



SAMUEL WAXMAN CANCER RESEARCH FOUNDATION
Institute Without Walls

Lung Cancer Research 2007-2008

Lung cancer is the most common cause of cancer-related death, annually causing over 160,000 deaths in the US and over a million deaths world wide. Treated by surgery, radiation therapy and chemotherapy, it is also one of the most intractable, with a 5 year survival rate of 14%. Below are highlights of two SWCRF sponsored research projects on lung cancer treatment and prevention.

PHASE I AND II CLINICAL TRIALS OF DRUGS TO PREVENT AND FIGHT LUNG CANCER – Dr. Ethan Dmitrovsky, Andrew G. Wallace Professor of Medicine and Pharmacology, American Cancer Society Professor, Dartmouth Medical School

Vitamin A derivatives called retinoids are widely used in cancer therapy and chemoprevention, but they are not effective against lung cancer. Dr. Dmitrovsky is exploring the promising use of a non-standard retinoid, or rexinoid, which appears to circumvent the cell mechanism that causes resistance to retinoids. The rexinoid being studied is already approved by the FDA, which would accelerate the process of changing patient treatment if the drug is effective. The Foundation has supported this work since its original funding of tissue studies that showed that the rexinoid had anti-cancer effect in lung cancer tissues and was worth investigating. Patients with advanced lung cancer and no other treatment options showed a positive response in a Phase 1 clinical trial testing the combination of rexinoid treatment with another FDA-approved drug, Tarceva. The research is now in Phase II clinical trials, in conjunction with Dr. Waxman's team, where the effectiveness and safety of the multi-drug regimen is being evaluated in lung cancer patients. In addition to offering a new approach to treatment, this work shows promise as a means by which lung cancer may be prevented. The significance of this line of research is demonstrated by the fact it was the basis on which Dr. Dmitrovsky was awarded a highly competitive American Cancer Society Professorship this year.

NEW WAY TO FIGHT AND PREVENT LUNG CANCER IDENTIFIED - Dr. Reuben Lotan, Deputy Division Head for Research, Cancer Medicine; M.D. Anderson Cancer Center

Genes produce proteins that tell a cell how to behave. Dr. Lotan's lab identified a gene which produces a lung-specific tumor suppressor protein. They demonstrated that the absence of this protein is associated with a higher level of cancer development and with an inflammatory environment in the lung that promotes cancer development. The laboratory has shown that use of an already-approved anti-inflammatory asthma drug reduced tumors in mice that lacked the protective protein. Once again, the use of a drug already approved by the FDA will accelerate the eventual implementation of this research, if further work supports a change in patient care. Controlling inflammation opens a new approach to prevention of lung cancer in addition to its treatment.



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Liver Cancer Research

Liver cancer is the third leading cause of cancer deaths world-wide. Among the most intractable of cancers, it has a 5 year survival rate of less than 10% in the United States. It is both more common and more deadly in developing countries. Surgery remains the primary treatment. Other therapies may improve quality of life, but can have significant side effects and do not offer a cure.

The Samuel Waxman Cancer Research Foundation played a key role in establishing the Mount Sinai Liver Cancer Program in 2005, which is now the leading center in the nation. Mount Sinai evaluates more new liver cancer patients than any other hospital in the US. Drawing on strengths both in treating patients and in basic molecular research, this program focuses on “translational research” designed to move lab research into improved patient care. To this end, they have recently led the first randomized clinical trial of a targeted molecular therapy for liver cancer with positive results (Llovet et al, NEJM 2008). In 2009, they will lead four international clinical trials. Between 2006 and mid 2008, the program has generated over 30 publications. Dr. Josep Llovet is Director of Research of this group, and is also Professor of Research at Hospital Clinic of Barcelona.

The Mount Sinai Liver Cancer Program also leads the HCC Genomic Consortium, an international collaboration funded in part by SWCRF. (HCC is hepatocellular carcinoma or liver cancer). Other participants include Dana-Farber/MIT-Broad Institute, Hospital Clinic of Barcelona and National Cancer Institute of Italy. They have outlined a research program to identify the distinctive genetic characteristics of liver cancer in patients with Hepatitis C and cirrhosis.

SWCRF-funded “revolutionary” breakthrough in treating liver cancer and in methods of basic medical research Dr. Llovet led a team whose work produced a breakthrough in how medical research on any surgically-treated disease can be conducted. During all surgery at any hospital, tissue samples are taken from the patient. The samples are preserved using formalin and embedded in paraffin. These samples constitute a pool of potential research material collected over decades. Investigation into the genetic causes of disease is one of the most exciting areas in medical research today. It has not been possible to conduct genetic research on these samples because of the method of preservation. Dr. Llovet’s team developed a way to do genetic analysis on these preserved tissues, opening up great possibilities for a broad variety of research.

Dr. Llovet’s team used this method to identify a genetic signature that indicates a liver cancer patient’s prognosis, so that appropriate steps can be taken in higher risk cases, such as targeted surveillance programs and personalized chemopreventive therapy. This study was published in New England Journal of Medicine in October 2008.



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Breast Cancer Research 2007-2008

Breast cancer is the most common cancer among women in the United States, other than skin cancer. The chance of a woman having invasive breast cancer at some point is about 1 in 8. It is the second leading cause of cancer death in women, after lung cancer.

IDENTIFYING A NEW WAY TO FIGHT BREAST CANCER: Although tamoxifen cuts the recurrence of breast cancer by half in post-menopausal women with estrogen sensitive breast cancer, it may be less effective in some pre-menopausal women with estrogen sensitive breast cancer. **Dr. Doris Germain (Mount Sinai Medical Center)** has explained how the presence of tamoxifen may amplify the effect of certain proteins that control cell growth. Her laboratory is now investigating an alternative approach for those pre-menopausal women and for all women resistant to tamoxifen, using two drugs which already have FDA-approval, fulvestrant (Faslodex) and bortezomib (Velcade). Because the drugs are already on the market, this research could lead more quickly to an exciting new anti-hormonal treatment for breast cancers which resist existing medicines.

PROMISING APPROACH TO PREVENTING BREAST CANCER: Vitamin A significantly inhibited the growth of some breast cancer cells in the laboratory, but not in clinical trial patients. **Dr. Lillian Ossowski and Dr. Eduardo Farias (both at Mount Sinai Medical Center)** demonstrated that the loss of effect was due to a decrease in Vitamin A receptors in the breast cancer cells and investigated ways to overcome that. They then studied the protective effect of a form of Vitamin A in mice genetically engineered to develop 2 different types of breast cancer. This derivative was more effective than Vitamin A, showing a significant reduction in the overall incidence of cancer and an increase in cancer-free survival.

IDENTIFYING HIGH RISK BREAST CANCER PATIENTS WITH A VERY POOR PROGNOSIS: Here is an exciting example of how the close collaboration in the *Institute Without Walls* speeds the pace of research by encouraging the application of insights gained in research on one kind of cancer to another kind of cancer. In studying how to predict the prognosis of breast cancer patients, **Dr. Julio Aguirre-Ghiso (Mount Sinai Medical Center)** is applying knowledge about genes that have been found to induce head and neck cancer cells to become dormant. He is investigating a particular gene to determine whether the level of activity predicts the breast cancer patient's condition in five years. Risk identification like this is critical to taking protective measures. This study correlated historical data about the genes in a tumor with information on a patient's actual disease activity. The next step is to investigate specifically how the gene determines cell behavior in order to identify where a drug can be applied to reprogram the cells to behave like normal cells.



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Melanoma Research 2007-2008

Melanoma is the deadliest of all skin cancers, and effective therapy in its later stages continues to be a formidable challenge. Surgery remains the primary treatment. Chemotherapy and available immunotherapy may improve quality of life, but have significant side effects and do not offer a cure.

CLINICAL TRIALS INVOKING AN EFFECTIVE IMMUNE RESPONSE IN HUMANS TO FIGHT MELANOMA – Dr. David Baltimore, Nobel Laureate, Robert Andrews Millikan Professor of Biology, California Institute of Technology; **Dr. James Economou**, Professor and Chief, Surgical Oncology, Deputy Director, Jonsson Comprehensive Cancer Center, UCLA

Nobel Laureate David Baltimore and Lili Yang demonstrated several years ago that, in mice, it was possible to engineer an immune response that effectively fought experimental tumors. A team composed of scientists at University of California at Los Angeles, California Institute of Technology, University of Southern California, University of Connecticut and Children's Hospital of Los Angeles is investigating whether it will be possible to invoke a comparable immune response in humans that will fight melanoma, using a groundbreaking gene therapy strategy. Because they are focused on turning on a particular gene, this method is expected to have many fewer side effects than currently available therapies. Their work ranges from basic biological research, through development of improved methods of analysis, to clinical trials involving patients with advanced melanoma. Based on data from early research funded by SWCRF, the team has obtained substantial additional funding for this ambitious project.

PHASE I AND II CLINICAL TRIALS OF POTENTIAL DRUGS TO FIGHT MELANOMA – Dr. Neal Rosen, Memorial Sloan-Kettering Cancer Center

Dr. Rosen's laboratory has identified a gene mutation which has been found in 80 percent of all melanomas and which drives tumor growth. The Foundation is funding investigation of compounds that target this mutation in order to prevent melanomas from growing. There are several Phase I and II clinical trials underway to determine safety, effectiveness and side effects in humans. The potential drugs being tested act on different parts of the chain of signals by which the mutation sends the cell instructions to behave like a cancer cell.

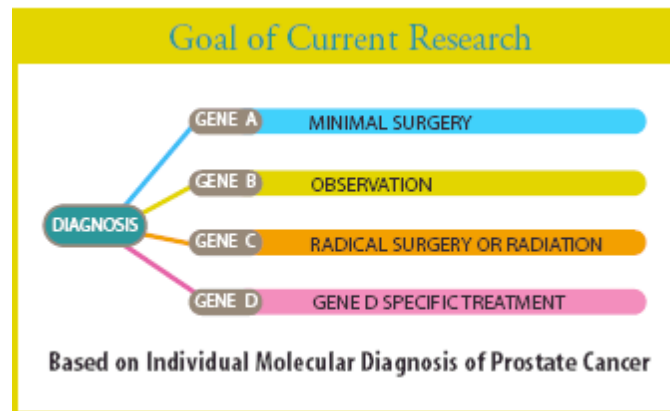


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Prostate Cancer Research 2007-2008

Prostate cancer is the most common type of cancer found in American men, other than skin cancer. 1 in 6 men will develop prostate cancer in their lifetime, and 1 in 35 will die of it. In 2008, the federal Agency for Healthcare Research and Quality surveyed the most common treatments and came to a frustrating and startling conclusion: it could not recommend one treatment as working better than any other for all men.

SWCRF funds research to identify an individual's most effective treatment based on a molecular level analysis of that person's specific tumor



Dr. Charles Sawyer of Memorial Sloan Kettering Cancer Center is developing ways to identify two common gene mutations that cause prostate cancer because targeted treatment would be different for cancer caused by different mutations. There are currently drugs available which target tumors with PTEN mutations, but they would not be effective against tumors caused by MYC mutations. Without the kinds of tests that Dr. Sawyer is working on, all prostate cancer patients are given the same drugs. One possible outcome of the research might be a blood test, comparable to the PSA test, which would catch cancer earlier and identify the genetic flaw for targeted treatment.

Dr. Sawyer's lab is also participating in promising clinical trials for a drug to help men who have developed resistance to the antiandrogen drugs commonly used to fight prostate cancer. The drug may delay progression of the cancer or possibly even induce a partial or complete remission.