Eyes on the goal

How Johns Hopkins Medicine turns research investment into new treatments, breakthrough discoveries and greater public good.
Medical research can seem far removed from our everyday lives. But much of it, whether it involves studying strands of DNA or electrical signals in the brain, is driven by the conviction that someday the insights will be used to restore people’s health—or even better, to help ensure that they don’t get sick in the first place.

Johns Hopkins has always been home to researchers who have thrown themselves into the hunt for new treatments and cures, with all the frustrating setbacks and exciting leaps that are part and parcel of these quests.

They know all too well that what they find may not turn out to be the hoped-for break.

But just having a shot at relieving human suffering is their great underlying motivator.
What we do here at Johns Hopkins goes far beyond basic research that’s driven simply by the passion to find out how a cell or a protein or an organism does what it does. What we really want is to have our discoveries make a difference in people’s lives.

So we come here every day to help the sick, to take what we learn into the clinic.

For instance, pulling together the results of several genetic research projects, our cancer scientists and clinicians developed a personalized treatment for a patient with a hereditary form of pancreatic cancer who was not expected to live more than three months. Genetic analysis of the tumor showed that it would likely be responsive to two particular drugs, and after several cycles of treatment, the patient went from having a grim prognosis to being symptom free.

Our research thrives at both ends of the spectrum. On one end, we have scientists who probe the most basic aspects of our biology. On the other, we have clinical researchers who test new treatments where they can actually make an impact—in our patients.

To go from finding a misbehaving molecule, to finding a treatment that can neutralize that molecule, to proving that it really helps people is what we call translational research. We take the basic ideas and then test to see whether the treatments we've developed are safe and can really cure the disease. But our research ideas also flow in the other direction. Observations we make in taking care of our patients drive us back to the laboratory to pursue studies that help explain what we see in the clinic. Translating between basic research and clinical investigation—in both directions—is at the heart of what we are working to achieve.

But it’s not only dedicated clinicians and scientists who contribute to this spectrum of discovery and patient care: We are fortunate to live in a time and at a place where society values what we do by providing substantial federal funding and philanthropic support for biomedical research. These are precious and increasingly scarce resources. At Johns Hopkins, we are proud of the success our faculty and clinicians have in securing grants from the National Institutes of Health and other state and federal agencies and our donors. Many of the success stories that unfold in the following pages were made possible by research funded by the National Institutes of Health.

Our doors—in our labs and in our clinics—have always been open to this kind of collaboration because it’s how we make great discoveries. We link the thinking together. It’s just the way this place works. It is the soul of Johns Hopkins Medicine.

Landon King, M.D.
Vice Dean for Research
Johns Hopkins Medicine
Diagnosed with sickle cell disease as a little girl, Ware had spent most of her life coping with crippling outbreaks of pain—called crises—occasionally interrupted by calm periods of a normal existence. By the time she reached adulthood, sickle cell had slowly taken over her life. Sudden temperature changes would send her spiraling downward. She was afraid for her family to hug or touch her. And the air conditioning or heat had to be set precisely to the right temperature or else she would risk another pain crisis. It was, she says, like being in prison.

Born at The Johns Hopkins Hospital, Ware had long relied on the institution for her medical care. Over the past two years, her dependency on Hopkins had increased exponentially. She estimates at least 20 emergency room visits in 2010 and five hospital admissions. Something, she says, had to give. She consulted her physician, Hopkins hematologist and sickle cell expert Sophie Lanzkron, the founder and director of the hospital’s sickle cell infusion center. Lanzkron directed Ware to her colleague Robert Brodsky—also a hematologist—who was leading a promising research trial that could potentially offer a cure for sickle cell patients.

After meeting with Ware and reviewing her medical history, Brodsky agreed that she was eligible for the trial. And, even though it called for a highly invasive and risky procedure—a bone marrow transplant—Ware didn’t hesitate. "By that point, my quality of life had become so low," she says. "I wanted to be able to be there for my children."

Once a bone marrow donor was identified and the procedure scheduled, Ware was ready to undergo the transplant. In the days and weeks that followed, she was carefully monitored for any signs of rejection and placed on a regimen of immunosuppressant drugs, just as organ transplant patients would be.

Fast forward three and a half months, and Ware’s life barely resembles that of a sickle cell patient. By all appearances, she seems to be cured of the disease and hasn’t experienced a crisis since the transplant. Her lab work, so far, shows no traces of the disease. "I’m not having pain, I’m able to function and get out more," she says. "Now I’m feeling normal. After all of these years, I can finally call myself normal.”

The pain, Shannon Ware says, is something akin to being run over by a Mack truck, set on fire and stabbed simultaneously.
a patient’s view
Sickle Cell Disease

Johns Hopkins Research Milestones

1890 Surgeon William Halsted devises an operation to cure inguinal hernia, an affliction regarded until then as almost incurable.

1897 Pharmacologist John Jacob Abel discovers epinephrine (adrenaline), a first-line treatment for heart attacks, severe allergic reactions and other conditions.

1906 Anatomist Ross Granville Harrison creates the first tissue culture. Harrison’s student John Enders uses this method to devise a test for mumps and to grow polio virus cultures, leading to later development of the Salk polio vaccine.
It’s called a pain crisis.
Unimaginable agony pounds through the body—sometimes hitting specific parts, sometimes more diffuse. One patient describes his crises like “a severe thunderstorm. The steady beating rain is like the pain beating all over your body, and there’s also lightning flashes in the midst of this pain storm.”

Unlike a real storm, however, the pain of a crisis can last days or even weeks without letting up.

Sickle cell disease is one of the first genetic diseases ever described. Researchers have known since the mid-1950s that patients with the condition have a glitch that affects a single amino acid in their hemoglobin, the molecule that carries oxygen in blood.

As a result, their blood cells frequently become “sickled,” taking on the thin, half-moon shape of an old-time farming tool. These sickled cells can’t squeeze through narrow blood vessels as easily as typical round blood cells. When they get trapped, they cut off blood flow, leading to the intense pain of a crisis and organ and tissue damage that accumulates over time, curtailing life short.

In the mid-1980s, two Johns Hopkins researchers came up with an effective way to help. Over the previous few decades, scientists had discovered that patients with naturally high levels of fetal hemoglobin—an immature form of the oxygen-carrying molecule—had significantly less sickling of their blood cells, and hence, fewer pain crises. Searching for a way to increase fetal hemoglobin in patients with less of the molecule, hematologists Sam Charache and George Dover looked for existing drugs that might do the trick. After numerous false starts, they finally hit the jackpot in a drug called hydroxyurea.

They started a pilot study of 39 patients to see how they’d fare on the new drug. Nearly all the patients showed significant increases in fetal hemoglobin, and a follow-up study showed a steep drop in patients’ pain crises—so much so that the study was halted four months early to give every sickle cell patient the option of using the drug.

Now, more than 30 years later, hydroxyurea remains the only drug approved by the U.S. Food and Drug Administration to alter the course of sickle cell disease.

100,000
• Sickle cell disease affects about 100,000 people in the United States and millions more around the world.
• Besides agonizing pain, sickle cell disease also causes ulcers, strokes, joint degeneration and blindness.
• Daily use of hydroxyurea cuts the frequency of pain crises in half.

1909
Neurosurgery pioneer Harvey Cushing finds the surgical passage that allows removal of a malfunctioning pituitary gland.

1913
Pharmacologist John Jacob Abel invents the first “artificial kidney” dialysis device.

1915
Medical student Jay McLean discovers the anticoagulant heparin, vital for preventing dangerous blood clots.
Every year, thousands of people are told that they need a bone marrow transplant from a donor. Unfortunately, only a fraction will actually receive one.

That’s because, for years, bone marrow transplants from donors needed to be a perfect “match” for the recipient, sharing all the major proteins that affect tissue compatibility. Without that match, the body’s immune system gears up to reject the new tissue, or the new healthy tissue can attack the recipient in graft-versus-host disease, or GVHD.

Even in siblings, there’s only a 30 percent chance that all these protein markers will match. And though millions of potential marrow donors have signed on with international registries, the chance that a patient will find at least one completely matched donor is still only about 50 percent to 60 percent. For some ethnic groups, such as African-Americans, the odds are as low as 20 percent.

As a result, patients who could benefit from bone marrow transplants—those with leukemia, lymphoma, aplastic anemia, or a slew of other blood, bone marrow or immune diseases—can wait for months, time that most patients who need a transplant don’t have. Many never find a lifesaving match.

More than 40 years ago, Johns Hopkins physician George Santos developed the first modern method for doing a bone marrow transplant. He used a combination of drugs, including one called cyclophosphamide, to clear out a patient’s diseased bone marrow to make way for the donor’s.

Decades later, two other Johns Hopkins physicians, Ephraim Fuchs and Leo Luznik, and their colleagues came up with a new spin on giving patients cyclophosphamide that opened up new options for bone marrow transplants—making it possible for patients to accept transplants with as little as half the matched proteins.

The big difference is giving cyclophosphamide after the transplant.

Fuchs and Luznik found that doing so takes advantage of the time when the immune cells, called T-cells, that are getting ready to attack the mismatched tissue are really vulnerable. And not only does this approach target the problem T-cells, it doesn’t wipe out the patient’s whole immune system in the process, which means that patients are better able to fight infection.

Because a perfect match is no longer needed, the researchers say, this technique opens up bone marrow transplants to almost anyone who needs one.

- Each year, more than 20,000 patients receive bone marrow transplants in the United States.
- Johns Hopkins has performed more than 5,000 bone marrow transplants.
- Johns Hopkins physicians have now done over 300 half-matched transplants, including about 65 last year alone.
Reproductive endocrinologist Georgeanna Seegar Jones shows that the pregnancy hormone originates in the placenta, laying the foundation for the pregnancy tests that are used today.

Urologist Hugh H. Young shows the effectiveness of sulfanilamide in treating gonorrhea and later uses it and other sulfa drugs to treat genitourinary infections.

Pharmacologist Eli Kennerly Marshall Jr. develops sulfaguanidine, a powerfully effective treatment for dysentery, and determines the proper dosage of quinolines to combat malaria.
Surgeon I. Ridgeway Trimble performs the first one-stage pancreaticoduodenectomy (removal of the pancreas and duodenum) in the United States.

1944
Surgeon Alfred Blalock, cardiologist Helen Taussig and surgical technician Vivien Thomas develop the “blue baby operation,” a procedure that corrects a deadly congenital heart defect and marks the beginning of cardiac surgery.
Why single out pancreatic cancer?
Because the odds are grim: Less than half of patients survive two years after diagnosis—even if the disease hasn’t spread. If the cancer can be operated on, surgery and chemotherapy can help, but modestly. Most see a pancreatic cancer diagnosis as a death sentence.

Contrast that with the latest result of a possible new approach—a vaccine that’s moving up the therapy pipeline—and it feels like the cavalry is on its way. In a study of 60 patients given the vaccine, 88 percent survived a year. Some 76 percent were alive after two. And a small number remain disease-free since the vaccine’s original testing in 1997.

This vaccine is far from typical. It’s taken Johns Hopkins cancer immunologists Elizabeth Jaffee and Daniel Laheru and their team since 1996 to get it through early clinical trials, not from a lack of effort but simply because of cancer’s complexity. The problem lies in recognition. Immune systems are equipped to recognize what they haven’t seen before—like measles viruses. Cancer cells, though, are enough like healthy cells that they don’t elicit an immune response. Worse, as tumors progress, immune systems grow more comfortable with cancer’s presence, developing a dialogue with the very cell pathways that turn the immune system off.

Training the immune system to react to cancer, then, has proved a huge challenge. Even so, progress has been sure. Sound basic science studies guided Jaffee and Laheru to use whole pancreatic tumor cells as their starter, rather than try to get immune systems riled by a few proteins taken from the cells’ surface. They radiated the tumor cells to make them harmless, and engineered them to display a molecule that lures immune cells close enough to tumors to recognize them as foreign. The result is an attack on cancer cells in the pancreas and throughout the body.

Now wider vaccine testing is slated nationwide as Jaffee and Laheru continue to investigate variations. Adding the chemotherapy cyclophosphamide, for example, appears to make the tumor more responsive to the vaccine. “We want to get the disease to a point where we control it,” says Jaffee, “not the other way around.”

The tabletop sign in the Johns Hopkins waiting room says it all:
Don’t be alone if you get a diagnosis of pancreatic cancer.
One issue facing nearly all people with Marfan syndrome is that sooner or later, they will need heart surgery.

In the 1950s, when a young Johns Hopkins physician named Victor McKusick began studying the heart defects in his patients with Marfan syndrome, he ended up launching an entire field that today is known as medical genetics.

McKusick’s idea was that Marfan’s major features—distortions of the skeleton, eyes, lungs and aorta—were due to a mutation that affected connective tissue, the “glue” that holds the body’s cells together. Back then, there was no way to prove it.

By the 1980s, surgical repairs could lift the death threat imposed by Marfan’s propensity to cause heart valves to leak and the aorta to balloon and rupture. Still, physicians caring for Marfan patients could offer little else to help.

Enter Harry “Hal” Dietz, another young Johns Hopkins physician who wanted to do more for his Marfan patients. Though he hadn’t started out to be a researcher, Dietz found in 1991 the mutations—in a gene that encodes fibrillin-1, a protein needed for formation of elastic fibers in connective tissue—that McKusick had suspected.

Yet Dietz’s “aha” moment turned quickly to near despair when he realized that the finding opened no real pathways for treatment. If Marfan patients were born with a structural predisposition to tissue failure, then they were “like a house with a rotten frame that could only be fixed by tearing it down and starting over.”

Still, Dietz couldn’t shelve the problem of how a structural deficiency alone could explain all of the problems that Marfan causes. Heading back to the lab, he and his colleagues created a mouse model of Marfan and showed that fibrillin-1 also regulates a molecule called TGF-beta, and it is an excess of TGF-beta that triggers most of the features of Marfan syndrome—including aortic enlargement and tear.

With the help of cardiologist Dan Judge, Dietz began scouting for a drug that would block TGF-beta. Their search turned up the well-known blood pressure medication losartan. Now, thanks to their careful studies showing that Marfan mice treated with losartan are essentially like normal mice, a multicenter clinical trial is under way to find out whether losartan can prevent aortic aneurysm in people with Marfan.

1:5,000

- Marfan syndrome affects 1 in 5,000 people worldwide.
- Nine out of 10 people with Marfan syndrome have heart problems.
- Treatments for Marfan syndrome could also help other forms of aortic aneurysm—a condition responsible for 1 to 2 percent of all deaths in industrialized countries.

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1953
Hematologist C. Lockard Conley and dermatologist Ernest W. Smith create a simple device for separating the components of hemoglobin, a protein in red blood cells that carries oxygen.

1968
Microbiologist Hamilton O. Smith discovers restriction enzymes, the proteins that can cut DNA at precise points in its genetic sequence, and molecular biologist Daniel Nathans uses the discovery to analyze the DNA of a virus that causes cancer in animals.
1969 Cardiologist Kenneth Lewis implants the first heart pacemaker that could be recharged from outside the body. The device was designed by Johns Hopkins physicist Robert Fischell.

1971 Orthopedic surgeon Lee Riley Jr. performs a total knee replacement using an artificial knee he designed with four other surgeons.

1972 Neuroscientist Solomon Snyder and his student Candace Pert discover opiate receptors in the brain, the means by which brain cells “talk” to one another.
1980
Heart surgeon Levi Watkins Jr.
implants the first automatic heart
defibrillator in a human patient with
life-threatening irregular heartbeats.

1984
Urologist Patrick Walsh performs the
first nerve-sparing prostatectomy to
remove a cancerous prostate gland
while protecting the patient against
incontinence and impotence.

1991
Surgeon John Cameron refines the
enormous operation known as the
Whipple to the point that hospital
mortality for the procedure at Johns
Hopkins is less than 2 percent.
In 1984, a young molecular biologist named Carol Greider wasn’t looking to find something so stunning that it would win her a Nobel Prize. But when she took on the challenge of how organisms maintain the genetic material at the ends of their chromosomes, the answer she found was deemed as basic as figuring out how cells divide.

Since then, Greider, who heads the Department of Molecular Biology and Genetics at Johns Hopkins, and other scientists have not only shown that her discovery—telomerase—plays a role in cancer, but that understanding how it behaves offers new targets for treatment. Yet, as basic discoveries so often do, the story of telomerase has also taken surprising twists.

For Johns Hopkins medical oncologist Mary Armanios, the bolt of telomerase excitement came when she unearthed a clue to a devastating disease called idiopathic pulmonary fibrosis (IPF) that leaves lungs swelled with scarring.

Armanios had been studying a young man who had symptoms of IPF, which can in some ways resemble early aging, including hair that grays before high school and a thinning of some kinds of blood cells. (In fact, IPF was identified by William Osler, Johns Hopkins’ first professor of medicine, who in 1892 noted that certain patients appeared to have succumbed to a disease that left their lungs gray and shrunken.)

The link between IPF and premature aging had always been hazy, but Armanios took a closer look at her patient’s genes and found a distinctive pattern in the ends of the DNA known as telomeres—a pattern that proved to turn up in many others with IPF. Clearly, this telltale problem in the telomere was the source of the disease. At last, the “I” in IPF could be dropped and the search could begin for treatments less drastic than today’s only option: a lung transplant.

Armanios is now using her new insights to search for ways to stop the disease and repair its damage. And Carol Greider has yet another reason to smile.

To physicians, the word idiopathic is like a red flag before a bull. “When we call a disease idiopathic, it basically means we have no idea what causes it,” says Mary Armanios. “And when we don’t know what causes it, we usually can’t even begin to treat it.”

• **100,000**
  - Idiopathic pulmonary fibrosis affects more than 100,000 people in the United States alone.
  - IPF is a disease of aging, with most people affected after age 60.
  - Telomerase mutations are the most common identifiable defect in inherited forms of IPF.

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1993 Urologists Alan Partin and Patrick Walsh develop the Partin tables, which can help predict the stage of prostate cancer to determine the best treatment approach.

1994 Hematologist Peter Agre and colleagues discover aquaporins, the proteins that allow water to move into and out of cells—paving the way for potential new treatments for glaucoma, cystic fibrosis and congestive heart failure.

At Johns Hopkins, that day is here.

But it began in the 1980s, when molecular biologist Bert Vogelstein and colleague Kenneth Kinzler started exposing cancer as a genetic disease—one in which inherited gene errors merge with environmental assaults to a person’s DNA and build to a tipping point. Now, of the 100 cancers studied, the Vogelstein-Kinzler team has mapped the genetic blueprint of 90 of them.

Tracing the effects of the altered genes in cells, the researchers have not only discovered that each person’s cancer shows a distinct genetic profile, they’ve developed a blood test that picks up DNA abnormalities all cancers have in common, as well as individual patients’ own patterns.

Universal, precise and specific, their test can pluck one abnormal cell from within a sea of 400,000 normal ones. It sees cancers invisible to CT scans, X-rays and other known ways to detect cancer. It is, in fact, a personalized and accurate test that can tell when surgery alone has truly wiped out a cancer. Equally important, for people who still have telltale cancer DNA in their blood, the test means there are cancer cells left behind that will require additional treatment.

“If this test says there is cancer,” Vogelstein says, “cancer is definitely there.”

And that, says William Nelson, director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, is only the beginning of personalized cancer medicine. “In the case of cancer genetics, we are on the cutting edge of the cutting edge. We are at a point where we can begin to alter the course of cancer in ways we could only imagine just a few decades ago.”

Ultimately, Vogelstein predicts, their advances could lead to true cancer prevention. “We know most of the major genes involved,” he says, “and virtually all the pathways through which they act.”

“The greatest achievements are yet to come as we use this information to help people.”

Just like fingerprints, every cancer is unique. What if someday we could translate that knowledge into a personalized test of whether a cancer really has been cured?
Transplant surgeon Robert Montgomery and colleagues use plasmapheresis to filter antibodies from the blood of kidney patients and prevent rejection of a kidney transplanted from an incompatible living donor.

Cardiologists Hal Dietz and Bart Loeys identify a previously unrecognized genetic disorder of connective tissue that is named Loeys-Dietz syndrome.
An important part of the mission of Johns Hopkins Medicine is to prevent and treat the diseases we see in the patients we care for every day. That process often starts with a discovery in the laboratory of one of our basic or clinical scientists, and then moves along the translational pathway before it evolves into a potential treatment. It is also important to know that treatments are more than just drugs. Treatments may include devices like pacemakers, new diagnostic tests, vaccines, diets and behavioral interventions. The translational steps may include testing a treatment in animals and normal humans before giving it to humans with diseases.

However, no new drugs are approved for use in humans without testing them in randomized clinical trials. In these studies, patients with the disease of interest are given either the best currently available treatment or the new experimental treatment. To conduct these trials, we need a large research team that includes physicians, nurses, pharmacists, research coordinators and biostatisticians. In 2010, we started about 425 randomized clinical trials involving both children and adults at Johns Hopkins Medicine. These studies included new research treatments for cancer, hepatitis, diabetes, stroke and schizophrenia. All of these randomized clinical trials are supervised by our Institutional Review Board to make certain they are conducted as safely and ethically as possible.

Randomized clinical trials are vital to answer these questions: Does this treatment improve patient outcomes? Which patients have better outcomes? How safe is this treatment? How does it compare to other treatments? These questions are important to both doctors and patients.

We all need to say thank you to the patients who agree to join these clinical trials. All of the successful treatments we have so far were based on patients agreeing to take part in a research study. The faster these studies are completed, the sooner we have the knowledge we need to improve care for everyone.

Daniel E. Ford, M.D., M.P.H.
Vice Dean for Clinical Investigation
Johns Hopkins Medicine
At Johns Hopkins, we pride ourselves not only on the quality of our patient care, but on the research that informs it. Our physicians believe that patients deserve the best treatments available—and their mission is to always look for ways to make the best available treatments even better.

Yet that kind of research and those kinds of results demand more than just good intentions. It takes tools and space, the brightest minds and substantial financial support to sustain our innovative research. So many of our successes began with a private gift from a single grateful individual who believed that the physician or program he or she supported could change and improve the field of medicine. Our supporters invest in us because they believe in what we do and want to be part of something that will improve the world around them.

From the inner-city child with asthma to the infant in South America with cleft palate to the adult across the world with head and neck cancer, there is no one untouched by dollars spent on medical science.

It’s an investment in human health, not only here in Baltimore, but throughout the country and around the world. And as such, it is one of the most gratifying investments you can make.

Janie Elizabeth Bailey
Johns Hopkins Medicine Board of Trustees
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