

Advancing Cancer Therapy at UCLA Through the Human Genome Project

By Dan Gordon

n his fifth-floor laboratory in UCLA's Gonda (Goldschmied) Neuroscience and Genetics Research Center, Dr. Stanley Nelson is analyzing tumors by going directly to the source: the genes that control cellular behavior in normal times, and that, by going awry, result in cancer. Nelson's work, and the work of researchers in laboratories and clinics throughout UCLA's Jonsson Comprehensive Cancer Center, is quite different from what it was a few years ago. And a few years hence, it is sure to bear little resemblance to what it looks like today.

In the past three decades, cancer researchers have employed the powerful techniques of molecular biology to discover that cancer is a genetic (though, in at least 90% of cases, not inherited) disease. It occurs when changes in the genetic blueprint — DNA — cause certain genes to become altered in cells, which then proliferate out of control.

The search for cancer-causing genes has been laborious. Researchers have groped around seeking a candidate, then spent months, often years, on the tedious task of cloning and mapping the order of the tens of thousands of chemical components that make up the gene before moving on to the more interesting and potentially fruitful questions at hand, such as how to use the information to benefit cancer patients and those at risk for the disease

Today, with the completion of a decade-long national quest whose grandiose ambition drew comparisons to the effort to land a man on the moon, scientists like Nelson can cut straight to the chase. The human genome, consisting of some 3.1 billion chemical building blocks that comprise our DNA, providing the instructions needed to assemble the human body and give it life, has been sequenced. Now that cancer researchers have the ultimate reference guide, the same information that once took years to gather can be obtained with a couple of mouse clicks.

The hard part, given the explosion of data available at researchers' fingertips, is knowing where to start. An area drawing immediate attention is the search for additional cancer-related genes. One of the major discoveries of the past 30 years is of the existence of cancer-promoting oncogenes that are activated by gene mutations, as well as tumor suppressor genes that are inactivated as a result of alterations. Approximately 100 oncogenes and some 30 tumor suppressor genes have been identified, but scientists believe many more are yet to be found.

"Sequencing the genome will greatly expedite the discovery of new cancer genes," says Dr. Leena Peltonen, chair of UCLA's Department of Human Genetics. She notes, for example, that genes identified with prostate and breast cancer have been pinpointed at several chromosomal sites, but their precise characterization remains to be accomplished. Now researchers can go online and find the listing of the sequenced genes residing on a particular chromosome, immediately providing "candidate" genes for further study.

Peltonen expects that investigators will use the sequenced genome to discover currently unknown genetic steps leading to cancer. "We understand only some of the metabolic pathways of the human body," she says. "Being able to study *all* of the genes involved in the cancer process will probably result in the identification of pathways about which we currently don't even have a clue."



esearchers have long held as an article of faith the notion that learning the processes and specific genetic alterations involved in cancers could result in more rational, targeted approaches to treating the disease — treatments that would be both less toxic and more effective. Two promising new therapies developed at UCLA provide some of the first proof that the researchers' faith was well founded. Herceptin, which targets a genetic mutation found in 25 to 30 percent of breast and ovarian cancers, was approved in 1998, the culmination of nearly two decades of work by a team headed by Dr. Dennis Slamon, director of the Jonsson Cancer Center's Division of Clinical/Translational Research. Gleevec (formerly known as STI-571), which was approved last May by the Food and Drug Anministration after clinical trials at UCLA and elsewhere, targets a mutation in a gene that causes a form of adult leukemia; pioneering research on this genetic alteration was conducted at UCLA by Drs. Owen Witte, Charles Sawyers and their colleagues.

"These treatments prove the principle that once we've identified the genes that are altered, we can develop the proper technology to

target therapies specifically to fix what's broken, as opposed to traditional chemotherapy and radiation, which are nonspecific," explains Dr. Judith Gasson, director of the Jonsson Cancer Center.

Or, as Slamon says of Herceptin: "Instead of build-

ing bigger bombs, we've developed a smart bomb to target a specific problem."

The specific problem that Herceptin attacks: extra copies of the HER-2/neu oncogene that cause overproduction of a protein receptor on the surface of breast and ovarian cells. Slamon discovered the problem after launching a "fishing expedition" in the early 1980s, using a human tumor bank at UCLA to look for patterns of alterations in known oncogenes. The discovery of the HER-2/neu alteration, which he then correlated to outcome — the more copies of the gene in the tumor, the more aggressive the cancer and the worse the prognosis — led Slamon to reason that attacking HER-2/neu might produce therapeutic benefits. Working with a genetically engineered antibody produced by the pharmaceutical company Genentech, he successfully locked onto the protein and interfered with its function, inhibiting the growth of tumor cells in the laboratory. By 1991, Slamon had begun clinical trials to test the antibody in humans; by decade's end he presented evidence of the largest survival impact ever for a drug used to treat metastatic breast cancer.

"The Human Genome Project could have significantly expedited our work with HER-2/neu," Slamon says. "But it also could have made it significantly more difficult. Everyone thinks that, because we have the gene sequence, we've got the only key we need. But it's like having a big bunch of words. The words aren't important until you put them into sentences. Then they can be *very* important."

In the 1980s, when Slamon and his colleagues discovered the relationship between the HER-2/neu gene and breast cancer, there were only 50 to 60 genes known to play critical roles in growth regulation. "We were looking for a needle in a relatively small haystack," Slamon says. "Now, thanks to the Human Genome Project, there are several thousand genes we know are important to growth regulation. So the haystack is orders of magnitude bigger."

He points out that the saving grace — what makes the thousands of sequenced genes useful and workable — is essential new technology that enables researchers to analyze large numbers of genes very quickly.

"In the future, there is no question that the combination of the human genome sequence and new technology to analyze the sequenced genes will vastly increase the pace of medical research and lead to important new cancer therapies," Slamon says. "I am very optimistic about that."

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"hen I was a kid and my parents bought the Encyclopædia Britannica, it didn't make me smarter just because they bought it, but it was a tool I could use to get smarter," says Dr. John Glaspy, director of UCLA's Oncology Center at the Jonsson Cancer Center. "In the same way, the availability of the human genome is a tool that we can use to create other tools that will lead to revolutionary developments."

Nelson, a professor of human genetics and co-director of the Jonsson Cancer Center's Microarray Core Facility, has been developing one of the most potent of those tools. DNA microarray technology enables researchers to detect quickly which of thousands of genes are expressed in a particular tissue sample. In one project, Nelson and his colleagues are analyzing hundreds of archived brain tumors, looking at which genes are turned on and which are turned off. They are correlating that information with the severity of the tumor and its response to treatment. "The notion is that, as we do this, we're identifying molecular targets that wouldn't otherwise be detected, targets that we can use to develop new therapies," Nelson explains.

In addition to yielding the sequence of the estimated 30,000 to 40,000 human genes, the Human Genome Project has revealed approximately one-fifth of the estimated 10 million DNA polymor-

phisms — the minute chemical variations that account for many of the differences in traits among humans. "The raw material is now there for us to analyze many different humans and ask why it is that people have varying susceptibilities to cancer," Nelson says. He believes the next great challenge is to develop a quick, inexpensive and reliable test to detect known genetic markers for cancer susceptibility. "In each test, we need simultaneously to look at 100,000 or more of these polymorphisms, densely located across the genome," Nelson says. "If we can develop a test at very high throughput, so that we can quickly analyze hundreds of thousands of people, we can begin to use the genome sequencing information with great effectiveness. This could dramatically accelerate the rate at which we could design specific therapies to disrupt the cancer process."

That acceleration has already begun. "Especially in the last five years, we have seen a very steep rise in the number of drugs being developed that are focused on cancer-specific targets," Glaspy says. The completion of the Human Genome Project means that such therapeutics can be identified and developed even more rapidly.

Glaspy believes another major immediate impact of the Human Genome Project will be in the area of cancer epidemiology and prevention. "Up until now, efforts in those areas have been hampered by not being linked tightly enough to biology," he says. "Having the ability to look at genetic differences between high risk and low risk populations will lead to a much clearer understanding of the interaction between the genome and the environment in the development of cancer."

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For many years, cancer researchers have probed the connections between diet and cancer susceptibility, with mixed results. "We are now in a position to identify differences in gene expression in our tissues across various diets, and finally prove that diet affects the molecular biology of benign cells," says Glaspy, who has shown that a particular diet can alter breast tissue, potentially reducing breast cancer risk. "Genomics will be a powerful tool for helping us explore the relationship between gene/diet interactions and the development of cancer in those target cells."

ndeed, the sequenced genome has enormous potential for uncovering vital information that seems likely to lead to better cancer treatments, and even to preventing some cancers from occurring. For example, it's been several years since the BRCA-1 and BRCA-2 genes were cloned and found to be associated with an increased risk of breast and ovarian cancers. Yet, Gasson notes, two sisters could inherit the identical BRCA mutation; one might develop cancer in her 30s, while the other might live a full life without ever getting the disease. Why? "They didn't just inherit the BRCA gene; they inherited the entire genome, and the pattern of other genes clearly affects how the altered BRCA gene functions," Gasson explains. "In addition, they're probably going to lead different lifestyles. They might live in different regions, have different diets, different exposures to environmental influences such as tobacco, asbestos and sunlight. We need to know exactly what the critical environmental influences are and

how they interact with the genes we've inherited."

The decoded genome promises to help researchers devise better strategies to prevent cancer from occurring. It has already proved feasible to develop prophylactic therapies for people with inherited genes that predispose them to cancer. The drug Tamoxifen was shown in clinical trials at UCLA and other centers to reduce the chance of developing breast cancer by about half in a study of pre- and postmenopausal women at high risk for the disease. UCLA is currently participating in the Study of Tamoxifen and Raloxifene (STAR) to examine whether the osteoporosis drug Raloxifene, which is similar to Tamoxifen, is also effective in preventing invasive breast cancer in women who have not had the disease but are at high risk.

"We now have a road map that will help us home in on genes that might interact with genetic syndromes we've already identified, or discover new genes that might be associated with an inherited predisposition," says Dr. Patricia Ganz, director of the Division of Cancer Prevention and Control Research at UCLA's Jonsson Cancer Center and principal investigator for the UCLA arm of STAR.

Ganz also expects the sequenced genome to serve as an extremely useful tool in efforts to provide more fine-tuned and tailored information about what behaviors might increase or reduce one's cancer risk. "As we learn that certain genes associated with cancer risk are turned on or off when someone is exposed to, say, tobacco smoke or has high levels of estrogen, we can make more specific recommendations," she explains. "We can also refine our target audience. Some people may be more sus-

ceptible to DNA damage from the sun due to their genetic profile; once we know that, we can tell them, 'For you, this is critical.' Messages tailored to an individual's risk are more likely to be persuasive than the mass messages we deliver today."

Ithough sequencing the genome is hugely impressive, in a sense that was the easy part. The challenge now shifts from defining the location and structure of genes to determining how they function. "We know the genome anatomy," says Peltonen, "but we have no idea about genome physiology — how genes communicate with each other during development...or during the malignancy process."

Peltonen, who has spent years investigating the genetic culprits behind complex diseases such as multiple sclerosis, cardiovascular diseases and cancers, says she and her colleagues have been forced to rethink their strategies by the new genome-wide tools that make it possible to identify the overall genetic profiles that predispose families and individuals to complex traits. "Now we have to recruit not only people who are talented in the lab with a pipette, but also people who are experts in biocomputing," she says.

Whereas success stories in genetics have involved single-gene disorders, the sequenced genome will enable researchers to get a much better grasp of complex, multifactorial diseases, such as most cancers. But capitalizing on the new information will require changing the old ways of conducting research. "If scientists are not clever and visionary, they will lose a lot of the benefits of the Human Genome Project," Peltonen asserts. The new circumstances call for more communication across different fields of expertise. They call for shared facilities that provide all cancer researchers with access to both the emerging technologies and the experts who implement them. Peltonen notes

that UCLA, where clinicians and basic researchers from all schools and departments are located on the same campus, and where shared facilities are the norm, is ideally situated to seize the moment.

Says Gasson: "For several years it's been clear that the image of a scientist working alone late into the night and then shouting 'Eureka!' no longer applies. I used to be envious of my colleagues in freestanding cancer centers — their lives seemed so much simpler — but now I'm grateful to be in a matrix cancer center, where we have all of the mathematicians, computer scientists, engineers, chemists, etc. at UCLA to bring into the cancer research family. It's a great time to be at a great university, and to be able to take advantage of all of these strengths."

UCLA's efforts to develop systems that effectively harness the decoded genome include the DNA Microarray Core Facility, headed by Nelson, along with a new proteomics program being developed in the School of Medicine under the leadership of Dr. Leonard Rome. "Now that we have the solution to the DNA puzzle, the next big question is how do the proteins encoded by the genes talk to each other, and what kinds of networks and circuits are formed?" Gasson explains. "It requires yet another kind of expertise to analyze proteins from complex biological systems."

Then there's the formidable challenge of developing information systems that aggregate the raw data generated by microarray experiments, organizing it in a way that enables scientists to find patterns that they can build on in further experiments. A new Jonsson Cancer Center Gene Expression Core, made possible by a generous

gift from a cancer center board member, is taking on that challenge. Nelson, Dr. Christopher Denny, and Dr. Robert Dennis, a software developer, co-direct the new core. "With some of these new technologies, you can assay the activity of 12,000 genes at once," says

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or, perhaps, attached to one's medical record. "The question is, who do you want to share this with?" Grody says. "I think most of us wouldn't want it to be part of the medical chart, open to anybody."

Predictive tests, including those for genes identified with familial cancers, create myriad possible problems, including the risk of adverse psychosocial impact from receiving bad news, potentially unneeded medical and surgical intervention (a positive test result not necessarily guaranteeing cancer), and the possibility of future discrimination if an insurer or employer gets the information.

At UCLA's Familial Cancer Registry (See related story on page 20.), patients at high risk for cancer can request genetic testing and genetic counseling with absolute assurance that their records will remain confidential because of a special "certificate of confidentiality" that the registry obtained from the National Institutes of Health. The NIH, which is an arm of the federal government, has rendered it illegal for registry records to be subpoenaed or in any other way acquired without permission from the patient.

Grody, fearful that genomic knowledge is being released at a clip that far outpaces the ability of geneticists and genetic counselors to deliver appropriate services, is part of an effort to educate primary care physicians on genetic testing issues. But, despite his concerns, he is convinced that the potential benefits of the new information far outweigh the risks. "To me," he says, "knowledge is power."

If knowledge is indeed power, the sequenced human genome instills in cancer researchers the strength of Hercules — along with



Denny, a pediatric oncologist. "That's all well and good, but the problem is that if you start doing multiple experiments, the data begins to stack up and it's difficult to break it down and actually analyze it."

So Denny, Dennis and Nelson are leading an effort to establish a database that will enable researchers to compare results of microarray experiments. "The power of this technology is in the comparisons," Denny says. "Up until now, everyone has been very focused on trying to get the experiments to work. Now, we need to better understand what all of the data means."

r. Wayne Grody is among those trying to understand what it all means from a different perspective. The UCLA pathologist and medical geneticist is taking an active role in the national discussion of how to tackle the many ethical, legal and social issues raised by genetic tests.

Most experts suspect that by the end of this decade, genetic testing will move to the next generation of technology, in which tens of thousands of genes will routinely be screened simultaneously. "It's estimated that we all carry, on average, about six genetic mutations," says Grody, who has served on numerous national committees examining ethical issues raised by genetic testing. "With genetic technology in common use, we would know what they are, and we might have some idea of what diseases we'll get 10, or 80, years from now." The genomic information might be contained on a magnetic strip, like that on a credit card, to be carried around by a person

the Herculean task of deciding how to put the knowledge to best use. "Our problems are different now," says Glaspy. "It used to be that we would spend much of our time developing a small amount of information, which we would analyze before moving on. Now it is very easy, within a short time, to have more information from an experiment piled up on your desk than you can hope to sort through in a lifetime. A lot of it is straw, but there may be a needle in there. Sorting through it all expeditiously is the new challenge for science."

-Dr. John Glaspy

Gasson notes that cancer researchers have moved at an everincreasing speed in their efforts to make the disease more preventable and treatable. The sequenced human genome kicks the effort into a higher gear.

"When the tools of molecular biology came along, enabling us to clone and sequence genes and look at their expression, we partially opened an important door in cancer research that allowed us to understand more about alterations in genes that regulate cell growth," Gasson says. "The sequencing of the genome is the next step in our ability to further open that door and see inside cancer cells. Now, we must harness what we see to more effectively treat this disease, or prevent it from occurring in the first place.

"The changes that have occurred within our lifetime in our ability to diagnose, treat and prevent cancer have been nothing short of a revolution. And I believe that the sequencing of the human genome, given the power of that information, will usher in the second revolution in cancer research."