

A Surgeon's View of Prostate Cancer

Robert Reiter, M.D., M.B.A., is a Professor of Urology and Molecular Biology, Director of the Prostate Cancer Treatment and Research Program, and Director of Urologic Research at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA). After studying medicine and completing a residency in general surgery at Stanford University, Reiter went to Baylor College of Medicine for training in urology. Reiter undertook additional fellowship training in urological cancer in CCR's Surgery Branch; he also conducted postdoctoral research focused on the molecular biology of prostate and kidney cancer with W. Marston Linehan, M.D., Chief of the Urologic Oncology Branch. In addition to his clinical practice, Reiter runs a large basic and applied research program in prostate cancer. He is currently the Principal Investigator of UCLA's prostate cancer Specialized Program in Research Excellence (SPORE), which has been successfully renewed twice. In 2007, he completed his business degree at UCLA, and he has been involved in three start-up companies to translate his discoveries into improved outcomes for patients with prostate cancer.

Looking back, I thought I wanted to be an academic clinician-scientist and thought I needed the intellectual stimulation of an academic setting, but I was not sure what kind of research I wanted to do or even if I wanted to do research. I had done three years of clinical training at Baylor, so I stepped out and explored something different. I had two fantastic years at NCI.

I trained at NCI on the recommendation of our chair at Baylor, who had also spent time there. I was looking to explore research and find what I wanted to do. In the clinical service, we were doing immunotherapy and taking care of patients with an inherited form

of kidney cancer, Von Hippel-Lindau (VHL) disease. The lab was trying to clone the *VHL* gene at the time, and I worked on number of projects, including one of my own to look at mutations in the *p53* gene in kidney cancer.

Personally, I found the link between what I was doing clinically and what we were doing in the lab rewarding; and that is what got me interested in an academic medicine career. It set me on a course that I continue today.

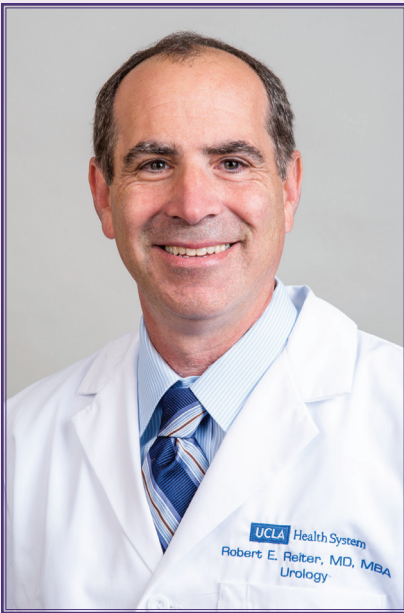
Markers of Success

My research remains highly translational; it is about taking insights from the clinic into the lab, whether from the operating

room or patient management. Today, I spend about 60 percent of my time doing surgery and taking care of patients, and about 40 percent of my time on running the laboratory and administrative work. Our lab has been focused on identifying new therapeutic and imaging targets in cancer. We have developed a series of different antibodies against prostate cancers, aimed both at therapies and at imaging for surgery or disease monitoring.

We have a definite interest in cancer stem cells. In the late 1990s, we first identified prostate stem cell antigen (PSCA) as a cell-surface marker overexpressed in prostate cancer. Early on, I wrote a number

(Photo: Courtesy of R. Reiter)



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of papers with the hypothesis that prostate cancers arise from stem cells in the basal cell layers, and, interestingly, the field has evolved to suggest that this is actually true! We are still interested in understanding the evolution of differentiated cell types from these stem cells, in particular, the evolution into neuroendocrine tumors.

In 2010, we published a paper in *Nature Medicine* in which we showed that N-cadherin, a mesenchymal cadherin associated with epithelial-to-mesenchymal transition (EMT), was reproducibly upregulated in several models of castration-resistant cancer. We showed that the ectopic expression of N-cadherin is sufficient for converting androgen-dependent prostate cancer into invasive, metastatic, and castration-resistant prostate cancer in animal models, and that these effects can be inhibited

by N-cadherin-specific antibodies. We are now trying to understand the role N-cadherin plays in the transdifferentiation process.

Surgical Strikes

Prostate cancer can be successfully eradicated through surgery, but a major correlate or predictor of failure is the presence of cancer at the margins of a tumor that is excised. Surrounding the prostate are nerve bundles that control the bladder, urethra, etc..., making surgery particularly challenging. You are always trying to split hairs: preserving normal function while getting cancer out. It is almost impossible to do that perfectly. If we could see the edges of the cancer, we could do a better job of excising it.

In order to address this problem, we are engineering antibodies to PCSA that are conjugated to different fluorophores that could help us visualize the cancer cells in the operating theater. In addition, we have developed different animal models that can replicate the kinds of problems we see in the operating room in order to test our antibodies.

Over the years, my closest collaborator has been Anna Wu, Ph.D., Professor of Molecular and Medical Pharmacology at UCLA. She has a background in radioimmunotherapy. I have clinical insight into the problems that can be addressed through antibody targeting; she has expertise in antibody engineering and radiobiology. My lab does the target identification and animal modeling; her lab reengineers the antibodies.

We have taken several antibodies into clinical trials and even started a few companies. My first commercial experience was with an antibody company spun out of my department; it licensed one of the antibodies that was developed in our laboratory. Then I went to business school, and eventually started a company in 2007 to develop

a prostate imaging agent and an imaging agent to track the immune system during immunotherapy. The company is venture backed and currently testing agents in the clinic. We have also started a virtual company to commercialize some of our newer antibodies. The whole purpose of my research is to try and make a difference for patients, and, in my opinion, start-up companies are vital channels for translation into the clinic and a way to maintain some control over the translational process once it leaves academia.

Surgeons and Science

If you look at the evolution of different fields across medicine, success has depended on discoveries that emanate from those fields. Urology has seen these successes many times, whether in the treatment of kidney stone diseases or the management of prostate cancer by castration (for which Charles Huggins, M.D., was awarded the Nobel Prize in Medicine).

Surgical fields have not been as adept at recruiting, fostering, or training clinician-scientists. I was just at a molecular biology course sponsored by the American Association for Cancer Research this summer and 90 percent of the students were medical oncologists. Research is a more established career path in medical oncology, so it is not surprising that most of the major advances in cancer treatment and biology (with notable exceptions) are coming from medical oncology or basic science, and less so from urology and even surgery. Add to that the economics of our time, which result in residency programs dropping their research year requirement, and research experiences like I had at CCR are fewer and farther between. I hope this trend reverses because the future of these fields depends on not just clinical practice but on research conducted by those practitioners.

“We have taken several antibodies into clinical trials...”