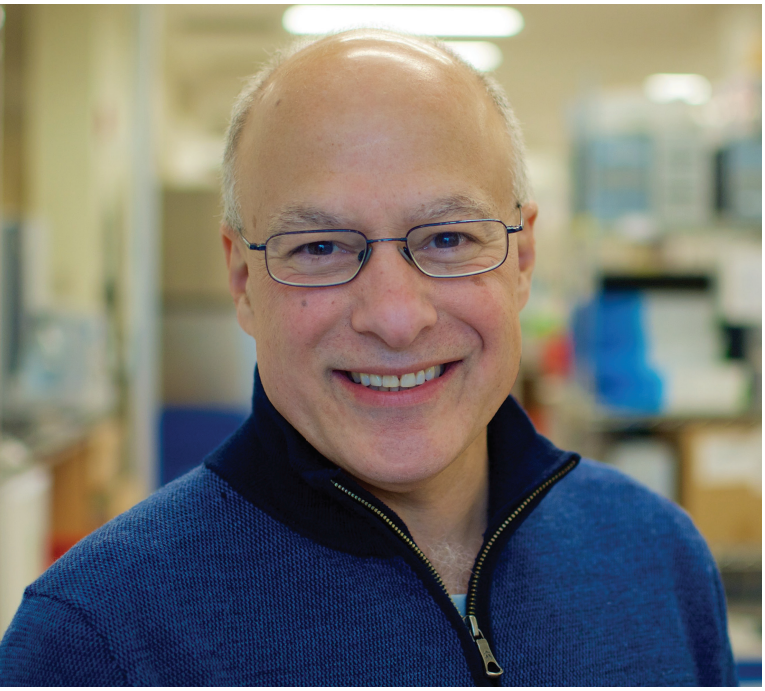

First Person Profile: William Sellers, MD

Dr. Sellers has helped to shape the field of cancer genomics and, alongside his colleagues, is working toward its ultimate goal—to move from therapy to cure

Matthew Meyerson, MD, PhD, recalls the moment circa 2005 when his colleague and collaborator William Sellers, MD, mentioned that he suspected a kinase mutation was responsible for hairy cell leukemia. Although neither had time to pursue that theory, it proved to be correct. In 2011, Italian researchers who had conducted a systematic genetic sequencing study discovered that BRAF kinase mutations were a disease-defining genetic event in hairy cell leukemia. They published their findings in *The New England Journal of Medicine*.[1] The anecdote, according to Dr. Meyerson, is vintage Dr. Sellers. "It's an example of Bill being very insightful and having a lot of predictive power," he says.

Based in Cambridge, Massachusetts, Dr. Sellers is a core member of the Broad Institute of MIT and Harvard, a senior advisor to the president for experimental therapeutics at Dana-Farber Cancer Institute, and a professor of medicine at the Dana-Farber Cancer Institute and Harvard Medical School. He is widely recognized for his groundbreaking findings in cancer genomics and therapeutic drug discovery and his research that homes in on the functions of tumor suppressor genes and oncogenes and cancer's molecular pathways through the use of high-throughput genetic sequencing and other methods.

In the early 2000s, Dr. Meyerson, who is also a member of the Broad Institute and is currently the director of the Center for Cancer Genome Discovery at the Dana-Farber Cancer Institute, partnered with Dr. Sellers on a gene sequencing project. "Bill and I were talking about cancer genomes, and he said, 'We should sequence the kinase genes where we might find something that's immediately treatable and could make a big difference in cancer,'" Dr. Meyerson recalls. "Bill has a lot of scientific courage—he just dives right in and is not deterred by anything."

They brought their project, which they initially began at the Dana-Farber Cancer Institute, to the Broad Institute, leading to its first cancer genome sequencing efforts. The two worked with other investigators to identify epidermal growth factor receptor (*EGFR*) mutations in lung cancer, and their discovery resulted in the standard use of *EGFR* inhibitors in treating the disease.

In addition, Dr. Sellers' laboratory, along with colleagues Levi Garraway, MD, PhD, and Gad Getz, PhD, discovered melanocyte inducing transcription factor (*MITF*) as an important oncogene in the development of melanoma. They also predicted that NK2 homeobox 1 (*NKX2-1*) was another potential oncogene. In fact, on the very same day that their article was published in *Nature*,[2] Dr. Meyerson and his colleagues found evidence that *NKX2-1* was amplified in lung adenocarcinoma in the exact location that the investigators had anticipated.

Finding His Path

Growing up in Reading, Massachusetts, Dr. Sellers was encouraged to cultivate his intellectual curiosity. His mother, an ardent believer in education, began teaching him before he was old enough to start school. He eventually discovered a love of mathematics and "figuring out how things worked."

During Dr. Sellers' high school years at Phillips Academy in Andover, Massachusetts, an influential biology teacher piqued his interest in the subject. At the time, the model for how people thought the plasma membrane was arranged changed dramatically, and the idea that biology was a puzzle to be deciphered captured Dr. Sellers' imagination. He majored in biology at Georgetown University in Washington, DC, and went on to the University of Massachusetts Medical School in Worcester, Massachusetts. In 1986, he began his internship and residency in internal medicine at the University of California, San Francisco.

His residency colleagues included the noted cancer researcher Charles Sawyers, MD, and David Hung, MD, a pharmaceutical

industry veteran who founded the biotechnology companies Medivation and Nuvation Bio. "Charles Sawyers and David Hung were in the year ahead of me and already interested in cancer, and that influenced me," Dr. Sellers says.

Following a series of genetic discoveries in the oncology world, Dr. Sellers became convinced that a better understanding of cancer's mechanisms would help to develop new, less toxic therapies. This would ultimately become a guiding philosophy for his career.

In 1990, he joined the Dana-Farber Cancer Institute and Harvard Medical School as an associate professor of medicine. Some 15 years later, he shifted to industry and became vice president and global head of oncology for the Novartis Institutes of BioMedical Research in Cambridge. "The transition from leading a lab to overseeing 250 biologists was a big one," he says. "By the end, I was overseeing 3 research sites and 600 FTEs (full-time equivalents). From a leadership perspective, I learned a lot."

Shaping and Improving Cancer Research

In Dr. Sellers' early years at Novartis Institutes, the technology of next-generation sequencing was just beginning to emerge, and he would play a key role in helping to improve research methods. Although he and his colleagues had discovered the *EGFR* mutation, he recalled how laborious the process had been. "Researchers would develop their ideas and test inhibitors in 1 or 2 cell lines, and part of the reason *EGFR*s were not known was because you would have needed a lot more cell lines," he says. "To be predictive, you have to have a substantial set of models that match human data, and they need to be much more annotated."

As part of a joint effort with the Broad Institute, Dr. Sellers also led Novartis Institutes to fund the development of a cancer cell line encyclopedia that generated systematic data across large numbers of cell lines. Dr. Sellers says that he is quite proud of the 10-year effort: "I think it had a big influence on how people look at targets, target validation, and profiling of drugs."

Along with his colleagues Dr. Garraway and Neil Rosen, MD, PhD, Dr. Sellers, using the NCI-60 cancer cell line panel, conducted one of the first studies to pilot this idea. "That was the inception, and then our group at Novartis built the capability to screen our compounds against 400 to 500 cell lines every few months," he notes. Since then, new technologies have enabled researchers to grow hundreds of cell lines much more cheaply, but the process resulted from these original ideas, Dr. Sellers adds.

Throughout his 11-year tenure at Novartis, Dr. Sellers pioneered genetic and functional genomic approaches to cancer therapeutic development and created an oncology drug discovery unit that became world-renowned. Nearly 40 of the company's molecules were approved for phase 1 clinical trials, and they have led to 8 marketed drugs. "I think we've impacted patients' lives," he says. "I'd be prouder if some of those were cures, but we're still a long way from that."

Also at Novartis, Dr. Sellers partnered with Carl June, MD, the Richard W. Vague Professor in Immunotherapy at the Perelman School of Medicine of the University of Pennsylvania, after he published dramatic results for patients with chronic lymphocytic leukemia who were treated with chimeric antigen receptor T-cell therapy. Recognizing the importance of this therapy early on, Novartis invested funds into the research. Subsequently, many other pharmaceutical companies made significant investments as well.

More recently, Dr. Sellers and his colleagues published findings in Nature indicating that the combination of ABL001 (asciminib), a potent inhibitor of ABL proto-oncogene 1, non-receptor tyrosine kinase (*ABL1*) in chronic myeloid leukemia, with the chemotherapy drug nilotinib led to complete disease control for chronic myeloid leukemia without recurrence in mice.[3] "It will take a while to do the combination studies in humans, but that could be a map for how to think more systematically about putting molecules together in curative combinations," he says.

Returning to Academia

Dr. Sellers returned to the Broad Institute and the Dana-Farber Cancer Institute in 2017 as a faculty member. Reflecting on the differences between industry and academia, he notes that each has its unique advantages and disadvantages. When he first arrived at Novartis, he relished the freedom of not having to worry about publishing and seeking grants. At the same time, if data on a particular project were not very robust, researchers were able to move onto another one quickly.

"Traditionally, academia is more individualistic and less team-oriented, and you're relatively underpowered with the resources you can bring to a given problem," he says. "When you get to industry, the whole concept is team-oriented."

Noting that he was lucky not to experience what he says is the downside of industry, "having the rug being pulled out from under you every year and changing direction," Dr. Sellers says that he joined Novartis at a fortuitous time when he and his colleagues were able to take a long-term view of their work. Now that he has returned to academia, he is focusing on the potential that his new roles bring.

"In academia, instead of other drug companies being your competitors, they are all potential collaborators, and the more of them that pick up on an idea we're working on, the better," he says.

One objective that he and his team are pursuing is to discover drug targets comprised of pairs of redundant genes that serve the same function using combination CRISPR screens. "The current single-gene knockout screens are likely to miss interesting and druggable gene pairs," Dr. Sellers says. For example, although mitogen-activated protein kinase kinase (MEK) inhibitor therapeutics target both *MEK1* and *MEK2*, the current CRISPR gene knockouts target just one or the other. To that end, Dr. Sellers and his colleagues are building next-generation CRISPR libraries to disrupt pairs of related genes.

In addition, they are exploring potential ways to develop new therapeutics. Rather than solely focusing on gene inhibitors or antagonists, the group is interested in exploring intrinsic conflicts between active genes. The hope is to discover whether activating certain genes could actually fight cancer growth. Successfully doing so would expand the world of drug discovery to include gene activators in addition to inhibitors, Dr. Sellers notes.

The biggest challenge for cancer research now is the ability to move from therapy to cure, he adds. "We have such an assembly

of ways to target cancer—more than we had even 10 years ago, but we're driven by a lot of empiricism," Dr. Sellers says. "If getting to a cure involves only random trial and error, it's going to be a while before we get [there]."

Instead, he says, researchers should begin to focus on why and how some patients have been cured. He cites testicular cancer as a good example, with 90% of patients able to be cured with short cycles of chemotherapy. "It would be good if we studied that and not just resistance," he says.

When he is not contemplating these significant challenges, Dr. Sellers enjoys cycling and hiking. He recently met a personal goal of climbing all 48 of New Hampshire's 4000-foot peaks. Dr. Sellers also loves cooking and spending time with his family, which includes his wife and 2 adult children, who both moved home to work remotely during the coronavirus disease 2019 pandemic. That, he says, has been "a blessing in disguise for us."

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Screening Entire Populations for Breast and Ovarian Cancer Could Prevent Millions of Cases Worldwide, Study Says

Screening entire populations for genetic mutations related to breast and ovarian cancer could prevent millions of more cases worldwide and would be cost-effective in high- and upper-middle–income countries according to an international study.

Led by researchers from Queen Mary University of London and published in the journal *Cancers*, the study examined the most well-known cancer-causing genes, *BRCA1* and *BRCA2*, which occur in approximately 10% to 20% of ovarian cancers and 6% of breast cancers.[1] Researchers note that if these mutations could be identified before people develop the disease, most cancers could be prevented with drugs, increased screening, and prophylactic surgery.

At present, global clinical guidelines recommend genetic testing only for high-risk women who either have a family history of the disease or meet other key criteria. However, more than 50% of women with *BRCA* mutations do not fall into the high-risk category. According to the authors, more than 97% of *BRCA* carriers in the UK population have not been identified.

In the study, investigators estimated the cost-effectiveness and health impact of *BRCA* testing in the general population in comparison with testing only for high-risk women in high-income countries (the United Kingdom, the United States, and the Netherlands), upper-middle–income countries (China and Brazil), and low-middle–income countries (India).

The researchers assessed cost-effectiveness from both societal and payer perspectives. Societal costs include the impact of income lost from an inability to work as well as shorter life spans. Payer costs include genetic testing, screening, prevention, and cancer treatment.

In high- and upper-middle–income countries, findings have shown that population-based testing is extremely cost-effective for payers. Societally, such testing is cost-saving in high-income countries and cost-effective in middle-income countries. To be cost-effective in low-income countries, the cost of *BRCA* testing

would need to be approximately $172. At present, *BRCA* tests range in cost from $475 to $4,000.

Results show that population-based *BRCA* testing can prevent an additional 2319 to 2666 breast cancer cases and 327 to 449 ovarian cancer cases per million women in comparison with the current clinical strategy. Over the course of a lifetime, those figures translate to preventing an additional

- 57,700 breast cancer cases and 9700 ovarian cancer cases in the United Kingdom
- 269,000 breast cancer cases and 43,800 ovarian cancer cases in the United States
- 15,000 breast cancer cases and 2500 ovarian cancer cases in the Netherlands
- 1,050,300 breast cancer cases and 154,700 ovarian cancer cases in China
- 156,300 breast cancer cases and 25,170 ovarian cancer cases in Brazil
- 570 breast cancer cases and 97,650 ovarian cancer cases in India

Lead researcher Ranjit Manchanda, MD, PhD, a gynecological oncology professor at Queen Mary University's Wolfson Institute of Preventive Medicine, notes that because costs of cancer genetic testing have fallen, significant opportunities exist for cancer prevention.

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