



INNOVATIVE MEDICINE

RESEARCHERS DEVELOP ADVANCED TREATMENTS
THROUGH CUTTING-EDGE SCIENCE

BY DAYTON FANDRAY



We live in an age of innovation wonders. We have smartphones, smart cars and global connectivity through the Internet. And if there isn't an "app" for something today, there will almost surely be two apps for it tomorrow. Science and technology have turned the world into a place that once existed only in the imaginations of our best science fiction writers. Nowhere are these changes manifested more profoundly than in the field of medicine, where scientists and engineers are creating entirely new classes of health care solutions.




* * * Dr. David Kerr, the director of research and innovation at the William Sansum Diabetes Center, in Santa Barbara, demonstrates an artificial pancreas device to a woman with Type 1 diabetes. The device, which is still being tested, may help patients by automating insulin delivery using cellphone technology.

Medical drug-delivery systems that work at the molecular level enable physicians to attack diseases at their sources. And prosthetic devices that tap into the abundant computing power we routinely carry in our pockets (in smartphones) can give patients who suffer from chronic medical conditions a chance to live normal lives.

Dr. Thomas Brown, the executive director of Swedish Cancer Institute in Seattle, is one of the industry leaders who believe that recent advances in molecular biology and computer technology are ushering in a new age in the practice of medicine.

“We’re at an inflection point in medical history,” he says. “This is not unlike the era when modern antibiotics came into play, when for the first time people began to assume that most young children would grow into adults. This is that kind of change—but with molecular medicine—and it’s just beginning to unfold.”

CHANGING CHANNELS

 Sometimes the search for new medications leads in unexpected directions and hinges on chance encounters.

At the Center for Immunity and Immunotherapies at Seattle Children’s Research Institute, Dr. Anne Stevens is exploring the possibility of treating lupus, a potentially deadly autoimmune disease, with a drug originally derived from sea anemone venom.

Stevens credits researchers led by George Chandy at the University of California, Irvine for making the discovery that made her research possible. She explains that Chandy found a sea anemone

protein that binds to a particular ion channel—a channel that controls the flow of ions through a cell membrane. Other researchers found that this ion channel, *Kv1.3*, is found on T lymphocytes (T cells) associated with lupus and other autoimmune diseases.

Treatments for lupus include steroids and chemotherapy, and the side effects of these treatments can be severe. As bad as the side effects are, however, treatment must be administered to prevent the inflammation associated with lupus from damaging a vital organ—lupus can be fatal if it affects the brain, heart or kidneys.

Stevens’ work aims at attacking a disease at its root, minimizing collateral damage to healthy tissue, while reducing the side effects. She believes that the synthetic compound *ShK-186*, modeled after the sea anemone compound, is an important step forward.

The compound, she says, has been shown to block the *Kv1.3* channel in the cell membrane of T cells. Through an intricate dance of biological processes, blocking the channel blocks the overproduction of inflammation hormones called cytokines.

“It just shuts everything down,” Stevens says.

In lupus patients, inflammation gets out of control, with the immune system attacking healthy tissue rather than the agents that it is supposed to attack—bacteria, viruses and cancer cells. So a treatment that shuts down the overproduction of cytokines could be a very good alternative to current therapies.


Stevens heard about *ShK-186* when Seattle-based Kineta Inc. asked for help locating patients with another autoimmune disease.

She realized that the T cell that Kineta was targeting was the same type she saw in lupus patients.

Working with Kineta, Stevens is now in the preclinical phase of testing the efficacy of ShK-186 for lupus treatment: “We know that the molecule binds and inhibits these types of lymphocytes,” she says. “But nobody has shown that the molecule blocks the lymphocytes in lupus patients.”

Stevens believes the connection will be there. And if the lab tests bear this out, she and her colleagues will be able to start planning a clinical trial. This research could lead to a treatment for lupus that spares patients from adverse side effects.

PUMPING IT UP

 To say that diabetes is a growing threat to people worldwide is an understatement.

“The rates of diabetes across the world are rising exponentially,” says Dr. David Kerr, director of research and innovation at the William Sansum Diabetes Center in Santa Barbara, California. He cites a recent statement by the Centers for Disease Control and Prevention (CDC) that says that two of every five Americans are expected to develop Type 2 diabetes during their lives. At the moment, Kerr notes, about 29 million Americans have diabetes, and it is estimated that close to 90 million have prediabetes and are at risk for the condition.

This represents a tremendous toll in human suffering. It is also becoming a huge burden for health care systems, not only in dealing with diabetes itself, but also in treating associated complications, including heart disease, vision loss and kidney failure.

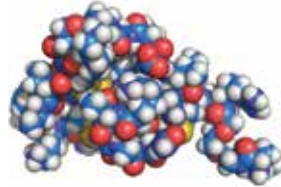
For Type 2 diabetes, treatment can range from simple changes in lifestyle—a better diet, more exercise—to a number of pharmaceutical solutions ranging from oral medicines to injections to infusions. The condition demands that a patient adapt to a changed set of circumstances, but it is manageable.

For patients with Type 1 diabetes, however, survival hinges on one thing—insulin. There are several methods for administering this vital hormone—injection, infusion from an insulin pump, and delivery via inhaler (an option introduced recently). The key is delivering the right amount of insulin from an external source to replace insulin that isn’t being produced by the patient’s pancreas.

Because all delivery systems require regular monitoring of blood glucose levels and a conscious effort to deliver insulin into the bloodstream, patients suffering from Type 1 diabetes are essentially forced to be in control of their condition around the clock.

Kerr and his team of researchers hope to relieve this burden by developing a fully automatic artificial pancreas.

At this point, though, the term “artificial pancreas” is a bit misleading. The system currently under development is not a mechanical organ tucked inconspicuously inside the body. Rather, it consists of three distinct components worn externally.



* * * Researchers at the Center for Immunity and Immunotherapies at Seattle Children’s Research Institute, in partnership with Kineta Inc., are exploring medical uses for a synthetic protein originally derived from the sun anemone (above). The protein (red, white and blue at left) blocks channels in the membranes of cells that cause autoimmune diseases. Blocking the cells could alleviate diseases’ effects without disabling immune defenses.

RESEARCH PIONEERS



Learn more at the following websites about the research and institutions featured in this article:

Center for Immunity and Immunotherapies at Seattle Children’s Research Institute.

CIIT researchers study disorders that yield powerful insights into the immune system. Visit seattlechildrens.org/research/immunity-and-immunotherapies.

Swedish Cancer Institute, Personalized Medicine Program. Research in gene sequencing allows specialists at Swedish to identify gene abnormalities in many different types of cancer cells to personalize cancer treatments for those specific abnormalities. Visit swedishcancerinstitute.org.

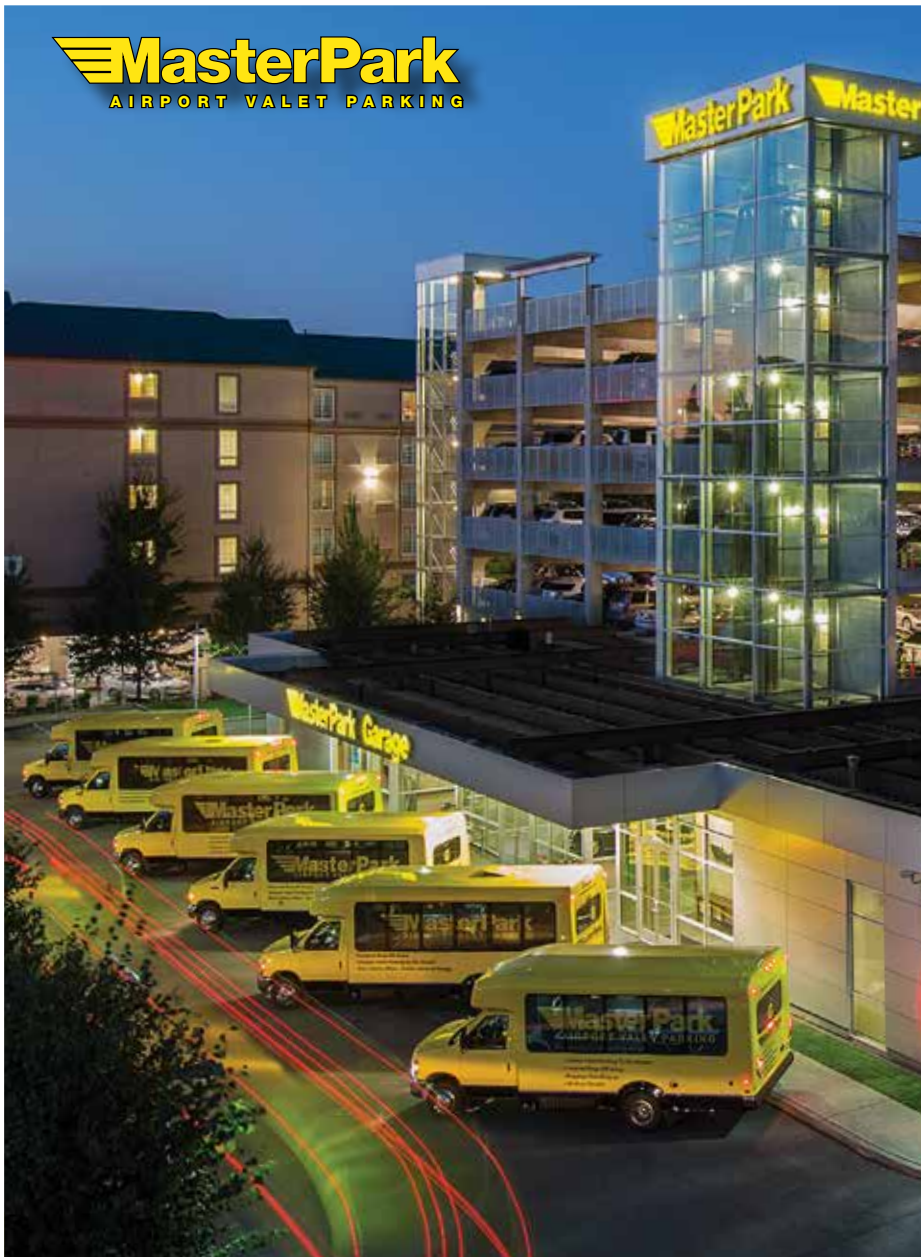
University of Washington Department of Bioengineering. Bioengineering faculty and

students conduct research that involves collaborations across engineering, physical sciences and medicine. Visit depts.washington.edu/bioe/research.

University of Washington Institute for Protein Design.

The Institute for Protein Design develops and applies methods for designing a variety of synthetic proteins. Visit ipd.uw.edu.

William Sansum Diabetes Center. Clinical trials include programs addressing Type 1 diabetes, Type 2 diabetes, diabetes prevention and diabetes during pregnancy. Visit sansum.org. For information developed by director David Kerr about traveling with diabetes, visit voyagemd.com.



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"It is a device," explains Kerr, "that has algorithms that automatically adjust the rate of insulin delivery by a pump, based on data from a real-time continuous glucose monitor." There is also a "computer brain" that talks to both devices, Kerr says.

People with diabetes have been using insulin pumps and glucose sensors for years. The key evolution is the computer brain that automates insulin delivery. Kerr suggests that this brain can be found in a device that is practically ubiquitous these days—a smartphone.


Even if the hardware is available, though, the artificial intelligence necessary for coordinating the delivery of insulin is still being developed.

"What we want is a fully automated, 24-hour, closed-loop system where the person doesn't have to do anything at all," says Kerr.

The challenge, he explains, is getting the math right. Insulin sensitivity varies from one individual to another. In any given patient, a range of variables—including changes in weight, activity levels and even mood—can affect insulin sensitivity. But Kerr believes that with the application of computer technology, accurate data about the individual can be collected and insulin levels can be adjusted accordingly.

The system has been tested in the lab, and the results have been encouraging, with glucose levels falling within the target range around 70 percent of the time. This, Kerr notes, is a much better result than patients achieve when they use injections or a pump by itself. The researchers hope to soon move on to tests involving patients "in the comfort of their own homes."

DESIGNER MOLECULES

 Erik Procko, a senior fellow at the University of Washington (UW) Institute for Protein Design, describes his work as being "very much in the realm of science fiction," and it does sound like something that could have come from the imagination of Philip K. Dick or William Gibson. Proteins, Procko explains, are the



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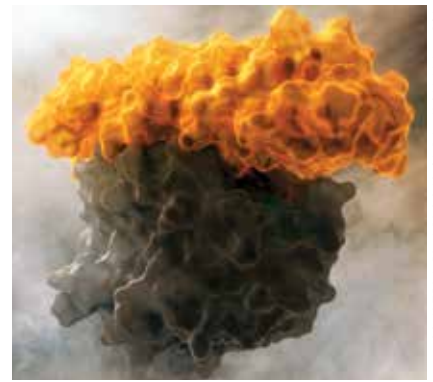
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COURTESY: ERIK PROCKO AND VIKRAM MULLIGAN

* * * Scientists at the University of Washington Institute for Protein Design created the BINDI protein (in gold in the rendering above) to bind to the Epstein-Barr virus (gray), which may prevent the virus' harmful effects.

complex molecules that make life possible. They replicate DNA. They catalyze metabolic reactions. They transport other molecules between locations.

"They are essentially performing many of the functions inside living cells," he says. "And that means that for viruses and bacteria, they are important for causing disease. But, also, proteins are important in our bodies for fighting diseases."

Procko explains that he and his colleagues design brand-new proteins to target disease-causing agents. And they have achieved impressive results with a protein to treat cancers tied to the Epstein-Barr virus. In the Western world, this virus is most commonly associated with infectious mononucleosis ("mono"), and infections are seldom fatal. But in Africa and other parts of the world, the virus has been linked to certain cancers.

Under normal circumstances, cells are programmed to fight viral infections by simply destroying themselves. The Epstein-Barr virus survives by thwarting this defense. "The virus prevents cells from killing themselves," Procko says. "The cells no longer die, and that makes them prone to becoming cancerous."

Epstein-Barr keeps host cells alive by producing a protein—BHRF1—that overrides cells' normal immune response. The challenge for Procko and his team was to design a protein that would in turn neutralize BHRF1.

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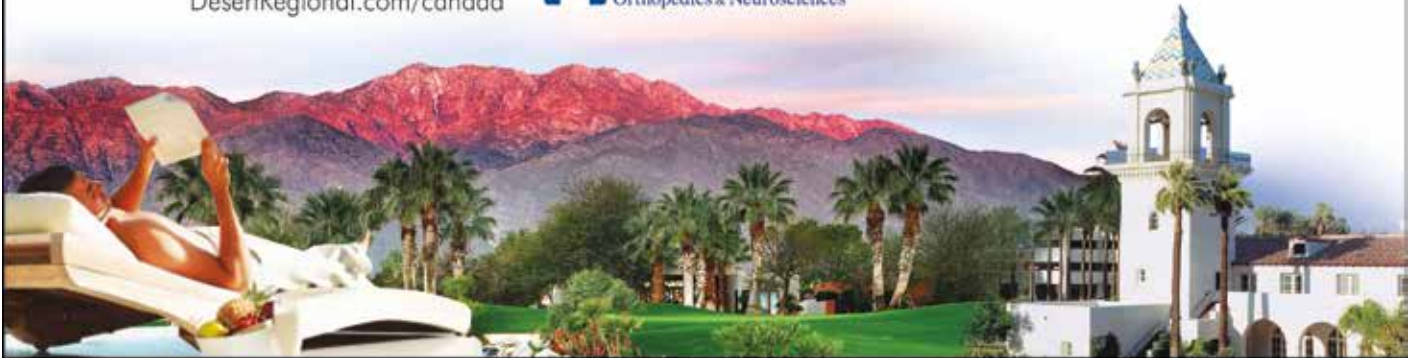
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Designing a protein from scratch is no small feat. It involves creating a chemical composition that, working within the laws of physics and chemistry, falls into a predetermined shape, or fold. This shape is crucial because proteins essentially function by binding to specific locations on their target cells or on other proteins. The shape determines whether or not the key fits the lock. Fortunately, with enough computing power—a resource in ample supply these days—the challenge of finding the right shape is surmountable.


“We’re trying to get an ideal shape with the ideal chemical composition,” says Procko. “That way we can make a molecule that knocks out the part of the virus that causes cancer.”

Once the researchers determine a protein configuration they want to test, they use artificial genes to create strands of DNA that encode the protein. Then they insert the DNA into bacteria that serve as “factories” to make the protein.

The team has demonstrated that a protein known as BINDI, which can be synthesized in the laboratory, has promising results in preclinical tests against Epstein-Barr virus–positive lymphoma.

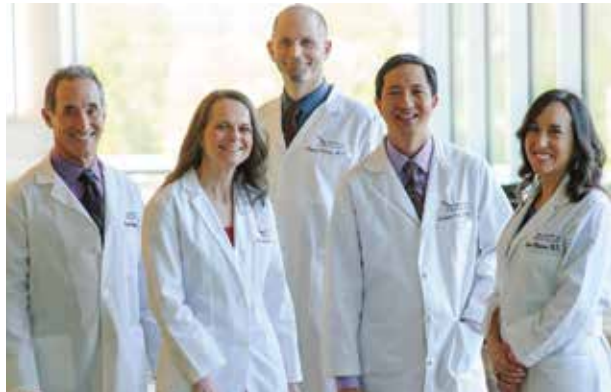
Procko says that this is one of the early cases of taking a protein design through validation in a test tube and through initial efficacy tests. “That’s quite a significant development,” he says.

UNTANGLING ALZHEIMER’S

 At Professor Valerie Daggett’s lab in the UW Department of Bioengineering, her team of researchers is also hard at work creating novel variations on the basic building blocks of life. For Daggett’s team, however, this involves designing *pieces* of proteins: the short chains of amino acids called peptides. The researchers believe that these peptides will be effective in preventing the damage caused when normal proteins cease to function as they should. This sort of breakdown can cause proteins to form so-called amyloid plaques and twisted fibers, or *fibrils*, that block communication among nerve cells (among

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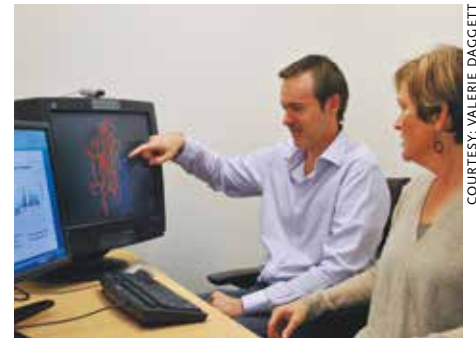
other functions). Such blockages appear to be factors in the form of dementia known as Alzheimer's disease. Catching rogue proteins in an intermediate state, which they pass through on their way to forming these plaques and fibrils, might well be the key to treating early-stage Alzheimer's patients.

"We already know that targeting the endpoint fibrils and plaques is not effective," explains Daggett, "because the damage has already been done by the intermediate structures."

Hoping to intervene in the process before the plaques and fibrils form, Daggett and her team have synthesized peptides that attach to an abnormal protein and prevent it from finishing the transformation. The results have been promising.

Daggett and her team believe this approach could ultimately provide better diagnostic tools and perhaps even drugs that could be used to effectively treat a variety of amyloid diseases.

"There is still a lot to do on the research




COURTESY: VALERIE DAGGETT

* * * Valerie Daggett (right) and Gene Hopping, at the University of Washington Department of Bioengineering, work on designing compounds to prevent the formation of plaques associated with Alzheimer's and other diseases.

front," she admits. "But we have many more new designs, many that are more potent than what we have published so far. ... I hope we are on the scale of years not decades."

PERSONALIZING MEDICINE

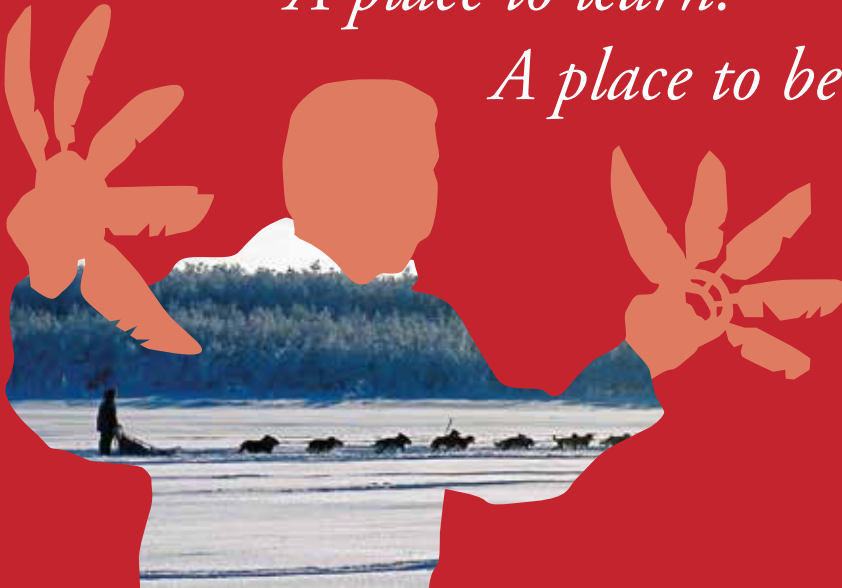
 The Human Genome Project, an immense international effort, changed biology forever by mapping the human genome in the 1990s and early 2000s. This work has also changed how doctors view cancer. The idea of customizing treatment based on a cancer's genetic signature is at the heart of the new Personalized Medicine Program at Seattle's Swedish Cancer Institute (SCI). The program involves Next-Generation Sequencing, an approach that is yielding increasingly more genetic information.

"I've been a medical oncologist since 1984," says Swedish's Thomas Brown. "During those 30 years we've been focused on where the cancer starts. Generally speaking, if you have colon cancer, you're treated in a certain way or ways. If you have breast cancer, you're treated in a certain way or ways. And so on. Increasingly, though, we're beginning to learn that there's a molecular fingerprint to one's tumor. And also, the patients themselves have a unique molecular fingerprint. Those features can inform treatment."

Based on insights from the Human Genome Project, Brown says, physicians

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can now see how changes in DNA, or changes in the proteins that result from that DNA, connect to cancer. And in understanding the mechanisms that can make normal tissue turn cancerous, better treatments become possible.

Dr. Evan Ong, a surgical oncologist at SCI, believes this could have important implications for his patients. Ong routinely treats patients diagnosed with abdominal cancers. The treatment, known as Hyperthermic Intraperitoneal Chemotherapy, involves administering chemotherapy in the abdominal cavity. Ong typically uses a drug called mitomycin, but he notes that some patients have a resistance to this drug.

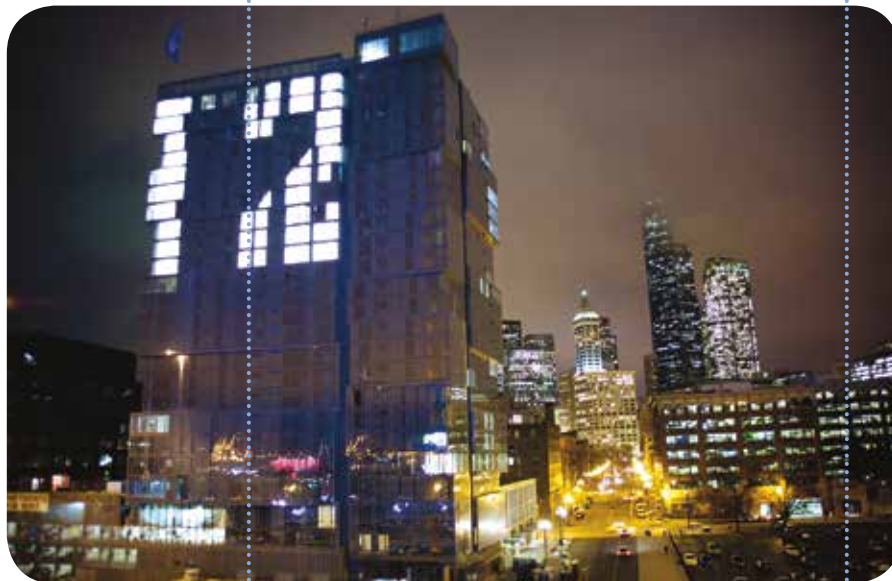
“One of the things that we’d like to do,” says Ong, “is have patients tested to see if they have resistance to the chemotherapy that I use. Then you can direct the chemotherapy and select the treatment that is most likely to be effective.”

This, according to Brown, is where the evolving worlds of information technology and data management cross paths with medical practice: “You take all of the molecular information, and you try to sort out what are the important gene sites and associated proteins, as well as where the most frequent changes occur that can cause problems,” he says. “And you try to bring that down to the individual patient.”

Ever since researchers took on the challenge of mapping the human genome, people have been wondering where that journey would lead. Personalized and targeted medicine are two of the tangible results of that research. And you’d be hard-pressed to find a medical professional who thinks the journey wasn’t worth the effort. For researchers developing medical approaches at the cutting edge—where science verges on science fiction and new treatments are catalyzed by sea anemone toxins, cell-phone technologies and esoteric research about life’s building blocks—the chances to positively affect so many people’s lives make the quests worthwhile. ▲

Dayton Fandray frequently writes about science and medicine for the magazine.

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