Paul Mischel: All about brains

Paul Mischel studies the molecular signatures of brain cancer to come up with targeted therapies.

Paul Mischel took the long way around to scientific research. He started out as a philosophy student, switched to medicine, specializing in neuropathology, and then switched again to molecular biology research. He now keeps a foot in both the clinical and research camps, studying the molecular biology of glioblastomas—the most common malignant brain cancer—in the lab and suggesting treatments based on those studies in the clinic.

His research includes gene expression and mutation profiling to identify glioblastoma subtypes (1) and analyzing commonly disrupted signaling pathways in brain cancers (2). As no two cancers are identical, the ultimate aim is to devise tailored therapies for patients based on the particular defects driving their cancer (3). By studying tumors with disruptions in the epidermal growth factor receptor (EGFR) signaling pathway, for example, he and his colleagues discovered why it is that some patients respond well to inhibitors of this pathway while others don't (4).

"The answers for how to treat these patients must be locked inside this tissue. We've got to get at it."

Mischel, who now runs a laboratory at the David Geffen School of Medicine at UCLA, is a man who has clearly found his niche. He spoke in a recent interview of the decisions and influences that shaped his career path and that landed him at just the right spot.

SEARCHING FOR A PURPOSE

Why did you choose to study philosophy?

The simple answer is that my father was a philosophy professor, and I was fascinated by him and by what he did. So, when I was 18, 19, it seemed to me the most meaningful or interesting thing you could possibly do—study philosophy and think about the mind.

So why the switch to medicine?

My father passed away from stomach cancer when I was 14, and it had a profound effect on my life. When I was in my late teens, I had a vague notion of wanting to use my life to try to do something about cancer, but I didn't really know how. After graduating at age 21, however, it really kicked in. I thought, "This is my life and my chance to do something."

That decision entailed going back and taking all my science courses at night school at Harvard. After that, I started medical school at Cornell. I was determined that I'd somehow end up doing something for patients with cancer, though I was a little unclear as to what that would actually be.

But your residency was in neuropathology, not oncology. Why was that?

The theme of the mind had also remained very central to me. Around the time that I was getting ready to graduate, I even considered becoming a psychiatrist, because I thought it would be a great way to link the mind and the brain. My father's brother, who continues to have a huge impact on my life, is a very famous psychologist, Walter Mischel—he's a member of the National Academy of Sciences. I spent a lot of time talking to him about my career. I still do.

Then I got to witness a brain-cutting session—I watched a human brain being dissected. I immediately thought, "This is important, this is something that I want to do."

You had still not quite found your calling.

No. At the end of the residency, I was offered a faculty position at UCLA, but I asked to defer because I felt at the time that the most interesting thing that I could do was to move into molecular biology. I had a systems level understanding of the brain, an anatomical and pathological understanding, but not a molecular understanding. And that's the way the world

Paul Mischel

was moving. This was 1996.

I applied to do a postdoc in Louis Reichardt's lab. Having absolutely zero background in molecular biology, my first year in Lou's lab alternated between comedy and tragedy. It was often very frustrating, but I have a fantastic wife, and she said, "Believe in yourself; you can get this done." In addition to being the mother of my two daughters, she is also a scientist herself—Deborah Kado, here at UCLA. I have learned to always listen to her!

Being in Lou's lab, watching how he and the people in his lab operated, how they approached problems, was an absolutely transformative experience for me. It really turned me into a scientist. I owe a great deal to Lou.

I rejoined the faculty at UCLA in 1998 and started working on some basic signal transduction biology in *Xenopus* oocytes. But I also had a clinical role of diagnosing brain tumors in patients. There was a disconnect between my research life and my clinical life. I would be looking at patient biopsies and often giving a diagnosis that carried a death sentence. I thought to myself, "The answers for how to treat these patients must be locked inside this tissue. We've got to get at it."

Around that time, Charles Sawyers at UCLA was pioneering the treatment of

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leukemia patients using signal transduction inhibitors. After a series of conversations with Charles, I realized that being able to find deregulated signal transduction pathways in our patients was the key to successful targeted therapies. That was a major turning point in my career, and I've never looked back.

SETTLED AT LAST

You found your niche. So do you think of yourself primarily as a scientist or a doctor?

I view myself as both—my being a physician profoundly influences the kind of science that I do. And the kind of science that I do profoundly influences the kind of physician that I am.

I do very little with regard to the clinic. However, I'm constantly surrounded by clinical material, analyzing tumors for their molecular patterns, particularly their signal transduction patterns. And the information is then used to decide how to treat patients. Consequently, I've found myself becoming more of a doctor than I expected. I have patients' family members or other physicians calling me saying, "We have this patient with this and that. How might we treat them?"

As an example, a colleague called me out of desperation about two years ago and said, "Can you look at this biopsy from a child with a rare tumor and help us come up with something?" Based on our molecular pathway analysis, they treated the child who had what should have been a lethal tumor. And two years later, the child is still doing well, with no recurrence.

Glioblastoma (upper left) is the devastating brain cancer that is the focus of Mischel's work.

What was the molecular signature of the tumor and how did you treat it?

Our particular interest has been on the EGF receptor/PI3-kinase signaling pathway. This is often up-regulated in tumors, but inhibitors targeted at EGFR frequently don't work as treatments. We showed in a *New England Journal of Medicine* paper that this failure can be due to the loss of a downstream tumor suppressor, called PTEN. If the tumor has lost PTEN activity, the downstream pathway stays active even if you target the signal at the receptor.

In the case of that child, we were able to show that PTEN was intact, suggesting he would respond well to an EGFR inhibitor. And indeed, he's doing great.

That must be very gratifying.

Yes. But we're just at the tip of the iceberg, because we need to help a lot more people, and these patient-specific treatments need to become standard practice in medicine. I find it very exciting that we're now in an era where science can profoundly influence what we can do for patients.

That's one of the reasons that I'm honored to be interviewed for *Journal of Cell Biology*. I've been saying over and over again in meetings that cell biologists are going to become increasingly important for understanding the molecular circuits that drive cancer and for being able to use that information to treat patients in the clinic.

FUTURE FORAYS

Is there any hope for patients whose tumors have lost PTEN activity?

Yes. We've been working very hard to understand what are the key downstream effectors of EGFR/PI3K. And we're asking whether we can develop ways of hitting these effectors. We have pretty strong data to indicate that we can, so this might now potentially widen the window of response from something like 15% of patients to over 50% of patients.

EGFR is up-regulated in many types of cancer, so is there a reason you focus on brain cancers?

There are two reasons. One is my own historical narrative—I went from neuropathology to fundamental neuroscience, to working on brain tumors. It's where my knowledge base comes from. The second is that this is a group of patients that is desperately in need of hope.

"Brain tumor cells often grow through the brain like single cell–infiltrating soldiers."

Until very recently, people would say of a patient with a brain tumor, "Forget it, there's nothing you can do. Forget about doing research in this area, it's too dreadful of a disease." This is partly because there's no early detection—by the time a person is diagnosed, the cancer is already advanced in most cases—and partly because, unlike other tumors that can potentially be surgically removed, brain tumor cells often grow through the brain like single cell–infiltrating soldiers.

Brain cancers are also notoriously nonresponsive to traditional chemotherapies and radiation therapies. So finding ways to target the pathways is a real hope.

One thing that pleases me immensely is that now, at national meetings, brain tumors have become a hot topic, because the science is becoming tractable at last. The pharmaceutical companies are now interested in helping move their drugs to trials in these patients. This is all good news for patients.

All of that said, however, what we're doing in brain tumors is entirely transferable to virtually any kind of cancer. So we're also becoming involved in many collaborative projects outside of the brain. JCB

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