SPRING 2008

VOLUME ELEVEN / NUMBER ONE

THE SCRIPPS RESEARCH INSTITUTE

ENDEAVOR

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FEATURES:

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This issue of *Endeavor* magazine features a few of the Scripps Research investigators who are working to understand cancer – and to develop new and better ways to fight it.

Up Front

Researchers Identify Potential New Target for Treating Metastatic Cancer

A team at The Scripps Research Institute has identified a human protein that may be a new target for future cancer therapies. By experimentally blocking the action of this protein, called CD151, the team showed they could stop cancer cells from metastasizing, or spreading from one tumor to establish new tumors elsewhere.

Metastasis is a hallmark of late-stage cancer and contributes significantly to the large number of cancer deaths each year in the United States. In a cover article of the the journal *Cancer Cell*, Scripps Research Professor James Quigley, PhD, and colleagues describe how blocking CD151 stopped the spread of human cancer cells within fertilized chicken embryos—an experimental model used for studying cancer metastasis.

"Targeting this protein keeps the cancer cells tied to their tumors," said Quigley. "This may be the first time anyone has shown a potential way of blocking cancer metastasis at its very earliest stage—as the cells are first pulling away from their tumors of origin."

While these results provide only a proof of concept, they suggest it may be possible to design new ways of fighting cancer by treating people with drugs that block CD151. Any new cancer treatments based on this discovery would likely take years to develop and would have to prove effective in numerous preclinical experiments and in human safety and efficacy trials before finding their way into the clinic.

In a separate study, Quigley and colleagues found that a specific type of white blood cell carries with it an unusually potent catalyst of tumor growth. The catalyst—protease matrix metalloproteinases type 9 (proMMP-9)—promotes angiogenesis, the formation of new blood vessels, which are critical to tumor growth. The catalyst is carried by inflammatory neutrophils, white blood cells known as granulocytes that are filled with granules or tiny sacs of enzymes that cells use to attack various microorganisms.

The study raises the possibility that neutrophils and their payload could be used as targets for future cancer therapies.

REFERENCES: *Cancer Cell*, 13(3) (March 11, 2008); *PNAS*, 10.1073/pnas.0706438104 (December 11, 2007).

Human Antibodies Prevent Hepatitis C Virus Infection

A team has found that certain antibodies can prevent hepatitis C virus infection in a "humanized" mouse model, opening the door to the use of antibodies as a human therapeutic and the development of a preventive vaccine for the disease.

The study's authors, who include Scripps Research Professor Dennis Burton, PhD, University of Alberta Professor Norman Kneteman, MD, and an international team of colleagues, identified a group of special antibodies that can broadly neutralize hepatitis C virus. Antibodies (proteins produced by the body's immune system in response to a foreign substance) are considered to be broadly neutralizing when they are effective against many different strains of a pathogen.

Hepatitis C, which is spread by contact with the blood of an infected person, remains the leading cause of liver cancer and the leading indication for liver transplants in the United States.

REFERENCE: *Nature Medicine*, 14, 25-27 (January 1, 2008).

Scientists Discover New Gene Linked to Fragile X Syndrome

Scientists have discovered a new gene, FMR4, involved in fragile X syndrome, a condition that often shares many symptoms of autism. The discovery may lead to new tests or treatments for several neurological disorders.

Prior to this research, FMR1 was the only gene known to be associated with the condition.

"FMR4 is a novel gene that is located in the same chromosomal neighborhood as FMR1, a well established causative gene in fragile X syndrome," said Claes Wahlestedt, PhD, a professor at the Scripps Research campus in Jupiter, Florida. "Like FMR1, FMR4 is silenced in fragile X patients and up-regulated in FXTAS (fragile X-associated tremor/ataxia syndrome), a disease that resembles Parkinson's disease."

Fragile X syndrome affects thousands of patients worldwide with severe learning disabilities, often accompanied by anxiety disorders, obsessive-compulsive behavior, and attention deficit hyperactivity disorder. There are currently no therapeutic treatments available.

REFERENCE: *PLoS ONE*, 3(1): e1486 (January 23, 2008).

"Though in the last couple of decades there has been a concerted war on cancer with a lot of improvements in early diagnosis and treatment, we still don't have a breakthrough in metastatic cancer—and this definitely needs to happen."

BRUNHILDE FELDING-HABERMANN, PhD.

Tracking Breast Cancer Metastasis

BRUNHILDE FELDING-HABERMANN SETS HER SIGHTS ON THERAPIES TO STOP TUMORS FROM SPREADING

Scripps Research Institute scientist Brunhilde Felding-Habermann, PhD—known as "Brunie" by her friends and colleagues—knows exactly when she got bitten by the science bug.

"In high school in Germany, where I'm from, I found myself spending a lot of time hanging around the biology department," says Felding-Habermann, an associate professor who came to Scripps Research as a senior research associate in 1993. "I was intrigued by the aquariums and displays and became very curious about how life works and how it can go wrong when disease happens."

Building on a foundation of work in physiological chemistry, cell biology, and protein biochemistry, she is currently focusing her work on the spread of breast cancer from the primary tumor to other parts of the body, a progression called metastasis, which is still poorly understood and poorly treated. Why cells metastasize and why they tend to colonize particular organs, especially the brain, are the specific questions Felding-Habermann hopes to answer.

"Brain metastases are among the most feared complications in breast cancer," she says. "And though in the last couple of decades there has been a concerted war on cancer with a lot of improvements in early diagnosis and treatment, we still don't have a breakthrough in metastatic cancer—and this definitely needs to happen."

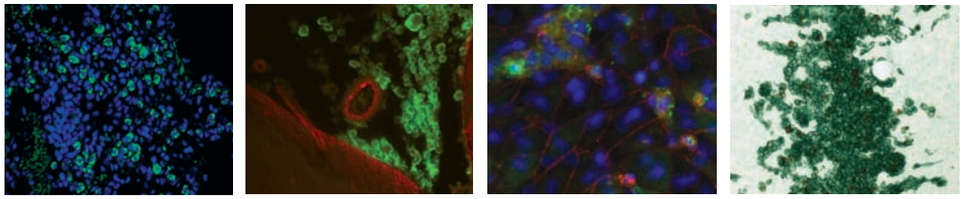
This urgency is underscored by the latest statistics and the human suffering behind them: There are about 1,350,000 new cases and 160,000 deaths from brain metastases in the United States each year.

EXPLAINING SATELLITE CANCERS

Scientists have a rough picture of the metastatic cascade: tumors break free from the original site and slide into the lymphatic system or the bloodstream, flow someplace else, attach themselves there, and often begin to thrive. Felding-Habermann and her research team—PhDs Mihaela Lorger, Karin Staflin, Joseph Krueger, Leontine Galante, Giulio Cattarossi, and Deirdre O'Sullivan, together with BAs Jane Forsyth and Melissa O'Neal—are working to understand the specifics of this insidious breakaway invasion so that strategies can be devised to stop metastasis in its tracks.

Using blood samples from breast cancer patients who had metastatic disease, Felding-Habermann and her team examine the samples, hoping to find and study circulating tumor cells. As the tumor cells circulate, they exhibit special characteristics that help the researchers understand how cancer spreads.

After finding out that the tumor cells isolated from patient blood samples can spread to the brain of experimental mice at an astonishing rate, the team has recently developed a special interest in brain metastasis. Brain lesions have been difficult to study because appropriate models were missing →



Researchers are beginning to understand critical facts about tumor cells. *Left*: Immune cells (green) can infiltrate a metastatic lesion (blue), but may inadvertently help the tumor cells grow. *Center left*: Tumor cells (green) invade the brain tissue, where blood vessels provide nutrients for the growing cancer. *Center right*: A model of the human blood-brain barrier helps illustrate how circulating tumor cells enter the brain. *Right*: Metastatic tumor cells that can grow rapidly and invade healthy brain tissue (dark stain) are the most dangerous.

in basic and clinical research. Recognizing the importance of their new cell and animal models, the team hopes to help further the understanding of how breast cancer cells spread to the brain.

To better understand how the tumor cells interact with the blood-brain barrier, the team observes this cellular structure in a culture system using human brain endothelial cells. These cells tightly line blood vessels in the brain and protect it from chemicals and cells in the blood, while still allowing essential metabolic functions.

"We present these endothelial cells in culture in a three-dimensional way to generate a model of the blood brain barrier, similar to how the cells might actually be presented in a blood vessel of the brain," Felding-Habermann explains. "Then we co-culture the cells with other cell types present in the human brain that are known to be constituents of the blood-brain barrier." The focus of this intensive work is to study if and how the tumor cells penetrate the blood-brain barrier to gain access to the brain tissue.

Felding-Habermann mentions one "very surprising" and significant finding made by Mihaela Lorger in her lab. In establishing cell lines from cancer patients' blood samples, the researchers noted that one patient donated samples at two different times and that the cancer cells from the samples behaved differently. One cell line penetrated the blood brain barrier easily; the other did not.

"This unexpected result tells us that circulating tumor cells can be quite different and have distinct functions. Because these cells came from the same patient and therefore share the same genetic background, this cell model helps the team to identify genes and, down the road, proteins that control these different abilities of tumor cells."

Pinning down the capabilities of cancer cells is a key to developing better, more targeted therapies.

TRACKING THE SPREAD OF CANCER

After the researchers establish these proliferating cell lines and study their functions in culture systems, the cells are prepared for use in experimental mice. Even though the culture- and test-tube models often involve high-tech approaches that can provide a lot of information, key steps of the metastatic cascade can be fully studied only in the complexity of an animal model.

The *in vivo* work begins with some genetic tinkering. The Felding-Habermann team engineers the tumor cells to express an enzyme called firefly luciferase. This enzyme, which is responsible for a firefly's ability to glow in the dark, can produce sparks of light, known as bioluminescence. With a special light-sensing camera and imaging system attached to a computer, the researchers can use this bioluminescense to locate cancer cells inside a mouse's body non-invasively.

"The light signal shows us a primary tumor forming, and we can see if tumor cells spread to other sites. Although we're looking at tumor movement in the entire body, we're primarily interested in what's happening in the brain."

Brain metastases are a growing concern in breast cancer, as well as in lung and some skin cancers. The prognosis is poor if patients develop brain lesions, and effective treatments are urgently needed.

"We need to understand this process [of metastasis] so that the best therapies can be developed to fight the cancer and potential new treatments for prevention can be given at the right time."

BRUNHILDE FELDING-HABERMANN, PhD.

WHAT'S GOING ON IN THE BRAIN?

As tumor cells make their rounds in the bloodstream, some of these cells may interact with the blood vessels of the brain and form secondary tumors in the brain tissue. The Felding-Habermann team monitors this process closely to see if blood cells, particularly platelets, help tumor cells lodge in the tiniest blood vessels in the brain and if they respond to treatment.

"What we've noticed is that some tumor cells not only can lodge in vasculature but also penetrate the blood-brain barrier," says Felding-Habermann. Still, these cells may not cause any harm unless they are able to survive and grow in the brain tissue. These properties are controlled by yet another set of genes and proteins that the team is studying. In monitoring the behavior and abilities of cancer cells, the researchers are addressing a central question about the nature of metastasis: Do primary tumors directly seed satellite tumors to the brain, or do these brain tumors come from metastases that have settled in other organs?

"We're focusing on these alternative scenarios, but it's also possible that both progressions are manifested in a given patient," she says. "From a clinical standpoint, it matters. We need to understand this process so that the best therapies can be developed to fight the cancer and potential new treatments for prevention can be given at the right time."

SEARCH-AND-FIND MISSION

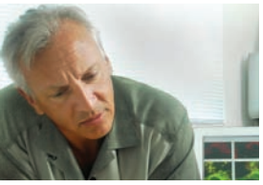
In the lab's work with mice, the team has made some interesting discoveries using stem cells to help develop new treatments for spreading cancer. Team member Karin Staflin implanted breast cancer cells into one hemisphere of the mouse brain and neural stem cells into the other hemisphere. The stem cells, the researchers were pleased to see, went on a search-and-find mission for cancerous lesions.

"We've shown that you can implant neural stem cells into either side of the brain, and they'll seek out disease; so we're trying to engineer the stem cells to express therapeutic antibodies that we have developed against aggressive breast cancer. If all goes well, the cells would then travel to brain lesions, produce the antibody, and eliminate the tumor cells."

This antibody approach was furthered, as many projects are at Scripps Research, Felding-Habermann points out, through collaboration with other Scripps Research scientists. "I was talking with Dr. Kim Janda, a professor of chemistry, and told him we have evidence that one of our target molecules is expressed primarily on metastatic breast cancer," Felding-Habermann recalls. "He said, 'Why don't we team up and mine our antibody library to see if any of the patients who have donated a blood sample to our library made an antibody that will recognize this molecule?'"

Out of that discussion came a project that has led to the discovery of two antibodies that have the potential to interfere with metastatic disease. "We're using these antibodies now in our mouse model," Felding-Habermann says. "If we're successful, we hope these can be used in the clinic to see if they can help cancer patients."

→ *Continued on p.15*



"At Scripps Florida, every department is based on the fundamental principle that you can apply research to human medicine."

JOHN CLEVELAND, PhD.

Moving Forward

JOHN CLEVELAND SEIZES OPPORTUNITIES IN CANCER RESEARCH AT SCRIPPS FLORIDA

John Cleveland, PhD, heads up the Department of Cancer Biology at The Scripps Research Institute's Florida campus. He arrived in the fall of 2006 from St. Jude's Children's Research Hospital with big plans for both the department and his lab and a fairly straightforward approach to accomplishing them. To a great degree, it all comes down to the phrase "translational science."

"With translational science you try to move—translate—basic discovery in the lab toward applications in human medicine," Cleveland says. "For us, that means we identify novel targets that could be used to treat cancer. Then we develop assays that will identify small molecules, and make sure they're hitting the right target. Then we take those small molecules to the chemists upstairs and they make it into a drug. If that works, we go to Phase I trials [the first human trials necessary for drug approval by the U.S. Food and Drug Administration] in collaboration with academic partners.

"Scripps Florida is the perfect spot for doing this—because basically you can do it all in your own building."

In any conversation with Cleveland, the phrase "translational science" is often used in conjunction with the phrase "big science," which, he explains, boils down to interactive, and often interdisciplinary, research—The Scripps Research Institute's strengths.

"Right now, we are the only academic research institution that combines basic research with the capabilities to develop drugs," Cleveland says. "You don't find that anywhere else. At Scripps Florida, every department is based on the fundamental principle that you can apply research to human medicine."

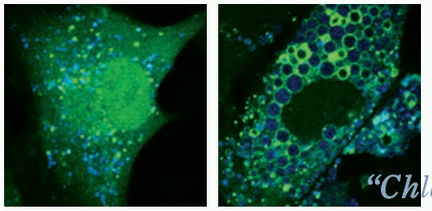
EXPANDING HORIZONS

Cleveland's pursuit of cancer treatments at Scripps Florida is a logical (albeit expansive) extension of the work he's been doing most his life, first at the National Institutes of Health and then at St. Jude's Children's Research Hospital. Cleveland joined the famed Memphis-based research facility in 1989 and became a full professor in its Biochemistry Department in 2000.

The difference this time around is the scope of the opportunity he has on his hands. "We were a basic research lab at St. Jude's," he says, "very good at target discovery, but we didn't do much with those discoveries—but that wasn't our goal."

Now, at Scripps Florida, he is expanding his research focus to include adult disease as well as more applied research, re-defining the basic goals of his laboratory. For him, this is all for the better.

This shift in his program has also been a lure for his laboratory colleagues—most of whom followed him to Florida. Additional attractions included the sunlit geography, he admits, but more so the technology Scripps Florida has to offer. →



Choloroquine has a potent effect on cancer cells. Compare untreated cells (left) with those treated with chloroquine for just four hours (right), which show a massive accumulation of large, dysfunctional lysosomes preceding cell death.

"Chloroquine and other agents that target the autophagy pathway may turn out to have very broad applications."

JOHN CLEVELAND, PhD.

"The technology here sold my postdocs on the move," he says. "Their eyes lit up when they witnessed the technology. That's because high-throughput screening has affected the way science looks for targets. It basically allows you to interrogate the whole genome."

Scripps Florida has established a high-throughput-screening system that, while common in the pharmaceutical industry, is far less so in the world of biotechnology and research. What Cleveland likes about the technology (aside from its accessibility) is what he calls the "ping pong effect"—using the technology on a regular basis reveals a great many things that were simply unknown before, which feeds other aspects of an investigator's research program.

Another part of ensuring the future of his research program has been keeping an eye towards funding. To this end, Cleveland has been building partnerships with industry as well as relying on more traditional means of support, such as grants from the National Institutes of Health (NIH). "We have to diversify our sources of funding if we are to be really successful," he notes.

Funding remains a critical factor in research, one that walks hand-in-hand with scientific advances. One way to look at it is to consider how close we would have come to reaching the moon without adequate funding.

"Doing great science takes a serious investment," Cleveland says. "There has to be a big investment to get big results."

And big results are precisely what Cleveland is after.

FIGHTING THE BEAST

In 2007, Cleveland's lab produced eight papers dealing with various aspects of cancer, a normal output for his team. ("I tell them I want 10 papers a year, but we don't always get it, so maybe eight is the right number.")

His big target is *MYC*, a serious villain. *MYC* is a proto-oncogene, a molecule that under the right circumstances can cause cancer, a transcription factor that regulates the expression of approximately 15 percent of all genes and is believed to be responsible for some 70 percent of human cancers, including of the breast, ovaries, lung, prostate, and skin, as well as leukemias and lymphomas. In almost all rapidly dividing tumors, it is overexpressed.

Cleveland simply calls *MYC* "The Beast." Over the past several years, his lab has discovered a great deal about *MYC*; for example, it is an essential regulator of tumor angiogenesis, and it regulates many other pathways that control the fate of cells.

"One of the major discoveries of the laboratory was that proto-oncogenes like *MYC* actually promote apoptosis or cell death when they are overexpressed in normal cells," he said in an earlier interview. "This point of view was very radical at the time the work was being done—in the late '80s and early '90s—yet now it is widely accepted. We also discovered how *MYC* induces apoptosis and showed that this pathway is overcome during tumorigenesis, that is, tumor cells undergo mutations that bypass this pathway. Obviously, if we could reactivate this pathway, we would have a therapeutic. This is one of the areas we're spending a lot of time on."

In studying *MYC*, Cleveland and his colleagues also stumbled across another intriguing pathway, the autophagy pathway. Autophagy is a complex adaptive cellular response that enhances cell survival in the face of starvation or other stresses, and is induced by most drugs that are used in cancer treatment. Inhibiting this pathway could overcome the problem of drug resistance and perhaps even prevent cancers from developing in the first place.

A NEW USE FOR AN OLD DRUG

In early 2008, Cleveland and some former colleagues at St. Jude's published a new study that proved just that and offers what may be the perfect crystallized idea of what translational science is all about.

In the study, published in *The Journal of Clinical Investigation*, he and his colleagues showed that a commonly prescribed anti-malarial drug effectively prevented the development of cancer in two models of distinct human cancer syndromes, Burkitt lymphoma and ataxia telangiectasia, a rare and progressive immunodeficiency disease that predisposes patients to cancer, especially lymphoma and leukemia.

The drug is chloroquine, which has been in worldwide use since 1946, and the work pointed towards a new and effective way to treat blood cancers that are difficult to treat otherwise—and to do so without raising the complicated and ever-present specter of cytotoxicity (a chemical's ability to kill cells) towards normal cells.

"Chloroquine can be combined with most agents that are used to treat cancer patients," Cleveland said when the study was released. "Our recent studies (published in *Blood* in 2007) in drug-resistant chronic myelogenous leukemia—a significant clinical problem—provide proof that drugs that disable the autophagy response can overcome treatment resistance. During autophagy, cells consume their own constituents to survive. Drugs used to treat cancer activate the autophagy pathway; chloroquine gums it up. We believe this strategy can be applied to nearly all refractory human tumors, and we are testing this notion in the lab."

With that clearly established, Cleveland is working to find derivates that may work more effectively than this drug, and if they hold up in the laboratory, to push them into Phase I trials as quickly as is humanly possible, emphasis on the human.

"That's the ethical thing to do," he said, "because chloroquine and other agents that target the autophagy pathway may turn out to have very broad applications."

"SOMETHING NEW AND EXTRAORDINARY"

In addition to bringing most of his lab from St. Jude's with him, Cleveland, as head of the Department of Cancer Biology, is also looking to bring other cancer scientists and their laboratories to Scripps Florida. He has a clear grasp of whom he wants.

"When you think about recruiting, you want investigators who have the potential to become stars in their field," he said. "In five years I want a fully functional, highly collaborative department that generates research that we can take to the pharmaceutical industry and which can generate large government-funded program project grants. That's part of big science. The other benchmark is to get compounds into the clinic—that's a huge focus for us and our partnerships. These are the key measures of success."

But not the only ones.

"The most satisfying aspect of the job is making sure the faculty and postdocs do well; that's leaving a legacy. If you do that well, and manage to be a good mentor, the studies and papers will come."

Cleveland has taken to his roles at Scripps Florida ("I'm busier than ever but happier than ever."), working to establish his laboratory and his department, as well as significant collaborations with investigators on the Scripps California campus. For Cleveland, being at Scripps Florida is about "the chance to build something new and extraordinary."

It's also about fulfilling the promise of his research.

"Cancer affects all of us. You know why you're coming to work every day."

ERIC SAUTER

"We've already started to get the network in place to do the kind of research that will lead us to this promised land of personalized medicine."

NICHOLAS SCHORK, PhD.

Putting Together the Big Picture

NICHOLAS SCHORK SEARCHES THE GENETIC CODE FOR CLUES ABOUT CANCER

Few would consider the works of Friedrich Nietzsche a logical starting point for a career in genomics research, but that's where Nicholas Schork, PhD, began. It wasn't the 19th century German philosopher's thoughts on morality, religion, or even science, though, that shifted Schork to the path that would ultimately lead him to The Scripps Research Institute, where he is helping to lead a medical revolution destined to transform how cancer and other diseases are treated. It was something decidedly less esoteric: the need for cash.

Schork was working on a graduate degree in philosophy at the University of Michigan with a family to support. Having picked up some experience with computers while an undergraduate, he was able to secure a job at the nearby medical school writing programs to analyze medical data.

As it happened, a number of scientists who would ultimately prove to be pioneers in genetics research, such as Francis Collins, who went on to lead the Human Genome Project, were working at the medical school at the time. Schork began attending their lectures and they effectively changed his life.

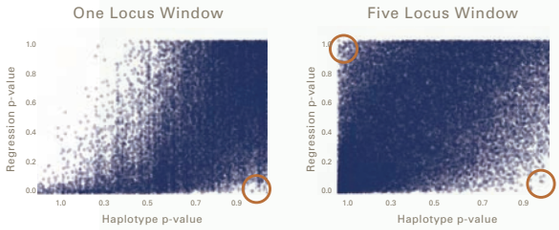
"There was a kind of revolutionary vision that was given off by these talks," he says, "suggesting all sorts of insights into disease could be obtained in unprecedented ways by unleashing the secrets of the genome, and that just excited me."

It excited him so much, in fact, that he would ultimately spend his professional life developing strategies for culling useful information from the human genome. Now, as a professor in the Department of Molecular and Experimental Medicine at Scripps Research since March 2007, and the director of research for genomic medicine at Scripps Health, Schork is working to bridge the gap between producing that information and using it to develop new life-saving treatments for cancer and other diseases.

TOO MUCH INFORMATION

One hurdle often discussed for the coming medical revolution Schork learned about at the Michigan talks was the need to figure out new ways to process and analyze what at the time seemed to be huge quantities of genetic data becoming available. Some of the researchers he came in contact with at the school, including his own father, who was a professor in biostatistics, encouraged him to consider shifting his education in a direction that would enable him to tackle this barrier.

Schork began working toward a PhD in epidemiology, while also continuing his philosophy studies. Ultimately, though, he decided that doing both was unfeasible. So, he began to focus on the genetics, though he still enjoys reading philosophy in his spare time. →



Regions where data disagree about significance.

As Schork neared completion of his epidemiology studies at Michigan, he made the welcome discovery that his skills were in demand. There were few people at the time with both the biological and computer knowledge required to understand genomics, as well as the complex statistics and computer programming facility necessary to process the data involved. With several faculty position offers, he was able to bypass the standard postdoctoral fellowship years and move straight to Case Western University.

Schork's time there included a leave of absence to work at the genetics startup GenSet, which originally aimed to sequence the entire human genome before the federally sponsored Human Genome Project program focused on the same target and squelched the company's efforts. Later Schork moved to the University of California, San Diego. It was there that he received a call from a former University of Michigan colleague who made what would prove to be an irresistible invitation to join a unique program developing at Scripps Research.

GENOME SLOGGING

In the simplest terms, Schork's talent and exceedingly complex job is, as he puts it, "developing appropriate mathematical models to slog through the genome." In other words, developing innovative ways to identify the specific letters in the genetic code that, when altered from the norm, can either cause diseases such as cancer, or create susceptibility to them. For good reason, it's a task that has been compared to finding a needle in a haystack on Earth using a telescope on Mars, though the reality of the task is probably more like having to find several needles in the haystack, all of different colors, and picking out the only one that is aquamarine.

When researchers such as Collins first inspired Schork, the field was overwhelmed by datasets of hundreds or thousands of genetic code letters in the search for useful information. Today, such concerns seem almost quaint, because now researchers can generate a billion of those letters in a day.

Beyond the challenge of volume, to figure out which letters are important in controlling or causing disease, researchers must also contend with countless other factors. Patients with similar medical conditions are likely to have a staggering variety of ancestral genetic backgrounds and environmental histories, all of which can be the source of numerous variations not tied to disease. To further complicate matters, numerous genetic variations might play a role in causing a particular disease, and some variations unique to those with a disease might be caused by the disease rather than responsible for it. Collectively, these complicating factors create a cacophony of background noise.

Schork and his team have, in recent years, achieved major advances that have made it possible to see past at least some of the genetic noise to analyze huge sets of genomic data from thousands of people. At a broad level, Schork tries to think of new analyses, or improvements on old ones, that will enable the identification of genetic differences shared by some or all members of a group suffering from the same disease. Other tests are aimed at measuring how robust the connection is between a variation held in common by disease sufferers and the disease itself, because some seemingly promising connections can prove to be insignificant. Additional work focuses on integrating genetic data analysis techniques with other potentially helpful information, such as the levels of certain proteins in the blood.

Though Schork has a team that includes talented computer programmers, he still does substantial programming himself, even if others in his group find his preference for Fortran, a computer language most consider hopelessly outdated, humorous. "I'm a dinosaur," says Schork with a laugh, "I admit it."

FROM DATA TO DRUGS

As daunting as the task of identifying the important variations may be through the analyses Schork develops, that identification is only a first step toward the ultimate goal of using genetic information to inspire or enable new disease treatments. "In order to actually prove to the world a discovery has some utility, you've got to conduct the appropriate clinical studies," says Schork. Toward that end, he has teamed with others at Scripps Research and Scripps Health, such as Eric Topol, MD.

It was Topol who called Schork at UC San Diego to ask if he would join a new Scripps Research program called the Scripps Advanced Clinical Trials program aimed at closing the gap between more basic genetics research and actual clinical studies.

"When I came to La Jolla, he was the first person to recruit without question," says Topol of Schork, "There is this torrential flood of data the likes of which we've never seen, and we are so fortunate to have someone like Nik who can make heads or tails out of it. There are only a few people like him in the world."

This clinical effort, which is only now getting under way, will include work on heart disease and health problems associated with ageing. But a key focus will be identifying genes and variations tied to different forms of cancer and then working with collaborators to develop targeted drugs or other treatment strategies that exploit these discoveries to fight disease.

The team is working to amass tissue samples from tumors removed from cancer patients and may also study existing tissue collections at Scripps Research or elsewhere. Schork's initial work to zero in on cancer causes will include two main components. One task will be analyzing the levels of thousands of proteins in samples to identify those whose production may be lower or higher than normal. The second goal will be to analyze DNA found in the tumor cells to identify variations and mutations that can be tied to a disease. In short, the work will be a miniature version of the same kinds of data analyses for which Schork is now world-renowned. But instead of studying databases of thousands of people's DNA as he has in the past, he'll focus on perhaps a few dozen patients suffering from the same disease.

According to Schork, once the mutations and protein abnormalities are identified, "that's where the fun and games begins." Even if a particular protein's level is high in a tumor cell, that doesn't mean it's the cause of the cancer. For instance, the protein's overproduction might be tied to a by-product, referred to as a passenger, of a mutation in another gene that is actually the tumor-causing culprit, or driver.

Once an important driver is identified, the team will then work with collaborators to develop potential treatments, such as a drug that blocks overproduction of a protein. "We've already started to get the network in place to do the kind of research that will lead us to this promised land of personalized medicine," says Schork.

GETTING PERSONAL

While there are no guarantees the hoped-for revolution will come, Schork says encouraging findings to date at labs around the world suggest the strategy is likely to work for many diseases.

The field is referred to as personalized medicine because a given driver is not likely to be shared by everyone suffering from a disease, and there have already been examples of using this basic strategy successfully in cancer research. The drug Herceptin, for instance, is used to block production of a protein that can cause breast cancer. But it's only one route to the disease because the mutation is shared by only about a fourth of breast cancer patients.

Herceptin is a form of personalized medicine because doctors can now screen potential patients to see if they have the mutation that would make the drug effective. The Scripps Research team will initially →

"We anticipate this revolution, and we intend to be leaders."

NICHOLAS SCHORK, PhD.

concentrate its cancer research on developing similar potential treatments for patients suffering from prostate and breast cancers.

It's not clear yet just how personalized genetics-based treatments for prostate, breast, or other forms of cancer will have to be. It could be that with some forms each tumor is so unique that it requires its own tailored treatment. Or, treatments like Herceptin that apply to a significant subset, but not all people suffering from a disease, might be identified.

Though the team will begin with a deliberately narrow focus, ultimately Schork says the research should have much broader impact. It's likely that similar gene defects lead to a variety of types of cancer, because most forms involve similar problems with unchecked cell proliferation leading to tumor growth. So, while in early stages some of the work may lead to experimental treatments that work for only a handful of people, discoveries should ultimately apply to larger groups and a variety of cancers. Schork envisions a point in the future where cocktails of drugs might be chosen from a larger menu of drug options and tailored to specific drivers identified in a given patient.

PROVIDING BALANCE

One likely challenge in developing the menu of drugs needed to fully realize the potential of personalized medicine is the tendency for a given treatment to work on only a small subset of disease sufferers. This could mean fewer potential profits for a pharmaceutical company and less inclination to foot the bill for developing the drug.

"I think there are certainly going to be some growing pains in these areas," says Schork, "but I think there is a growing acceptance of the biological reality that drugs don't work ubiquitously."

Personalized medicine is already having both commercial and regulatory impacts that hint at more to come. Just a few months ago, the Federal Drug Administration approved a blood-clotting drug that requires genetic screening to determine proper dosage for a particular patient. Another recent precedent-setting approval for a drug used to treat skin rashes includes a warning that those of Asian descent have been shown to have especially adverse reactions to the drug.

But an even greater sign of things to come may be found in the recent launching of several companies that analyze their customers' genetic codes for variations that research has tied to susceptibility to cancer and other diseases, as well as physical traits such as sensitivity to bitter tastes. Huge questions remain open, such as how useful such information may be, given that susceptibility does not guarantee affliction and that most doctors are currently ill equipped to address the information in meaningful ways.

Schork says that as interest in individual sequencing and personalized medicine is growing, research like that he is conducting with Topol and other colleagues can offer an important balance.

"I think programs like ours can do the science to see if this stuff works," he says. "We anticipate this revolution, and we intend to be leaders. We want to spark this revolution in a way that doesn't create more problems than it's solving."

MARK SCHROPE

Tracking Breast Cancer Metastasis

(continued from page 05)

TRANSLATING RESEARCH INTO BETTER HEALTH

The ultimate objective of Felding-Habermann's research is nothing less than targeting tumor cells in order to kill already-existing tumors and to prevent cancer from spreading. "This is the goal of thousands of cancer researchers out there. Everything we do is aimed at that goal."

Treatment of brain tumors can be tricky, even for the most skilled surgeon. Chemotherapy is often problematical because the blood-brain barrier, which serves to protect the brain and spinal cord from damaging chemicals, also keeps out many types of potentially beneficial drugs. Surgery can be difficult if the tumor is near a delicate portion of the brain or spinal cord, and radiation therapy can damage healthy tissue.

"Current treatment typically involves surgery to remove a well-defined tumor," says Felding-Habermann. "There's also focal radiation with x-rays with the objective of getting treatment as localized to the tumor as possible." She adds that in many of these cases, a patient doesn't have only one well-defined lesion but multiple lesions. "So, ideally, we want a chemical or a therapy that can be distributed in a way that allows it to reach all of the tumor cells, while leaving healthy brain cells intact."

Her team's use of innovative antibody delivery methods and stem cells as agents to deliver chemotherapy and specifically kill brain metastases may do exactly this. "Based on results from the literature and our own findings, we think that combining a neural stem cell approach with therapeutic antibodies could well be the most effective way to reach breast cancer metastases in the brain. Antibodies normally do not cross the blood brain barrier, but neural stem cells, engineered to express antibodies with therapeutic potential, could deliver the blocking molecules to the metastatic sites."

THE HUMAN ELEMENT—FRONT AND CENTER

One thing that drives her forward in this work, Felding-Habermann says emphatically, is her direct connection with patients and cancer survivors. She maintains this contact through the California Breast Cancer Research Program, which is currently funding her work, and she has often been a reviewer on study sections that include women who are non-scientists but knowledgeable about cancer research, many of whom have had breast cancer.

Recently, Felding was contacted by the National Breast Cancer Foundation, a group that educates breast cancer advocates, which was presenting a one-week course for advocates who had come from all over the country. Would it be possible for them to visit her lab?

"I was very glad to get this call and said 'yes, of course,'" says Felding-Habermann. "So about 60 people came over to our lab for an afternoon seminar I'd prepared with some colleagues here at Scripps. We got tremendous positive energy from these people—the human element front and center. Interactions like these have always been my prime motivation for the work I do."

JEFF WORLEY

Behind the Scenes

In recognition of Phillip and Patricia Frost's donation, the foyer of a key building will be named the Frost Lobby.

"The Scripps Research Institute deserves our full support."

PHILLIP FROST, MD

PHILLIP AND PATRICIA FROST GIVE $1 MILLION TO SCRIPPS FLORIDA

Miami physician, businessman, and philanthropist Phillip Frost and his wife, Patricia Frost, an ardent supporter of education and the arts, have donated $1 million to Scripps Florida.

In recognition of the Frosts' donation, the foyer of the building that will house laboratories for a key component of Scripps Florida research—making strategic scientific discoveries, then accelerating their development into new drugs and treatments to improve human health—will be named the Frost Lobby, announced Scripps Research President Richard A. Lerner, MD.

"The Scripps Research Institute deserves our full support," said Phillip Frost. "By minimizing the bureaucratic aspects of advanced medical research, Scripps President Dr. Richard Lerner has attracted an unequalled group of scientists who will continue to be responsible for many of the advances in this century."

"Phil's experience as an entrepreneur and his history of success in drug development have made him a very valuable member of our Board of Trustees as we've expanded our operations from California to Florida," said Lerner. "Now, his and Patricia's generosity will further enable us to make Scripps Florida the center of a vibrant biomedical and biotech community in the state."

The first phase of Scripps Florida—three buildings totaling 350,000 square feet of laboratories and space for cutting-edge technologies, biomedical support services, and administration now under construction on Florida Atlantic University's Jupiter campus—will be ready for occupancy in early 2009. Currently, 240 researchers and support staff are working in two buildings and three trailers on the FAU campus. The temporary laboratory facilities built for Scripps Research will ultimately be integrated into FAU's campus.

Hans and Dagny Wiener have established a charitable gift annuity with The Scripps Research Institute.

BENEFIT FROM A GIFT ANNUITY

Join The Scripps Legacy Society by establishing a charitable gift annuity with The Scripps Research Institute. You can get an immediate tax deduction, receive a fixed income for the rest of your life, and support our scientists' present and future research.

Hans and Dagny Wiener have taken advantage of this option, establishing a charitable gift annuity with The Scripps Research Institute.

"My husband, Hans, and I wanted to create a lasting legacy for the future of medical research at Scripps Research by creating this charitable gift annuity, while also enjoying increased income in our retirement years," said Dagny. "I've always been aware of the importance of medical research. We had many doctors in the family, including my father, one of my sons, and my uncle—in fact, I worked for my uncle performing research on the effects of radium at the Karolinska Institute in Sweden."

Hans, who has since passed away, had an illustrious career in international relations and received the Commander of the Swedish Royal Order of the North Star from the King of Sweden.

In addition to supporting biomedical research, your Scripps Research charitable gift annuity can supplement your retirement income. If you are 80 years old, for example, and establish a $50,000 gift annuity with Scripps Research, you will receive $4,000 per year for the rest of your life, some of it tax-free, while also receiving an immediate tax deduction of $25,618.

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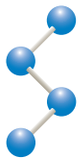
The Scripps Research Institute has launched, "At the Forefront," a monthly e-newsletter for donors to the institute. If you would like to receive the newsletter, please sign up at www.scripps.edu/philanthropy.



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A PUBLICATION OF
THE SCRIPPS RESEARCH INSTITUTE

Office of Communications—TPC30
10550 North Torrey Pines Road
La Jolla, California 92037
www.scripps.edu

PUBLISHER:
Keith McKeown

EDITOR:
Mika Ono Benedyk

DESIGN:
Studio 32 North

PRODUCTION:
Studio 32 North
Kevin Fung

COVER ILLUSTRATION:
Yuko Shimizu

INTERIOR ILLUSTRATIONS:
Meg Mateo Ilasco

PORTRAIT PHOTOGRAPHY:
Dana Neibert

PORTRAIT PHOTOGRAPHY:
Bruce Hibbs

PRINTING:
Precision Litho