

Center for Cancer Research

The Center for Cancer Research (CCR) was founded in 1974 by Nobel Laureate and MIT Professor Salvador Luria. It is one of eight National Cancer Institute (NCI)-designated basic (nonclinical) research centers in the US. CCR's mission is to apply the tools of basic science and technology to understanding how cancer is caused, progresses, and responds to treatment. The CCR is both a physical entity and an organizing body for MIT's cancer research community-at-large, which is comprised of over 500 researchers across the Institute. It grows out of MIT's proven strengths in molecular biology, genetics, cell biology, and immunology, and stimulates extensive collaboration among the Institute's schools. The Center is comprised of 33 member laboratories from four departments.

The year 2006–2007 marked the beginning of a major shift in CCR's 30-year history. In September 2006, MIT president Susan Hockfield announced a major campus development program that included plans for a new Center for Cancer Research facility. The new facility, which will house CCR's biologists and a dozen MIT engineers working on the frontiers of cancer research, signals a major effort to change the way that cancer research is approached. While the facility is still in its early planning stages, the possibilities are exciting and the kinds of results that new collaborative projects between CCR's biologists and engineers can have can be seen in such projects as the Center for Cancer Nanotechnology Excellence, started in 2005.

In the technology-rich environment of MIT, the CCR is uniquely poised to bring the best science and the best minds to bear on cancer and cancer treatment. The Center is committed to carrying forward one of MIT's proudest traditions: the transfer of basic science out of the laboratory and into the world, where innovation has its real impacts.

Research Highlights and Ongoing Activities

Collaboration is critical to CCR's approach to research, and the broad range of disciplines represented among our membership has lent itself well to healthy and fruitful collaborations over the year. Indeed, this breadth of talent in science and engineering has been recognized in the form of multi-investigator grants from NCI and others. In addition to a grant in the Integrative Cancer Biology Program (ICBP) funded in 2004 and an NCI Center of Cancer Nanotechnology Excellence funded in 2005, the Center received new collaborative project funding in 2006–2007 including:

- A \$20 million dollar gift from the Ludwig Fund, a major philanthropic foundation primarily focused on cancer research, to establish the Ludwig Center for Molecular Oncology, administered through the CCR. The Ludwig Center is led by CCR member [Robert Weinberg](#) of the Whitehead Institute, who is joined by CCR director Tyler Jacks, Richard Hynes, Frank Gertler, Jacqueline Lees, and David Housman (all CCR members from E17/18).
- NCI funding of a \$6 million, multiyear grant to study tumor cell microenvironment in 2006 with Richard Hynes as the principal investigator with coinvestigators Tyler Jacks, CCR director; Robert Weinberg of the Whitehead Institute; and Ralph Weissleder of Massachusetts General Hospital.

- Funding from Alnylam Pharmaceuticals, Inc., a leading RNAi therapeutics company, who signed an agreement to sponsor a five-year research program at CCR focused on the delivery of RNAi therapeutics. Robert Langer and Daniel Anderson are the coinvestigators of the research program and Alnylam will provide research funding for approximately ten post-doctoral researchers annually over the five-year term.

In addition, over the last year CCR members from the MIT community have made significant contributions in the following areas of research, which have broad impact on cancer research:

Systematic analysis of cancer pathways. In pioneering work in the emerging field of systems biology, three MIT teams have used complex network analysis to bring important new insights into pathways critical to tumor development. Focused on processes related to the control of cell death, signal transduction, or the response to DNA damage, these groups have used a powerful combination of proteomic and genomic analysis combined with computational and mathematical modeling to begin to unravel the intricate complexities of these key cancer pathways.

Regulating gene expression in embryonic stem cells. Two papers from the Richard A. Young and Rudolf Jaenisch laboratories and their collaborators have pinpointed the location of key regulators of gene expression across the genome in embryonic stem cells. Using stem cells of both mouse and human origin, they have demonstrated that the class of Polycomb transcriptional repressors bind to the control regions of a wide range of developmentally important genes in stem cells, keeping them silent. In this way, programs of gene expression associated with specific developmental programs required later in development are switched off in the stem cell. The new insights shed light on the mechanisms of pluripotency of embryonic stem cells and may lead to new methods to induce stem cells to differentiate into cells of specific lineages for therapeutic purposes.

Tiny new tools in the anti-cancer arsenal. Research from the laboratory of Robert Langer has led to the development of a novel class of targeted nanoparticles for cancer therapy. The Langer group has developed nanoscale smart bombs engineered to deliver their payload of chemotherapeutic compounds directly to cancer cells. Using a targeting molecule engineered to specifically bind to a protein overproduced on the surface of prostate cancer cells, they have been able to direct the binding and uptake of nanoparticles harboring the anticancer drug to human cancer cells growing in mice, leading to significantly improved tumor responses. This work may herald the arrival of a powerful new tool in the battle against cancer.

MicroRNAs and development. A recently discovered class of gene regulators, termed microRNAs (miRNAs), are now appreciated to be critical for the control of a high percentage of cellular genes. Using a very sensitive method of miRNA cloning, the group of Phillip Sharp has profiled the expression of this class of molecules during the development of white blood cells. They have shown that certain miRNAs are dynamically regulated during the transitions as cells develop along these lineages, suggesting these miRNAs participate in the finetuning of gene expression program required for cells to adopt specific fates.

Probing mammalian cells with RNAi. Groups from the Whitehead and Broad Institutes and their collaborators have constructed and tested a large toolkit for probing the function of mammalian genes. Using a virus-based system, they have built an enormous library of inhibitory molecules, termed RNAi vectors, which can infect cells and shut down the function of individual genes of interest. This powerful new tool can be used to probe the genes required for normal cell behaviors and for studying the genes that contribute to cancer cell growth and the response of cancer cells to chemotherapy and radiation.

Keeping chromosomes together. Angelika Amon's group has dissected the molecular controls that regulate when chromosomes are held together and when they are allowed to separate during germ cell development. A breakdown in this process in humans can lead to chromosome missegregation, aneuploidy, and severe defects during embryonic development. Using the experimental organism baker's yeast, Dr. Amon and her group have uncovered the mechanism for the step-wise unzipping of the chromosomes at a critical juncture in formation of haploid germ cells.

Putting the anticancer police back on patrol. The laboratory of Tyler Jacks and its colleagues have shown that restoration of the anticancer pathway controlled by a key tumor-suppressor gene can lead to dramatic tumor regression in vivo. Using a genetically engineered mouse model of cancer, the Jacks group was able to switch on the function of the p53 tumor-suppressor gene in fully established cancers. Restoration of p53 function led to rapid cell death or arrest of cancer cell proliferation. These results provide proof-of-principle for the effects of restoring p53 function in human cancers, where the pathway is disrupted in the majority of cases.

Cancer cells deal with DNA damage differently. The groups of Michael Yaffe and Jacqueline Lees have provided evidence that cancer cells may differ from normal cells in the dependency on a key DNA damage response pathway, possibly revealing a specific vulnerability of cancers to chemotherapy. By manipulating the gene p38MAPK/MK2 in normal cells or cells lacking the key tumor suppressor p53, they show that p53-mutant cells are selectively dependent on p38MAPK/MK2 when challenged with the chemotherapeutic agent doxorubicin. Thus, inhibition of p38MAPK/MK2 might widen the therapeutic window for conventional chemotherapy, which would allow lower doses of chemotherapy to be used and reduce harmful side effects.

Mediating metastasis. Tumor metastases account for 90 percent of cancer deaths, but relatively little is known about the molecular control of this process. Recent work from the laboratory of Robert Weinberg has shown that a key developmental regulator, termed Gooseoid, can promote metastatic spread in cell-based model of the disease. Gooseoid is involved in a critical transition in early embryogenesis in which cells migrate from one site of the embryo to another. Reactivation of this developmental program in cancer cells may likewise aid in their spread throughout the body.

Other Events

In addition to its strengths in basic research, CCR performs an important role in training future researchers in biomedical science, including undergraduate and graduate students and postdoctoral and clinical fellows. The faculty of the Center fulfills critical roles in the educational programs of the Department of Biology. Extensive collaborations exist with medical schools, hospitals, and the biotechnology/pharmaceutical industries. Thus, the research in CCR has a major impact both on the fundamental understanding of cancer and on its translation to and from the clinical arena.

To further the Center's goal of bringing cutting-edge research to the cancer research community in the Boston area, on June 15, 2007, CCR will host its sixth annual scientific symposium, Systems Biology of Cancer. President Susan Hockfield will make closing remarks to over 1,100 individuals from MIT, other area academic institutions, and industry. The symposium features speakers from academia and industry, including Lee Hood, Morag Park, Bruce Ponder, Joe Nevins, Erin O'Shea, and Stephen Friend.

Faculty Growth

During this year CCR welcomed Michael Hemann. Professor Hemann came to MIT from Cold Spring Harbor Laboratories. He is a very bright and highly imaginative young scientist with an outstanding track record throughout his research training. His experimental plan uses cutting-edge methods in molecular genetics and modeling human cancer in the mouse. Moreover, his research is focused on one of the most pressing problems in oncology: the basis of chemotherapeutic sensitivity and resistance. Professor Hemann's laboratory has recruited two outstanding graduate students and one postdoctoral fellow, and they have successfully initiated several cell-based and whole animal screens. The early data look very promising.

Internal CCR Faculty Awards and Honors

Angelika Amon received the 2007 American Society for Biochemistry and Molecular Biology Amgen Award and the School of Science Prize for Excellence in Undergraduate Teaching.

Michael Hemann received the 2007 Rita Allen Foundation Scholars award.

Richard O. Hynes, Daniel K. Ludwig professor for cancer research and Howard Hughes Medical Institute investigator, was named scientific governor of the United Kingdom's largest charity, the Wellcome Trust. Professor Hynes was also the recipient of the 2007 E. B. Wilson Medal of the American Society of Cell Biology.

Phillip Sharp received the 2006 Inaugural Double Helix Medal for Scientific Research from Cold Spring Harbor Laboratory, a 2006 honorary doctorate from Ripon College, the 2006 American Association for Cancer Research Irving Weinstein Distinguished Lectureship Award, and the 2007 Winthrop-Sears Award from the Chemists' Club of New York.

Research Funding

Funding support for CCR has grown steadily in recent years and is currently at an all-time high. CCR has maintained its designation as an NCI-designated Cancer Center following the successful competitive renewal of its grant last year. Financial support for research in the Center comes from many sources. The core of this support, which provides much of the funds for administration, core research facilities (i.e., biopolymers, flow cytometry, specialized laboratories, and partial support for new faculty), is a center core grant from NCI. In addition to the core grant, CCR's resident faculty have a total of 59 fully funded projects (39 grants, 20 fellowships). This competitive support comes largely from the National Institutes of Health and the Howard Hughes Medical Institute,

industry, and a variety of foundations supporting research in particular disease areas, including the American Cancer Society and the Hereditary Disease Foundation. This latter type of support is particularly valuable for starting projects that later mature into federally funded grants. CCR's success in attracting grant support is a reflection of the excellence of the research and educational activities of its faculty members. The FY2007 research volume was approximately \$22.4 million, which does not include support from the Howard Hughes Medical Institute or the Ludwig Center funds.

Tyler Jacks

Director, Center for Cancer Research

David H. Koch Professor of Biology

Investigator, Howard Hughes Medical Institute

More information about the Center for Cancer Research can be found at <http://web.mit.edu/ccr/>.