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DISCOVERY'S EDGE

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BRIDGE THE GAP

INSIDE: Doctor^2 | One + One = Four | A New Center for Biomedical Discovery | Reflecting on the Past

A Map to the Past, Present, and Future

Why does a physician decide to become a researcher? At Mayo Clinic the answer is fairly obvious: to be of greater help to patients. There is also a driving curiosity involved and a strong sense that one can be doing more to find answers. At Mayo we like the model of the clinician-investigator because medical issues seen in the exam room can be addressed by motivated professionals eager to bring new therapies to patients. Research pursued by clinician-investigators is patient-centric, focusing on new and better therapies, in general, and on unmet clinical needs, in particular.

I remember what did it for me. It was 1981 when, as a resident, I became intrigued by a paper published that year by a kidney research team demonstrating that in response to stress, the kidney mounts responses that, in the short term, appeared beneficial (adaptive), but, in the long term, these responses proved injurious (and thus maladaptive). This concept that kidney disease persists and progresses by an interplay of adaptive and maladaptive responses was a major motivation for me to pursue a career as a nephrologist and as an investigator in kidney disease.

This issue of *Discovery's Edge* profiles some of our rising-star clinician-investigators, physicians with dedication, curiosity, and the commitment to address the unmet needs of patients. At Mayo, we encourage and train these types of doctors, who, by their research pursued today, may provide therapies for tomorrow.

Also in this issue, we explain how Mayo helps researchers bring discoveries all the way to practical applications, avoiding pitfalls along the way. We also look at two great research partnerships — one from today and one from the past — and how each made remarkable medical progress that almost immediately changed lives. And we reveal a long-kept secret: the identity and moving story of the young patient whose participation in science helped win the Nobel Prize.

Best wishes,

Karl A. Nath

Karl A. Nath, M.B., Ch.B.
Medical Editor

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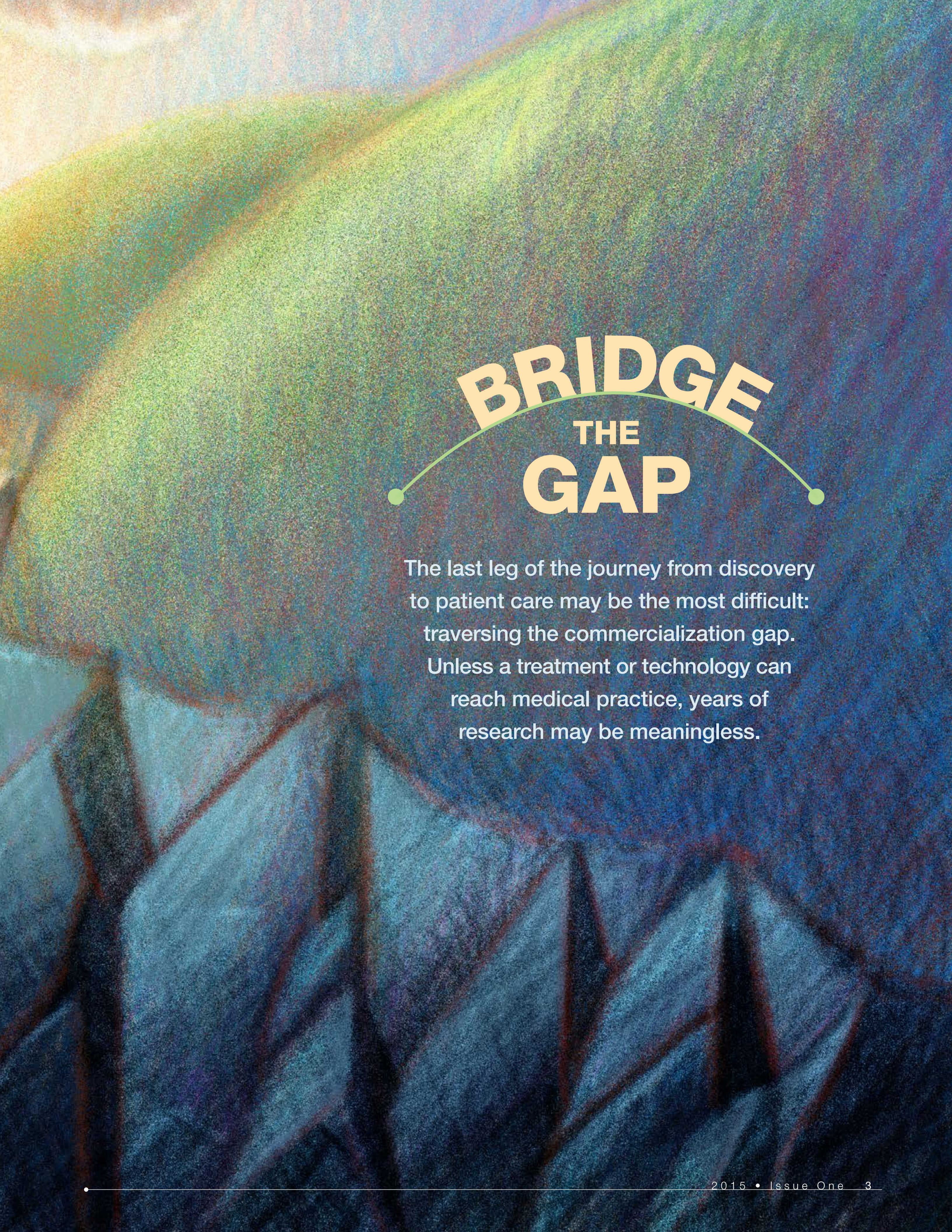
VALIDATED RESEARCH



BRIDGE THE GAP

The last leg of the journey from discovery to patient care may be the most difficult: traversing the commercialization gap. Unless a treatment or technology can reach medical practice, years of research may be meaningless.

Kidney disease patients on dialysis lose the ability to make hemoglobin, the iron-rich protein in blood that carries oxygen. They suffer from anemia (low hemoglobin) and feel run down and out of breath.

The standard treatment: doses of the hormone erythropoietin (EPO) to stimulate bone marrow to produce red blood cells, which contain hemoglobin. A red blood cell can survive for 100 days after it is produced, so repeated administrations of EPO can lead to accumulation of excessive numbers of red blood cells, and patients often end up with too much hemoglobin, which increases the chances of heart attack or stroke. In response, doctors throttle back on EPO. Often they guess wrong, causing patients to become anemic again. This roller-coaster effect, called hemoglobin cycling, is a major medical problem. Only about 45 percent of dialysis patients nationwide are managed within the proper hemoglobin range.

Now, a team of Mayo doctors and outside business consultants have developed a software program and algorithm that predict the effect of EPO in each patient and refine these predictions based on cumulative results.

"We were able to reduce our usage of the drug by almost 50 percent," says Mayo Clinic nephrologist James T. McCarthy, M.D., who helped develop the technology. "And we found that we could get approximately 80 percent of our dialysis patients using EPO in the desired hemoglobin range at all times."

James T. McCarthy, M.D., helped develop software to improve care for dialysis patients.

The software gained FDA approval and has been licensed by the start-up Physician Software Systems, which is offering it for sale to hospitals and clinics throughout the country. The impact on patient care and savings to the health care system could be huge. "If this particular approach were adopted throughout the U.S.A., we could see the bill for this drug, which is used in most dialysis facilities, drop nationally by $1 to $2 billion," says Dr. McCarthy. "It took the right convergence of skill sets — the hematology experts who know how blood is made, the system dynamics experts who know how to manage a complex system, and those of us who know where we want it to end up."

The software to reduce hemoglobin cycling is just one example of many Mayo Clinic inventions — new treatments, new devices, new procedures — that have the potential to improve patient care.

The challenge is finding ways to get these innovations outside Mayo's walls and into health care elsewhere, not just in the United States, but around the world. That's the job of Mayo Clinic Ventures — to translate research and new technology at Mayo Clinic into gains for patients.

"From a patient's standpoint you want to know that you're getting the best care," says James A. Rogers III, chair of Mayo Clinic Ventures. "And Mayo excels at giving you the best care. Part of that is, do you have the most up-to-date, the best, the cutting-edge technologies to help with whatever problem I have as a patient."

Says Rogers, "That's where we come in. We're facilitators who take great ideas and get them to the bedside quickly and efficiently."

TO IRELAND AND BACK AGAIN

Sometimes, novel and potentially valuable medical ideas face barriers that must be overcome by equally ingenious methods to bring the product to the public. The "Ireland deal" is a case in point.

Several years ago, Mayo Clinic gastroenterologist Vijay P. Singh, M.D., was a fellow at Mayo Clinic in Minnesota. He was studying pancreatitis, a debilitating disease in which the pancreas inflames and gradually dies bit by bit, causing

James A. Rogers III is chair of Mayo Clinic Ventures.

"We're facilitators who take great ideas and get them to the bedside quickly and efficiently."

- James A. Rogers III

"pain that is like a knife going from the front to the back of your belly," says Dr. Singh. The disease impacts 275,000 Americans each year. Many die. There's no effective treatment, says Dr. Singh, except to give painkillers, fluids, and the encouraging suggestion, "hopefully you'll get better."

Dr. Singh was examining tissue samples one day when he was called to a patient. "I put my samples on ice," he says. "That's what you have to do. You hold your reactions for an hour or two." His patient was due for a pancreas debridement — slicing away the dead tissue. "I thought of my patient and also of my samples and I thought, why not put ice on the pancreas to slow it down, like I'm doing with my samples?"

Working with lab rats, Dr. Singh developed a method to induce "local hypothermia." The stomach overlies most of the pancreas. By inserting a ballon into the stomach and circulating cool water through it, Dr. Singh could easily cool the pancreas about 10 degrees Celsius. In humans, Dr. Singh predicts, the cooling will have a "synergistic effect," slowing each of the reactions that would otherwise lead to a cascade of severe pancreatitis, and "thereby reduce hospital stay, reduce going to the ICU, and prevent mortality. That's the benefit to the patient. And also to the health care system, because the cost of acute pancreatitis in the United States is about $3 billion."

But then came a hurdle: Bridging the gap from using novel medical devices in lab animals to approval for human use is difficult and expensive in the United States. "There is not enough money for translational research like that," says

Vijay P. Singh, M.B.B.S, discovered how to put pancreatitis "on ice."

says Nair, "and then go into European market to sell it and then bring it back into the United States for FDA approval."

PARTNERING WITH INDUSTRY

Commercialization depends on good technology and a bit of luck. But a big factor, says Rogers, "is a very motivated, skilled business team."

Once a technology gains government approval, there are generally two ways to bring it to market. First is through a start-up (such as Physician Software Systems). Sometimes, physicians who develop a technology choose to form the new business themselves through Mayo's Employee Entrepreneurial Program. Otherwise, Mayo Clinic Ventures works with experienced entrepreneurs, often through its Entrepreneurs in Residence Program. "Their upside is getting equity in that company," says Rogers. "If that company is successful, Mayo wins and they win."

Manu Nair, Mayo's senior technology licensing manager who guided commercialization of Dr. Singh's device. "We call it the valley of death. That's where the good, cool technologies die because they don't have the money to advance them. You need to build a bridge between the early-stage basic research to a stage where venture capitalists or commercial enterprises will be interested in taking it on and running with it."

Says Nair, "I started looking to find money from sources that basically have money to advance technologies but don't have technologies." So he looked to Ireland. With a small population and university system, the country can't compete with countries like the United States on basic research. But it devotes considerable money to applied tech. Nair assembled a deal that brings together Mayo, Enterprise Ireland, and the National University of Ireland, Galway, to bridge the valley of death. If Dr. Singh's device is approved for human use in Europe, two venture capitalists have committed to create a spin-off company,

Mayo also commercializes new technology through existing companies. In return, Mayo negotiates for royalties on sales. Such was the case with a novel "elastography" technology developed by Mayo's Ultrasound Imaging Laboratory to diagnose changes in soft tissue.

Ultrasound, an oscillating sound pressure wave with frequencies generally far above dog-whistle range, is used to image tissues, such as a developing fetus. But ultrasound can also generate a "shear wave" in tissue. "Tissue moves and then releases," explains Mayo Clinic professor of biomedical engineering James F. Greenleaf, Ph.D. "That is like throwing a rock in a pond and causing a wave to propagate out away from where we pushed it."

Dr. Greenleaf and colleagues have developed a combination of software, hardware, and procedure that allows them to measure the speed that different frequencies propagate through tissue. "In order to analyze those shear waves, you have to do some fancy filtering and signal processing," says

"We call it the valley of death. That's where the good, cool technologies die because they don't have the money to advance them. You need to build a bridge between the early-stage basic research to a stage where venture capitalists or commercial enterprises will be interested in taking it on and running with it."

- Manu Nair

Dr. Greenleaf. The result is a visual image of differences in tissue stiffness and viscosity. That helps doctors diagnose and characterize the progression of various diseases.

"One of the huge potentials is in liver," says Dr. Greenleaf. For example, with hepatitis, the liver gets stiffer and stiffer. If the liver is very stiff, not much can be done. But at lower levels, treatment is possible. Ultrasound provides much more information than a needle biopsy. "The advantage of the ultrasound method is that it samples a lot of the liver, whereas if you stick a needle in, you get about 1/20,000 of the liver," says Dr. Greenleaf. Ultrasound elastography is also proving useful in examining breast and thyroid conditions.

Different facets of Mayo's elastography have recently been licensed to two well-known multinational corporations. Such agreements mean money for Mayo, of course, but also help patients who may never step foot on a Mayo campus.

"Every day, Mayo ideas are out there benefitting millions of people through companies like GE, Siemens, Medtronic, and DePuy," says Rogers. "I think there's a ton of benefit to society."

James F. Greenleaf, Ph.D., may be smiling about the "elastography" technology his lab developed.

Doctor²

A physician has no answers to a patient's problem but decides to personally seek out the solution. That's how a clinician-investigator is born. It's a plus for the patient and for medicine.

Harmeet Malhi, M.B.B.S., is one of Mayo Clinic's promising clinical-investigators.

Many Mayo Clinic physicians see patients in the morning and then don researcher's garb for an afternoon in the lab as a medical scientist.

This Clark Kent–like existence as a clinician-investigator enables your doctor to be on the discovery's edge of a given specialty. These dual-role professionals are one of Mayo Clinic's greatest strengths — physicians who seek solutions through science and apply that new knowledge in patient care as soon as possible. They're able to go beyond the existing medical literature for diagnoses and treatments because their published findings are changing medicine.

During residency and post-residency fellowships, emerging doctors can be overwhelmed with the responsibilities of caring for patients. As a result, they often abandon their research work in the laboratory. The Clinician-Investigator Training Program at Mayo Clinic provides physician-scientists with the time and mentoring to continue their research while establishing a robust clinical practice.

Mayo Clinic physician-scientists Lewis R. Roberts, M.B., Ch.B., Ph.D., David Dingli, M.D., Ph.D., and Harmeet Malhi, M.B.B.S., share a common goal: finding balance. They juggle the complicated medical needs of patients, the rigors of scientific precision in the labs, the demanding cycles of grant funding, staying abreast of rapid changes in their areas of specialty, and the

David Dingli, M.D., Ph.D., says Mayo's Clinician-Investigator Training Program made him a scientist.

expectations of mentoring younger scientists, all while trying to have time for family and friends.

This is the life of the clinician-investigator at Mayo Clinic.

Each, however, has been trained to excel in the dual role of physician and scientist. Drs. Roberts, Dingli, and Malhi have completed Mayo Clinic's Clinician-Investigator Training Program, a two- or three-year comprehensive educational experience for doctors doing their residency or fellowship at Mayo Clinic. The program is specifically designed to protect time for research, provide leadership through an active mentoring program, and assist the doctors in establishing a track record for publications and securing grant funding.

PROTECTING AN ENDANGERED SPECIES

In 1979, James Wyngaarden, M.D. (later to become director of the National Institutes of Health), rang the first alarm about physician-scientists becoming an endangered species. Practicing physicians have traditionally played a central role in research, advancing breakthrough treatments for innumerable diseases, from smallpox and cholera to polio, heart disease, and cancer. Much of this has been possible because of the unique perspective of their own experiences with caring for patients.

Shortly after, in 1980, Mayo Clinic began its Clinician-Investigator Training Program. Every two years, approximately 18 doctors are selected to participate. They may combine the M.D. degree with another advanced degree, such as a Ph.D. Their research can fall anywhere along the spectrum of biomedical inquiry, from highly specialized basic science through population-based studies.

Lewis R. Roberts, M.B., Ch.B., Ph.D., is a Mayo Clinic clinician-investigator and recently named Peter and Frances Georgeson Professor in Gastroenterology Cancer Research.

Steven H. Rose, M.D., dean of the Mayo School of Graduate Medical Education

TRANSLATING RESEARCH TO TREATMENTS

"Translational research" is biomedical research that attempts to turn scientific findings into practical applications that enhance human health and well-being. For example, doctors at Mayo Clinic hope to translate findings from the laboratory into better patient care and improved treatment options. Achieving that goal is not easy.

"It's very difficult for the clinician-investigator to stay current with the vast and rapidly developing body of biomedical science, while keeping up with all the major changes that are occurring in their area of clinical practice," says Steven H. Rose, M.D., dean of Mayo School of Graduate Medical Education. "However, the Clinician-Investigator Training Program provides residents and fellows with the time and the mentoring to develop their skills in both areas. The disappearance of physicians from the basic medical research workforce would cripple the translational process of medical discovery." Translational research, Dr. Rose proposes, is not a separate discipline but rather "at the very core of medical research at Mayo. The key is a dynamic, two-way partnership between clinical practice and biomedical researchers. That takes great discipline and commitment."

"The disappearance of physicians from the basic medical research workforce would cripple the translational process of medical discovery."

- Steven H. Rose, M.D.

FROM PATIENT TO LABORATORY AND BACK AGAIN

Imagine a two-lane road with one end being the research lab, the other the patient. Important medical discoveries in the laboratory need to reach the patient. The problems of the patient need to get back to the laboratory to guide and direct research. The key is the seamless flow of ideas and information back and forth between the two. Clinician-investigators drive the vehicles that travel back and forth along that imaginary highway.

"It can be a challenge trying to balance both," says Dr. Roberts, a hepatologist who has spent the past two decades studying how liver cancers develop, grow, and spread. "But I have a perspective in the lab that people who are 100 percent devoted to research don't have. The patient interactions are critical to my future research. I can bring their problems back to the lab, and it drives my research."

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> - Lewis R. Roberts, M.B., Ch.B., Ph.D.

THE GIFT OF TIME

Developing the expertise in both research and patient care takes a serious commitment on the part of the clinician-investigator. With the exacting demands of residency, a young doctor often will give up on his or her research to focus on patient care. Mayo Clinic's Clinician-Investigator Training Program protects the doctor's time to continue to work in the laboratory, as well as with the patient.

"It's like taking on two full-time jobs," says Dr. Roberts. "You want to achieve mastery in both, and mastery takes time. The CI program gave me that gift of time. It protected my time to continue my research in the laboratory without having to forego my commitment to my patients. Not many doctors have that opportunity."

Dr. Dingli, a hematologist whose research into the use of replicating viruses for cancer therapy lives at the interface between mathematical theory and experiment, is more succinct about the importance of the Clinician-Investigator Training Program to his career.

"The CI program made me a scientist," Dr. Dingli says. "Research takes time and money. The CI program protected my time to learn how to become a scientist. It also expanded my vision to see the importance of group or collaborative science and taught me how to compete for money. None of that would have happened without the CI program."

THE VALUE OF MENTORING

While acknowledging that the protected time was invaluable to developing her research into liver disease, Dr. Malhi found the mentoring she received in the Clinician-Investigator Training Program played a crucial role in her becoming a top-notch researcher. No one is accepted into the training program without the support of a mentor who is active in research and willing to spend the time necessary in training an emerging scientist. The mentoring goes far beyond how to design an experiment in the laboratory.

Dr. Malhi studied with Gregory J. Gores, M.D., Reuben R. Eisenberg Professor, now executive dean for research at Mayo Clinic. "Greg certainly made me a better researcher," Dr. Malhi says. "But he also taught me how to prepare manuscripts for publication, the ins and outs of grant writing and fundraising. He showed me how to be a better clinician and how to find balance between my professional and personal life. I'm more successful because of his mentoring, and I'm also a better person."

Becoming a scientist, just like becoming a clinician,"has a long apprenticeship," says Dr. Dingli. Working with a mentor "provided me with the guidance and advice to become an independent researcher. It helped hone my research skills. It also taught me the value of collaboration. A clinician's work cannot be done alone, just like a researcher's work cannot be done alone."

TAKING THE LESSONS HOME

One day, Dr. Roberts hopes to return to his native Ghana with news that he has discovered a means for early detection and subsequent treatment for liver cancer. The clinician-investigator understands how important this news would be to this sub-Saharan nation — and the world. According to Dr. Roberts, primary liver cancer, or hepatocellular carcinoma, is the second leading cause of cancer deaths, accounting for an estimated 750,000 deaths per year.

If he succeeds, it will be, in part, because of his work as a clinician-investigator. "My CI training and the Mayo culture of mentoring and collaboration has allowed me to care for patients and do my liver cancer research," Dr. Roberts says. "That was not possible if I had stayed in Ghana, but all of the people at home may still benefit from my work. Professional and departmental boundaries don't exist here. If I succeed or if a colleague succeeds, we all succeed. And people's lives are improved."

In the end, that's what Mayo Clinic's Clinician-Investigator Training Program is all about: directed research combined with clinical expertise to improve people's lives. It's the perfect balance.

Over 275 people have completed Mayo Clinic's Clinician-Investigator Training Program since its inception in 1980. Nearly 50 percent of the doctors who have finished the program still work at Mayo Clinic. Two clinician-investigators who completed the training are Carmen M. Terzic, M.D., Ph.D., and Gianrico Farrugia, M.D. Here they talk about their experiences in the Clinician-Investigators Training Program and answer some questions about their work at Mayo Clinic.

Carmen M. Terzic, M.D., Ph.D.

After completing the Clinician-Investigator Training Program in 2003, Dr. Terzic remained at Mayo Clinic to continue her work in cardiovascular research and physical medicine. The Venezuelan native now chairs the Department of Physical Medicine and Rehabilitation and plays a leading role in the development of stem cell therapy to repair damaged hearts.

"The Clinician-Investigator Program was the perfect program for me," Dr. Terzic says. "It helped me consolidate my research knowledge without leaving a time gap in research because of my clinical practice. And it helped me obtain the publications and preliminary data I needed to be competitive for extramural funding, which ultimately helped me launch my career as an independent clinician-investigator."

Q: What do you do at Mayo Clinic?

I conduct research in basic stem cell biology and cardiovascular rehabilitation. I also do clinical work in cardiovascular rehabilitation, general physical medicine and rehabilitation, and pediatric chronic pain program.

Q: What is your current research?

I study the role of nuclear transport in the differentiation and genetic shaping of cardiac cells during the differentiation process from stem cells.

Q: Why is this interesting to you?

I have been always interested in the basic mechanism of cellular function, and I have been also interested in muscles (cardiac, skeletal). Understanding basic stem cell differentiation is important as it will allow us to build tools and to define intervention that will allow a control and manipulation of the differentiation process to improve outcomes in stem cell therapy.

Q: What's the best advice you've ever received?

Get involved in science/research and apply to a Ph.D. program. This advice was given to me by my mentor in Venezuela.

Q: What's the most adventurous thing you've ever done?

I took a two-month backpack trip to Europe and was in Berlin at the time of the fall of the Wall. Although coming to live in Rochester, Minn., from a South American city of over one million people may also apply as an adventure.

Gianrico Farrugia, M.D.

Dr. Farrugia came to Mayo Clinic in 1988 from his Mediterranean homeland of Malta for his residency and stayed to complete the Clinician-Investigator Training Program in 1993. Today, he is a prominent gastroenterologist leading cutting-edge research that embraces enteric neuroscience. Dr. Farrugia also helped guide Mayo Clinic's advances in genome-driven individualized medicine as the director of the Center of Individualized Medicine. He is also the vice president of Mayo Clinic's campus in Florida.

"When I came to Mayo," Dr. Farrugia says, "I had good clinical skills, but I had no research skills at all. The CI program was fundamental to my career in research. I had two great and very different mentors, Joe Szurszewski and Jim Rae, who taught me good research techniques, introduced me to the right people, and taught me to obsess over every detail — from each sentence in a grant application to the smallest specifics of an experiment. I can't overstate it enough: The CI program made my career."

Q: What do you do at Mayo Clinic?

I am a gastroenterologist and see patients with motility disorders as well as perform endoscopy such as colonoscopy. I run a translational research lab focused on understanding normal gastrointestinal function, abnormal function in motility diseases, and discovering new ways to treat these diseases.

Q: What is your current research?

We are studying a cell type called the interstitial cell of Cajal that is the pacemaker cell of the gut. We also study how ion channels — cell membrane proteins that allow ions to move in and out of cells — open and close, including by mechanical forces. We are also very interested in how carbon monoxide is made by macrophages and other cells in the gut and protects key cell types from damage by diseases such as diabetes. These cell types are key to maintaining normal gut function and become abnormal in diseases such as diabetic gastroparesis, irritable bowel syndrome (IBS), and constipation. By studying them, we can come up with new ways to treat these diseases.

Q: Why is this interesting to you?

I am a physician first and want to cure the patients I see in my practice.

Q: What are the practical applications for better patient care?

We have identified the key abnormalities in diseases such as diabetic gastroparesis, IBS, and constipation. With all my colleagues in the motility interest group at Mayo, we are starting clinical trials to test disease modifying agents rather than only treat symptoms.

Q: What's the best advice you've ever received?

Be curious and always go to the source, never assume what you read is correct, find out who originally said it and what data they had to say it. That has given me the opportunity to see things in a different light from the literature.

Q: What might people not know about you?

I was a competitive windsurfer.

Vicente E. Torres, M.D., Ph.D.

Peter Harris, Ph.D.

Even if you're tops in your field, you may need a partner with skills you don't have.

That was the conclusion Mayo Clinic nephrologist Vicente E. Torres, M.D., Ph.D., came to about 15 years ago. As head of Mayo's Division of Nephrology and Hypertension, he had worked at Mayo for nearly a quarter century and was renowned as a clinician and researcher who specialized in polycystic kidney disease.

But as the importance of genetics to human diseases — especially PKD — became ever more obvious, Dr. Torres knew he needed the skills of someone who could understand the cause of disease at a molecular level.

"Medicine entered a new phase where genetics became really very important, not only for monogenic diseases like polycystic kidney disease, but for almost all diseases that have a genetic component,"says Dr. Torres, "In nephrology at that time, we really didn't have anyone who was trained in molecular genetics. So, I thought that it was a very good idea to try to attract people like that here to Mayo."

He recruited Peter Harris, Ph.D., a molecular geneticist from the University of Oxford whom Dr. Torres knew from various international conferences and meetings. Dr. Harris was head of a team that had identified the gene that causes the most common form of polycystic kidney disease.

Dr. Harris came to Mayo in 1999. The partnership has probably worked better than either investigator imagined. The two have coauthored dozens of scientific papers and have published scores of other studies individually or with other collaborators. Their research on PKD has lead to new understanding of the disease, its causes, and its progression. Their collaboration appears to be creating the possibility of treatment for a genetically determined disease that afflicts hundreds of thousands in the United States alone.

"What you have in that combination is one of the best examples of a clinician-scientist teaming up with a basic scientist, bringing their own complementary tools and expertise in the hope there will be new and better treatments," says Mayo Clinic nephrologist Karl A. Nath, M.B., Ch.B. "There's no redundancy. It's an instance of one and one makes four rather than two."

AN UNLIKELY PARTNERSHIP

The two scientists are a study in contrasts. Dr. Torres, the older man, is professorial in salt-and-pepper beard, his speech serious and measured, with a trace of a Spanish accent. Dr. Harris seems like an English schoolboy in comparison. He says Dr. Torres lured him to visit Minnesota in the middle of one of the warmest Minnesota winters on record, as though Dr. Harris had no idea what was in store for him. "I think it was 40 degrees when we were here," says Harris. "It certainly wasn't like the last winter."

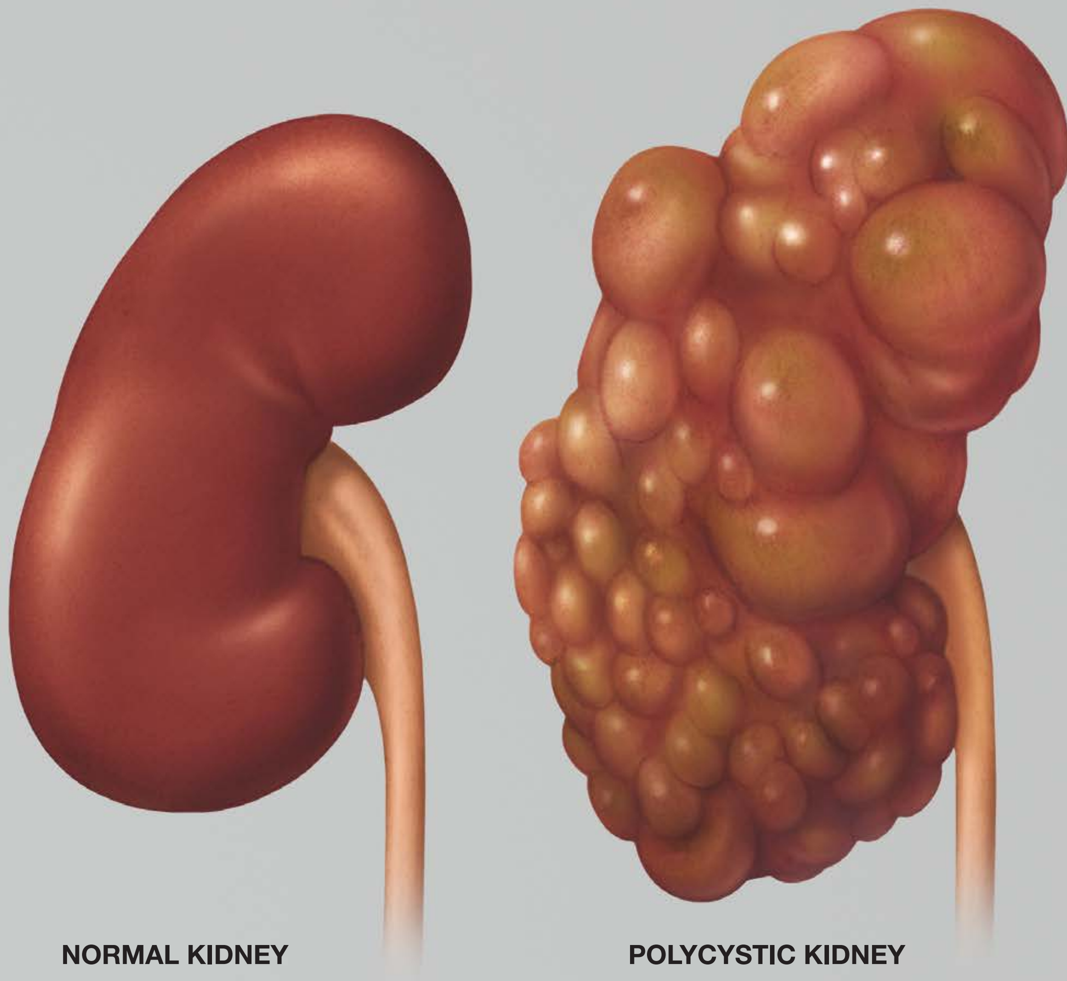
Not surprisingly, the two scientists came to specialize in PKD in entirely different ways.

For Dr. Torres, it was a matter of public health. He was already a nephrologist at Mayo Clinic when he had the opportunity to examine the prevalence and outcomes of the disease in Olmsted County (the southeastern Minnesota county that includes Mayo).

"I found polycystic kidney disease to be a fascinating field to work in because, although it's a kidney disease, it involves many other organs," says Dr. Torres.

"What you have in that combination is one of the best examples of a clinician-scientist teaming up with a basic scientist, bringing their own complementary tools and expertise in the hope there will be new and better treatments"

- Karl A. Nath, M.B., Ch.B.



Polycystic kidney disease or PKD can turn a healthy kidney into something almost unrecognizable. The cysts proliferate in clusters, usually causing the affected kidney to dwarf a normal organ. Mayo's research into the disease is part of the work ongoing in the Robert M. and Billie Kelley Pirnie Translational Polycystic Kidney Disease Center.

"To get the understanding of how the kidney works and how the kidney fails in polycystic kidney disease, there are also other organs and systems involved — the liver, the heart, and the vascular system."

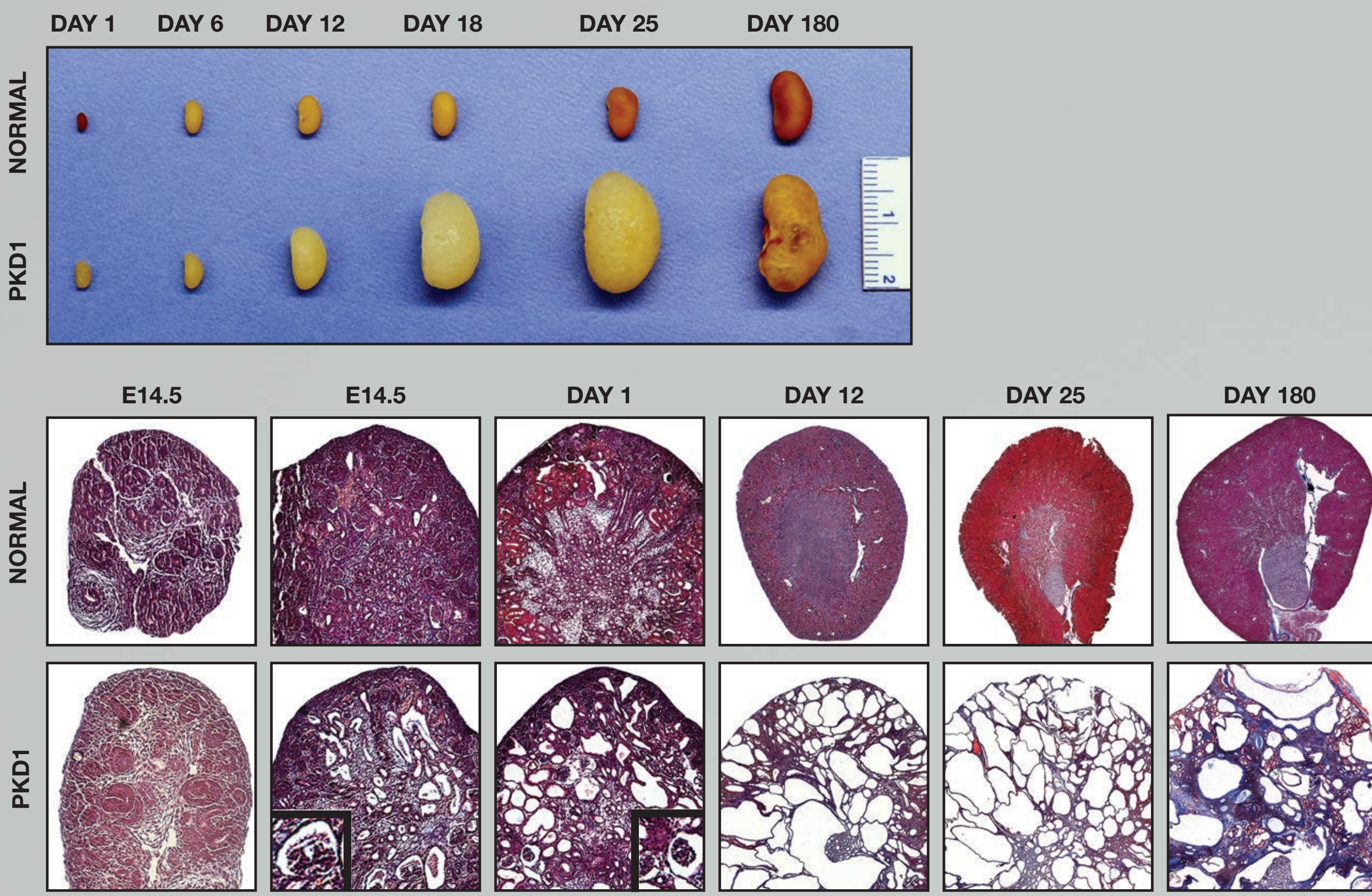
For Dr. Harris, it was all about genetics. "I was very interested in how we could use the new genetic methods—the identification of polymorphic markers. It's rudimentary now, but it seemed cutting edge at the time."

Their work has the potential to affect the lives of some 600,000 Americans with the disease. PKD is an inherited disorder that develops as clusters of cysts grow within the kidneys, which gradually fail, usually beginning in early middle age. The cysts can grow in the liver and elsewhere. Other complications include high blood pressure, brain aneurysms, heart abnormalities, and chronic kidney pain.

The autosomal dominant form of the disease is caused by an abnormality to one of two genes. A child with one affected parent has a 50 percent chance of getting the disease. Symptoms, such as gradually failing kidneys, usually show up in early middle age. Far less common is autosomal recessive PKD, in which both parents must have the genetic abnormality to pass the disease to their children. Abnormalities in kidney and liver function show up in infancy and childhood. Many victims die in infancy. Those who survive often suffer high blood pressure and need a kidney transplant in childhood.

At the heart of the problem, says Dr. Torres, are the one million filters and tubules that make up each kidney. PKD affects the tiny tubules. "When these genes don't work properly, these tubules don't know when to stop growing and form the cysts," says Dr. Torres. "As they grow, they destroy the tissue. The kidney gradually loses its function." About half of patients with the dominant form of PKD have end-stage renal disease by age 60. More than 2,000 will start kidney replacement therapy — such as transplant or dialysis — every year in the United States.

"Most patients know they are at risk because of family history," says Dr. Torres. As a result, there is a "psychological burden" to the disease. "Patients with



External and cross-section views of mice kidneys with PKD. *Analysis of an early onset mouse model of PKD1 (Pkd1RC/del2). (Top) Photo of the kidneys showing the rapid increase in the size of the kidney from day 1 after birth (P1) to P25 in the Pkd1 mouse compared to normal. Mice that survive to 6 months have kidneys with a shriveled appearance. (Bottom) Histological kidney images of the Pkd1 model compared to normal. Fetal kidneys from embryonic day (E14.5 and E16.5) and images after birth from day 1 to day 180. The kidney mostly consists of cysts by day 25 and by day 180 shows a high level of fibrosis (blue stain). Glomerular cysts are enlarged and inset at E16.5 and day 1. The scale is the same between the normal and Pkd1 kidney at time point.*

polycystic kidney disease can go through phases of denial, anger, and depression," says Dr. Torres. "Family members at risk of polycystic kidney disease often don't find out that they have the disease for a couple of reasons. One is that there is a natural tendency for families not to discuss it much. And second, which is more important, is that we don't screen children for polycystic kidney disease because there is nothing we can offer. So we recommend screening the at-risk family members when they are adults."

Doctors treat any high blood pressure or pain. They may control cholesterol and screen for intracranial aneurysms. Otherwise, there's little to be done until kidneys fail and a transplant becomes necessary.

"If we can slow down or stop the progression in these patients, then we can alleviate some of the problems by delaying renal failure, transplantation, or dialysis," says Dr. Harris. "Obviously, we'd like to completely cure the disease, but even if we could slow it down or slow down the progression of the disease by five or 10 years, that would be a big breakthrough."

FROM MOLECULES TO PATIENTS

Dr. Harris works at the most basic scientific level. He came to Mayo Clinic to continue researching the genetics of PKD because he knew "there are always a lot of new patients coming through the door. Many of those patients are involved in trials of some sort."

Dr. Harris examines "downstream signaling effects"— how genes, such as the abnormal PKD gene, create various molecules that "signal" or stimulate cell membrane receptors and affect the formation of tubules in the kidney. To conduct these inquiries, Dr. Harris engineers a variety of "genetically altered" animals, such as mice and zebrafish in which specific genes are removed or changed.

"Making the right mouse, one that really matches the way that the disease progresses in humans — or speeding it up a little bit so you don't have to wait 50 years — has been something we've spent quite a lot of time on," says Dr. Harris. The trick is to mimic the onset of the disease fast enough to be efficient but

slowly enough to keep the animal alive for study — "a Goldilocks level of the mutation."

Dr. Torres's work picks up where Dr. Harris's leaves off. He spends a quarter of his time seeing patients, the remainder in PKD research. That includes characterizing the progression of the disease and setting up drug and other therapeutic trials.

One important result of their collaboration: the discovery of a compound that inhibits the signaling of a particular molecule and slows by half the progression of PKD. The treatment has been approved for human clinical treatment in Japan (though not yet in the United States).

Meanwhile, says Dr. Torres, "there are a lot of candidate drugs that need to be tested — more that need to be tested than money available for clinical trials."

Another priority is developing new imaging technologies to examine the progression of PKD long before symptoms appear. "If you want to treat, you have to be able to measure," says Dr. Torres. "So to be able to measure before the kidney function goes down is something that is very important."

Other work focuses on preventing transmission of PKD to the next generation. Mayo Clinic has begun providing "preimplantation genetic diagnosis" for PKD. Doctors screen out embryos that carry the gene for PKD before implantation and pregnancy.

In the future, Dr. Harris says, the two researchers hope to find other genetic factors that influence the severity and progression of the disease. Even further in the future "there might be methods of gene editing," he says. "You can imagine that potentially you might be able to gene-edit at a very early stage. Those cells would go back and populate the embryo. It's looking more promising than it did even a couple of years ago."

AN ENVIRONMENT FOR DISCOVERY

What makes for fruitful collaboration between basic scientists and clinicians?

Partly, it's environment. Mayo Clinic's tightly knit campus helps."Here you have a lot of clinical departments, and you have researchers working side by side," says Dr. Harris. "Everything is just three or four minutes away."

"And it helps that in this collegial setting, a culture of collaboration has developed," says Dr. Torres.

Resources, especially human resources, are vital as well. Says Dr. Torres, "I think one of the things that Mayo brings to the equation is expertise in multiple areas. Polycystic kidney disease involves the kidneys, but it involves other organs." So he and Dr. Harris have studied problems with liver specialists and surgeons, neurologists and vascular surgeons, kidney radiologists and vascular radiologists. "I think all of these people are top in their areas, so having the ability to collaborate with these people is something that Mayo brings."

Most important, perhaps, are personal chemistry, skills, and knowledge. Dr. Torres and Dr. Harris bring different backgrounds and interests to bear toward a common objective — Dr. Torres with his years of clinical experience with patients and Dr. Harris with his genetically engineered lab mice and the ability to read the human genome.

"That's when collaborations work well, I think," says Dr. Harris. "If you're both trying to do the same thing, it doesn't really work out well. When you have different expertise and you can put it in and enhance the final product, which is what we've been doing I think, that's when collaboration really works — when you can make a much better product than either of us could make individually."

> *" . . . that's when collaboration really works — when you can make a much better product than either of us could make individually. "*
>
> - Peter Harris, Ph.D.

New Center for Biomedical Discovery Focuses on Basic Science

How do you starve cancer? How does the body recognize "self"? What makes cells stop producing insulin?

These are some of the unanswered but fundamental questions Mayo Clinic's new Center for Biomedical Discovery will be targeting. The center brings to the forefront the cellular and molecular expertise in Mayo's laboratories, along with the latest technologies, to gain a better understanding of what actually causes disease. Discoveries in the laboratory form the basis for tomorrow's clinical care, and Mayo's scientists have been teaming with physicians to explore the needs of patients for over 100 years.

With over 30 years of scientific experience and a decade as leader of Mayo's Department of Biochemistry and Molecular Biology, Mark A. McNiven, Ph.D., George M. Eisenberg Professor, is director of the new center. Dr. McNiven says finding the mechanism of disease is essential to curing it, rather than simply limiting damage or treating symptoms.

"Our goal is to work closely with clinicians to provide answers and solutions for patients everywhere," he says. "We want to combine the objectives so we understand the cause of disease while we treat the condition."

Mark A. McNiven, Ph.D., leads the Mayo Clinic Center for Biomedical Discovery. The goal is to find out how diseases start.

"Discovery science is a significant part of our research effort at Mayo Clinic, as it is the starting point in seeking help for our patients when current knowledge isn't enough," adds Gregory J. Gores, M.D., Ruben R. Eisenberg Professor and executive dean for research at Mayo Clinic.

Under Dr. McNiven's leadership, cross-disciplinary groups of researchers will be road mapping diseases to improve health in diverse fields. In the past year, teams at the center have published research on topics ranging from the progression of dysfunctional tau protein in Alzheimer's disease to identification of a key gene that, if inhibited, could halt development of pancreatic cancer.

Teams are organized around three platforms of excellence, which guide the center's research on disease processes spanning most organ systems.

- The Metabolism and Diabetes Platform, led by Lawrence J. Mandarino, Ph.D., studies diseases related to defects in metabolism, such as obesity, type 2 diabetes, and cardiovascular disease.
- The Immunity and Fibrosis Platform, co-led by Virginia M. Shapiro, Ph.D., and Edward B. Leof, Ph.D., Erivan K. Haub Family Professor of Cancer Research, investigates the role of immune system in disease, including the causes of organ fibrosis and cirrhosis.
- The Cancer and Cell Aging Platform, under the co-leadership of Daniel D. Billadeau, Ph.D., Edmond A. and Marion F. Guggenheim Professor, and Jan van Deursen, Ph.D., Vita Valley Professor of Cellular Senescence, explores the mechanisms that contribute to unchecked cell growth, as well as the impact of cell aging on diseases like arthritis and muscle wasting.

To maximize discovery knowledge, the platforms in the center bring together teams of investigators from across Mayo Clinic. While the team science is initially focused on investigators within Mayo Clinic, there are plans to create alignment strategies with external partners in industry, academia, and foundations as the center evolves. Dr. McNiven will also prioritize innovation and commercialization to help make new discoveries available to patients.

With team science and broad collaboration, Dr. McNiven plans to align the Center for Biomedical Discovery with the fundamental goal of Mayo Clinic — meeting the needs of its patients.

Debra Stockdale Prihoda holds a family photo. She is the baby on her mother's lap.

Reflecting on the Past

Mayo Clinic researchers conducted the animal and clinical studies on the first drug to combat tuberculosis. Then they successfully treated the first patient, published their findings—and co-authored a love story.

Patricia Thomas was trying to keep up her spirits. Her cough was not improving. Already thin, she was not gaining weight and the night sweats had returned. She tried to be optimistic, writing her boyfriend, Bob Stockdale, who was on a U.S. Navy destroyer in the Pacific fighting in World War II. She read his letters again and again. The nurses considered her the most spirited of their patients at Mineral Springs Sanitarium in Cannon Falls, Minn.

It is unclear whether Patsy, as she was called by family and friends, fully realized that she was dying, but her doctors did. It was 1944, and no effective treatment existed for tuberculosis.

About 45 miles away, in Rochester, Minn., however, two doctors at Mayo Clinic were about to make medical history.

FELDMAN AND HINSHAW

William H. Feldman, D.V.M., born in Scotland and transplanted to Colorado, eventually landed at Mayo Clinic as a laboratory researcher. His fixation on tuberculosis began early. His mother had allowed TB patients to sleep on their large front porch to take in the cold mountain air — thought to be curative for consumption, as TB was called in the 19th century. By the time Dr. Charles Mayo hired him in 1927, Dr. Feldman had had time to think about those patients and the path of his scientific career.

Corwin H. Hinshaw, Ph.D., M.D., was at first a parasitologist, studying birds and other animals at the University of California. He then spent time at American University of Beirut, finally deciding to enroll in medical school so he could "understand the host as well as the parasite." After a short two years in medical school, he was aiming at a specialty in gastroenterology, but in 1933 was hired at Mayo Clinic in pulmonology and soon became an expert in pneumonia, then still a common killer. He also came into contact with his share of tuberculosis patients referred to Mayo from surrounding sanitariums.

How Drs. Feldman and Hinshaw met is not recorded, but once they did, they joined forces against a common foe: tubercle bacilli.

Mayo collaborators William H. Feldman, D.V.M., and Corwin H. Hinshaw, Ph.D., M.D., proved the effectiveness of streptomycin against tuberculosis.

Sanitariums like the one at Cannon Falls sprang up around the globe. Note the screens on the front windows allowing cold air into the patient sleeping areas. Patricia Thomas went to Mineral Springs a few weeks after graduating from Austin High School.

LONG HISTORY OF TUBERCULOSIS

Few people today realize how deadly tuberculosis once was — and still is. TB, consumption, phthisis, scrofula, Pott's disease, and the White Plague are all terms used to refer to tuberculosis throughout history. Mummies from Egypt dating to 2400 BCE show tubercular decay in their spines. The list of people who have succumbed to tuberculosis includes such notables as Egyptian King Tut and American First Lady Eleanor Roosevelt, writers Jane Austen and George Orwell, religious leader John Calvin, and South America liberator Simon Bolivar. Tuberculosis has killed 1 billion people around the world over the past two centuries. In 2010, 8.8 million new cases were diagnosed, and over 1.2 million deaths occurred, most of them in developing countries.

Prior to 1950, however, the United States had its own TB epidemic. The country and other nations were dotted with sanitariums where those with the respiratory disease were sent, mainly to be isolated from the rest of the population. Fresh air, clean surroundings, and healthy food were all supposed to help. The idea was to bolster a patient's immune system to naturally fight off the infection. Some did better than others, but no one knew why. For many, it was months or years of upturns and declines as the bacilli slowly caused lung tissue to deteriorate, hindering breathing and making patients cough up blood. According to the Centers for Disease Control and Prevention, today, about 500 people die of TB in the United States, annually. In contrast, from the 1920s into the '40s, deaths exceeded 70,000 a year.

THE FIRST EXPERIMENT

That was the situation in which Drs. Feldman and Hinshaw began their work.

Scouring the latest medical literature for possible paths to pursue, the two became interested in a drug called Promin, a sulfone compound that had been tested against a range of diseases by drug maker Parke, Davis & Company, but no one had tried it against TB. The Mayo researchers were prepared. They had determined that the guinea pig was an ideal model as it easily contracted the virulent strain of human TB and the disease would take its course in a consistent fashion.

From May 1940 into the fall of the year, Promin was studied in the animals in Rochester. Early the following year, they reported in *Proceedings of the Staff of Mayo Clinic* the positive results. It was not anything close to curative, but there was significant modification of the disease. They had, in effect, bumped it off the "impossible mission" list. But according to Dr. Feldman, their peers, upon hearing their presentation at the American National Tuberculosis Association, were far from enthusiastic.

"Few in the audience believed what we said, many didn't understand, and some were sure we were wasting our time in searching for an effective chemotherapeutic agent," Dr. Hinshaw said in a later presentation.

The study provided two additional benefits. It signaled to others that this team in the Midwest had developed a good system for testing potential anti-TB compounds and it spurred the two of them to try a range of other formulas, including many pre-existing drugs that didn't work for other diseases but might work on TB.

In July 1943, Dr. Feldman wrote Selman Waksman, a Ph.D. scientist at Rutgers University to ask about drugs he was working on that they might test. The pair had been following his published papers on natural compounds that had antibacterial properties. He also asked if he could visit Waksman's lab in New Jersey. After some delay, Dr. Waksman extended an invitation and in a very cold November, Dr. Feldman made the long train trip to the East Coast.

At this time, the Waksman lab was working on a drug that had been isolated from microbes in the soil. His lab assistant, Albert Schatz, was working long hours

> *"Few in the audience believed what we said, many didn't understand, and some were sure we were wasting our time … "*
>
> - H. Corwin Hinshaw, Ph.D., M.D.

extracting the compound from solution in the basement of the lab building, often sleeping on the floor to ensure the process didn't stop. While not immediately identified to Drs. Feldman and Hinshaw, this compound was streptomycin.

That November visit is shrouded in mystery. According to physiologist and historian Julius Comroe, Jr., Dr. Feldman urged Dr. Waksman to include TB in any tests he would initially run on prospective antibacterial drugs, or antibiotics, as Dr. Waksman would label them. Dr. Feldman also asked him to make available any promising compounds so he and Dr. Hinshaw could conduct guinea pig trials.

At the time the doctors visited in New Jersey, the first paper on streptomycin might have already been in the works, perhaps even in the hands of journal editors. In January 1944, the paper was published, including some data of its effects on TB. There is no evidence, however, that the Mayo team even knew the drug existed.

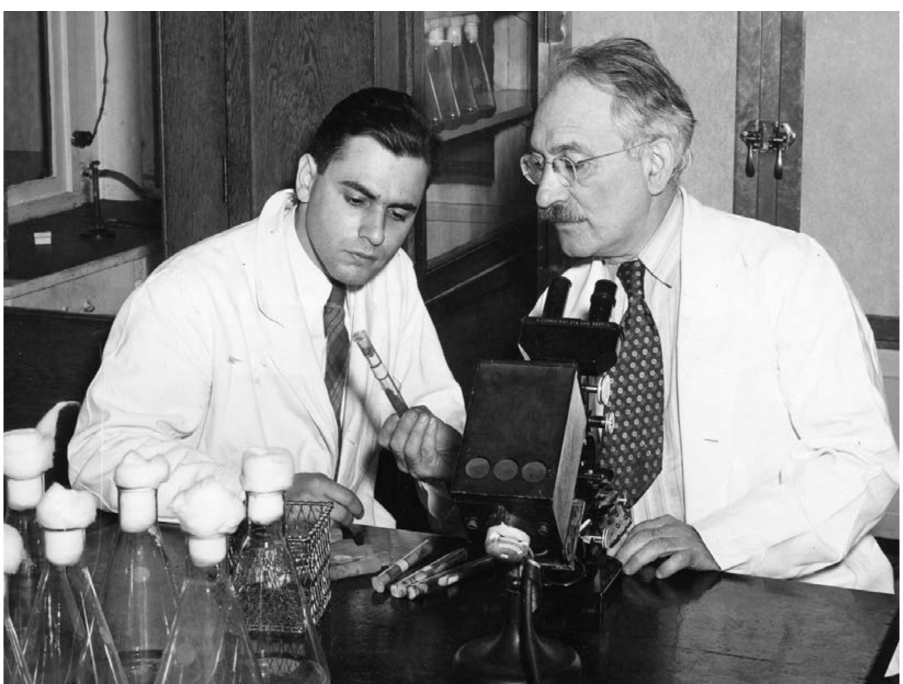
Finally, in March, Dr. Waksman wrote Dr. Feldman asking if he would test streptomycin. A microbiologist and biochemist whose work was founded in plant and soil research, Dr. Waksman could do cellular testing but had no way to conduct animal studies or human clinical trials. He needed the collaboration with Mayo Clinic for any rapid development of the drug.

TEN GRAMS AND THE BEGINNINGS OF A CURE

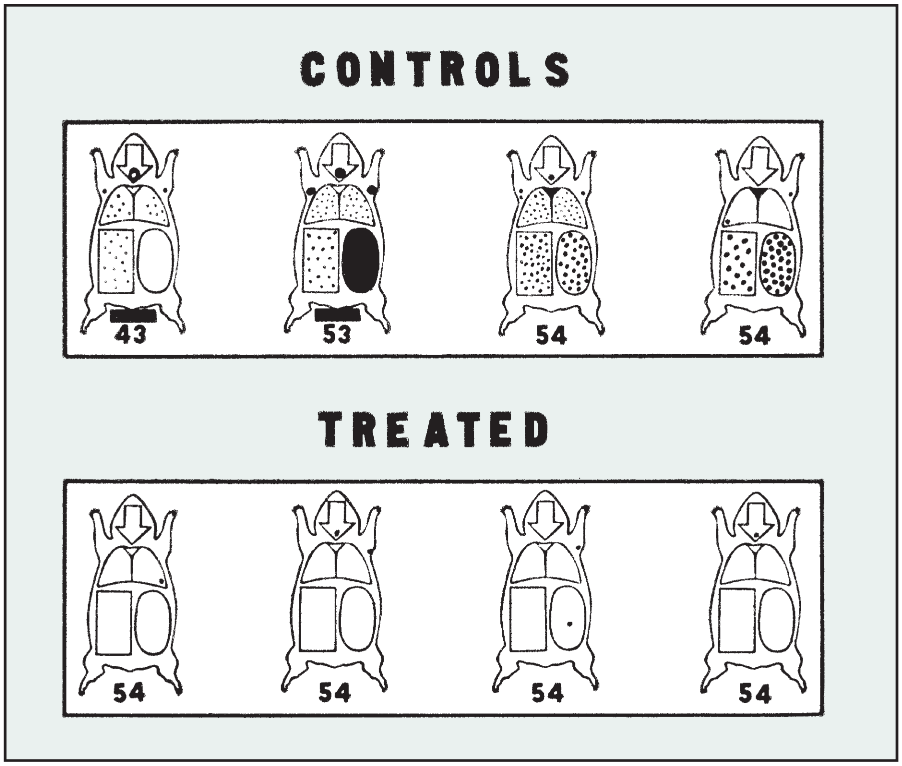
Drs. Feldman and Hinshaw, however, were given little of the drug to work with; the granules in the one vial they received weighed ten grams, equal to the weight to two U.S. nickels. To maximize its use, they split the drug into multiple doses that would last from early April until late June for four guinea pigs with TB. The small doses provided relief but did not cure the pigs. Still, this initial test achieved its goal: to show the drug was not overly toxic, unlike an earlier compound, actinomycin.

During this period, Dr. Waksman was in talks with Merck & Company, the New Jersey pharmaceutical firm. At a meeting in July, Mayo and Rutgers scientists tried to persuade Merck officials to produce enough streptomycin to supply the Mayo team. In the end, according to author Peter Pringle, it was CEO George Merck himself who consented to the plan as part of the war effort.

Now, the Mayo team could begin serious tests.



Albert Schatz and Selman Waksman, Ph.D., discoverers of streptomycin. (Courtesy, Rutgers University Archives)



A graphic was created to convey data in the published findings of the streptomycin guinea pig studies. The picture tells the story. American Review of Tuberculosis, *1945.*

Drs. Feldman and Hinshaw had gambled that they would obtain more of the drug and had infected a number of guinea pigs with the TB bacteria before they left for New Jersey. When they returned to Minnesota, they were able to immediately repeat the toxicology trial and received the same results. When World War II left them with a shortage of technicians, the two doctors maintained the dosing themselves, administering the drug every six hours for 61 consecutive days.

In August, they began a large trial of 25 guinea pigs infected with TB with 24 control animals. After 215 days they presented the findings to their peers, the staff of physicians and researchers at Mayo Clinic, probably in the 15th floor assembly room of the Plummer Building. It was two days after Christmas, 1944. They repeated the study in the following months and published their paper in the *American Review of Tuberculosis*.

Was streptomycin effective against tuberculosis? Almost in answer to their previous critics, Feldman and Hinshaw drew a very clear picture, literally (see graphic above).

NOTHING TO LOSE: THE PATRICIA THOMAS STORY

Dr. Karl Pfeutze knew he could do no more for Patsy Thomas. In October 1944, her right lung had worsened and a Mayo surgeon removed some ribs to try to limit the disease. Then X-rays showed deterioration in her left lung. Dr. Pfeutze told Patsy he was permanently transferring her to Rochester and into the care of Dr. Hinshaw at Mayo Clinic.

Dr. Hinshaw concurred with Dr. Pfeutze that the young woman was dying. It was clear that streptomycin was her only chance. The final animal tests weren't complete, but the data were sufficient. The doctors were confident an experimental treatment was reasonable. Patsy told Dr. Hinshaw to go ahead with the injections.

Consenting to what today would be called a "first in human study" appears a simple choice for someone with nothing to lose. Yet, it takes courage to undergo what may be stressful or painful treatments, knowing that one's life may be extended only briefly, if at all. Often patients agree to participate — in their words — "so it may help others."

Those who take part in research studies play as important a role as the scientists and physicians.

In November 1944, Patsy began her treatments. Dr. Hinshaw had to estimate the dosages, extrapolating from the animal trials and perhaps from two earlier patients. An elderly man may have received some injections at Colonial Hospital in Rochester, but his condition was far worse. He died after a few days. A second man, with bloodborne TB, was treated "for two or three months," according to Dr. Frank Ryan's history, *The Forgotten Plague*. That patient showed some improvement but died of an unrelated blood clot.

Patsy Thomas was the first human to receive a full schedule of streptomycin to treat her TB. In all, she received five courses of the drug with multiple doses over five months, each carefully administered, monitored, and adjusted, based on observations and X-rays. By April 1945, the disease had receded to the point that surgeons were able to remove the small portion of a lung still infected, leaving Patsy Thomas clear of the deadly disease.

OUTCOMES

Streptomycin was only the start, but it was the beginning of the end of a terrible disease that few people even remember today.

In December 1948, Dr. Feldman wrote to Dr. Waksman, with whom he had developed a constant exchange of letters, phone calls, and telegrams over the years, to say he was going to be leaving Rochester shortly for a stay in the woods of northern Minnesota. He had just completed his own course of treatment for tuberculosis. He had contracted the disease either from a patient or from his own testing, but he was under the able care of a quite competent Mayo specialist named Corwin Hinshaw. He had received what would be the standard treatment from then on — streptomycin and PAS (para-aminosalicylic acid). He was back at Mayo a year later, his life saved by the drug he helped develop and by his colleague and friend.

Dr. Selman Waksman won the Nobel Prize in Physiology or Medicine in 1952. Drs. Feldman and Hinshaw ended up celebrating by having a drink under the shade tree in the Feldmans' backyard.

And on October 8, 1947, Patricia Thomas became Patricia Stockdale, marrying her sweetheart, Bob, after he left the Navy. Patsy's daughter, Debra Stockdale Prihoda, says her mother never knew the full significance of her treatment or her involvement in the story of tuberculosis. She said her mother had no idea her name was in the medical history books or that she contributed to someone winning the Nobel Prize. Patsy might not have known that she was the first person successfully cured of TB with the new drug. She was grateful and happy to be able to marry and have a family.

Though her spirit never lagged, her condition weakened over the years and her overall health was never robust. Patsy died on June 10, 1966, at the age of 42. Now, after seven decades we can finally give Mayo Clinic patient Patricia Thomas Stockdale full credit for her historic contribution in the fight against tuberculosis.





(Clockwise from upper left) Patricia Thomas, high school senior; Bob Stockdale visits Patricia while on leave from the Navy; the engagement photo; the family she hoped for — Debra, Steven, and Kathy; Bob Stockdale in uniform.

Baxter Ventures, Mayo Clinic, and Velocity Pharmaceutical Development, LLC Form Vitesse Biologics, LLC

Baxter Ventures, the venture arm of Baxter International Inc., Mayo Clinic, and Velocity Pharmaceutical Development, LLC formed Vitesse Biologics, LLC, a unique collaboration to focus on the development of antibody and protein-based therapeutics in the areas of immunology, hematology, and oncology.

Mayo Clinic to Study 10,000 Patients for Drug-Gene Safety

Mayo Clinic's Center for Individualized Medicine, in collaboration with Baylor College of Medicine, will launch a study of 10,000 Mayo biobank members for potential risk of drug reactions or lack of drug effect based on each individual's genome. Researchers will be sequencing the DNA of the biobank members for 69 different genes that can influence how patients metabolize or react to different drugs. The goal is to determine which pharmacogenomic findings are relevant to that individual patient and to insert that information into their medical records – providing an "early warning system" to prevent adverse drug reactions or ineffective treatments.

Mayo to Study Cancer Survivorship

Mayo Clinic has received a five-year, $11 million grant to study survivorship in patients with non-Hodgkin lymphoma, a cancer that originates in the lymphatic system and spreads throughout the body. The Lymphoma Epidemiology of Outcomes Cohort Study will enroll 12,000 patients with the disease. The study will follow these patients for long-term prognosis and survivorship.

"With an increasing number of Americans living with non-Hodgkin lymphoma, we need to find new and better ways to improve the length and quality of their lives," says the study's principle investigator, James R. Cerhan, M.D., Ph.D., a Mayo Clinic epidemiologist.

According to the National Cancer Institute, about 70,000 cases of non-Hodgkin lymphoma will be diagnosed in the U.S. in 2015. The incidence has been increasing since 1950, although, over the past two decades, the rate of increase has slowed, and survival rates have improved. These trends have led to an increasing number of survivors — most recently estimated at 550,000.

the headlines

Woman's Day Red Dress Awarded

Virginia M. Miller, Ph.D., director of the Women's Health Research Center at Mayo Clinic, has spent her career researching how heart disease differs in women and men. On Feb. 10, she was honored for that work with a Woman's Day Red Dress Award in New York City.

Mayo Researcher Appointed to National Advisory Council

Sundeep Khosla, M.D., has been appointed to the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) advisory council. The NIAMS advisory council is responsible for giving advice to the institute on policy issues as well as making recommendations for research proposals.

"It is a tremendous honor," Dr. Khosla says. "Being part of the NIAMS council gives me an opportunity to provide key input into scientific directions and policies of the institute. It is also important for Mayo to have faculty represented on such leadership councils since it reflects the outstanding scientific environment Mayo provides for its investigators to succeed."

Launch of Regenerative Medicine Incubator

Mayo Clinic's Center for Regenerative Medicine, along with economic development groups in Rochester, launched the Advanced Product Incubator (API) in June. The API offers cell-free platforms — clean-room laboratories — to develop regenerative therapies. Built according to Current Good Manufacturing Practices set forth by the Food and Drug Administration, the API adheres to rigorous standards of facility design, monitoring, and process control. This multidisciplinary, first-of-its-kind facility bridges teams of researchers and physicians with scientific and industry experts to accelerate product development. API's unique approach is to develop low-cost, off-the-shelf, cell-free regenerative therapies that address chronic or incurable diseases.

On The Path of Discovery

NEW APPROACH TO BRAIN CANCERS

A new molecular classification may improve the methods used to diagnose and treat gliomas.
– *New England Journal of Medicine*

ONCOLOGISTS REVEAL REASONS FOR HIGH COST OF CANCER DRUGS, RECOMMEND SOLUTIONS

"Americans with cancer pay 50 percent to 100 percent more for the same patented drug than patients in other countries," says S. Vincent Rajkumar, M.D., of Mayo Clinic Cancer Center. "As oncologists we have a moral obligation to advocate for affordable drugs for our patients."
– *Mayo Clinic Proceedings*

TARGETED DRUG CAN 'DIMINISH THE SUFFERING' OF MYELOFIBROSIS

Use of the targeted agent pacritinib significantly reduced the symptoms and burden of advanced myelofibrosis in patients, say Mayo researchers.
– Annual meeting, American Society of Clinical Oncology, Chicago

CHEMOTHERAPY COMBO OFFERS LONGER LIFE TO PATIENTS WITH B-CELL CANCERS

Because of the significant benefit found in combining the targeted drug ibrutinib with standard chemotherapy for relapsed chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), researchers closed their clinical trial early. – Annual meeting, American Society of Clinical Oncology, Chicago

MAYO CLINIC RESEARCHERS IDENTIFY METHYLATED DNA MARKERS THAT MAY ONE DAY LEAD TO NONINVASIVE WHOLE BODY CANCER SCREENING

A team of Mayo Clinic researchers identified the source of cancer in patients' gastrointestinal tracts by analyzing DNA markers from tumors.
– Annual meeting, American Association for Cancer Research, Philadelphia

SAFE TO TRANSPLANT LIVERS FROM DECEASED PATIENTS

In the largest study of its kind, transplant researchers at Mayo Clinic in Florida found that liver cancer patients have the same beneficial outcomes using organs donated by patients who died of cardiac death.
– *American Journal of Transplantation*

NEW MOUSE MODEL FOR ALS RESEARCH OFFERS HOPE

Researchers at Mayo Clinic in Florida have developed a mouse model that exhibits the neuropathological and behavioral features associated with the most common genetic form of ALS.
– *Science*

MAYO IDENTIFIES FIVE KINDS OF OBESITY

Mayo Clinic researchers have identified five subcategories of obesity in an effort to determine the most effective, individual treatments. – *Gastroenterology*

MAYO CLINIC-LED TEAM IDENTIFIES MASTER SWITCH FOR CANCER-CAUSING HER2 PROTEIN

A team of researchers led by Mayo Clinic identified a small site in the HER2 protein that enables it to form a molecular switch that sets off a cascade of events that turn normal cells cancerous. – *Journal of the National Cancer Institute*

ASTHMA DISCOVERY MAY LEAD TO NEW THERAPEUTIC APPROACH

Mayo researchers and collaborators have discovered a key cellular mechanism that contributes to bronchoconstriction and inflammation in asthma.
– *Science Translational Medicine*

EFFECTIVE LEADERSHIP: ONE REMEDY FOR PHYSICIAN BURNOUT

A Mayo Clinic study suggests there's a correlation between physician burnout and the effectiveness of doctors' supervisors. – *Mayo Clinic Proceedings*

MAYO RESEARCHERS COMBINE COMMON GENETIC VARIANTS TO IMPROVE BREAST CANCER RISK PREDICTION

A Mayo-led team combined 77 common genetic variants from more than 67,000 women into a single risk factor to improve the identification of women with an elevated breast cancer risk.
– *Journal of the National Cancer Institute*

COULD A TAMPON HELP PREDICT ENDOMETRIAL CANCER? MAYO CLINIC RESEARCHERS SAY YES

Mayo researchers have shown it is possible to detect endometrial cancer using tumor DNA picked up by ordinary tampons. – *Gynecologic Oncology*

MAYO STUDY FIRST TO IDENTIFY SPONTANEOUS CORONARY ARTERY DISEASE AS INHERITED

Mayo researchers have identified a familial association in spontaneous coronary artery dissection, a type of heart attack that most commonly affects younger women, suggesting a genetic predisposition to the condition.
– *JAMA Internal Medicine*

MAYO STUDY OF THOUSANDS OF BRAINS REVEALS TAU AS DRIVER OF ALZHEIMER'S DISEASE

By examining more than 3,600 postmortem brains, Mayo researchers in Jacksonville, Florida, and Rochester, Minnesota, found that dysfunctional tau protein drives cognitive decline and memory loss in Alzheimer's disease.
– *Brain*

RISK OF PAINKILLERS

Mayo Clinic researchers studied how many patients prescribed an opioid painkiller for the first time progressed to long-term prescriptions. The answer: 1 in 4. People with histories of tobacco use and substance abuse were likeliest to use them longterm.
– *Mayo Clinic Proceedings*

Tablet X-tra Link to news releases for these discoveries in the tablet edition.

U.S. WOMEN'S AWARENESS OF BREAST DENSITY VARIES BY RACE AND ETHNICITY, EDUCATION AND INCOME, MAYO STUDY FINDS

Disparities in the level of awareness and knowledge of breast density exist among U.S. women, according to the results of a Mayo Clinic study.
– *Journal of Clinical Oncology*

MAYO IDENTIFIES GENE THAT PUSHES PANCREAS CELLS TO CHANGE SHAPE, A KEY STEP TO CANCER DEVELOPMENT

A team led by investigators from Mayo Clinic in Florida, and the University of Oslo, Norway, has identified a molecule that pushes normal pancreatic cells toward pancreatic cancer — one of the most difficult tumors to treat.
– *Nature Communications*

MOLECULE THAT PROVIDES CELLULAR ENERGY FOUND KEY TO AGGRESSIVE THYROID CANCER

Cancer researchers at Mayo Clinic's campus in Jacksonville, Florida, identified a molecule they say is important to survival of anaplastic thyroid carcinoma (ATC) — a lethal tumor with no effective therapies.
– *Journal of Clinical Endocrinology and Metabolism*

MAYO FINDS HOW HUMAN BEHAVIOR LEADS TO ERRORS

Mayo Clinic researchers identified 69 "never" events among 1.5 million surgical procedures performed over five years and detailed why each occurred. Using a system created to investigate military plane crashes, they coded the human behaviors involved to identify any environmental, organizational, job, and individual characteristics that led to the never events. Their discovery: 628 human factors contributed to the errors overall, roughly four to nine per event.
– *Surgery*

NEW BREAST EXAM NEARLY QUADRUPLES DETECTION OF INVASIVE BREAST CANCERS IN WOMEN WITH DENSE BREAST TISSUE

A new imaging technique pioneered at Mayo Clinic nearly quadruples detection rates of invasive breast cancers in women with dense breast tissue, according to a major study.
– *American Journal of Roentgenology*

MAYO RESEARCHERS FIND CANCER BIOPSIES DO NOT PROMOTE CANCER SPREAD

A Mayo study of more than 2,000 patients dispelled the myth that cancer biopsies cause cancer to spread. Findings showed patients who received a biopsy had a better outcome and longer survival than patients who did not have a biopsy.
– *Gut*

MOLECULAR CLASSIFICATION MAY HELP DIAGNOSE, TREAT BRAIN TUMORS

The molecular makeup of brain tumors can be used to sort patients with gliomas into five categories, each with different clinical features and outcomes, researchers at Mayo Clinic and the University of California, San Francisco have shown. The finding could change how physicians determine prognosis and treatment options. Previously, they relied on how patients' tumors look under the microscope.
– *New England Journal of Medicine*

DISCOVERY'S EDGE

We publish *Discovery's Edge* twice a year — four times online — to tell people how Mayo Clinic research and investigators are changing medicine.

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Art of Science

This gripping image, created by Mayo Clinic illustrator Steve Orwoll, is from the new website for Mayo's Center for Biomedical Discovery (see page 22) which is dedicated to uncovering the molecular causes of disease. The staff at the center say they are using basic science to build a roadmap of what happens in the body when things go wrong. It's well worth a "site visit" for more of this imaginative art.