

Two New Department Chairs Named

PEDIATRICS AND COMMUNICABLE DISEASES, ORTHOPAEDIC SURGERY GAIN NEW LEADERSHIP

The U-M Medical School recently selected two of its own to lead departments within the Medical School. Pediatric oncologist Valerie Castle, M.D., associate provost for academic and faculty affairs, was named chair of the Department of Pediatrics and Communicable Diseases and the first David Murray Cowie Professor of Pediatrics, effective September 1. On October 17, James Carpenter (M.D. 1984), associate professor of orthopaedic surgery, associate director of MedSport, and director of surgical services for the U-M Athletic Department, became chair of the Medical School's new Department of Orthopaedic Surgery and the first Harold W. and Helen L. Gehring Professor of Orthopaedic Surgery.

"Dr. Castle was clearly the most outstanding candidate. Her leadership will support the department's continued advancements in clinical care, research and education," says Allen S. Lichter, M.D., dean of the Medical School and



Valerie Castle



Photo: Martin Viebet

James Carpenter

Radiation, Radiation Oncology Rank No. 1 in NIH Research Funding

Researchers in the U-M Medical School's Departments of Radiology and Radiation Oncology have received research grants and contracts totaling over \$21 million — more than any other "Radiation-Diagnostic/Oncology" specialty at other institutions. Fiscal year 2002 NIH awards to U-M in this specialty represented a 64 percent increase over 2001.

During federal fiscal year 2002, the Medical School received a total of \$224 million in NIH research funding, accounting for 70 percent of all NIH awards to the University of Michigan.

—SFP

the Newman Family Professor of Radiation Oncology.

Born in Canada, Castle received her medical degree from McMaster University in Hamilton, Ontario, where she completed her pediatric residency. Castle joined the U-M faculty in 1990 after completing a fellowship in pediatric hematology/oncology at the U-M Medical School. Castle's research focuses on a pediatric solid tumor called neuroblastoma.

Regarding Orthopaedic Surgery, Lichter is "pleased that Dr. Carpenter has accepted

the offer to chair one of our newest departments. He is committed to expanding services for our patients, supporting pioneering research in orthopaedic medicine, and attracting the best and brightest students for a world-class education. His leadership will be invaluable as the department enters an important period of growth."

Carpenter joined the University of Michigan Medical School faculty in 1990. He specializes in shoulder, knee and arthroscopic surgery, as well as sports medicine. Carpenter was born in Ann Arbor and is a third-generation graduate of the U-M Medical School. He completed his residency in orthopaedic surgery at Massachusetts General Hospital and Harvard Medical School, where he also held a research fellowship in orthopaedic biomechanics.

—MBR

New Hope for Pancreatic Cancer Diagnosis and Treatment

Photo: Martin Vloet

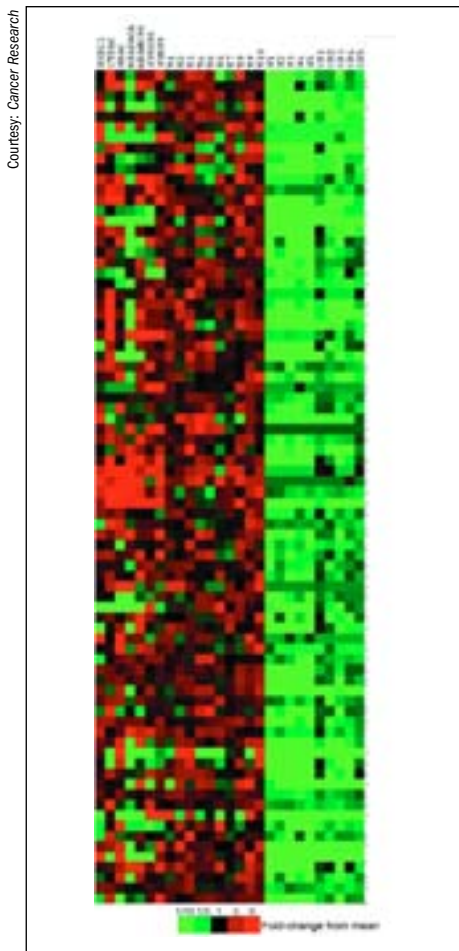
Every year, more than 29,000 Americans receive what amounts to a death sentence — a diagnosis of pancreatic cancer. Fewer than 20 percent are diagnosed in time to qualify for the only known treatment — an arduous operation — and only 3 percent of all patients live even five years.

“Pancreatic cancer is one of the swiftest and surest cancer killers, and not nearly enough has been learned about what, at the molecular level, makes it so deadly,” says Craig Logsdon, Ph.D., a professor of physiology in the Medical School and co-leader of a research team in the U-M’s Comprehensive Cancer Center.



Above: Diane Simeone and Craig Logsdon

Left: Gene expression patterns for 80 of the most promising genes identified in U-M research on pancreatic cancer



Courtesy: Cancer Research

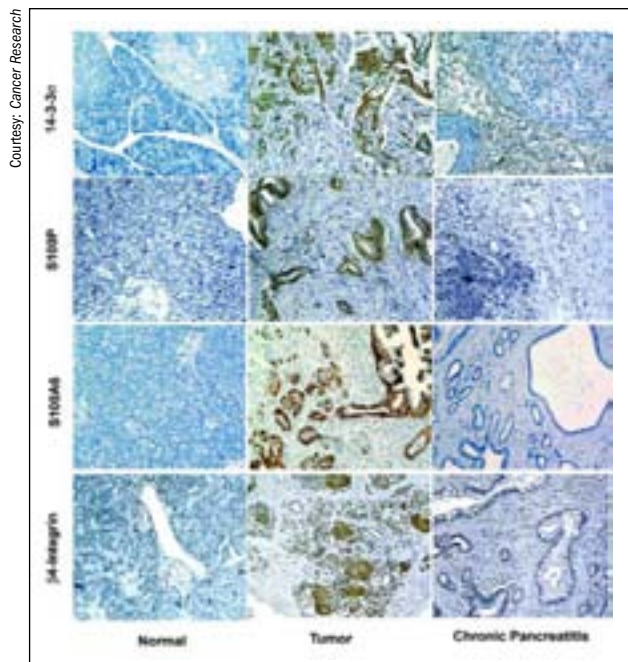
U-M scientists recently identified 158 genes specific to pancreatic cancer — the most accurate list to date. Unlike other scientists, U-M researchers have found ways to distinguish genes involved in cancer from those involved in a chronic inflammatory disease, pancreatitis, which often is mistaken for cancer. Determining pancreatic cancer’s protein “biomarkers” is the first step toward reliable diagnostic tests and more effective treatments for this disease, according to Logsdon.

Using their gene list as a roadmap, U-M scientists are cataloging proteins encoded by these genes and creating antibodies to detect proteins in the blood or saliva of cancer patients. Tissue samples from U-M patients with pancreatic cancer or chronic pancreatitis will be analyzed and added to the research database. Eventually, U-M scientists hope to use this information to develop and test new treatments in animals and, eventually, in human patients.

U-M scientists recently identified 158 genes specific to pancreatic cancer — the most accurate list to date.

“We need a better understanding of pancreatic cancer, to help improve the terrible odds these patients face and to spare pancreatitis patients unnecessary surgery because of misdiagnosis,” says Diane M. Simeone, M.D., an associate professor of surgery and co-leader of the research project. ➤

Pancreatic Cancer Diagnosis and Treatment (continued)



These stained tissue samples show how U-M scientists used proteins made by four of their target genes to confirm that these genes were expressed more often in cancerous tissue than in normal or pancreatitis tissue.

“We’re combining clinical and basic science in a way that we feel will help accelerate progress on this disease,” says Logsdon. “This gene list is a very promising start, but there is still far to go.”

The research project is funded by the Michigan Life Sciences Corridor, the Lustgarten Foundation for Pancreatic Cancer Research, the U-M’s Comprehensive Cancer Center, and the National Cancer Institute.

U-M research collaborators include Samir M. Hanash, M.D. (Ph.D. 1976), professor of pediatrics and communicable diseases; Thomas J. Giordano, M.D., Ph.D., clinical associate professor of pathology; Joel K. Greenson (M.D. 1984), associate professor of pathology; Charles Binkley, M.D., surgery resident; Thiruvengadam Arumugam, Ph.D., research fellow; David Misek, Ph.D., senior pediatrics research associate; and Rork Kuick, systems projects coordinator.

—KG

Read an expanded version of this story:

www.med.umich.edu/opm/newspage/2003/pancancer.htm

Learn more about pancreatic cancer and the U-M’s new Pancreatic Tumor Clinic:

www.med.umich.edu/1libr/aha/aha_pancan_crs.htm

www.cancer.med.umich.edu/clinic/pancreaticclinic.htm

Bexxar Approved by FDA

CANCER DRUG WAS DEVELOPED AT U-M

The final hurdle in a long journey from laboratory research to clinical treatment was crossed on June 30 with a simple announcement from the U.S. Food and Drug Administration. Bexxar® — a new cancer therapy conceived and developed by scientists at the University of Michigan Comprehensive Cancer Center — was approved for use in patients with non-Hodgkins lymphoma. In September, the drug also was approved for Medicare reimbursement.

Non-Hodgkins lymphoma affects the blood, bone marrow and lymphatic tissues and is the nation’s sixth-leading cause of cancer death. Bexxar combines an antibody that seeks out cancer cells with a radioactive form of iodine. The drug binds to a protein found only on the surface of tumor cells and delivers a high concentration of targeted cell-killing radiation, with minimal damage to normal tissue.



Mark Kaminski speaks with patient Richard Lowenthal, one of the first Bexxar recipients, as nuclear medicine technician Denise Regan administers the drug.

Mark Kaminski, M.D., professor of internal medicine, developed Bexxar with Richard Wahl, M.D., formerly at the U-M Medical School and who is now professor and chair of nuclear medicine at Johns Hopkins University Medical Center, in collaboration with scientists at Coulter Corporation, which was later acquired by Corixa Corporation. Bexxar will be co-marketed in the U.S. by Corixa and Glaxo-SmithKline.

For an expanded version:

www.med.umich.edu/opm/newspage/2003/medicarebexxar.htm

To learn more about non-Hodgkins lymphoma:

www.cancer.med.umich.edu/learn/lymphomainfo.htm

For more information on Bexxar from its manufacturer: www.bexxar.com

—KG

Hirschsprung's disease — a serious, sometimes life threatening, genetic disorder affecting one in 5,000 newborn infants — is caused by defective stem cells, according to new research by Medical School scientists.

Scientists know that Hirschsprung's is a genetic disease, and they have identified some of the mutations associated with the disorder. But no one knew exactly how these mutations affected the development of the intestinal nervous system. Based on new research, U-M scientists now say the basic problem is that neural crest stem cells, which give rise to nerves in the embryonic digestive system, never reach the lower part of the developing gut.

Babies with Hirschsprung's disease are born without ganglion cells — specialized nerve cells in the large intestine, which trigger contractions to eliminate feces. The result is chronic constipation and intestinal obstructions requiring surgery, sometimes immediately after birth.

"We found that the mutated genes causing Hirschsprung's disease act in neural crest stem cells to impair their ability to form a normal intestinal nervous system," says Sean J. Morrison, Ph.D., a Howard Hughes Medical Institute investigator and assistant professor of internal medicine in the U-M Medical School.

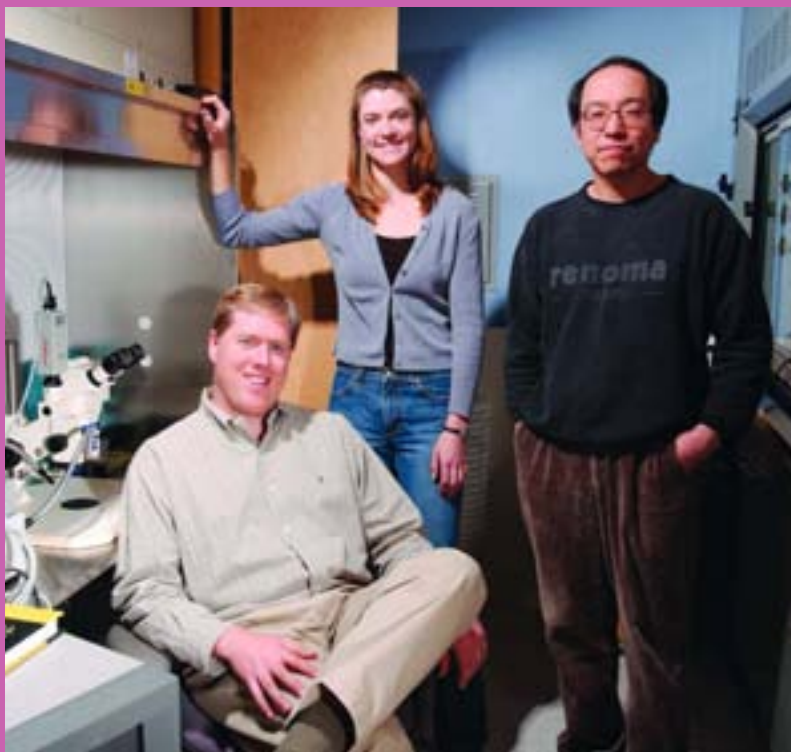


Photo: Martin Voet

Sean Morrison, Genevieve Kruger and Tashihide Iwashita

U-M Team Determines Defective Stem Cells Cause Rare Intestinal Disorder

Neural crest stem cells are one variety of "adult" stem cells. Unlike embryonic stem cells, which can become nearly any cell in the body, neural crest stem cells normally develop into the neurons and supporting cells of the peripheral nervous system — as well as connective tissues, such as dermis, bone and vascular smooth muscle. They first show up in the embryo's primitive neural tube, which forms the spinal cord. When everything goes right, neural crest stem cells then migrate through the developing gut, seeding the primitive digestive system with stem cells capable of generating a healthy, functioning intestinal nervous system.

But in embryos with Hirschsprung's disease, some or all of these stem cells get stuck and never migrate past the esophagus. U-M scientists say mutations in a gene called *Ret* are responsible for the cells' inability to move past the esophagus into the stomach and intestines of the developing embryo.

The study was funded by the Howard Hughes Medical Institute, the National Institutes of Health, the Searle Scholars Program and the U-M's Institute of Gerontology. Ricardo Pardal, Ph.D., a U-M research fellow, and Mark J. Kiel, a graduate student in the U-M Medical School's M.D./Ph.D. program, were collaborators in the study.

—SFP

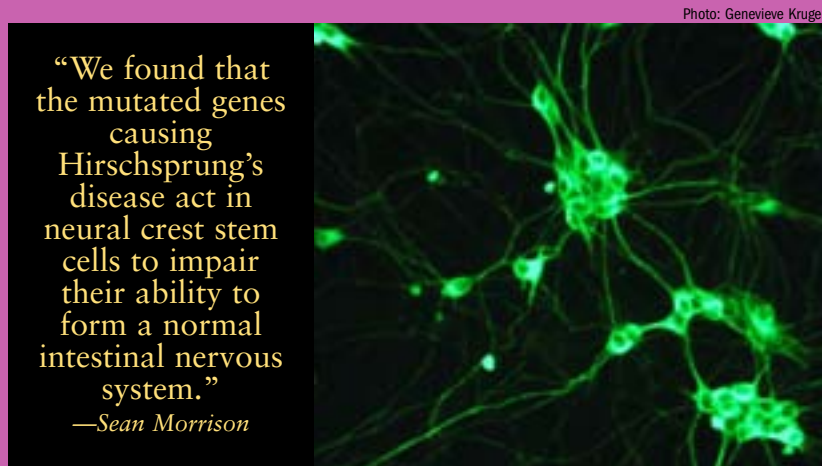


Photo: Genevieve Kruger

Neural cells grown from a single neural crest stem cell

For an expanded version of the story:
www.med.umich.edu/opm/newspage/2003/hirschsprung.htm

Learn more about Hirschsprung's disease:
www.um-pediatric-surgery.org/new_070198/new/Library/Hirschsprung/hirschsprung.html

Why Some People Get Sick ... and Others Get Sicker

Photo: Marcia Ledford



Michelle Trudeau, Miriam Meisler and David Buchner

A gene that turns a chronic inherited neurological disorder — which produces tremor and muscle weakness in laboratory mice — into a lethal disease that paralyzes and kills them within a few weeks of birth, has been discovered by U-M scientists. Called *Scnm1*, the gene is one of a small group of recently discovered “modifier” genes that interact with other genes to alter the physical effects of inherited diseases.

There are many inherited diseases — including cystic fibrosis, amyotrophic lateral sclerosis (ALS) and epilepsy — where symptoms vary widely, even between members of the same family. Understanding how modifier genes work could help scientists solve a fundamental mystery of genetics: Why do people with identical genetic mutations often differ in the severity or age of onset of the same inherited disease?

“In our study with mice, we found that the severity of neurological defects caused by mutations in a gene called *Scn8a* are determined by another gene, *Scnm1*, which is located on a different chromosome,” says Miriam Meisler, Ph.D., a professor of human genetics in the U-M Medical School. “*Scnm1* is expressed in many human cells, which suggests that it could modify the severity of a wide range of inherited disorders in humans, including other neurological diseases.”

Meisler’s research focuses on sodium channel genes that control the flow of electrical signals between nerve and muscle cells. Mutations in sodium channel genes produce a variety of neurological disorders — including several types of epilepsy, ataxia, poor muscle coordination, paralysis and cardiac arrhythmias like long QT syndrome.

“If we can find a way to change the secondary effects of modifier genes, we may be able to minimize the impact of the original genetic defect,” Meisler says.

The U-M study was funded by the National Institutes of Health. Meisler conducted the study with David Buchner, a U-M graduate student, and Michelle Trudeau, a U-M research associate.

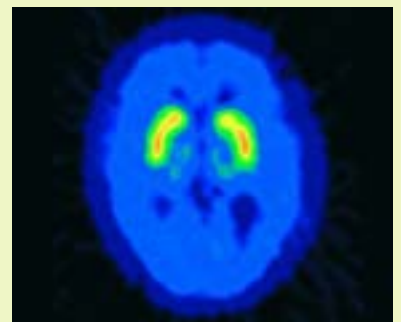
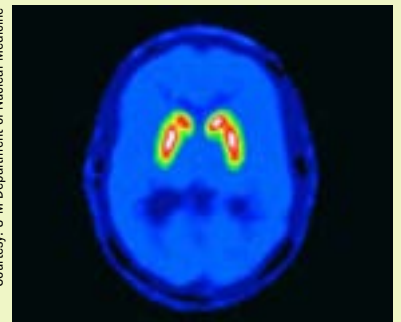
—SFP

Read an expanded version:
www.med.umich.edu/opm/newspage/2003/scnm1.htm

More information on modifier genes:
www.med.umich.edu/genetics/faculty/meislermore.htm

U-M researchers found that multiple system atrophy patients had a lower density of brain cells that produce important neurochemicals called dopamine and acetylcholine.

Courtesy: U-M Department of Nuclear Medicine



These PET scans show differences in brain chemistry between a normal brain (top) and the brain of a patient with sleep disorders associated with Multiple System Atrophy (bottom). The normal brain shows high densities (white and red) of dopamine-producing cells, while MSA patients have much lower densities (orange and green) of these cells in the same areas of the brain.

To Sleep ... Perchance to Dream?

Could chemical imbalances in the brain be related to sleep disorders? Possibly, according to recent research by U-M scientists who have discovered links between brain chemistry and two common conditions – obstructive sleep apnea and REM sleep behavior disorder.

Sleep disorders are a fact of life for millions of Americans. Up to 3 percent of adults have some degree of obstructive sleep apnea with repeated episodes of interrupted breathing during the night that lead to snoring and daytime sleepiness. REM sleep behavior disorder occurs less often, but is more dramatic. Patients literally act out their dreams during the rapid-eye movement, or REM, phase of sleep, moving their arms and legs, getting out of bed, talking and shouting, and even hitting or punching. REM sleep behavior disorder can endanger the sleeping person, or his or her bed partner.

In research directed by Sid Gilman, M.D., the William J. Herdman Professor and chair of Neurology in the Medical School, U-M scientists made positron emission tomography (PET) brain scans and conducted detailed sleep studies for 13 patients with multiple system atrophy, a rare and fatal degenerative neurological disease. People with multiple system atrophy were selected for the study because the disease is almost always accompanied by severe sleep disorders. Experimental data from studies of these patients – all of whom had sleep apnea and REM behavior disorder – were compared to data from 17 healthy volunteers.

U-M researchers found that multiple system atrophy patients had a lower density of brain cells that produce important neurochemicals called dopamine and acetylcholine. Patients with the fewest dopamine-producing neurons in the striatum of their brains had the most severe REM sleep behavioral symptoms. Patients with the fewest acetylcholine-producing neurons in the brainstem had the most interruptions in breathing during sleep.

“It’s exciting to show this major neurochemical deficit for the first time, and confirm what others have suspected,” says Gilman. “We don’t know if we will find this same effect in patients with other neurological diseases or in people who are otherwise neurologically well, but these findings are already suggesting further research opportunities.”

Gilman is careful to note that the research findings to date only show correlation, not causation, between brain chemistry and sleep disorders. U-M scientists are planning additional research, including a similar study of patients with Parkinson’s disease. Gilman says he and other specialists suspect that sleep disorders may be an early symptom in many cases of Parkinson’s disease.

Research collaborators include Robert Koeppe, Ph.D., U-M professor of radiology; Ronald Chervin, M.D., associate professor of neurology; Flavia Consens, M.D., clinical assistant

Photo: Martin Vloet



Sid Gilman

professor of neurology; Roderick Little, Ph.D., U-M professor of biostatistics; Larry Junck (M.D. 1976), professor of neurology; Hyonggin An, graduate student in biostatistics; and Mary Heumann, a research associate in neurology.

—KG

For an expanded version of the story:

www.med.umich.edu/opm/newspage/2003/sleepdisorder.htm

Learn more about snoring and sleep disorders:

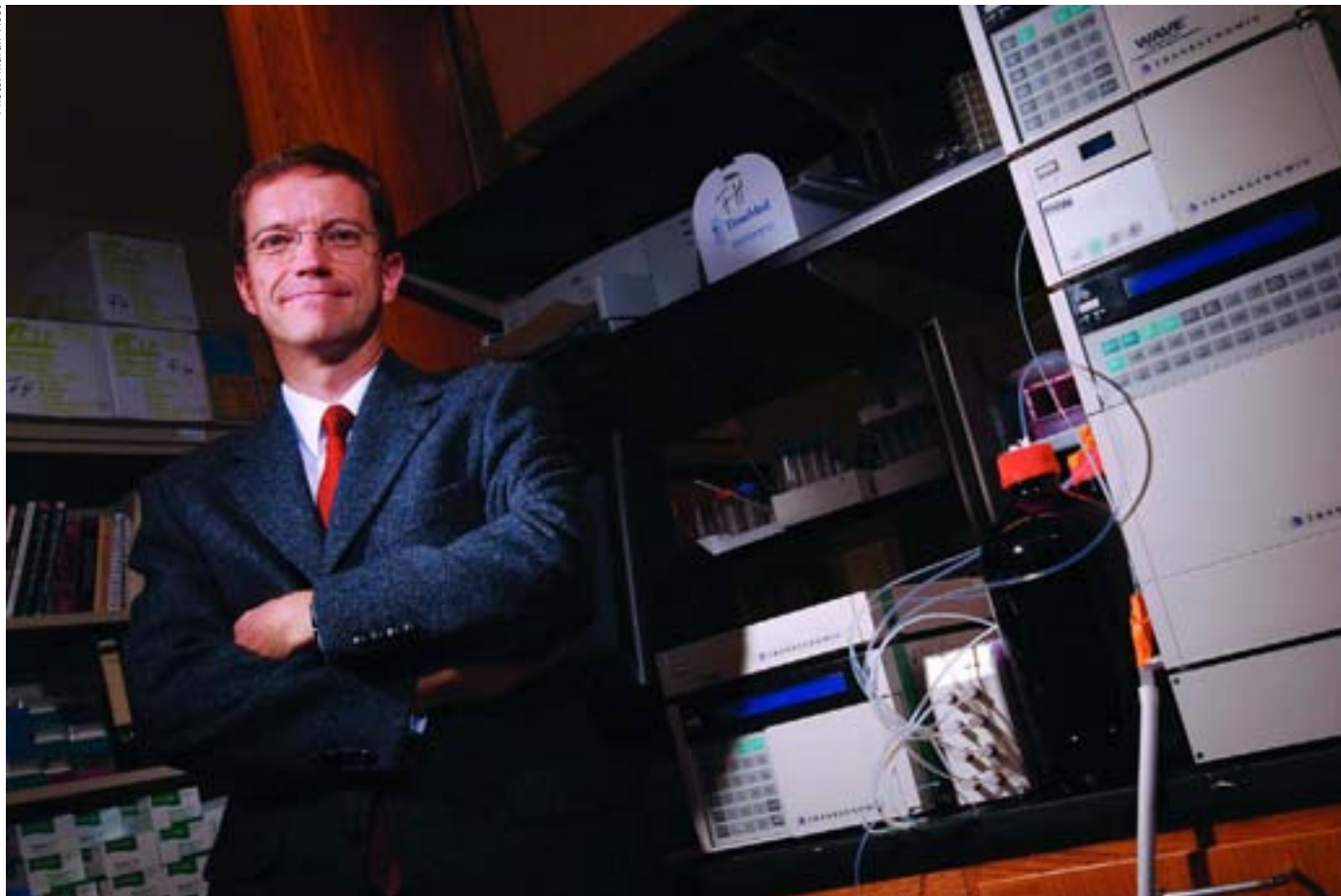
www.med.umich.edu/1libr/aha/aha_sleepapn_crs.htm

www.med.umich.edu/1libr/aha/aha_snoring_crs.htm

www.med.umich.edu/1libr/aha/aha_insomnia_crs.htm

Genetic Mutation Causes Lethal Kidney Disease

Photo: Martin Vioet



Friedhelm Hildebrandt

Scientists at the U-M Medical School have found a genetic mutation that causes one type of nephronophthisis, or NPHP – a rare disease that leads to kidney failure in infants, children and young adults. NPHP is the most common genetic cause of kidney failure in children and young adults. Other than dialysis or a kidney transplant, there is no treatment and no cure.

“We can do the diagnostics and confirm for the patient that this is the disease they have, but we cannot offer any treatment,” says Friedhelm Hildebrandt, M.D., the U-M’s Frederick G.L. Huetwell Professor for the Cure and Prevention of Birth Defects. “Our only hope is to work out the mechanism to understand where it comes from. Now that we have the gene, at least we know where to start asking questions.”

Working with an international team of scientists, Hildebrandt and Edgar A. Otto, Ph.D., a U-M research investigator, found that children who inherit, from both parents, mutated forms of a gene called *inversin* develop nephronophthisis type 2, which causes renal failure in infancy. Results from the U-M study were published in the August 2003 issue of *Nature Genetics*.

Finding the gene responsible for NPHP2 is important, not only because it could lead to a future treatment, but also because of intriguing links

between NPHP2 and a life-threatening genetic disorder called polycystic kidney disease, which affects 500,000 people, mostly adults, in the U.S.

The study was funded by the German Research Foundation (DFG), the National Institutes of Health and the University of Michigan. Other collaborators from the U-M Medical School were John F. O’Toole, M.D., a resident in internal medicine; research fellows Julia Hoefele, M.D., Rainer Ruf, M.D., and Matthias T. Wolf, M.D.; and research assistants Frank Beekmann, Karl S. Hiller and Adelheid M. Mueller.

—SFP

Read an expanded version of this story:
www.med.umich.edu/opm/newspage/2003/kidney.htm

Learn more about Hildebrandt and his research:
www.med.umich.edu/hg/RESEARCH/FACULTY/Hildebrandt/hildebrandt.htm

Read the published paper in *Nature Genetics* (34) 413-420, August 2003: www.nature.com/ng

Pap Smears after Hysterectomy:

SMALL BENEFIT FOR MANY WOMEN, HIGH COST TO THE HEALTH CARE SYSTEM

"Most women with hysterectomies don't need annual Pap smears," says Michael Fetters, M.D., an assistant professor of family medicine in the U-M Medical School. "Just because you have a test available, doesn't mean you should always use it."

Fetters directed the first cost-benefit analysis of Pap smear screening exams for cervical or vaginal cancer in women who had hysterectomies for benign disease. The study found that routine Pap screenings add no more than three weeks to these women's lives at a cost to the health care system of up to \$12 million.

U-M researchers still recommend regular Pap smears for women whose hysterectomy was linked to cervical cancer or those with special risk factors associated with lower genital tract cancers. And even though a Pap smear may not be necessary, an annual visit to the doctor still is.

Photo: Gregory Fox

U-M researchers still recommend regular Pap smears for women whose hysterectomy was linked to cervical cancer or those with special risk factors associated with lower genital tract cancers.



Michael Fetters

The study was funded by Blue Cross Blue Shield of Michigan Foundation, the American Academy of Family Physicians Foundation and the Robert Wood Johnson Foundation Generalist Faculty Scholars Program. U-M research collaborators included Richard W. Lieberman, M.D., clinical assistant professor of pathology and of obstetrics and gynecology; and Paul H. Abrahamse, research associate.

—NF

Read an expanded version of this story:
www.med.umich.edu/opm/newspage/2003/skipppap.htm

For more information on Pap smears:
www.med.umich.edu/1libr/aha/aha_papsmear_crs.htm

Photo: D.C. Goings



Amy Alderman

Miles Apart

PHYSICIANS DIFFER DRAMATICALLY IN RHEUMATOID ARTHRITIS TREATMENT PROTOCOLS

More than two million Americans with rheumatoid arthritis are caught in the middle of a debate between rheumatologists and surgeons over what the most effective treatment for their chronic, debilitating condition is. Anti-inflammatory medications work for many patients, but hand surgery has been proposed as an option for those who do not respond to medicines or whose hands are twisted and contorted.

Amy Alderman, M.D., a resident in plastic and reconstructive surgery, led a U-M research team that surveyed nearly 1,000 physicians in different specialties about how best to treat patients with rheumatoid arthritis. The survey found that physicians were miles apart in their treatment protocols and in their perception of how well surgery can help ease pain, restore function and prevent further problems.

"Treatment varies depending on where patients live, what type of physician they're referred to, how much cross-training and interaction those physicians have with others, and what an individual doctor personally thinks of other specialties," says Alderman. Only large studies evaluating the effectiveness of various hand operations, she says, will quell the debate and help patients get consistent and beneficial care no matter what kind of doctor they see or where they live.

Alderman's collaborators include Kevin C. Chung, M.D., associate professor of plastic and reconstructive surgery; Peter A. Ubel, M.D., associate professor of internal medicine; David A. Fox, M.D., professor and chief of rheumatology; and H. Myra Kim, Sc.D., an associate research scientist in the U-M School of Public Health. The study was supported in part by a grant from the Robert Wood Johnson Foundation and the American Society for Surgery of the Hand. Alderman is a former Robert Wood Johnson Clinical Scholar at the University of Michigan.

—KG

For an expanded version of this article:
www.med.umich.edu/opm/newspage/2003/handsurgery.htm

For more about rheumatoid arthritis:
www.med.umich.edu/1libr/aha/aha_rhearth_sha.htm

Protein Governs Spread of Prostate Cancer

It's not usually prostate cancer itself that kills — it's the spread of the cancer from the prostate to the rest of the body. But relatively little is known about exactly what makes some men's cancers spread, or metastasize, while other tumors stay put. A new study by scientists at the University of Michigan Comprehensive Cancer Center has revealed one crucial key to that deadly process.

The U-M team found that a protein called RKIP, for Raf kinase inhibitor protein, governs the ability of prostate cancer cells to leave their original location and enter nearby blood vessels, which then act as superhighways to the rest of the body.

The findings show that RKIP is vital to a process called vascular invasion, which is the first step in a cascade of events leading to

“Many cancer cells that enter the bloodstream don't go on to form successful metastases,” he says. Keller predicts that the U-M discovery will help scientists and clinicians better understand the complex process by which some cancers kill.

The study was funded by the Stuart and Barbara Padnos Endowed Research Fund, the Association for the Cure of Cancer of the Prostate, the Department of Defense and the National Cancer Institute through the U-M's SPORE (Specialized Program in Research Excellence) grant for prostate cancer research. U-M research collaborators included Zheng Fu (Ph.D. 2002), U-M postdoctoral researcher; Rodney L. Dunn, a U-M research associate; and Zhi Yao, a U-M visiting professor.

—KG

Keller predicts that the U-M discovery will help scientists and clinicians better understand the complex process by which some cancers kill.

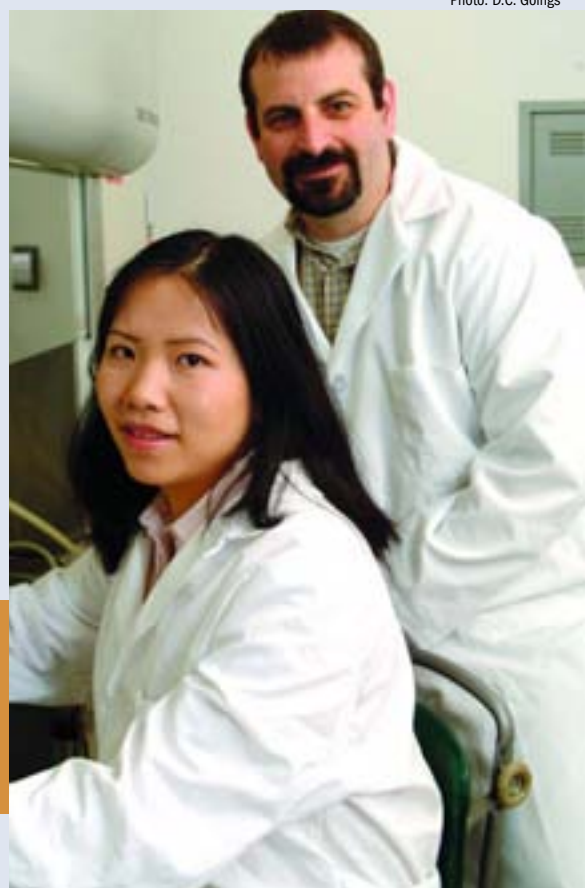
metastasis. Tumors that produce a normal amount of RKIP appear unable to make the jump to the vascular system, reports Evan Keller, D.V.M., Ph.D., an associate professor of comparative medicine and of pathology in the U-M Medical School, who led the research study. But if a tumor cell lacks RKIP, metastasis can take place.

Keller notes that vascular invasion is not the only action required for cancer to spread.

Read an expanded version of the story:
www.med.umich.edu/opm/newspage/2003/prostateprotein.htm

Find more information on prostate cancer:
www.med.umich.edu/1libr/aha/aha_metprost_crs.htm
www.cancer.med.umich.edu/learn/pwprostate.htm

Photo: D.C. Goings



Zheng Fu and Evan Keller