RICHARD WHITE

The zebrafish maven

Ludwig Oxford's Richard White models cancer in fish that are easy to manipulate genetically and enable the clear visualization of individual cancer cells as they spread

Richard White joined Ludwig Oxford in October 2023, moving from New York's Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, where he had been an associate professor of cancer biology and genetics since 2012. A physician-scientist and authority on the use of zebrafish to model cancer, Richard has developed a nearly transparent model of the fish named casper that has proved very useful to his studies. His research interests revolve around two major themes: how cancer cells co-opt the genetic programs of embryonic development, and how their microenvironment influences

their fate. Richard's studies have established, for example, that migrating melanoma cells often move in clusters, interacting with each other and with fat cells to seed metastatic tumors. His work on the role of developmental programs in cancer has, meanwhile, pegged genes that help determine a cell's anatomical location as potentially novel targets for cancer therapy. Richard's contributions have not gone unnoticed: he received in August the Outstanding Research Award from the Society for Melanoma Research. Ludwig Link recently caught up with Richard to learn a little more about his life, his many fascinations and, of course, his science. Here's an excerpt of what turned out to be a very engaging conversation.

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Tell us a bit about your background and family.

I grew up in Brooklyn, New York, and come from a slightly unusual background. A bunch of smart people in my family, but it's not a super educated family. I have two siblings, a brother, and a sister, and I was the oddball in the family. I was always pretty good at school and from a very early age knew exactly what I wanted to do, which was to become a doctor. My mom was a stay-at-home mom, but when I was around two or three, my dad, who worked for the U.S. Postal Service, developed what turned out to be lifelong mental illness, a psychotic disorder that made him violent. Eventually he was arrested and put in jail. He left the house when I was around 10 or 11 years old. That was pretty tough. So then, my mom had to go to work, because it's hard to raise three kids on public support. And she wound up working in an accounting department, rose through the ranks and did really well. She never went to college but just carried herself up and became a bookkeeper. I'm so proud of her.

Where did you go to college?

I was really focused on becoming a doctor,

so I joined the only six-year combined BS-MD program in the country at the time, at Rensselaer Polytechnic Institute and Albany Medical College in New York. I got to medical school when I was 19 and I really disliked it. It wasn't that I hated medicine. The reason, in retrospect, was that med school requires a lot of memorization but what I really enjoyed was the science part of medicine. I tried to quit four times and they told me, "No, that's not a good idea." But then I had a summer program with the person who became my PhD advisor, and I loved it, so I went back to the med school and said, "Okay, I won't quit if you let me join the MD-PhD program." There was a lot of controversy around that because they weren't sure if it was legal to do a combined BS-MD-PhD. But eventually they worked that out.

What did you study for your PhD and who was your advisor?

My advisor's name was Cathy Davison. What we studied was cell-cell communication: how endothelial cells interact with smooth

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muscle cells, and how that mediates the pathogenesis of hypertension. There's a direct line between that and what I do today, looking at how cell-cell communication governs nearly all aspects of physiology. Cathy was an amazing mentor. She gave me tons of freedom. What was a little bit frustrating was that the lab was small. It had three or four people and very little funding. This was because Albany wasn't primarily a research medical school. My advisor told me, "You need to go to a bigger institution, a place that has lots of resources for research, so you can do the sort of stuff you want to do."

Where did you do your medical residency?

I went to Yale for my residency. I totally blossomed at Yale. I did a very traditional residency track. I liked taking care of patients, and I felt I should learn how to be a good doctor. But I also met with lots of researchers and talked to them.

How did you start working on zebrafish?

I wanted to become an oncologist, so I decided to go to Harvard for my fellowship because it had an outstanding clinical cancer program but also world-class laboratories. My first year was at Dana-Farber Cancer Institute and Massachusetts General Hospital and I had remarkable clinical mentors. But there was no question I wanted to be a basic laboratory scientist. So I interviewed with 15 different labs and pretty much made up my mind where I wanted to go. And then changed it at the very last moment. A friend of mine said, "Oh, you should go talk to the zebrafish guy." I was pretty confused why I would care about a fish. But I wound up meeting with Len Zon, who runs a big zebrafish lab at Harvard. It was such a fun conversation but I had almost no idea what he was talking about—why would we study fish cancer? And then, two days later, he emails me and he just says, "That was a great conversation. When are you starting?" And I was a bit taken aback because I had no idea what I would do. But he told me not to worry, we could just do interesting stuff. And I said, "I'm sold."

The first two years were kind of a mess because I had no idea what I was doing. I didn't have a background in genetics. I knew nothing about zebrafish, and he just let me wander in the woods for two years. He told me, "You'll figure it out." To be given the freedom to just wander, scientifically, for two years—that was the best gift he gave me. Len's lab had just built the first melanoma model in zebrafish but I had no idea what to do with it. I began thinking about the strengths of the zebrafish, how we could use it to answer interesting questions in cancer. It seemed to me that the two interesting things were genetics and imaging. We could manipulate stuff in the fish and then we could image it. And so my work in the lab pretty much followed that logic—imaging and genetics.

Ludwig Oxford's Richard White has developed a nearly transparent zebrafish model, named casper, that has greatly facilitated imaging for his studies on cancer progression and metastasis.

What led to the development of casper?

I first turned my attention to the imaging side of things. Casper was pretty random, I've got to say. I'd become friends with a technician in the lab named Anna Sessa and we were on the T—the subway in Boston. There was a fish floating around Harvard called Roy Orbison that had these big black eyes and was sort of translucent. She said to me, "I wonder if we could make that fish transparent because then you could do cool imaging." We just started breeding this original fish with other fish and then, eventually, we came up with this fish called casper. And we thought, "Oh, that's clearly a pretty useful fish—it's not totally transparent, but it's pretty transparent." So now we had this fantastic tool for imaging, which we still use to this day. Nothing quite beats seeing things happen in real time.

So what are the most intriguing discoveries that you've made using zebrafish as cancer models?

After we made casper, I basically then turned to the genetics of the tumors. This interest started in Len's lab and then grew tremendously in my own lab at Sloan Kettering. The quality of my colleagues there pushed me to think about a more global view of what it means to be a cancer. It's not just genes, it is much beyond that.

There are probably three big buckets of discoveries we've made, and they're highly interrelated. The first was how, and why, cancers utilize developmental programs to get started. DNA mutations occur all over the body but we, and now others, observed that it's only the cells that adopt a configuration that turns on an embryonic gene expression program that eventually
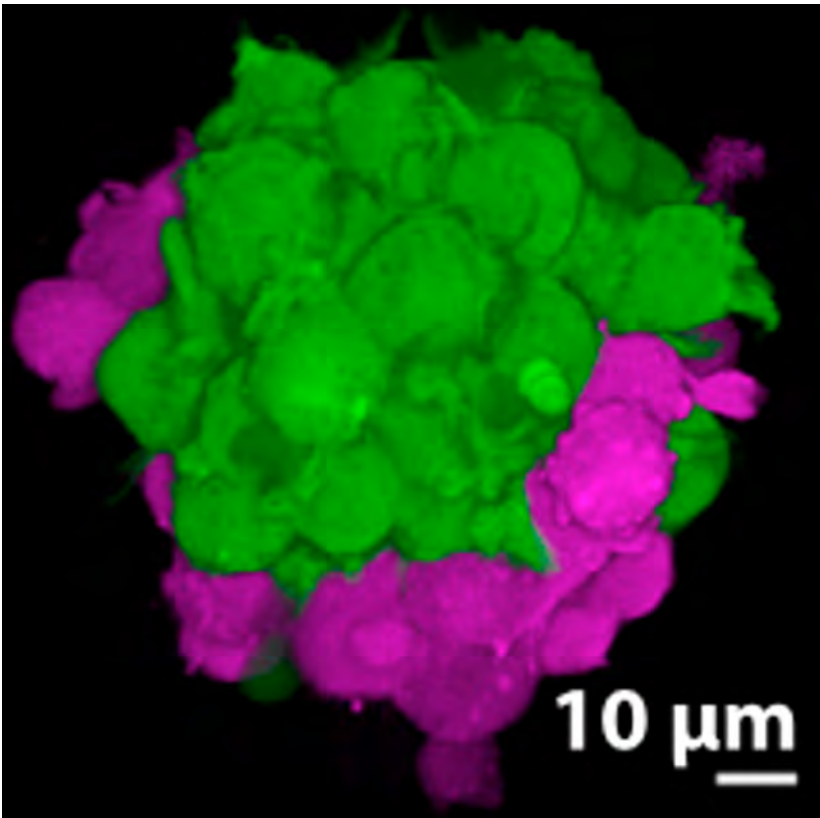
Image by the White lab

A cluster of cancer cells, with the green ones being more invasive, the red ones more proliferative. White's studies using the casper zebrafish revealed that such clusters metastasize more efficiently to distant organs, which implies that targeting the ways they stick together could help prevent metastasis.

take off and become cancer. What that told us was that DNA mutations will never sufficiently explain why cancer cells act like they do. You have to understand the epigenetic state of the cell because that's what turns on these embryonic programs, and that's as much a part of cancer as DNA mutations. So we developed this concept of *oncogenic competence*, where you get DNA mutations all the time but it's really the transcriptional state—especially these embryonic transcriptional states—that seem to be the special sauce that gives the cell its ability to form a cancer.

A second important finding was about anatomy. Some mutations can give you cancer in one part of the body but not in another. If the first concept was competence, this told us something about specificity. To explore this, we used a rare subtype of melanoma, called acral melanoma, which appears on the hands and feet. And these tumors turn out to have totally different mutations than melanomas in other parts of the body, and that's why they form where they do. So it's a very fundamental thing—that DNA mutations interact with where the cell is anatomically located in the body to cause cancer. And, again, that's governed by transcriptional and epigenetic programming. We call that concept *oncogenic specificity*. Competence is, can you become a cancer? Specificity is, why do certain mutations only cause cancer at certain anatomic sites?

And the third bucket?

The third one brings all of this together. If cancers only form from cells in certain places, under certain conditions, what brings that together is the surrounding cells—the local microenvironment that pushes a cell to become cancerous, or not cancerous. This led us into a whole series of studies looking at cell-cell interactions, how tumor cells in these different sites interact with their neighbors. In a way, that brought me full circle back to my PhD, where I worked on cell-cell communication, although in a totally different context. And that's been really exciting because I never fully appreciated how dominant the microenvironment could be—I grew up thinking about cancer as a cell autonomous thing, yet most evidence says it's a collection of cells acting in a coordinated manner. I think the real therapeutic opportunity in cancer is all the other stuff surrounding the cancer in these microenvironments.

Where is your research heading? Any new or emerging areas of interest?

We're developing a lot of tools to try and look in much more sophisticated ways at cell-cell communication. We're also trying to understand this very fundamental question of why certain genes that should be relatively ubiquitously expressed seem to exhibit extreme cell-type specificity. For example, many chromatin factors are expressed in pretty much every cell, or many, many types of cells, yet they have this extreme specificity, only exerting their effects in certain cells.

What are your avocational interests?

When I was around 19, right around the time I started medical school, I started traveling a lot. It became this way of really seeing the world that even books couldn't provide. And so, I began traveling extensively. My partner Theresa and I met over a shared love of traveling. One day, she propositioned me and said, "Do you want to go to India? And I said, "Sure, that sounds fun." And we started dating shortly after that. I'm very happy to say that we've given this love of travel to our daughter Harper. It's just a way of thinking about the world, and I'd like to think she gets that. So we all travel together.

What country would you most like to visit?

I really want to go to Sri Lanka, which has an incredible history, and a lot of natural beauty. I've always wanted to explore Russia because my grandparents were born in Russia.

Any favorite music?

Oh, yeah. It's terrible. We gravitate more towards folk music, which is kind of funny—another shared love between my partner and me. We bonded over this very obscure folk band, and I was like, "Oh, my God, she's heard

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of this band!" She had the same reaction. And we thought, "Well, clearly we should be together."

Who is your favorite author, and your favorite book, if you have one?

That's a tough one. The one that always pops into my head is Jose Saramago's Blindness. It's a perfect microcosm of, I think, what it means to be human. The other one is, A Little Life by Hanya Yanagihara. She does this amazing job of showing how that tiny little nucleus that is your world ultimately tells a bigger story about the things that everyone's going through.

The person I've read recurrently over the years is the Japanese author Murakami. He does an incredible job of showing how narrow the line is between reality and what might be considered fantasy, or magic, or something like that, and that it doesn't take much to cross that line.