Right for You

The effectiveness of some treatments is determined in your genes

Mayo Clinic
Cancer Center

Training Cancer-Killing Viruses
Mining the Genome for the Causes of Cancer
A Vaccine to Defend Against Breast Cancer
Our Mission
To relieve the burdens of cancer by promoting basic and clinical research on the incidence, causes and progression of cancer and translating discoveries into improved methods for prevention, detection, diagnosis, prognosis and therapy.

Our Primary Value
The needs of the patient come first.

Features

My Very Own Prescription
Personal differences, based on genetic variation, have led to the possible replacement of a prominent breast cancer medication.

Therapy in Action
Development of molecular imaging could offer a quick, clear view of treatment's biological impact on cancer.

Attack on Command
Genetic engineering can tame viruses and direct their ability to destroy cancer cells, creating new possibilities to treat the untreatable.

Quality & Quantity
Numbers show that Mayo Clinic Cancer Center plays a leading role in cancer research.

Digging Deep
Researchers are mining the mysterious human genome to find traces of the causes of various cancers.

Outreach to the Underserved
Why is America's increasing diversity accompanied by alarming disparities in the incidence and treatment of cancer?

Self-Defense Training
A potential vaccine for breast cancer instructs the immune system to fight back against tumor-promoting molecules.

Personal Best
National Marathon speeds progress toward individualized treatment of breast cancer.
A Nationwide Approach to Finding Answers

Mayo Clinic Cancer Center is “people finding answers for people.” I am so proud to be surrounded by physician-investigators, scientists and other personnel who help advance our search for those answers. Each of them understands our mission. We pursue it with a single, focused purpose — to prevent and eliminate the many diseases under the cancer umbrella and effectively diagnose and successfully treat patients using the newest and best therapies.

We are truly a “national” cancer center. Since 2003, the National Cancer Institute has designated our three campuses as one comprehensive cancer center — the only one of its kind in the nation. As one center, we are geographically diverse, while still reflecting regional populations. Our patients benefit from this in many ways. We have more people pursuing solutions to complex problems. Mayo Clinic Cancer Center researchers regularly collaborate across our campuses to leverage their expertise. That results in more discoveries and faster transition of findings into treatments.

We can simultaneously conduct clinical trials at three campuses, in three states. That broadens participation. More people can access potentially lifesaving research, producing more reliable data. Our patients benefit from the latest knowledge no matter where they live. A research discovery in Arizona can help patients in Minnesota or Florida and beyond.

Knowledge is the critical element. What we know and how soon can save lives. Does a new potential treatment work better than the standard therapy? Does it work better for some compared to others? Is a combination of therapies helpful? As soon as we have an answer, we share it with our colleagues. Physicians and scientists across Mayo Clinic can know — sometimes in hours — how to better care for their patients.

This inaugural issue of *Forefront* highlights our latest findings and ongoing research to save lives and prevent cancer from recurring. Many of our physicians have told me they became researchers because they wanted to offer solutions to patients — answers to some of the most difficult questions any of us will ever face. At Mayo Clinic Cancer Center, we want to answer a resounding “yes” when we’re asked, “Doctor, can you help me?”

Robert B. Diasio, M.D.
Director
Mayo Clinic Cancer Center
MY VERY OWN PRESCRIPTION

Personal differences, based on genetic variation, have led to the possible replacement of a prominent breast-cancer medication.

Tamoxifen, a medication legendary for reducing the recurrence of breast cancer by almost one-half, was routinely prescribed for most postmenopausal women following breast-cancer surgery — until investigators at Mayo Clinic took a closer look.

In a series of clinical and laboratory studies, Mayo investigators demonstrated that tamoxifen, when administered after breast-cancer surgery, was less effective in postmenopausal women who were unable to metabolize the drug to its most active form, endoxifen. Now these researchers are proposing to bypass the role for human metabolism by developing endoxifen as a drug.

The National Cancer Institute (NCI) has decided to collaborate with Mayo Clinic on development of endoxifen through the NCI Experimental Therapeutics Program. The clinical trial will be conducted at Mayo Clinic, where scientists and clinicians are partners in translating a basic science discovery into a change in medical practice.

“`The clinical trial will allow us to administer endoxifen directly, without the potential interference in metabolism,” says breast cancer oncologist Matthew Goetz, M.D. “Our hope is that endoxifen will be more effective than tamoxifen and will also be tolerated well by patients.”

In the body, tamoxifen metabolizes to form endoxifen.
“Once we saw the totality of the clinical and basic science data, we knew that the best way to proceed was to simply bypass tamoxifen completely and administer endoxifen directly.”

Medication Tailored to Genetics
The tamoxifen saga is a high-profile example of the new field of pharmacogenomics — the study of the role that individual genetics plays in the body’s response to medications. The goal of pharmacogenomics is individualized drug therapy that maximizes drug effectiveness. Determining the function of common genetic variations and knowing which are present in a patient would help prevent both toxicity and underdosing.

Not for Every Woman
The U.S. Food and Drug Administration (FDA) approved tamoxifen in 1977 for patients with advanced breast cancer and in 1990 to help prevent the recurrence of cancer. Then, pharmacogenomics and collaboration came into play.

James Ingle, M.D., the Betty J. Foust, M.D., and Parents’ Professor, provided Dr. Goetz an important head start: a bank of DNA — tumor samples from 250 breast cancer survivors who had taken tamoxifen for five years following surgery — from Dr. Ingle’s own tamoxifen studies in the 1980s and 1990s.

Dr. Goetz and his colleagues demonstrated that tamoxifen was less effective in patients with a common genetic variation. Because of that variation, these patients’ livers produce little or no CYP2D6, the enzyme needed to metabolize up to 25 percent of all drugs, including tamoxifen. In addition, tamoxifen appears to be less effective in women who also take certain antidepressants, which potently inhibit the activity of CYP2D6.

Mounting Evidence
Dr. Goetz partnered with Dr. Ingle, co-leader of the Women’s Cancer Program and principal investigator of the Breast Cancer SPORE; Matthew Ames, Ph.D., whose laboratory has studied the pharmacology and pharmacogenomics of dozens of cancer drugs; molecular biologist Thomas Spelsberg, Ph.D.; molecular biologist John Hawse, Ph.D.; and others to build on the research.

“We showed that endoxifen is extremely potent and is the main compound in tamoxifen metabolism,” says Dr. Spelsberg, the George M. Eisenberg Professor. “Tamoxifen is activated via the CYP2D6 enzyme into endoxifen, a completely different molecule that has a completely different mechanism of action from tamoxifen.”

“Once we saw the totality of the clinical and basic science data, we knew that the best way to proceed was to simply bypass tamoxifen completely and administer endoxifen directly,” says Dr. Ames, the Sandra J. Schulze Profes-
sor and chair of Molecular Pharmacology and Experimental Therapeutics. His laboratory has completed animal studies that suggest intravenous administration of endoxifen is safe and effective and has moved on to testing of oral administration.

A Rare Collaboration

For endoxifen to be eligible as a medication, large quantities need to be produced. Drs. Goetz and Ames presented the case for endoxifen to the NCI and won a spot in NCI’s drug-development program, a competitive, peer-review program. This is a major feat, according to Jerry Collins, Ph.D., the NCI’s associate director for Developmental Therapeutics.

“Although NCI is open to collaborations with academic, nonprofit or commercial organizations, only a small proportion of clinical projects for new molecules, such as endoxifen, arise from noncommercial collaborators,” Dr. Collins says.

The first phase of a clinical trial will be conducted at Mayo Clinic, using a supply of endoxifen produced by NCI. In this trial, endoxifen will be delivered to women with advanced estrogen receptor-positive breast cancer who have failed standard therapies. Drs. Goetz and Ames hope the trial will accomplish several tasks:

- Determine the safety profile of endoxifen
- Characterize the plasma pharmacokinetics of endoxifen, measuring plasma concentrations over time to document how the drug is absorbed, distributed in the body, localized in the tissues, and excreted
- Assess any clinical benefit of endoxifen
- Examine endoxifen’s effect on tumors at a molecular level

“Making endoxifen available for cancer patients is a series of stages,” says Dr. Collins. “We hope it fills the treatment gap that currently exists for patients who don’t benefit from tamoxifen.”

One for All

In this case, pharmacogenomics revealed that inherited differences make tamoxifen a poor choice for some women and discovered a possible replacement for all women.

“The endoxifen project goes beyond benefiting a single patient by creating a molecule that can be given to everybody,” says Dr. Collins. “Even so, the project wouldn’t have happened without pharmacogenomics.”

Mayo Clinic has a potential financial interest in technology related to this research.

The Right Drug for Me

Carol Wray received a prescription for tamoxifen after she underwent breast-cancer surgery, then recalled a lingering suspicion.

“Over the years, I noticed how some drugs seemed to have no effect on me,” says Mrs. Wray.

Her observation proved astute. Wanting the best prevention against a recurrence of breast cancer, she turned to the Internet and found information about Matthew Goetz, M.D., and his research on tamoxifen.

She called Dr. Goetz from her home in Virginia and arranged to send a blood sample to Mayo Clinic. Genotyping of the blood sample confirmed a variation in her CYP2D6 gene, placing her among the women who cannot metabolize tamoxifen — and unknowingly are vulnerable to a return of the cancer.

“I was so thankful to Mayo,” says Mrs. Wray, who switched to a newer class of cancer-fighting drugs that she was able to metabolize.

Supporting Research

Kappie Spencer is a 25-year supporter of Mayo Clinic research in breast cancer, which has affected many women in her family.

“One way I can personally make a difference is through philanthropy,” she says, noting that her annual contributions help fund newer treatments and advances in genetic predisposition to breast cancer. She has received recognition as a volunteer in various national women’s organizations and as a women’s activist.
The ability to tell if a therapy is working for a cancer patient rests with radiologists who increasingly feel the need for speed. They are developing advanced scanning tools and imaging techniques to virtually watch a tumor shrink or an oncolytic virus spread through tumors, destroying cancer cells. The molecular revolution has spawned molecular imaging — the marriage between molecular biology and internal imaging. Val Lowe, M.D., professor of radiology, defines molecular imaging as “pictures of where certain molecules are and how they are functioning in a living organism.”

At Mayo Clinic Cancer Center, radiologists are studying the use of molecular imaging not only to image the biology of cancer (its cellular characteristics, metabolism, growth, death and use of blood) but to detect cancer, help select molecular therapies and swiftly assess response to treatments.

Researchers say development of these tools is critical to understanding the effectiveness of the newest therapeutics. For example, using tracers to evaluate chemotherapy or targeted therapies can allow physicians to increase, reduce or stop treatment, depending on the cancer’s response as seen using specialized scanners.

“In molecular imaging, you need to figure out what tumor or organ you are trying to target with a given therapeutic, and then use one of a cornucopia of reporter genes and tracers,” says radiologist Stephanie Carlson, M.D. Visible with molecular imaging, these engi-

“\textit{This is the future of medicine. We have the techniques in imaging to keep up with molecular medicine.}”
neered genes and molecules bind to specific cells, such as cancer cells, providing a glimpse of their movement or accumulation or the location of a specific chemical reaction.

Physicians once relied on touch or exploratory surgery to diagnose what was happening inside the body. Then X-rays arrived that could “see” gross anatomy, followed by the more advanced toolkit — computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) — that radiologists now use to see both detailed form and function.

These devices have provided true breakthroughs in the diagnosis and management of cancer, but it can take weeks or months to see if a tumor shrinks after treatment. With molecular tagging and tracing of a drug, the benefit could be seen within days, if not hours.

“This is the future of medicine,” Dr. Carlson says. “We have the techniques in imaging to keep up with molecular medicine, and they’re beginning to have a great impact on patient management.”

For instance, breast cancer can now be imaged with specific molecules that target tumor receptors and provide data on whether that particular patient will respond to hormone therapy.

**Highest-Resolution PET**

Mayo works with PET device manufacturers to develop and test new scanners, including a prototype that will offer the highest resolution PET image ever produced. To date, PET can image tumors about 7 millimeters wide (0.27 inches). The new machine can detect cancers 2 millimeters wide (0.08 inches).

“We want to be able to image the molecular events in smaller and smaller sites of cancer or other disease,” says Dr. Lowe. “This will be a major advance.”

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**Therapy Guided by Imaging**

Stephanie Carlson, M.D., has found that molecular imaging modalities perfected in small animals can be used in human health to help guide the use of virotherapy.

Working on image-guided gene and virus therapy for pancreatic cancer, she experimented with a scanner that combines high-resolution CT anatomical images with functional images from single photon emission computed tomography (SPECT). She found that, within hours or days, micro-SPECT/CT can show if a therapeutic gene is being expressed and if it has a tumor-fighting effect.

“Normally we would wait weeks to months to see if a tumor shrinks,” she says. “This shows us where the therapeutic virus goes, what it infects and over what period of time.”

**Supporting Research**

Frank and Susan Borman, members of the Mayo Clinic Cancer Leadership Council, have established a charitable remainder trust to benefit Mayo Clinic for research into breast and prostate cancer. Col. Borman, a pioneer in the exploration of space as an astronaut on Gemini and Apollo missions, later rose to chairman of the board of Eastern Airlines. Among other endeavors, Susan Borman helped initiate the Red Ribbon Campaign, a national event dedicated to helping kids grow up safe, healthy and drug free.

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**Viewing Prostate Cancer**

Detecting prostate cancer and assessing the effects of treatment with current methods of imaging is difficult, says Val Lowe, M.D., who leads a group of investigators in the use of PET for prostate-tumor detection and therapy evaluation.

For most cancers, PET and an infusion of fluorodeoxyglucose (FDG), a sugary, biologically active molecule, can find and monitor tumor activity. FDG-PET usually offers a multidimensional image of tumors gobbling up sugar at a faster rate than other tissues because they need energy provided by sugar to grow.

But the large majority of prostate cancers, Dr. Lowe says, do not use glucose. “We have found that you don’t see anything on an FDG-PET scan,” he says.

Dr. Lowe and his colleagues have developed the use of a different PET tracer — a radioactive version of choline, a building block of cell membranes. Mayo Clinic is believed to be the only U.S. cancer center using choline PET imaging clinically to detect metastatic prostate cancer.

Researchers also are evaluating use of the fluorine-18 radioisotope in fluorothymidine (FTL) PET, which detects cell growth. Used before and after drug treatment, it can monitor changes in cancer growth.

“These are only a few of our ongoing clinical trials looking at how PET tracers can tell if a cancer drug is working,” Dr. Lowe says.
ATTACK ON COMMAND

Genetic engineering can tame viruses and direct their ability to destroy cancer cells, creating new possibilities to treat the untreatable

Viruses are undergoing a transformation as Mayo Clinic Cancer Center researchers turn them into allies in the fight against cancer.

Culled from microbes and engineered genetically, new “smart” viruses are reprogrammed to seek and destroy a specific type of cancer cell without harming surrounding, healthy tissue. Redirecting the destructive force of viruses to attack cancer, Mayo researchers are developing new therapies with potential to remove the “untreatable” label from some forms of cancer:

- Adenovirus, alias a common cold, combined with an iodine-absorbing gene for heavy-duty radiation to treat prostate cancer.
- Vesicular stomatitis virus (VSV), a cattle disease with no immune-response issues in humans, to treat liver cancer.
- Malignancy-seeking measles viruses to treat ovarian cancer; multiple myeloma, a cancer of plasma cells in bone marrow; and brain cancer.

“These are novel therapies for very advanced diseases, and we hope they will offer more effective treatment for patients,” says John Morris III, M.D., chair of the Endocrinology Department. “The Holy Grail we are seeking, of course, is to be able to treat metastatic disease — cancer that has spread beyond one organ.”

A Leader in Taming Viruses

Mayo Clinic has one of the oldest and largest clinical virotherapy and gene therapy programs in the world, and it focuses on the treatment of cancer patients, says Eva Galanis, M.D., an oncologist and chair of the Molecular Medicine Department. Mayo developed the first in-human use of modified measles strains, beginning with treatment of patients with ovarian cancer in 2004. This bench-to-bedside translational effort, which has shown promising early signs, now includes several trials — ongoing or in development — for a variety of tumor types.

“Homegrown” viruses developed by the Cancer Center’s Gene and Virus Therapy Program are being tested in five early-stage clinical trials, some at all three Mayo campuses. Mayo also is conducting virotherapy clinical trials in collaboration with other institutions and pharmaceutical companies.

The program excels at developing and testing oncolytic viruses, which destroy cancer cells. As one of the few academic medical centers with a Food and Drug Administration (FDA)-compliant facility to manufacture clinical-grade viruses and vectors and a pharmacology lab for FDA-required toxicity testing, Mayo can streamline the many cycles to develop and refine a new virus therapy for testing in cell models, animal models and humans.
Building a Program
Stephen Russell, M.D., Ph.D., the Richard O. Jacobson Professor of Molecular Medicine, came to Mayo Clinic more than 10 years ago from Cambridge University with a vision to build this new class of cancer therapies.

“I decided at medical school that what I wanted to do was cure cancer with viruses,” says Dr. Russell. “Coming to Mayo was the opportunity of the century for translational research. The environment here is perfect for gene therapy because you need many different types of expertise to coalesce. We have that expertise plus the infrastructure to support a pipeline of gene therapy studies.”

The Gene and Virus Therapy Program has grown to a team of more than 100 people. To generate funds for the program and spread the use of its technology, Mayo Clinic in September 2009 created NISCO International, a Minnesota company offering oncolytic-virus research and development, including manufacturing, toxicology testing, and clinical trials coordination.

Virotherapy at Work
Dr. Russell marvels at the killing power of viruses. “If you get a virus infection, it causes an illness because it destroys something in your body,” he says. “Hepatitis destroys your liver, HIV destroys your immune system and pneumonia destroys the lung. So, if viruses can destroy tissue, why not have them selectively do that to cancer tissue?”

Virotherapy is really a combination of gene and viral therapy. Given advances in viral genetics, it is easy to manipulate a microbe’s DNA to target only the diseased cells, Dr. Russell says. “Viruses are simple,” he says. “Typical viruses have fewer than 10 genes in their entire genome, and you can take the genes out that cause human harm and put extra genes in. You can create viruses with unique properties, such as the ability to enter specific receptors found on different cancers and to carry different genetic payloads.”

Through these genetic payloads, the team has achieved several improvements:

- **Massive cell death.** Previous cancer gene therapies affected only the single cells that took up the genes. The team invented a new approach that produces massive cell death by merging surrounding cells into a single protoplasmic mass.

  “In this way, a single virus-modified cell can cause death of many surrounding cells,” explains Dr. Russell. “We call it bystander killing.”

- **Noninvasive monitoring.** Mayo researchers have developed ways to monitor the effectiveness of treatment by doing a simple blood test or imaging investigation. They introduce a “marker gene” into the virus, and the expression of the marker gene shows up in a blood test, or a CT or MRI scan, indicating whether the virotherapy gene is performing as expected. Knowing the results of the blood test will allow physicians to adjust the virotherapy treatment.

The Latest Choice
The vesicular stomatitis virus (VSV) has great potential as a cancer-fighting drug for two reasons, Mayo Clinic researchers say.

1. VSV spreads faster and causes more rapid destruction of cancer cells.
2. VSV, a blistering disease in cattle, does not cause disease in humans, so it eliminates problems with immunity due to previous exposure.

Mayo Clinic plans to conduct at least two clinical trials of new VSV-IFN virotherapy with VSV plus a gene added to produce interferon, which will protect normal cells from infection.

**Liver cancer.** Even if the cancer is detected early, only 10 percent to 20 percent of patients with hepatocellular carcinoma (HCC) survive five years. Partly due to the difficulty of early diagnosis, less than 1 percent of patients with HCC are treated with radical, potentially curative treatments, such as liver transplantation or surgical resection. At all three Mayo campuses, patients who are not viable candidates for liver transplantation or surgical resection will be invited to participate in a clinical trial of VSF-IFN injected directly into the tumor site.

**Multiple myeloma.** Physicians will administer the VSV-IFN with the NIS gene added and monitor results.
test or image then allows researchers to adjust and improve the therapy.
In recent studies with mice, Dr. Morris put a gene called the sodium iodide symporter (NIS), which produces a protein that causes the thyroid gland to absorb iodine, into an adenoviral vector that was injected into prostate and breast tumors. Following a dose of radioactive iodine, a gamma camera tracked the spread of radioactivity in the tumor.

- **Targeted radiation.** Dr. Morris also determined that virus therapy bolstered with the NIS gene and a therapeutic dose of radiiodine led to significant shrinkage of tumors in mice. Because the versatile NIS gene helps produce a double impact of virus therapy and radioiodine therapy, Mayo Clinic has started a clinical trial involving patients who have relapsed prostate cancer, plans to test the gene in patients with multiple myeloma, and is introducing it into other cancer therapy vectors.

Despite the flurry of clinical trials, Dr. Russell acknowledges that virus therapy is probably several years from widespread clinical application.

**A Preview of New Models**
In conventional drug development, the new drug advances through the clinical trial process without changes. Dr. Russell sees gene and virotherapy as an ongoing process that requires a different model for human testing.

“It’s much like building motor cars. Just because you build something that works does not end the need to design better models,” explains Dr. Russell. “There are multiple components in the new gene therapy vectors, and we can continually improve them because we have control over all stages of production.”

Meanwhile, the team is investigating the oncolytic potential of a number of additional viruses — herpes; Coxsackie A21, which causes hand, foot and mouth disease; A21, which is related to polio; and Sindbis, a relative of West Nile virus.

“Every virus is different from the next virus,” says Dr. Russell. “They have different mechanisms by which they bind to cells, enter cells, take over cells, destroy cells, and spread.

“One virus does not trump all others,” he says. “Every virus is potentially a drug.”

**A Foundation Built on Measles**
Mayo Clinic Cancer Center became the world leader in researching the measles virus as a potential cancer-fighting agent by first noting documented cases of patients with blood cancers who developed measles and had a spontaneous regression of their cancer. A series of discoveries and inventions followed:

- Kah-Whye Peng, Ph.D., and Eva Galanis, M.D., demonstrated that measles virotherapy could shrink a variety of solid tumors with minimal damage to healthy tissue.
- Stephen Russell, M.D., Ph.D., Roberto Cattaneo, Ph.D., and Richard Vile, Ph.D., The Richard M. Schulze Family Foundation Professor, invented a technique that exploits the characteristics of viral fusogenic membrane glycoproteins (FMGs), which produce massive cell death by merging surrounding cells into a single protoplasmic mass.
- The team deleted the pathogenic coding for two genes in the measles virus that cause illness in humans.
- Drs. Peng and Russell developed blood-test monitoring of viral gene expression. They genetically engineered the measles virus vector to express carcinoembryonic antigen (CEA), a substance produced by some cancers. The engineered virus, called MV-CEA, can be monitored in cancers that do not produce CEA.
- Dr. Russell and John Morris III, M.D., demonstrated that adding the NIS gene to the measles virus enables the use of PET imaging because radioactive iodine can act as a tracer.

**Protected by Measles**
Diane Fleshin, 55, was diagnosed with ovarian cancer in early 2009. Following surgery and six months of chemotherapy, she and her husband, Rick, both retired U.S. Army nurse practitioners and parents of a 13-year-old son, Sam, wanted something to prevent a recurrence. When Mayo Clinic in Rochester, Minn., a 4.5-hour drive from their 80-acre farm in Iowa, suggested a clinical trial on measles-based MV-NIS virus therapy, the couple jumped at the chance.

“It’s all about Sam,” Diane Fleshin says. “We read all the research, and it seems like the cutting edge. We know the odds on ovarian cancer and recurrence and the effectiveness of standard therapy. . . We are very realistic, but also optimistic, and this is definitely the right path for us. If the cancer recurs, we won’t look back and say, if only we had done that.”
Clinicians, specialists and researchers uniting for the good of the patient make Mayo Clinic Cancer Center a worldwide leader in translating cancer research into increasingly effective treatment for patients.

The Cancer Center challenges internationally recognized physicians and scientists to solve questions spanning the cancer continuum — from prevention and early detection to treatment and end-of-life care — and, ultimately, to reduce cancer’s burden on society. Although merely hinting at the impact on patients and their families, numbers help measure Mayo Clinic Cancer Center’s prominent role in the fight against cancer.

Mayo Clinic Cancer Center’s rank on U.S. News and World Report’s 2010-2011 “America’s Best Hospitals” list for cancer.

Estimate of new cancer patients every year at Mayo Clinic, making it one of the largest cancer treatment facilities in the nation.

Number of cancer-related clinical trials currently led by Mayo Clinic scientists. Mayo-based cooperative groups — North Central Cancer Treatment Group, Phase I Program, Phase II Consortium and the Cancer Prevention Network — that speed the search for new treatments and therapies by enabling Mayo investigators to recruit patients for clinical trials being conducted around the world.

Number of members in Mayo Clinic Cancer Center, including physicians and scientists representing 55 departments on all three campuses. They collaborate across programs and specialties beyond Mayo Clinic, using their collective knowledge to accelerate progress and increase potential for breakthroughs.

Campuses (in Phoenix/Scottsdale, Ariz.; Jacksonville, Fla.; and Rochester, Minn.) that distinguish Mayo Clinic as the only NCI-designated comprehensive cancer center with a multisite presence.

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Forefront
Shared Resources are available to researchers for cutting-edge technologies, services and scientific consultation. These core facilities include Biospecimens Accessioning and Processing, Bioinformatics, Biostatistics, Clinical Research Office, Cytogenetics, Electron Microscopy, Flow Cytometry/Optical Morphology, Gene Analysis, Gene & Virus Therapy, Genotyping, Pharmacology, Pharmacy, Protein Chemistry & Proteomics, Survey Research, Tissue & Cell Molecular Analysis, and Transgenic & Gene-Targeted Mouse Models.

The number of endowed professorships among Cancer Center members.

Collaborations with peer scientists at institutions across the United States, including NCI, two dozen NCI-designated cancer centers, the Translational Genomics Research Institute (TGen) in Phoenix, the Minnesota Partnership for Biotechnology and Medical Genomics and the Biodesign Institute at Arizona State University.

The total of cancer-related manuscripts by Mayo Clinic physicians and scientists selected for publication in high-impact clinical and science journals in a recent five-year period.

Number of highly competitive NCI Specialized Programs of Research Excellence (SPORE) at Mayo — out of 67 nationwide. SPOREs promote interdisciplinary research on novel ideas with potential to reduce cancer incidence and mortality, increase survival, and improve quality of life.

- Brain Cancer
- Breast Cancer
- Ovarian Cancer
- Pancreatic Cancer
- Prostate Cancer
- Lymphoma (shared with the University of Iowa Holden Comprehensive Cancer Center)
- Multiple Myeloma (the nation’s only one, shared with Dana-Farber Cancer Institute)

The number of Mayo’s NCI-sponsored cancer research programs. Mayo is one of just five centers with at least a dozen formal programs that boost productivity through collaboration.

- Hematologic Malignancies
- Cell Biology
- Genetic Epidemiology & Neuro-oncology
- Gene & Virus Therapy
- Risk Assessment
- Prostate Cancer
- Developmental Therapeutics
- Cancer Prevention & Control
- Women’s Cancer
- Immunology & Immunotherapy
- Gastrointestinal Cancer
- Cancer Imaging

How many Mayo has received in competitive peer-reviewed National Institutes of Health grants in the past year, including $91.5 million from NCI.

How many benefactors gave donations totaling more than $270 million to the Cancer Center in the past five years.
As high-tech prospectors, Mayo Clinic researchers Robert Jenkins, M.D., Ph.D., and Ping Yang, M.D., Ph.D., are mining for the ultimate sources of cancer among the 12 million potential genetic variations along the human genome.

Based on genome scanning of nearly 4,700 people, they have linked seven variations in the DNA sequence to significantly increased risk of developing glioblastoma, the most aggressive and common brain cancer.

Determining where to look is important progress that can guide further drilling into the genome and further panning for the gene function that triggers a specific cancer. Genome mining can be used to look for a number of links to cancer, such as genetic factors that influence cancer treatment outcomes. However, its greatest power may be in uncovering the subtle genomic variations that likely consort with environmental factors to initiate cancer development in an individual.

“These variations are present in the genome from the beginning, before cancer develops. If we knew how these slight effects work together, we could start to think about cancer prevention,” says Fergus Couch, Ph.D.

A Genome Powerhouse
Genome mining requires biological samples from a large number of patients. Mayo Clinic has been collecting samples in its tissue registry since 1905 and now at Mayo Clinic Biobank. It also requires rapid genotyping of samples and building custom tools to look for specific gene patterns. Mayo Clinic can do both through its Genotyping Shared Resource.

That combination has made Mayo a go-to powerhouse for genome studies. Mayo researchers lead national and international consortiums looking for links to the development of breast, brain and ovarian cancers, among other solid tumors, as well as multiple myeloma and chronic lymphocytic leukemia.

These searches always begin with a genome-wide association study (GWAS). Researchers test the blood of thousands of participants using premanufactured chips to examine up to a million genetic variations, known as single-nucleotide polymorphisms (SNPs). Comparing scans of patients with a particular cancer to cancer-free individuals can reveal unexpected associations.

“GWAS just tells us there is something in the neighborhood that is interesting. The next step is fine-mapping by using gene chips that are customized for those particular regions,” says Ellen Goode, Ph.D. “You can often find a much stronger signal that way.”
“These variations are present in the genome from the beginning, before cancer develops. If we knew how these slight effects work together, we could start to think about cancer prevention.”

**Finding the Prime Suspect**

The most definitive Mayo-led genome-mining study to date found a gene that could explain development of lung cancer in people who have never smoked.

In March 2010, researchers from five institutions, led by Ping Yang, M.D., Ph.D., reported in *Lancet Oncology* that about 30 percent of patients who never smoked and who developed lung cancer had an uncommon variant of a gene known as GPC5. The investigation involved four levels of research:

1. A GWAS that examined 300,000 SNPs found 44 SNP hits in 377 lung cancer patients who never smoked and 377 never-smokers who did not have lung cancer.
2. Testing on three independent populations involving thousands of never-smokers with and without lung cancer narrowed the 44 SNPs to two SNPs.
3. The remaining two SNPs were tested in yet another group of patients and controls. The research team used fine-mapping to precisely locate the SNPs and discovered they were adjacent to each other on the same gene, which was later identified as a variant of GPC5.
4. In laboratory experiments, researchers found that reduced expression of the gene led to lung tumors.

“The findings suggest that GPC5 has an important tumor-suppressor-like function and that insufficient function can promote lung cancer development,” says Dr. Yang.

**Closing in on the Cause**

In the GWAS on glioblastoma, Drs. Jenkins and Yang and colleagues at the University of California, San Francisco, looked at 250,000 SNPs in 692 adult patients with brain cancer and compared them to 3,992 individuals without brain cancer. The findings, reported in *Nature Genetics* in July 2009, were validated using independent data from 176 glioblastoma patients and 174 controls from Mayo Clinic.

Since then, they have used fine-mapping to look more closely at 13 SNPs in five regions. They learned that one SNP is involved in development of high-grade glioblastoma. They also determined that one region is linked to development of oligodendroglioma, a type of tumor found in about 9 percent of adult brain cancer patients. The other regions may also be involved in promoting these cancers as well, Dr. Jenkins says. The findings have not yet been published.

**Revealing More Mystery**

Since decoding the genome, scientists have realized that one gene may produce many different proteins and each protein can act differently, depending on the cell it inhabits. Sequences not associated with genes — once thought to be junk DNA — are now called gene deserts. These vast areas are thought to contain different sorts of elements that also guide life but in exotic forms still largely unrecognized. Most of the genome is made up of deserts with scattered oases of genes.

“We have found over the past 10 years that there are likely regulatory elements that guide gene expression in these areas that we had no idea existed or that would ever be important to health and disease,” says James Cerhan, M.D., Ph.D. “Now we think they hold many important answers.”

Consequently, most GWAS researchers don’t expect to find a powerful ge-
nentic effect. Their SNP hits are either in gene deserts or are genes likely influenced by other factors, such as response to chemical modifiers or bundling within chromosomes that causes genes or sequences to touch and regulate each other.

“It’s all new biology, all new genetics,” says Dr. Jenkins. “We now know that there are pieces of DNA that interact with each other at a long-range distance because of the way DNA is packaged, which changes from cell to cell and which is influenced by environmental factors such as age, nutrition, smoking, and so on.

“These are very interesting times.”

Groups Share DNA in Large Studies

Finding subtle genome variation that places a person at risk of cancer development requires more DNA than any one institution possesses. Therefore, the world comes to the researcher, and in notable cases, those researchers are at Mayo Clinic.

Fergus Couch, Ph.D., leads two large, international consortiums designed to look at molecular factors that influence two different and relatively rare kinds of breast cancer:

- **Consortium of Investigators of Modifiers on BRCA1/2 (CIMBA).** Forty-four international research groups are combining DNA samples from women who have been diagnosed with BRCA1 mutations — a rare defect that causes breast cancer in 65 percent of women who inherit it. The goal is to discover what genetic factors protect women with the mutation against developing the cancer. So far, about 12,000 samples have been collected, and a GWAS has found a group of candidate SNPs that seem to modify cancer risk.

- **Triple-Negative Breast Cancer Consortium (TNBCC).** The 20-group consortium is scanning the genomes of 1,600 patients with triple-negative breast cancer, which is very aggressive and largely untreatable. Dr. Couch says none of this work is possible without a global effort. “We pooled our efforts because we had to, and now we know how beneficial this shared interest can be,” he says. “It sets a model for other research fields.”

Mayo epidemiologist Celine Vachon, Ph.D., who leads the triple-negative breast cancer GWAS with Dr. Couch, also recently initiated a collaborative effort in the United States and the United Kingdom to look for susceptibility factors for development of myeloma, a tumor of the bone marrow.

“There is a misperception that investigators work alone in their ivory towers,” she says. “Collaboration is the only way we are able to identify these genetic variations important to rare cancers.”

Leading a Global Search

Looking for genetic differences that predispose a woman toward developing ovarian cancer, Ellen Goode, Ph.D., evaluated more than 600,000 SNPs in a GWAS of women with ovarian cancer and women without the cancer, all from similar communities.

Working with three other institutions, she found 13,000 SNPs that seemed to differ most in 2,000 ovarian cancer patients and 2,000 control subjects.

Now, in a study led by Dr. Goode and colleagues at the Moffitt Cancer Center in Tampa, Fla., 25 institutions from around the world, all members of the international Ovarian Cancer Association Consortium, are sending DNA samples to Mayo Clinic for genotyping. The study will evaluate these 13,000 SNPs in 22,000 women with ovarian cancer and 22,000 women without cancer and then drill deeper.

Dr. Goode says collaborative efforts help satisfy the need to replicate results.

“The only way to move science forward is to see consistency of results across multiple GWAS using different populations, which requires consistency of methods that everyone agrees to,” she says.
Outreach to the Underserved

Why is America’s increasing diversity accompanied by alarming disparities in the incidence and treatment of cancer? Researchers seek answers and solutions.

Cancer ranks first or second in cause of death among every racial and ethnic minority group in the United States, according to the Centers for Disease Control and Prevention (CDC). Disparities in the quality of health care across racial and ethnic groups may be impacted by socioeconomic status, geography, age, disability and sex.

Striving to eliminate disparities and to help prevent and reduce illness and death in minority populations, Mayo Clinic Cancer Center has committed to conduct more research involving women and minorities. America’s only multisite comprehensive cancer center has a unique ability to reach out to the nation’s diverse populations through practices based in Minnesota, Florida and Arizona.

Research begins with outreach initiatives to improve patient care for the underserved and uninsured. Through patient education, screening and other services, Mayo has built relationships with key communities. For instance, Mayo researchers have been working with Native American and Alaska Native community leaders for more than a decade. Earning trust, researchers say, is an essential first step toward expanding participation in research activities.

To assess and address the health needs of underserved populations, Mayo Clinic investigators have used an approach called community-based participatory research — the kind that matters to the community and results in ongoing health improvement. In partnership with local organizations and local health professionals, Mayo researchers design projects to address local priorities. They meet often with community leaders, who help interpret findings and offer guidance on culturally sensitive interventions. In the end, nurturing the community’s sense of ownership on research projects increases participation and compliance with actions that lower risk of cancer.

- Reaching Out
  During cancer-education events at African-American and Hispanic churches in northeast Florida, Mayo Clinic offers instant access to specific cancer studies. Mayo Clinic’s mobile research lab helps include more diverse populations in studies by offering a convenient way to give a medical history and blood sample. One study will determine how frequently an abnormal protein associated with a common blood cancer, multiple myeloma, and an acquired genetic abnormality associated with another blood cancer, lymphoma, are found in the blood of the population in northeast Florida.

- Including the Uninsured
  The Volunteers in Medicine (VIM) Clinic, with several Mayo Clinic oncologists and clinical staff as regular volunteers, provides free primary care to the working uninsured in the Jacksonville, Fla., area. More than half of the patients are minorities. Eligible patients are invited to participate in breast cancer clinical trials led by Mayo Clinic researchers.

- Personnel for Data Collection
  As part of its partnership with Mountain Park Health Center (MPHC), a federally funded network of five clinics serving a largely Hispanic population in Phoenix, the Cancer Center supports a data manager for electronic data collection in a community-based cancer screening program and is developing clinical trials on cancer prevention.
• **Staffing for Regional Studies**
  Through collaborative recruitment, the Cancer Center is helping Maricopa Integrated Health System (MIHS) add hematologists and oncologists in central Phoenix. In addition to helping new cancer patients get appointments sooner, this initiative will provide opportunities for a diverse, regional population to participate in cancer research and clinical trials.

• **Language Barriers**
  Sandhya Pruthi, M.D., *(right)* started a breast clinic in a local public school in Rochester, Minn., to create a nonthreatening environment for predominantly immigrant women. Sending physicians and interpreters into the community has attracted hundreds of uninsured or underserved women originally from Somalia, Vietnam, Mexico, Croatia, Poland, South America and other countries. Research on a female population representing more than 20 languages could answer questions about levels of understanding and how they affect health care choices.

• **Care and Recruitment**
  For more than six years, physicians from the Division of Hematology/Medical Oncology at Mayo Clinic in Arizona have staffed the Cancer Clinic at Phoenix Indian Medical Center (PIMC), a unit of the federal Indian Health Service. Clinical research coordinators were added to the care team to prepare for clinical trials on cancers prevalent among tribes in the Southwest.

• **Culture or Lifestyle?**
  How do cultural beliefs affect decision-making on follow-up care for 100 Native American and Alaska Native men after a diagnosis of an elevated prostate-specific antigen (PSA) level or prostate cancer? Interviewing men at four sites, including three tribes in Minnesota, and evaluating their medical records will help identify patterns of care. Jon Tilburt, M.D., and Wesley Petersen, Ph.D., co-principal investigators of a CDC-funded pilot study, seek to understand what factors contribute to efficient follow-up care for men with an abnormal prostate-cancer blood test. Their partnerships with community leaders will lay the groundwork for future research designed to improve care processes for men in these communities.

• **Risk and Screening**
  In an ambitious study on breast-cancer screening, researchers are collecting and reviewing mammograms and screening records for more than 1,200 Native American women, about 20 percent of the screening-eligible population from two Minnesota and two Wisconsin tribes. Overall, the communities have low screening rates. Dr. Petersen, the principal investigator, is documenting the risk of breast cancer in each community to find any associations between personal risk of breast cancer and adherence to screening guidelines. Identifying factors that separate those who do and don’t adhere to screening guidelines could point toward effective interventions.

• **Lung Cancer**
  In the Yukon-Kuskokwim Delta region of western Alaska, home to 25,000 Alaska Natives in 56 remote villages, prevalence studies by Mayo researcher Christi Patten, Ph.D., *(left)* found that over 50 percent of children age 15 to 18 regularly use tobacco and 79 percent of women use tobacco during pregnancy. Based on teens’ preferences, staff from Mayo and the regional hospital in Bethel, Alaska, designed a weekend cessation program in Bethel — away from home villages — with other teens and fun activities. A larger study with 100 teens from 10 villages will assess the program’s effectiveness.
SELF-DEFENSE TRAINING

A potential vaccine for breast cancer instructs the immune system to fight back against tumor-promoting molecules

Survivors of breast cancer worry about their disease returning, especially in the first five years after treatment. What if the chances of recurrence could be dramatically reduced with a vaccine?

A team of Mayo Clinic researchers is pursuing that goal, testing a combination of peptides in a vaccine now in a clinical trial at all three Mayo Clinic campuses. Hope runs high. If the team’s approach works, it could prevent recurrence for more than 2 million breast-cancer survivors in the United States and eventually could protect against numerous other cancers as well.

With funding from the U.S. Department of Defense, the clinical trial began in fall 2008 with a small number of women who were cancer-free for at least three months after completing traditional treatment. Testing has not produced enough data to conclude anything definitive, but researchers are observing a response by the patients’ immune systems that, at least in theory, could be helpful in protecting them from breast cancer, says Sandra Gendler, Ph.D., of Mayo’s Arizona campus.

Mayo Clinic physicians diagnose and treat more than 1,300 new patients with breast cancer each year. Nationwide, an estimated 40,000 women will die this year from the disease — the most common cancer diagnosed in women, especially as they age.

Directing the Immune System

Dr. Gendler, Svetomir Markovic, M.D., Ph.D., of Mayo Clinic’s Minnesota campus, and former colleague Pinku Mukherjee, Ph.D., collaborated to create the vaccine. It is designed to trick the immune system into killing cancer cells that express MUC1, a sugary molecule that is overproduced in the presence of cancer.

“We are trying to get an optimal vaccine,” Dr. Gendler says. “Once we know that we have something that stimulates the immune system and stimulates a response, then we will have to combine that with other drugs that are known to act to reduce immunosuppressant effects of a tumor.”

Ideally, that means the cancer would not return or would have less vigor. It also would open the way for this approach, known as immunotherapy, to be used against other cancers.

Immunotherapy aims to stimulate or manipulate the body’s immune system to repel the growth of cancerous tumors. At Mayo Clinic, 23 scientists and physicians from multiple departments pursue and test substances that provide such a response without being toxic to healthy cells. In addition to the clinical trial on breast cancer, Mayo researchers are using immunotherapy to target malignant melanoma, non-Hodgkin’s lymphoma and other cancers.

MUC1 expression is shown (red color) lining a normal duct in the breast (left). The localization of MUC1 changes on metastatic breast cancer cells in a lymph node (right), where MUC1 is found everywhere, all around the surface and inside the tumor cells, which are disorganized. Adapted by permission from Macmillan Publishers Ltd.: Oncogene 22, 1324-32, 2003.
Linked to Many Cancers
MUC1 is a mucin, a protein normally produced by epithelial cells lining body organs such as the breast, lung, stomach, intestines and reproductive tract. When cancer strikes, cell architecture collapses and MUC1 production intensifies, promoting tumor formation. MUC1 appears on more than 90 percent of breast cancers and played a role in about 70 percent of all cancer-related deaths in 2009.

As with breast cancer, all malignancies originating in glandular tissue overexpress MUC1, Dr. Gendler says. The MUC1 vaccine, she says, thus could be used against many other cancers—lung, stomach, colorectal, pancreas, prostate, kidney, endometrial, ovarian and gallbladder. More than 90 percent of multiple myelomas and about 60 percent of lymphomas also overexpress MUC1, she says.

Designed to Trigger Response
Dr. Gendler was the first scientist to clone MUC1. Dr. Markovic, the principal clinical investigator, specializes in the development and clinical testing of cancer vaccines and immune-boosting agents.

Their team created a vaccine of specially crafted synthetic peptides derived from MUC1 and another molecule, HER-2/neu, which is overproduced in 25 percent of breast cancers. These peptides are delivered with adjuvants, ingredients that help trigger the production of white blood cells and other immune responses.

The clinical trial is being coordinated across Mayo campuses by Donald Northfelt, M.D., in Arizona, Edith Perez, M.D., in Florida, and Dr. Markovic in Minnesota.

Dr. Gendler and colleagues caution that, even if this clinical trial proves successful, it will take several years before such a vaccine would find its way into widespread clinical application. Studies are under way to fine-tune the vaccine, using “sugary” peptides and longer peptides that should induce immune memory.

“Ultimately, if things go well, we could have a preventive vaccine that could be used to vaccinate high-risk patients earlier,” says Dr. Gendler. “That’s not here at the present time, but if we are able to see immune responses, then this could become possible. Our goal is to prevent and treat spontaneous tumors and keep cancer from spreading.”

An Empowered Patient
A longer, fuller life is exactly what Marcella hopes to realize from her participation in the clinical trial of a breast cancer vaccine. Marcella, 58, who lives in Iowa and works as a respiratory therapist at a university medical center in neighboring Nebraska, entered the trial in December 2009.

Marcella was diagnosed in mid-2007 with triple-negative breast cancer, an extremely aggressive form that lacks the three receptors commonly targeted for treatment. It is more likely than most other subtypes to return and spread.

“When I found out, I was devastated,” she recalls. “I had no family history of breast cancer. I am in the medical field, so I was quite aware of what the diagnosis meant.”

Marcella’s treatment near home included a lumpectomy, chemotherapy and radiation. Then she searched the Internet for “a way to empower myself, so that I could feel like I had some control of my life.” A description of the immunotherapy clinical trial on Mayo Clinic’s Web site provided that avenue of support.

“I understood going into the trial that the other participants and I are pioneers, and we may not know for many years what our outcomes will be,” Marcella says. “Just having that opportunity to participate gave me great hope of extending my life and having a better quality of life.”
Focused on a Malignant Molecule

Born and raised in Minot, N.D., Sandra Gendler, Ph.D., grew up knowing all about Mayo Clinic. But her route in getting there took many turns over many miles:

- Bachelor's degrees in microbiology and chemistry from the University of Minnesota in 1966.
- Serving as a technician for DNA-discoverer James Watson, Ph.D., in Boston. A doctorate with honors in 1984 from the University of Southern California, where she launched her studies on breast cancer.
- Postdoctoral work at the Imperial Cancer Research Fund (ICRF) in London in the laboratory of Joyce Taylor-Papadimitriou, Ph.D., where she launched her long-running probe of breast cancer and MUC1, the protein linked to many cancers. She was first author on the 1987 paper that described the cloning of MUC1.
- Head of the Molecular Epithelial Cell Biology laboratory at the ICRF from 1987 to 1992.

In 1993, Mayo Clinic called. Drawn by Mayo Clinic’s team approach to medicine, Dr. Gendler joined the faculty as a professor of biochemistry and molecular biology. At the Arizona campus, she developed appropriate mouse models for the next stage of her research — testing MUC1 as a potential drug.

At Mayo Clinic, Dr. Gendler twice has been named Educator of the Year and in 2004 was named a Distinguished Investigator. Since 2008, she has been the David F. and Margaret T. Grohne Research Professor of Therapeutics for Cancer Research. Dr. Gendler has trained more than 50 students and postdoctoral fellows, many of whom remain involved in research on MUC1.

In 2009, Dr. Gendler was elected a Fellow in the American Association for the Advancement of Science, the world’s largest general scientific society, in recognition of meritorious efforts to advance science or its applications.

Supporting Research

The Regis Foundation for Breast Cancer Research was founded in 1990 by Anita Kunin, a breast cancer survivor and wife of Myron Kunin, founder of Regis Corporation, a global leader in beauty salons, hair-restoration centers and cosmetology education. The Foundation’s annual Clip for the Cure raises millions of dollars for breast cancer research and education when thousands of Regis stylists volunteer their time and talents to give reduced-rate haircuts. In addition to other gifts to Mayo Clinic, the Foundation established the Regis Professorship in Breast Cancer Research.

‘Doctor, You Have Breast Cancer’

Sandra Gendler, Ph.D., was about to launch a clinical trial on the potential breast cancer vaccine in June 2008 when, at age 64, she was diagnosed with the disease.

Dr. Gendler went through chemotherapy and radiation to knock out Stage II cancer that had affected just one lymph node. Late-onset breast cancer runs in her family, so getting it was not a surprise.

“It wasn’t a fun event, but it was mind expanding,” she says. “I have been thinking about breast cancer in an entirely different fashion.”

Tissue typing found Dr. Gendler ineligible for her own clinical trial, but the experience hardened her resolve to succeed in the laboratory.

“It has made me even more committed to get a translational phase working for patients,” she says, “and it has made me really want to get what I am doing into the clinics.”
Florida Campus Adds Extended-Stay Housing

The Gabriel House of Care, a 30-room, outpatient housing facility, is scheduled to open on the Mayo Clinic campus in Jacksonville, Fla., in spring 2011. The $8.8 million project, being built on a 4-acre lakefront, will provide extended-stay housing for visiting organ-transplant patients, cancer patients receiving radiation therapy and their families.

Jorge and Leslie Bacardi of the Bahamas made the lead gift to express their gratitude to Jorge Bacardi’s organ donor, Christopher Gregory, a 19-year-old college student from Baltimore who passed away unexpectedly.

The Gabriel House of Care will be owned by Mayo Clinic and leased to and operated by St. Andrew’s Lighthouse, a Jacksonville organization that houses some Mayo Clinic patients and their families in two smaller housing facilities and coordinates a hotel lodging program for patients.

Ovarian Cancer Becomes Seventh SPORE

Investigators at Mayo Clinic Cancer Center received a five-year, $11.5 million grant to translate research into treatments for women with ovarian cancer. The Specialized Program of Research Excellence (SPORE) grant, awarded by the National Cancer Institute (NCI), is the seventh SPORE grant to support cancer research at Mayo Clinic.

The Ovarian Cancer SPORE, one of only five in the nation, consists of several projects, including:

- Combining a new enzyme inhibitor with topotecan, an established chemotherapy drug for ovarian cancer, to augment topotecan’s effectiveness
- Determining inherited factors that control a woman’s immune response to ovarian cancer

Lynn Hartmann, M.D., co-leader of the Women’s Cancer Program, is lead investigator of the Mayo Ovarian Cancer SPORE and the Blanche R. and Richard J. Erlanger Professor of Medical Research. The SPORE’s co-leader, Scott Kaufmann, M.D., Ph.D., is a laboratory scientist who specializes in mechanisms of chemo-resistance in cancer cells and Helen C. Levitt Professor.

NCI Renews Major Grant

Mayo Clinic Cancer Center (MCCC) has received an additional five years of National Cancer Institute (NCI) funding and designation as a comprehensive cancer center. Mayo Clinic has the only NCI-designated comprehensive cancer center that conducts research at three distinct locations across the United States.

The NCI Cancer Center Support Grant award totals more than $28 million over five years for infrastructure and administrative support for Cancer Center researchers across Mayo’s three campuses.

100 and Counting

A 75-year-old man with leukemia became the 100th and oldest patient at Mayo Clinic to receive an autologous stem-cell transplant since the program began in 2003. The Arizona resident had previously battled both prostate and pancreatic cancer, but his healthy lifestyle and fit condition kept him healthy enough to undergo the transplant at Mayo Clinic’s campus in Arizona.

Dr. Molina Receives NCI Team Leadership Award

Oncologist Julian Molina, M.D., Ph.D., was one of 11 researchers honored by the National Cancer Institute (NCI) with its new Cancer Clinical Investigator Team Leadership Award.

Dr. Molina’s research focuses on Phase I clinical trials addressing drug development for treatment of lung cancer and head and neck malignancies, including thyroid cancer. NCI selected the recipients for “exceptional contributions to the advancement of effective new therapies through their collaborative team science approach.”

Five Honored as Named Professors

Gifts to Mayo Clinic from benefactors have created five named professorships for members of Mayo Clinic Cancer Center since January 2009.

As endowments, the gift funds provide income to support Mayo Clinic
programs in medical education and research.

Named professorships, which recognize distinguished achievement in a specialty area and service to Mayo Clinic, represent the highest academic distinction for Mayo faculty members:

**The Vasek and Anna Maria Polak Professorship of Cancer Research** Named for The Vasek and Anna Maria Polak Charitable Foundation of Torrance, Calif. Awarded to Keith Stewart, M.B., Ch.B., a consultant in the Division of Hematology and Oncology at Mayo Clinic in Arizona and a professor of medicine. Dr. Stewart’s research focuses on the biology and treatment of multiple myeloma, including autologous stem-cell transplant. He leads a nationally funded laboratory research program in genomics and target identification in myeloma.

**The Regis Professorship of Breast Cancer Research** Named for the Regis Foundation for Breast Cancer Research of Minneapolis. Awarded to Charles Loprinzi, M.D., an oncology physician/scientist and professor of oncology. Dr. Loprinzi has served as chair of the Division of Medical Oncology and vice chair of the Department of Oncology. A nationally renowned breast cancer expert, he is director of the North Central Cancer Treatment Group (NCCTG) Cancer Control Program and co-director of the Mayo Cancer Center Prevention and Control Program.

**The Getz Family Professor of Cancer** Named for Sandy and Bert Getz of Scottsdale, Ariz., and Libertyville, Ill. Awarded to Rafael Fonseca, M.D., a physician/scientist in the Division of Hematology/Oncology, a professor of medicine, deputy director of Mayo Clinic Cancer Center, site director for the Hematologic Malignancies Program at Mayo Clinic in Arizona, and leader of Mayo’s multiple myeloma team. Dr. Fonseca’s practice has focused on diagnosing and treating plasma-cell disorders.

**The Vita Valley Professorship of Cellular Senescence** Named for a nonprofit foundation created by the Noaber Foundation of the Netherlands to accelerate innovation in health care. Awarded to Jan van Deursen, Ph.D., a consultant in both Pediatric and Adolescent Medicine and Biochemistry, director of Mayo’s Transgenic and Gene Knockout Core Facility, and Cellular Senescence Research Program leader for the Robert and Arlene Kogod Center on Aging. Dr. van Deursen’s research focuses on mechanisms that regulate development of cancer and aging-related disorders.

**The Charles F. Mathy Professor of Melanoma Research** Named for the late Charles Mathy, a leading businessman in the La Crosse, Wis., area. Awarded to Svetomir Markovic, M.D., Ph.D., a professor of medicine and associate professor of oncology. Dr. Markovic’s research interests include applying developments in basic immunology to hematology/oncology clinical research and practice. He also conducts laboratory research on the immune system as a therapeutic tool in the treatment of metastatic melanoma and lymphoma.

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**Dr. Sargent to Head Statistical Center**

Mayo statistician Daniel Sargent, Ph.D., has been named director of the Statistical Center of the Cancer and Acute Leukemia Group B (CALGB), a national association of clinical cancer researchers funded primarily by the National Cancer Institute. He will be integrating functions at Duke University with those NCI-funded groups already coordinated by Mayo Clinic — the North Central Cancer Treatment Group (NCCTG) and the American College of Surgeons Oncology Group (ACOSOG). Dr. Sargent will be principal investigator on the NCI grant that provides in excess of $5 million annually to operate the center. He will also direct 90 researchers conducting NCI-funded research. Using the same system for all three groups will reduce duplication of research efforts that would have happened without collaboration.
BRaIN-TaMOR RATE DIFFERS BY RACE
The incidence of a rare and deadly tumor called primary central nervous system lymphoma is two times higher in African-Americans, ages 20 to 49, than in white Americans, according to a Mayo Clinic study — the first to quantify incidence of the tumor by racial groups. The number of American Indians, Alaska Natives and Asian/Pacific Islanders diagnosed with the lymphoma was too low to draw any conclusions.

Based on a review of the records of 2,665 patients between 1992 and 2002 in 13 U.S. communities, the prognosis for those with the tumor is poor and appears worse for African-Americans. In the study, the 12-month survival rate for white Americans was 34 percent, compared to 19 percent among African-Americans. (Journal of Neuro-Oncology)

MEASURING RISk OF BREaST CANCER
Mayo Clinic researchers found that certain structural features within breast tissue can indicate a woman’s risk of developing breast cancer. They first studied tissue structures in 85 patients with breast cancer and their earlier, noncancerous breast biopsies, then compared them to 142 age-controlled samples from Mayo’s repository of benign biopsy tissues.

The team determined standard measurements for healthy breast tissue. Examples include the size of lobules, the many, small glands in a breast, and the number of acini, the milk-producing elements, in each lobule. According to the model they developed, the percentage of acini present per lobule at a given age indicates cancer risk. In testing, the new method was more accurate on five-year risk predictions than the National Cancer Institute’s risk assessment tool. (Journal of Clinical Oncology)

MULTI-ORGAN SCReENIng
Mayo Clinic researchers demonstrated that a single, noninvasive test can detect digestive cancers in multiple organs, including cancers that currently are not screened.

In 70 patients with cancers throughout the digestive tract, stool DNA testing detected 100 percent of both stomach and colorectal cancers, 75 percent of bile duct and gallbladder cancers, 65 percent of esophageal cancers, and 62 percent of pancreatic cancers. Early-stage cancers were just as likely to be detected as late-stage cancers. In 70 healthy patients, the test was negative.

Stool DNA testing, developed at Mayo Clinic, analyzes a stool sample for gene mutations in cells that are shed continuously from the surface of cancers throughout the digestive tract. In future development, researchers will strive for significant improvements in accuracy, processing speed, ease of patient use and affordability.

SINGLE INCISION FOR TOTAL COLECTOMY
A 32-year-old Arizona woman at risk for colon cancer is believed to be the first patient in the United States to undergo single-incision total colectomy. The patient has a condition in which the colon develops multiple polyps that will progress to cancer if the colon is not removed.

The landmark procedure, performed by a surgeon at Mayo Clinic in Arizona, removed the right colon, transverse colon, descending and sigmoid colon, and then joined the small bowel directly to the rectum. The laparoscopic surgery required a 3-centimeter incision around the navel.

GENE VARIANTS LINKED TO ADULT LEUKEMIA
A national team of researchers led by Mayo Clinic found that patients with chronic lymphocytic leukemia (CLL) are more likely to have similar DNA changes or variants in up to six genes, compared to people who do not have the cancer. The findings validate an earlier European study and demonstrate a genetic basis for the development of CLL, the most common adult leukemia in the United States.

Using blood samples from 399 CLL patients and 632 participants who did not have the cancer, investigators conducted a genome-wide association study, looking for genetic variants that may be associated with risk of developing the disease. (American Association for Cancer Research)

BIOMARKERS PREDICT OUTCOME FOR KIDNEY CANCER
Researchers at Mayo Clinic in Florida and Minnesota have developed a biomarker panel to more accurately predict the outcome for patients with clear cell renal-cell carcinoma, the most common cancer to develop in the kidney.

Using tumor specimens and data on 634 patients who underwent surgery at Mayo Clinic, the team found that the ex-
pression levels of three proteins in this type of tumor tissue can be used to predict which patients will ultimately die from their cancer. They found that patients with the highest combined values for the three biomarkers were five times more likely to die from the cancer than patients with low values. (Clinical Cancer Research)

**STATINS MAY PREVENT PROSTATE CANCER**

A Mayo Clinic study found that men who did not take statins were three times more likely to develop prostate cancer than statin users, suggesting statin use may prevent development of prostate cancer. Statin medications are widely prescribed to lower cholesterol or to help prevent heart attack and stroke in high-risk patients.

The findings came from data in a large cohort study of 2,447 men, ages 40 to 79, living in Olmsted County, Minn. The study has followed the men from 1990 to the present to assess various urologic outcomes. (American Urological Association annual meeting)

**DRUG COUNTERS THYROID CANCER**

Mayo investigators report that cancer in about two-thirds of 37 patients with aggressive differentiated thyroid cancer treated with the drug pazopanib either stopped growing or quickly shrank. Pazopanib is an experimental agent that helps stop the growth of new blood vessels.

All patients had thyroid cancer that had spread to their lungs. In half, the cancer involved lymph nodes and in 39 percent it spread to their bones. Most of the patients in the multicenter clinical trial were enrolled at Mayo Clinic in Minnesota and Florida. (American Society of Clinical Oncology annual meeting)

**MRI FINDS TUMORS IN UNDIAGNOSED BREAST**

Using MRI to screen an undiagnosed breast when tumors have been found in the other breast increases cancer detection in postmenopausal women, say Mayo investigators in Florida. In the study, MRI detected cancer in the undiagnosed breast — cancer not found with a clinical or mammographic examination — in 3.8 percent of 425 women. MRI detected cancer in the second breast in 5.4 percent of women age 70 and older.

Detecting and treating cancer at the same time in both breasts may save costs, patient stress, and the potential toxicity from having to treat cancer again later. (The Breast Journal)

**OBESITY WORSENS COLON-CANCER OUTCOMES**

Obesity has long been linked to increased risk of developing colon cancer, and now researchers at Mayo Clinic have found that obesity is associated with worse outcomes in patients already diagnosed and treated for the cancer.

Based on data culled from thousands of patients, obesity was significantly associated with a greater number of tumor-containing regional lymph nodes and worse survival rates, independent of other tumor features. Varying levels of obesity were associated with an increased risk of death, ranging from 19 percent to 35 percent, compared to non-obese patients. The effect was stronger in men than in women. (Clinical Cancer Research)

**HORMONE THERAPY PROTECTS COLON**

Women who reported using hormone therapy had a 28 percent lower incidence rate of colorectal cancer than women who did not use these drugs, according to a large, prospective study. But women who said they used other hormone preparations, such as oral contraceptives, did not appear to derive any colorectal-cancer-prevention benefits.

The investigation, headed by a Mayo Clinic researcher, is part of the Iowa Women’s Health Study, which enrolled 41,836 women from Iowa, aged 55 to 69. (American Association for Cancer Research annual meeting)

**TURNING OFF LUNG CANCER**

Researchers at Mayo Clinic in Florida discovered that a specific gene is required for the earliest steps in the development of lung cancer — expansion of cancer stem cells. These stem cells appear to be the major drivers in many common lung cancers.

The researchers previously discovered the gene that is genetically altered and overexpressed in a majority of lung cancers, then screened thousands of approved drugs that might target the gene. A clinical trial at Mayo Clinic in Minnesota and Arizona will gauge the ability of aurothiomalate, once used to treat rheumatoid arthritis, to turn off the expansion of cancer stem cells in patients with lung cancer. (Cancer Research)

**THE KEY TO METASTASIS**

Research at Mayo Clinic in Florida revealed that a molecule known as protein kinase D1 (PKD1) is key to the ability of a tumor cell to “remodel” its structure, enabling it to migrate and invade. If PKD1 is active, tumor cells cannot move, the researchers found. PKD1 is silenced in some invasive cancers.

Now that PKD1 has been recognized as a key regulator in mechanisms that allow invasive tumor cells to spread, the researchers say they can try to design treatments to stop invasive cancer cells from metastasizing — the process that often leads to death from the disease. (Nature Cell Biology)

**Supporting research**

Molly and Carly Houlahan, ages 17 and 15 respectively, founded Hives for Lives six years ago in memory of their grandfather, who died from esophageal cancer. The young beekeepers sell their honey and donate the profits — over $160,000 so far — to cancer research, including research at Mayo Clinic. Their honey, lip balm and beeswax candles are sold through retail outlets, such as hospital gift shops, and on their website www.hivesforlives.com.
PERSONAL BEST

National Marathon speeds progress toward individualized treatment of breast cancer

Researchers at Mayo Clinic Cancer Center are behind the wheel of new equipment that speeds across the human genome like a Ferrari on an empty straightaway, thanks to thousands of runners averaging less than 10 miles per hour.

The “next-generation sequencer” can scan a person’s entire genome — all 3 billion base pairs of DNA, the building blocks for every cell in our bodies — in about three days. As recently as two years ago, compiling such a mountain of genetic data would have taken months.

The Race to End Breast Cancer

Proceeds from “26.2 with Donna, the National Marathon to Finish Breast Cancer,” enable Mayo cancer researchers to take advantage of the high-speed equipment. The marathon is the brainchild of Donna Deegan, longtime evening news anchor in Florida and a disciplined runner. She also is a three-time breast-cancer survivor and Mayo Clinic patient.

First run in 2008, the marathon starts and finishes at Mayo Clinic’s Florida campus. The annual February event attracts more than 8,000 runners, and 70 percent of race proceeds support Mayo breast-cancer research.

Thinking Big

A big idea drives the value of the technology’s big capability. Edith Perez, M.D., the Mayo Clinic oncologist leading the marathon-funded research, wants to create a future where breast-cancer care is far more individualized and more effective. To reach this goal, she has assembled a team of collaborators from all three Mayo Clinic campuses, as well as industry partners and other medical centers.

Working together, the team strives to pinpoint minute genetic changes that fuel breast cancer in each individual patient. The discovery of that information has the potential to change all aspects of breast-cancer care — from diagnosis to treatment to prognosis.

“We need to make cancer care more effective and more compassionate, and science is the way to reach that goal,” says Dr. Perez, Serene M. and Frances C. Durling Professor. “Identifying the genes and proteins causing breast cancer in each patient will help us predict the benefits of treatment and develop new therapies.”

New Discoveries

It will take many years to achieve the goals that Dr. Perez and her colleagues have for the future of breast-cancer care. But they already are discovering exciting leads about the genetic factors that influence breast cancer.

For example, the team has already identified several fusion gene products — when two previously separate genes become one and sometimes cause cancer — that have never been seen before in breast-cancer tumors.

Meanwhile, Mayo researchers in other cancers are learning quickly from the team’s growing expertise and using the gene-sequencing equipment to launch projects in cancers of the lung, pancreas, colon and thyroid.

“In other places you would see new projects germinate based on one team’s experience, but not like this,” says E. Aubrey Thompson, Ph.D., a scientist and member of Dr. Perez’s team. “Collaboration is just part of the DNA here.”
MAO CLINIC CANCER CENTER
directory
cancercenter.mayo.edu
e-mail: cancerresearch@mayo.edu

Arizona
13400 East Shea Boulevard
Scottsdale, AZ 85259

Florida
4500 San Pablo Road
Jacksonville, FL 32224

Minnesota
200 First Street S.W.
Rochester, MN 55905

Administration
Robert Diasio, M.D.  Director
Robert Smallridge, M.D.  Deputy Director at Large
Edith Perez, M.D. Deputy Director, Florida
Rafael Fonseca, M.D. Deputy Director, Arizona
Charles Elrichman, M.D. Deputy Director, Clinical Affairs
Daniel Billadeau, Ph.D. Associate Director, Basic Sciences
Robert Jenkins, M.D., Ph.D. Associate Director, Translational Research
Gloria Petersen, Ph.D. Associate Director, Population Sciences
Edith Perez, M.D. Deputy Director, Florida
Rafael Fonseca, M.D. Deputy Director, Arizona
Charles Elrichman, M.D. Deputy Director, Clinical Affairs
Daniel Billadeau, Ph.D. Associate Director, Basic Sciences
Robert Jenkins, M.D., Ph.D. Associate Director, Translational Research
Gloria Petersen, Ph.D. Associate Director, Population Sciences

CANCER RESEARCH PROGRAMS

Cancer Imaging
Val Lowe, M.D.  Program Co-Leader
Richard Ehman, M.D.  Program Co-Leader

Cancer Prevention and Control
Richard Hurt, M.D.  Program Co-Leader
Charles Loprinzi, M.D.  Program Co-Leader

Cell Biology
Mark McNiven, Ph.D.  Program Co-Leader
Alan Fields, Ph.D.  Program Co-Leader

Developmental Therapeutics
Scott Kaufmann, M.D., Ph.D.  Program Co-Leader
Matthew Ames, Ph.D.  Program Co-Leader

Gastrointestinal Cancer
Heidi Nelson, M.D.  Program Co-Leader
Stephen Thibodeau, Ph.D.  Program Co-Leader

Genetic Epidemiology and Risk Assessment
James Cerhan, M.D., Ph.D.  Program Co-Leader
Mariza de Andrade, Ph.D.  Program Co-Leader

Gene and Virus Therapy
Stephen Russell, M.D., Ph.D.  Program Leader

Hematologic Malignancies
Thomas Witzig, M.D.  Program Co-Leader
Rafael Fonseca, M.D.  Program Co-Leader

Immunology and Immunotherapy
Larry Pease, Ph.D.  Program Co-Leader
Eugene Kwon, M.D.  Program Co-Leader

Neuro-Oncology
Brian Patrick O’Neill, M.D.  Program Co-Leader
Joseph Loftus, Ph.D.  Program Co-Leader

Prostate Cancer
Donald Tindall, Ph.D.  Program Co-Leader
Bradley Leibovich, M.D.  Program Co-Leader

Women’s Cancer
James Ingle, M.D.  Program Co-Leader
Lynn Hartmann, M.D.  Program Co-Leader

SPECIALIZED PROGRAMS OF RESEARCH EXCELLENCE (SPORES)

Brain Tumor SPORE
Brian Patrick O’Neill, M.D.  Principal Investigator
Robert Jenkins, M.D., Ph.D.  Co-Principal Investigator

Breast Cancer SPORE
James Ingle, M.D.  Principal Investigator

Lymphoma SPORE
(Shared with the University of Iowa)
Thomas Witzig, M.D.  Mayo Lead Investigator

Multiple Myeloma SPORE
(Shared with Dana-Farber Cancer Center)
Leif Bergsagel, M.D.  Principal Mayo Project Investigator
Rafael Fonseca, M.D.  Principal Mayo Project Investigator

Ovarian Cancer SPORE
Lynn Hartmann, M.D.  Principal Investigator
Scott Kaufmann, M.D., Ph.D.  Co-Principal Investigator

Pancreatic Cancer SPORE
Gloria Petersen, Ph.D.  Principal Investigator

Prostate Cancer SPORE
Donald Tindall, Ph.D.  Principal Investigator
Brian Davis, M.D., Ph.D.  Co-Principal Investigator

AFFILIATIONS AND COLLABORATIONS

American Cancer Society
American College of Surgeons Oncology Group
Biosdesign Institute - Arizona State University
Cancer and Leukemia Group B
*Cancer Prevention Network
Children’s Oncology Group
Coalition of National Cancer Cooperative Groups
Eastern Cooperative Oncology Group
GLOIOGENE
Gynecologic Oncology Group
Hormel Institute - University of Minnesota
Indian Health Service
Minnesota Partnership for Biotechnology and Medical Genomics
Native Programs
National Cancer Institute
*North Central Cancer Treatment Group
Ontario Institute for Cancer Research
Pancreatic Cancer Genetic Epidemiology
Pharmacogenetics Research Network
*Phase I Program
*Phase II Consortium
Radiation Therapy Oncology Group
Translational Genomics Research Institute (TGen)

* Based at Mayo Clinic

Mayo Clinic Department of Development
Toll-free: 1-800-297-1185
e-mail: development@mayo.edu
www.mayoclinical.org/development
Cancer survivors, families, friends and medical staff enjoyed a rock and roll theme party at Mayo’s Rochester campus in June. It was part of the 23rd annual National Cancer Survivors Day, which is celebrated across the country. Mayo cancer educator and event organizer Janine Kokal says, “Having the opportunity to meet other cancer survivors — especially the many long-term survivors — is inspiring for us all.”