Solving cancer's secrets

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Chuck Perou. Credit: Max Englund, UNC Medical Center News Office

Some fathers play ball with their sons. Or take them fishing. Chuck Perou's father took his son to his pathology lab to show him how a pathologist conducts tests and runs experiments. Perou, a nature junky at a young age, learned precisely how things go wrong in the human body to cause disease. He learned what could be done about disease and what sometimes couldn't. Fascinated, the young Perou seemed destined to study what makes one kind of tumor deadly and another curable.

Since his days as a postdoc at Stanford, Perou has led the charge to characterize the genetic differences between the four major breast tumor subtypes. Widely regarded as a seminal breakthrough in breast cancer research, Perou's findings have led to better diagnostic tools – one of which he created – while pointing his lab and other researchers toward specific targets for better breast cancer treatments.

For his work, Dr. Perou has earned numerous awards and has been recognized with a May Goldman Shaw Distinguished Professorship and, most recently, a Hyman L. Battle Distinguished Cancer Research Award. He has also been featured in publications, such as the *New York Times*.

We sat down with Dr. Perou to ask him about his scientific pursuits, the genetics of breast cancer, and his hope for better treatments.

Why did you pursue a degree in biology at Bates College and eventually cancer research as a postdoc at Stanford?

I was always attracted to biology and how biological systems and organisms work, and I loved being outdoors as a kid. I loved nature shows—Nature, Cosmos, Nova; I was a PBS junky and still am. It was that love of nature that was the driving force behind becoming a biology major and pursuing a graduate degree.

It wasn't until after graduating from college , where I conducted genetics experiments as a technician in a molecular biology lab – that I really developed a huge love for science. Once I manipulated genes myself I was just totally hooked. I was only working with yeast, but I was amazed that I could manipulate biological organisms. And it's still amazing to me.

For my graduate work I spent five years hunting down a single gene implicated in Chediak-Higashi syndrome, a very rare disorder but well-known in the pathology world because of its stereotypical set of phenotypes. It was very interesting, and I learned how to become a scientist. I just loved doing the science. That's the overriding thing for me. There's never a dull moment.

But after spending five years working on just one gene I thought that was too limiting. This was around the advent of genomics – the study of all genes at once instead of just one gene at a time. There was this new technology called DNA microarray, which was invented by Pat Brown at Stanford; it allowed researchers to look at thousands of genes at once to see which ones were dysregulated in a specific sample. I thought this would have a huge impact on cancer biology research.

I'll never forget sitting in David Botstein's lab at Stanford interviewing for a postdoctoral fellowship, and at the end he says, "Oh by the way I'm starting this new project with Pat Brown to use DNA microarrays to study human cancers." I almost said, on the spot, "Where do I sign?" It was a dream project. Fortunately, he took me.

Our first focus was breast cancer. We thought we had the perfect new tool to apply to this very complicated disease.

In 2000, you were first author on a Nature paper in which you describe that breast cancers fell into four basic subtypes – luminal A, luminal B, basal-like, and HER2 type. Could you explain these findings and how they relate to treatments for breast cancer patients?

The four basic subtypes we've found are really indicative of underlying genetics. And it's underlying genetics that dictate the behavior of tumors

and their sensitivities to therapies.

Now we have found very strong links between mutations of specific genes and the specific subtypes, suggesting that if you get this mutation, then you have this subtype. We've now identified some of the genetic causes of these subtypes. This is important from a biological perspective because it gives us some molecular understanding of why we have different subtypes. From a therapeutic perspective, some of these genetic causes are targetable by current therapies. So when we say you have this subtype, we know it's linked to that particular drug target. So, patients with a specific tumor subtype will get a specific drug and people with another subtype won't; they'll get a different treatment.

We know that some of the gene mutations responsible for the tumor growth aren't targetable with known drugs.

For instance, endocrine therapy targets the estrogen receptor. That's one important protein. Most breast cancer cells are dependent on estrogen for growth. So, you give the drug, it interferes with the estrogen receptor, and those cells stop growing. Tamoxifen, the oldest drug that does this, has probably saved more lives than all other cancer drugs combined. It's very effective, and very specific.

And Herceptin, which targets the HER2 receptor, is another targeted therapy for one subtype. But basal-like tumors – or triple-negative tumors – lack the proteins that those therapies target. So we use chemotherapy, which nonspecifically targets all rapidly growing cells.

In patients with basal-like tumors, about 30 to 40 percent will have complete response to chemo, which means that the likelihood of cancer reoccurrence appears low. Then, some patients have an initial positive response to chemo, but they fall short of a complete response. These patients are much more likely to see the disease return. Then some basal-

like patients see no response. These patients are a major focus of our lab efforts because we have little to offer them right now and we need to do better. We need to find the biological pathways we can target to improve outcomes for these patients.

Finding better drug targets and treatments takes a lot of time and effort. Could you explain how your lab works toward creating better cancer treatments?

The way we approach trying to improve therapeutics is we have well-selected animal and cell-line models for each of our subtypes. We then do these extensive genomic characterizations so that we learn about every gene that's mutated in these models. We try to characterize the derangement of genes and the signaling pathways of these cancer cells. Then we use that information to figure out what we believe to be the Achilles heel of that particular type of cancer based on the underlying genetics. Then we test our hypothesis.

In the lab, we get drugs or compounds that we think will target that critical change that turns a normal cell into a cancer cell. Sometimes these experiments work and much of the time they don't. If an experiment doesn't work, then we try to figure out why. If it does work, then of course we're very encouraged and we might combine that drug with the current standard of care to see if there's a synergy between the two. This is what we're trying to do for the triple-negative patients for whom chemo is their only option.

We've had some exciting results here at UNC regarding why some drugs haven't worked, especially seminal studies done in Gary Johnson's lab in pharmacology. He's helped figure out that when you give a drug to target a particular point in the cell's signaling pathway, the cell sometimes reroutes the signal around that drug target. So now that we can see how

the cell reroutes the signal, can we target that adaptive response as well the original drug target. This might be how we overcome some of the resistance we see in the most aggressive cancers.

The Prosigna test was based on your work. What is this test and how will it help patients?

This test is based on the past 10 years of our work; it identifies different biological tumor subtypes, and based on that it provides a risk score – the probability of whether a patient will have a disease relapse or not within a given time frame.

We take a sample of tumor, run our 50-gene assay, and get an assessment of the patient's risk. For many patients we have really good news. For the low-risk group, the test might reveal that a patient has a 95 percent likelihood of not having the disease occur within ten years. This is almost the natural incident breast cancer rate. These patients, we now know, do very well on endocrine therapy and probably won't need any further systemic treatment. Of course, we watch each patient individually, but you can use this test to help make treatment decisions.

For breast cancer, one of the difficult decisions is whether to get chemotherapy or not. We know that most breast cancer patients probably don't need chemotherapy, but it's hard to figure out who does or doesn't need it. You can use risk as a means to make that decision. If you're highly unlikely to have the disease reoccur, then there's almost no reason to get chemo. But patients perceive risk differently. Some patients might think a 5 percent risk isn't low enough and will want chemo. Another person will say it's only a one in 20 chance, so the odds are in their favor. So they might forego chemo. The FDA approved the Prosigna test this year for use as a prognostic tool for ER+ patients receiving endocrine therapy.

Are you hopeful for better cancer treatments over course of next 10 or 20 years?

I'm quite hopeful that over the next five to 10 years we'll make significant progress in the development of diagnostic assays so we can better define diseases using genetics, mutations, and genomics. And I think this will go hand-in-hand with developing new drugs and improving our use of older drugs.

For example, right now, we give drugs to patients based on large-scale studies. We know that a given drug may benefit just half of all patients. But these studies don't tell us which patients will benefit and which ones won't. Better diagnostics will allow us to identify the patients who will benefit and the ones who won't before we give them the drug.

We know that cancer is a hundred different diseases. But in the past we didn't know what these 100 diseases really were. Now we know what they are, and this will allow us to better analyze what treatment works and why, and in other cases, why we're falling short. This is the sort of information we need in order to come up with better treatments for all types of cancer.

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