



Spotlight on Research

Memorial Sloan-Kettering is dedicated to advancing the understanding of the biology and management of cancer through innovative programs in basic science and clinical research.



Robert Benezra

BREAST CANCER

Cell biologist **Joan Massagué** and colleagues identified a group of genes that may be responsible for breast cancer metastasis to the bone. The researchers inoculated mice with human metastatic breast tumor cells that suggested a poor prognosis based on their genetic profile and discovered a set of genes that work together to promote cancer spread to the bone. If one or more genes in this set was missing or expressed at low levels, the cells spread to the bone less aggressively.

Magnetic resonance imaging (MRI) is a highly sensitive screening tool that may detect breast cancers missed by mammograms in women who are at increased risk for developing the disease, according to a study led by medical oncologist **Mark E. Robson**. However, MRI yields a significant number of false-positive results, leading to additional exams and biopsies, which may have a negative psychological impact on women who are already anxious because of their elevated risk. Researchers reported that MRI should not be recommended to the general population at the present time because its specificity is not yet adequate, and the majority of abnormalities detected in average-risk women would turn out to be false positives.

Work by **Robert Benezra** and colleagues showed that targeting the proteins required for the formation of new blood vessels (a process called angiogenesis) was not sufficient to stop cell growth. The investigators created mouse models that have a genetic abnormality similar to that which is present in 25 to 30 percent of human breast cancers and engineered the mice to also be deficient in the protein Id, which is required to develop the blood vessels that tumors need to grow and spread. They then tested the ability of a drug called 17-AAG to attack the viable cells in these mice and found that tumor growth was completely inhibited in Id-deficient mice that received 17-AAG, indicating that two cell mechanisms must be disrupted in combination to suppress aggressive breast cancer.

CANCER GENETICS

A rare genetic syndrome, dyskeratosis congenita (DC), may hold the key to understanding a mechanism that causes premature aging, anemia, and cancer. Recreating DC in genetically modified “knockout” mice, cancer geneticist **Pier Paolo Pandolfi** and colleagues unexpectedly showed that DC is caused by a disruption in ribosome function and not by shortened telomeres, as previously hypothesized.



Pier Paolo Pandolfi

Kenneth Offit and colleagues at MSKCC and The Rockefeller University showed that brain tumors can develop in children in the rare instance that both parents carry mutations of the *BRC A2* gene, which has been linked to breast and ovarian cancers. The findings were the first to establish childhood brain cancers, predominantly medulloblastoma, among the diseases that can occur if both parents carry *BRC A2* mutations.

DEVELOPMENTAL BIOLOGY

Developmental biologists **Kathryn V. Anderson** and **Lee Ann Niswander** led a multi-institutional team of investigators in research that shed new light on the mechanisms of the hedgehog signaling pathway, which determines when and where cells grow during embryonic development and is linked to several types of cancer. They found that intraflagellar transport (IFT) proteins — which control the formation of hairlike extensions, or



Kathryn Anderson

cilia, on the surface of cells that mediate movement and sensation — are necessary for normal hedgehog signaling in mice.

CANCER VACCINES

Immunologists **Jedd D. Wolchok**, **Alan N. Houghton**, and colleagues developed



Alan Houghton (left) and Jedd Wolchok

a vaccine that dramatically extended the lives of dogs with canine malignant melanoma. Treatment with this vaccine, made from human DNA, increased the median survival for nine dogs with the disease from an expected 90 days to an average of 389 days. The vaccine is currently the focus of a clinical trial for patients with a high risk of melanoma recurrence.

IMAGING SCIENCES

Thoracic surgeons **Valerie W. Rusch** and **Robert J. Downey**, radiologist **Timothy J. Akhurst**, and colleagues demonstrated that positron-emission tomography (PET) scanning, which measures metabolic differences between cancer and healthy tissues, can detect the response to chemotherapy in patients with esophageal cancer. The researchers found that PET scans performed at the time of diagnosis were able to detect metastases that other imaging methods missed.

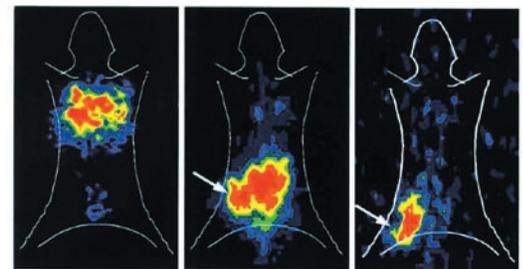
Researchers **Steven M. Larson** and **Juri G. Gelovani**, working with **Richard J. O'Reilly** and colleagues, developed a method to track the migration, survival, and function of transplanted T cells in mice. The cells were transduced with a reporter gene and labeled with

radioisotope tracers, then tracked using advanced imaging techniques.

IMMUNOLOGY

Investigators **Michel Sadelain**, **Renier J. Brentjens**, **Isabelle Rivière**, and colleagues developed a novel approach to instruct human T cells to recognize and kill cancer cells in mice. This is the first time that this approach, called adoptive immunotherapy, has succeeded using genetically targeted human T cells.

Work by investigator **David W. Golde** and colleagues provides new insight into how the body's defense cells are activated at sites of tissue injury. The researchers discovered that the laminin receptor protein regulates the granulocyte-macrophage colony-stimulating



MSKCC researchers used a gamma camera to produce images of T cells that have been tagged with radioisotope tracers as they are injected into a mouse (left) and migrate to and then attack a tumor in its leg (center and right).



Marcel van den Brink

factor (GM-CSF) signal by binding to and modulating the GM-CSF's receptor function. The researchers believe that laminin at the blood vessel wall binds to the receptor on two types of white blood cells, allowing GM-CSF to activate these cells as they enter the tissues.

Marcel R. M. van den Brink and several MSKCC collaborators demonstrated that treatment with interleukin-7 enhances the reconstitution of immune cells called T cells in mice that have received allogeneic stem cell transplants. For cancer patients who receive this type of transplant, most often for treatment of lymphoma or leukemia, the faster reconstitution of T cells could mean a shorter recovery period after the procedure.

LEUKEMIA

Using microarray technology, which allows researchers to study the expression of tens of thousands of genes simultaneously, researchers **Stephen D. Nimer**, **Agnès Viale**, and colleagues elucidated the role of the nuclear protein CCAAT/enhancer binding protein alpha (C/EBP α). This protein is involved in the differentiation of blood stem cells and is mutated in some cases of acute myelogenous

leukemia. Their analysis found that the level of C/EBP α activity ultimately affects whether a stem cell in the bone marrow becomes a white or a red blood cell.

LUNG CANCER

Peter B. Bach, **Colin B. Begg**, and colleagues developed a statistical tool to accurately predict which patients are at the highest risk of lung cancer. Using an individual's age, sex, and smoking history, they found that among smokers aged 50 to 69, the ten-year risk for developing lung cancer ranged from a low of less than 1 percent to a high of 16 percent — a finding that may help individuals decide whether to undergo lung cancer screening.

An anti-cancer agent designed to block the signals responsible for telling cancer cells to grow has shown promising results for patients with advanced non-small cell lung cancer. The double-blind, randomized study of the compound gefinitib (IressaTM) was led by medical oncologist **Mark G. Kris**. The compound,

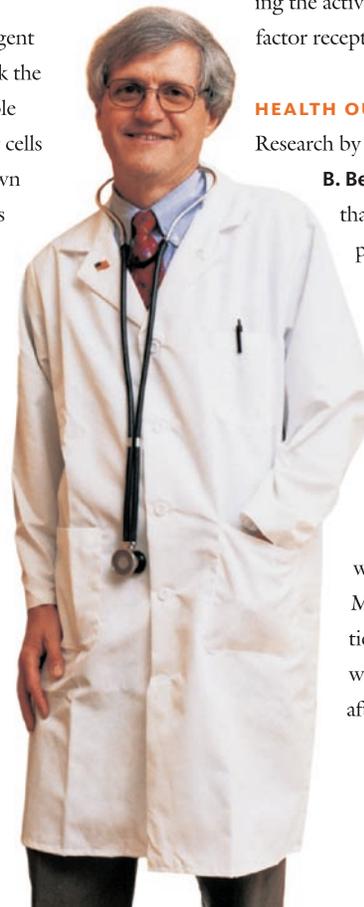
initially developed at MSKCC and approved in 2003 by the U.S. Food and Drug Administration, targets and blocks an enzyme called tyrosine kinase, part of the epidermal growth factor receptor. Found on the cell surface, the epidermal growth factor receptor is overexpressed in many non-small cell lung cancers.

A study by investigator **Vincent A. Miller** suggested that a drug called erlotinib (TarcevaTM) has promising activity in patients with bronchioloalveolar cell carcinoma, a type of non-small cell lung cancer generally considered to be resistant to chemotherapy. Erlotinib is a small molecule that also works by blocking the activity of the epidermal growth factor receptor tyrosine kinase.

HEALTH OUTCOMES

Research by **Deborah Schrag**, **Colin B. Begg**, and colleagues found that only 40 percent of older patients who had received non-surgical treatment for superficial bladder cancer received follow-up cystoscopic examinations every three to six months, as recommended, to detect disease recurrence early. Their conclusions were based on a review of Medicare records of 6,700 patients aged 65 and older who were followed for three years after their diagnosis.

Mark Kris





James Eastham (left) and Colin Begg

PROSTATE CANCER

In a study of nearly 1,000 men who had five consecutive prostate-specific antigen (PSA) tests over a four-year period, **James A. Eastham, Colin B. Begg,** and colleagues found that levels of PSA commonly fluctuated above and below the normal range. Although elevated PSA levels often lead to follow-up biopsies to confirm or rule out cancer, their study suggests that biopsies not be performed until the PSA test is repeated.

Research from **Michael J. Zelefsky, Steven A. Leibel,** and colleagues showed that men with localized prostate cancer who were treated with high-dose levels of three-dimensional conformal radiation therapy achieved long-term survival with minimal side effects. Researchers studied data from 828 MSKCC patients treated over a ten-year period and demonstrated improved outcomes in all subgroups of patients treated with high doses of radiation, compared with those treated with lower conventional dose levels.

Using mouse models, geneticist **Pier Paolo Pandolfi** and colleagues demonstrated that the dose of a protein called Pten determines whether a prostate tu-

mor will become an aggressive cancer or remain benign. In 70 percent of patients with prostate cancer, one or both copies of the *PTEN* gene are found to have been lost at the time of diagnosis.

RADIATION THERAPY

Research by **Zvi Y. Fuks, Richard N. Kolesnick,** and colleagues provided the first genetic evidence that radiation therapy causes tumor shrinkage by damaging the blood vessels that feed tumor growth. Using genetically engineered mouse models, they found that radiation targets the endothelial cells that line small blood vessels, causing a special form of programmed cell death called apoptosis.

Research by **C. Clifton Ling, Gloria C. Li,** and colleagues suggested that a new type of gene therapy sensitizes cancer cells to ionizing radiation, potentially increasing the effectiveness of treatment. Working in mouse tumor models, the investigators introduced and then expressed antisense



Dinshaw Patel (left) and Stephen Nimer

Ku70 RNA, which reduces the level of the protein Ku70, a component of a protein complex that identifies and repairs DNA double-strand breaks. The reduction of Ku70 levels made the tumor cells more radiosensitive and enhanced the likelihood of cell death following radiation treatment.

STRUCTURAL BIOLOGY

Dinshaw Patel, Stephen D. Nimer, and colleagues published the first images of a protein structure thought to be linked to leukemia and related cancers and that may be a target for future anti-cancer drugs. Using x-ray crystallography, they visualized a segment of a protein encoded by h-l(3)mbt, or human lethal malignant brain tumor, the product of a gene found on chromosome 20 that is deleted in some cases of leukemia, myelodysplasia, and myeloproliferative diseases.

THERAPEUTIC CLONING

Biologist **Lorenz P. Studer** and colleagues described a novel way of producing therapeutic nerve cells that can cure mice with Parkinson's-like disease. The goal of therapeutic cloning is to manipulate stem cells that have been generated through the cloning of a patient's own cells into specialized cells needed to repair a failing organ. In this case, the researchers developed mouse stem cells into nerve cells called dopamine neurons, which are lost in patients with Parkinson's disease.