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At Work: Human Oncology and Pathogenesis Program Chair Charles

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Charles Sawyers

Charles Sawyers is an internationally recognized expert in the development of targeted therapies, especially for leukemia and prostate cancer. We spoke with him in 2006, shortly after he became the inaugural Chair of Memorial Sloan Kettering's Human Oncology and Pathogenesis Program.

Both of my parents are physicians, so I was exposed to clinical medicine and the biological sciences early. I majored in history at Princeton University and had no idea I wanted to be a scientist — until I got to medical school [at The Johns Hopkins University]. Although I went to medical school to become a doctor, I became captivated by the growing possibilities that molecular biology could bring to medicine, and in particular to cancer medicine.

At that time in the early 1980s, there weren't many concrete examples of what was possible, but to me it seemed like the next great thing. So from then on I did everything I could to get experience in the lab. I spent a year of medical school working in a pharmacology lab. During my residency training at the University of California, San Francisco, I was able to do the same for six months.

During my internship, I was greatly affected by the time I served on the leukemia ward. It was the first time I took care of patients my age. Leukemia

treatment is very intensive. Patients spent a month in the hospital, and you get to know them well. Based on that experience, I decided to work on leukemia.

My interest in prostate cancer came when I was starting my own lab in the early 1990s. I felt the progress we had made in understanding the genetics of leukemias could be applied to other types of cancer. And I wanted to work on a disease that was, in my view, underserved scientifically. Although I had minimal clinical experience treating patients with prostate cancer, I was interested in many unique features of the disease: it depends on hormones for growth and it has a unique pattern of metastasis only to bone.

Fascinating Clinical Questions

These are fascinating clinical questions that seemed very solvable. Our first step was to derive human xenograft models (growing human tumors in mice). These tools have been critical to helping us learn why prostate cancer cells develop resistance to drugs that target the androgen receptor pathway. That problem has been a major focus of my lab.

At the same time we were making progress in our work on prostate cancer, I became involved in 1996 in the initial testing of a drug that became imatinib (Gleevec®) for the treatment of chronic myeloid leukemia (CML). CML is unique in that it is caused by a single mutant protein called BCR-ABL, which results from a genetic abnormality called the Philadelphia chromosome. As a postdoctoral fellow I had worked on how BCR-ABL activates the cascade of intracellular signaling that leads to CML. Brian Druker [of Oregon Health and Science University], Moshe Talpaz [then at M.D. Anderson Cancer Center], and I wrote the first clinical trial and tested imatinib in CML patients.

Gleevec is a pill taken once a day with few side effects. It worked so well so early in the trial that it was obvious to all of us involved that it had to be moved forward as quickly as possible. The clinical impact was so dramatic that we became evangelists, trying to get the resources to speed up the clinical testing. Not only did we see almost instant improvement in patients in the chronic [early] phase of CML, we also saw results in patients who were in blast crisis, the most advanced stage of the disease.

We live in a unique time where you can just taste how molecular understanding in the lab is applicable to things in the clinic.

Charles Sawyers
Human Oncology and Pathogenesis Program Chair

I'll never forget it. Some of these patients were hospitalized, in wheelchairs, and on oxygen with only weeks or months to live. Within a week or two, they were walking out of the hospital in complete remission.

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Solving the Puzzle of Resistance

But the sad part was that these patients were the first to develop resistance, and they relapsed quickly. We eventually would learn that patients treated in the early stage of CML could relapse as well, and that CML cells were still present in patients at low levels. So we set out to solve the puzzle of why patients were developing resistance.

We learned that in some patients there were many more copies of the Philadelphia chromosome, and that BCR-ABL was able to flood the blood cells and out-compete the drug. But in most patients, an additional mutation was occurring in the BCR-ABL protein, which affected the drug's ability to block the protein's activity. At first we didn't know how this occurred, but about that time, in 2000, structural biologist John Kuriyan [then at The Rockefeller University and now at University of California, Berkeley] published a paper showing how imatinib bound to BCR-ABL. That work gave immediate insight into how mutations could prevent that binding.

I have to confess that I was not someone who paid much attention to structural biology. I thought it was fascinating, but I never envisioned the impact it would have on what I do now. However now, if I had the opportunity to take a sabbatical, I would study structural biology. Clearly, it can guide how we develop these new small-molecule inhibitors, which will be a major part of cancer treatment in the future.

My lab began collaborating with the Kuriyan lab, and we eventually published a paper showing that these additional mutations resulted in BCR-ABL

changing shape from what is known as a closed conformation to an open conformation. Soon after that we got a call about another drug — which became known as dasatinib (Sprycel®) — that inhibited BCR-ABL in the open conformation.

Clinical trials with dasatinib began very quickly, but this time we changed the way we conducted them. We determined the BCR-ABL genotype on every patient to give us additional insight into what mutations each patient had. Today when we treat CML, we can use these gene-based measurements to instruct us about which drug to use and to predict how each patient will do.

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Incorporating Genotyping into Clinical Trials

As we understand more about cancer genes, it's increasingly important to incorporate molecular measurements into clinical trials for all kinds of cancer, and to use genotyping to guide clinical management. One of the missions of HOPP is to encourage this approach and develop the tools to make these measurements.

Memorial Sloan Kettering Cancer Center has all the pieces necessary to pull it off: outstanding clinical care, genomics technology, a computational biology and bioinformatics infrastructure, and biologists and clinicians who can sit at the same table and look at the data together.

We live in a unique time where you can just taste how molecular understanding in the lab is applicable to things in the clinic. Memorial Sloan Kettering Cancer Center is a place where that genetic medicine revolution should happen, and HOPP will be home to the next generation of physician-scientists who have one foot in each part of the problem.

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