne.

Sales of therapeutic products based on GM-CSF were in the order of USD 75 million for 2004. These products are currently sold by Schering-Plough Corporation under the trademark Leucomax and by Schering AG through its wholly owned subsidiary company Berlex, Inc. under the trademark Leukine.

Sales of other products licensed from the Institute for research and diagnostic purposes were in excess of USD 4 million.

The gross income to the Institute from license fees and royalty income totaled USD 7.6 million for 2005 and USD 3.9 million after co-owner and inventor sharing.

The Institute is also working to facilitate the start-up of new companies using Institute-owned technology as appropriate.

Human Resources

An important aspect of the Institute's developing programs is the training of outstanding young scientists who will in time join an emerging new generation of cancer investigators. During the year, 29 PhD students started and 42 completed their postgraduate training with the Ludwig Institute.

At December 31, 2005, the Institute was acting as sponsor to 133 postdoctoral fellows and 142 PhD students.

The quality of the Institute's science continued to be internationally recognized. In the last year, the following distinctions and awards were received: -

- Dr. Thomas Perlmann (Stockholm Branch) was elected to the 50-member Nobel Assembly responsible for electing the Nobel Prize laureates in Physiology or Medicine;
- Dr. Benoît Van den Eynde (Brussels Branch) was awarded the honor of presenting a cycle of conferences for the Francqui Chair, Louvain University, Brussels;
- Dr. Antony Burgess (Melbourne Branch) was awarded the Leach Lecture Medal;
- Dr. Serhiy Souchelnytskyi (Uppsala Branch) was awarded a Roche Award by the Human Proteome Organization (HuPO) Conference.

Formal academic review to assess the quality and impact of the research performed by LICR staff members was conducted in 2005 by the Scientific Advisory Committee and Scientific Directorate.

Three staff members underwent external review for Associate Member rank and were promoted:- Dr. Stefan Constantinescu (Brussels Branch), Dr. Weisan Chen (Melbourne Branch) and Dr. Ian Davis (Melbourne Branch).

One staff member, Dr. Andrew Clayton (Melbourne Branch), underwent review for Assistant Member rank and was appointed.

One staff member, Dr. Karen Arden (San Diego Branch), underwent review for Senior Investigator rank and was appointed.

One staff member, Dr. Brian Stevenson (Office of Information Technology, Lausanne), underwent review for Associate Investigator rank and was appointed.

Three staff members underwent review for Assistant Investigator rank and were appointed: -
Dr. Christian Iseli (Office of Information Technology, Lausanne), Dr. Zhanqi Liu (Melbourne Branch) and Dr. Carina Hellberg (Uppsala Branch).

Proposal to carry forward excess of income over expenditure

The Statutory and Consolidated Financial Statements of the Ludwig Institute for Cancer Research as of December 31, 2005, together with the Reports of the Statutory Auditors and the Group Auditors, KPMG Fides Peat, dated April 7, 2006, are hereby submitted to the General Meeting of Shareholders.

The balance sheet of the Consolidated Financial Statements shows total assets of CHF 1,754,587,247 and the statement of income and expenditure shows an excess of income over expenditure for the fiscal year of CHF 21,181,369.

The balance sheet of the Statutory Financial Statements shows total assets of CHF 42,794,371 and the statement of income and expenditure shows an excess of income over expenditure for the fiscal year of CHF 4,522,253.

In accordance with Article 8 of the Statutes, the Board of Directors proposes that the Shareholders of the Institute authorize the carrying forward of the accumulated available excess of income over expenditure as at December 31, 2005 in the amount of CHF 15,621,240. In this regard, it is noted that according to Article 8 of the Statutes of the Institute, no distribution may be made to the Shareholders.

Ludwig Institute for Cancer Research

On behalf of the Board of Directors

R. Palmer Baker Jr.
Chairman

May 8, 2006