Profile of Daniel A. Haber

Beth Azar, *Science Writer*

Research oncologist Daniel Haber may not have treated patients in years, but they are never far from his mind. "When I started my MD/PhD program at Stanford I thought I could be both a physician and a researcher," says Haber, director of the Massachusetts General Hospital (MGH) Cancer Center, where he also runs a cancer research laboratory. "But at some point the research became dominant in terms of my interest and my ability. I tried to make up for it by directing my research toward very clinically relevant questions."

Haber's research focuses on using human genetics to tackle cancer through early diagnosis and targeted treatments. He was among the first to find targetable genetic mutations that cause cancer, discovering a mutation in lung cancer that helped lay the foundation for widespread testing of cancers with treatable mutations. He is also making strides in detecting rare cancer cells circulating in blood, with the goal of early detection and treatment. Haber's Inaugural Article (1) identifies a signaling pathway that switches on dormant metastatic tumor cells that have spread through blood. This work could lead to ways to prevent cancer from spreading through blood.

Daniel A. Haber. Image courtesy of Mark Karlsberg (Studio Eleven, Newton, MA).

Haber is the Kurt J. Isselbacher Professor of Oncology at Harvard Medical School and has been a Howard Hughes Medical Institute investigator since 2008. He was elected to the National Academy of Sciences in 2018.

Finding His Mission

Haber's father taught him the importance of helping people. The elder Haber worked for an organization founded in 1881 to assist Jews fleeing pogroms and that today resettles refugees in the United States. "He had a sense of mission," Haber says of his father. "He wanted his life to be about doing something that was larger than himself, something meaningful. That was inspiring to me." Haber's mother had a successful career in financial investing. Haber and his sister were raised in Paris until they moved to Geneva, Switzerland when Haber was 5 years old. The family spoke French at home, although Haber's mother spoke French and English with an equally terrible Hungarian accent, quips Haber. By the time Haber reached high school, his English was broken at best. That quickly changed when he enrolled in the English program at the International School of Geneva, where he excelled in science.

For college, Haber decided to explore his American roots and applied to the Massachusetts Institute of Technology, thinking he would study biomedical engineering. Once there, he realized he preferred biology and medicine, so, as a sophomore Haber began volunteering in William Thilly's cancer biology laboratory. He completed his undergraduate degree in life sciences in 3 years and spent his fourth year working in the laboratory, earning a Master's degree in genetic toxicology in 1977.

Unable to decide between being a physician and a researcher, Haber set his sights on a medical degree and Doctorate of Philosophy, and applied to Stanford University. "It was an exciting new time and the science there was really unequalled," recalls Haber. At Stanford, he worked in the laboratory of biochemist Robert Schimke, a pioneer in developing ways to clone DNA. Just before Haber arrived, Schimke's graduate student, Fred Alt, discovered that cancer cells can amplify their DNA as they become resistant to chemotherapy drugs.

"The assumption had been that DNA was stable and no cell could change its DNA," says Haber. "Fred discovered that as the chemotherapy drug methotrexate blocks its target enzyme, called DHFR, the cell becomes resistant by amplifying the number of *DHFR* gene copies until there are hundreds of *DHFR* genes making massive amounts of proteins to overcome the drug inhibition."

Haber was fascinated by the idea that the genome could be so plastic and decided to study the process of gene amplification. For his graduate thesis, Haber

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discovered a mutant DHFR enzyme with altered binding to methotrexate (2). With that work, Haber was hooked on cancer research.

Stepping Away from the Clinic

Haber had found his research passion, but he still had to finish medical school. He landed an internship and residency at MGH and an oncology fellowship at Dana Farber Cancer Institute. After 4 years of clinical work, Haber returned to research as a postdoctorate in David Housman's cancer research laboratory at the Massachusetts Institute of Technology. He wanted to expand his earlier research studying cancer genetics.

"The work that David was doing discovering new human disease genes through positional cloning really excited me," says Haber. "And he was a wonderful person and mentor, very inspiring for me."

Haber's research (3) helped identify the gene *WT1*, which causes the childhood kidney cancer, Wilms tumor. Haber's main goal was to test the "Knudson hypothesis," which postulates that inherited cancers occur only if both alleles of a tumor-suppressor gene have a mutation and that, in familial cases, earlier and multiple cancers arise because a mutant allele is transmitted in the germline. His research supported the hypothesis. The *WT1* gene has now emerged as a major immunogenic target in leukemia vaccine therapy trials.

Haber moved to MGH in 1989 to work in its newly created cancer center. "I was the seventh faculty member hired," says Haber, who was recruited by Kurt Isselbacher, the center's first director. "It was a phenomenal atmosphere in which to conduct research." There, he continued working on Wilms tumor biology, eventually cloning a second Wilms tumor-suppressor gene, *WTX*, located on the X chromosome (4). Meanwhile, researchers had cloned another tumor-suppressor gene in breast cancer, *BRCA1*. Haber's colleague Stephen Friend had collected blood samples from 400 women who had developed breast cancer before age 40. Haber's team tested these samples for germline mutations and discovered that 10% of the women had a *BRCA* gene mutation, irrespective of their family history. In addition, a single "founder" *BRCA1* mutation accounted for up to 20% of early-onset breast cancer in Ashkenazi Jewish women (5).

"Testing for *BRCA* mutations was quite controversial back in 1996, since it wasn't clear what to do with that knowledge," explains Haber. "Now, *BRCA* mutation carriers are extensively screened, and if they do develop cancer, their specific targeted treatments are based on the fact that they have a *BRCA* mutation." Following up on this laboratory work, Haber helped start genetic counseling programs in breast, colon, melanoma, kidney, and endocrine cancers at MGH.

Although Haber continued to see patients, "after a while my research became too intensive and also the care of patients became too complex and demanding," he explains. "At some point you have to pick what are you going to be really good at. That's when I decided to step back from my clinical responsibilities."

Shaping Cancer Research and Treatment

When Isselbacher stepped down from directing the cancer center in 2003, Haber was recruited to take his place. Meanwhile, his research team has helped shape MGH's approach to cancer treatment by pushing the idea of mutation-driven therapies.

Haber's most important discovery was inspired by a profile in *The Boston Globe*. A woman with lung cancer had been treated at MGH with an experimental drug and her tumor appeared to melt away. The same drug was ineffective for most patients with lung cancer. The drug targeted a growth factor called EGFR, which is expressed by almost all cancers, so Haber wondered whether tumors that responded to the drug might have a mutation in the *EGFR* gene. His laboratory tested tumor samples from nine people who had dramatic responses to the drug; eight of those cases had *EGFR* gene mutations. There were no mutations in any of seven nonresponding tumors (6). This discovery, along with a paper from another laboratory group (7), not only transformed the treatment of lung cancer but also helped launch national efforts to test tumors for rare mutations at the time of diagnosis, setting the stage for genetically targeted precision oncology.

"We learned that 10% of lung cancers have *EGFR* mutations, and this is the single oncogenic driver in most cancers that arise in nonsmokers," says Haber. "The tumor is 'addicted' to the mutant *EGFR* oncogene, and depends on it for growth."

However, targeted drugs are only effective until cancer cells develop new mutations that make them resistant. The trick, says Haber, is to catch the cancers earlier, when there may be fewer resistant cancer cells, and the treatments have a chance to be curative. Hence, Haber recently turned his research toward early cancer detection.

With his bioengineering colleague Mehmet Toner and his collaborator Shyamala Maheswaran, Haber developed and tested microfluidic devices to find rare circulating tumor cells (CTCs) that invasive cancers shed into the bloodstream, long before they establish distant metastases. The newest generation device removes normal blood cells, leaving behind viable cancer cells for molecular analysis (8). Those cancer cells from the blood can be cultured and tested for drug-sensitivity patterns (9). Importantly, they can be analyzed at the single-cell level for DNA, RNA, and protein (10). "We are now trying to push the technology using advanced sequencing approaches to see if we can diagnose early, potentially curable, invasive cancers in individuals who are at high risk, either because of genetic or environmental factors," says Haber.

For his Inaugural Article (1), Haber examined how blood-borne CTCs that have landed in distant tissues and initially appear dormant reactivate and grow to generate a metastasis. Haber and his colleagues used a mouse cancer model to track CTCs in the blood and in the lung, before and after they started to grow. They

found that growing cancer cells expressed the prolactin receptor. In addition, the tumor cells secreted the prostaglandin PEG2, which triggered the surrounding normal lung cells to make prolactin. This is interesting, explains Haber, because PEG2 is produced within tumor cells by the enzyme COX2. COX2 inhibitors—nonsteroidal antiinflammatory drugs like aspirin—are known to suppress cancer initiation. Unfortunately, epidemiological studies have shown COX2 inhibitors increase the risk of heart attacks, making them too risky for cancer prevention. "Cancers are very heterogeneous and we know that one drug doesn't fit all," says Haber. "We need to define whether there are specific subtypes in which prostaglandin suppression can prevent metastatic recurrence and others where it is not effective."

As for the future, Haber is committed to the idea that a cure for cancer will come from early diagnosis. "I see that as the place where I would like to make an impact," he says.

In the end, much like his father, Haber is motivated by the goal of helping people in need. "For me, it's the idea of applying molecular biology to solving challenges that impact the care of cancer patients," he says. "But far beyond what I can accomplish myself, is the real legacy of having trained students and postdocs who are now maturing, doing their own thing, and taking this further than I would ever have dreamed."

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