



Bradley Bernstein

LUDWIG WORKING FROM HOME

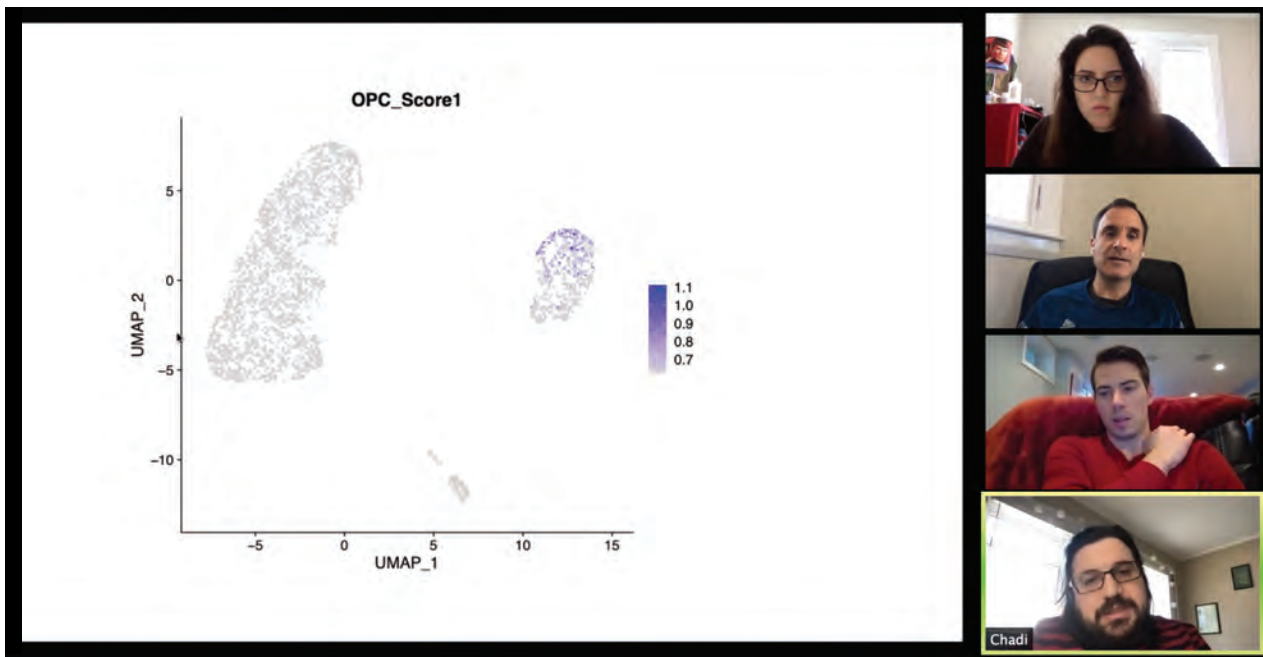
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Surveyor of genome structure

GROWING UP IN SEATTLE, WASHINGTON, Ludwig Harvard's Bradley Bernstein always knew what he wanted to do when he grew up. "For as long as I can remember, at least from the time I was five years old, I wanted to be a physician," he recalls. There was a phase in college, at Yale University, when physics caught his fancy. But it didn't last. "Around quantum mechanics, I realized that I might not be cut out to be a theoretical physicist," he says dryly. One thing he retained from this early training, however, was a love of quantitative analysis, which he channeled into structural biology as a novice researcher in the Yale laboratory of Thomas Steitz, who won the Nobel Prize in chemistry in 2000. "It really grabbed me," he says, "this application of math and physics to biology."

The fascination endured, ultimately propelling Bernstein into a career detailing and mapping

the chemical and structural changes to DNA and its protein packaging—or chromatin—that govern gene activity. His pioneering work in this field has helped illuminate how such processes orchestrate human development and how their dysfunctions fuel cancer. In one study published in *Cell* in 2019, Bernstein and his colleagues generated an atlas of cell states in acute myeloid leukemia (AML) that could inform new treatments for the aggressive cancer. In another, done in collaboration with Center Co-director George Demetri and reported in *Nature*, Bernstein described how a structural change to chromatin—as opposed to a classical mutation to a growth-promoting gene—drives a subtype of abdominal tumors known as GISTs. The study revealed a possible new strategy for treating these sarcomas and furnished further proof for a surprising mechanism of carcinogenesis.



Bernstein leads his team through a virtual research meeting.

Functions of structure

After graduating from Yale, Bernstein enrolled in an MD/PhD program at the University of Washington, Seattle, where his doctoral research under the guidance of structural biologist Wim Hol focused on the structure of an enzyme expressed by the trypanosome parasite. Upon the suggestion of pathologist Stephen Schwartz—who in March 2020 died of complications from COVID-19—Bernstein picked pathology as his medical specialty, moving to Brigham and Women’s Hospital in Boston, Massachusetts, for his residency. “Pathology seemed very connected to disease mechanism and close to the type of science that fascinated me,” he says.

Bernstein then joined the Harvard University laboratory of Stuart Schreiber, where as a postdoctoral fellow he developed new technologies to elucidate the structure of chromatin in yeast. When the complete sequence of the human genome was reported in 2003, Bernstein saw a golden opportunity to map human chromatin on

a large scale—and to get a step closer to linking his scientific interests to his medical ones.

“The human genome is about six feet in length, and it has to fit into this tiny nucleus inside a cell,” says Bernstein. “But it also has to fit in a way that makes all the right genes accessible.” Cells do this by winding DNA around protein spools and packing away unneeded stretches, while unraveling and opening for business genes that are essential to their identity and function. Targeted chemical—or epigenetic—tags placed on chromatin determine which stretches of the genome are open and which are closed. Distinct epigenomic landscapes are an essential part of what make, say, a pulsing heart cell so different from a firing neuron or a crawling immune cell. Epigenetic aberrations, on the other hand, can cause disease, not least cancer.

In 2005, Bernstein and Schreiber, in partnership with MIT’s Eric Lander and other researchers, reported in *Cell* the

first large-scale map of human chromatin structure, charting the distribution of a pair of epigenetic tags on two chromosomes and providing an early glimpse of how epigenetics regulates gene expression. Later that year, Bernstein joined the faculty of Harvard Medical School, set up his own lab at the Massachusetts General Hospital and became a member of the Broad Institute of MIT and Harvard.

In 2006, Bernstein, Schreiber, Lander and their colleagues published another landmark study in *Cell* on how genes that orchestrate embryonic development are epigenetically tagged to perform their functions. “At the time, people thought a gene sits in either an open or a closed state,” says Bernstein. “What we showed was that embryonic stem cells keep their options open by ensuring that master developmental genes exist in this dynamic, bivalent state, poised to either switch on or stably turn off, depending on which lineage their progeny choose.”

Into the cancer genome

Around then, researchers were noticing that tumor progression too seemed to depend on stem-like cells. Eager to parlay his experience in stem cell biology into more applied medical research, Bernstein began working with MGH colleagues to chart the regulatory circuits that push the stem-like cells of the brain cancer glioblastoma (GBM) into a proliferative state. They reported in *Cell* in 2014 four transcription factors—master regulators of gene expression—responsible for that capability. Their over-expression, the team showed, could turn an ordinary GBM cell into a cancer stem cell. Another study Bernstein and his team published in *Science* that year profiled global gene expression of individual GBM cells. The tumors, they found, are often driven by several distinct stem-like cancer cells, explaining in part the brain tumor’s notorious resistance to a variety of individual therapies.

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In exploring the mechanisms underlying GBM, Bernstein also applied his team’s expertise in mapping regulatory elements of DNA, which encode no proteins but instead switch genes on and off or modulate the intensity of their expression. There are about a million such switches, known as enhancers and repressors, scattered across the genome.

In 2016, Bernstein and his colleagues discovered a novel way in which one such switch, through the agency of disrupted chromatin structure, drives a subtype of brain tumor. The tumors in question puzzled researchers because they lack mutations in any of the usual growth-promoting genes that cause cancer. They are instead characterized by mutations to a metabolic enzyme named IDH.

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How this might fuel cancer was unclear, but one clue was that the DNA in such tumors bristled with an abnormal number of epigenetic tags known as methyl groups. This increased methylation of the DNA, Bernstein and his colleagues reported in *Nature*, disrupts a recurrent element of genomic structure, known as an insulator, that partitions entire neighborhoods of the genome from each other. “When the insulator is knocked out, the genome refolds in such a way that a giant ‘on’ switch comes in contact with an oncogene called PDGFRA, turning it on and driving tumor growth,” says Bernstein. The researchers also showed that a chemotherapy that reverses methylation could suppress the growth of the tumors in culture.

“Cancer has traditionally been thought of as a genetic disease, in which a mutation to DNA creates an oncogene that drives the formation of a tumor,” says Bernstein. “But here we were showing that you can have a nongenetic mechanism—this is, an epigenetic one—that switches on an

oncogene.” Most exciting for Bernstein is that the findings have led to the launch of a clinical trial to evaluate the use of DNA demethylating drugs for the treatment of brain tumors.

Structure and dysfunction

Since aberrant methylation of DNA has long been associated with cancer genomes, the chances were high that similar epigenetic mechanisms might drive other cancers as well. One likely candidate emerged in Bernstein’s conversations with Ludwig Harvard Co-director George Demetri, an authority on sarcomas. A type of sarcoma known as a gastrointestinal stromal tumor (GIST) is often driven by mutations that activate the oncogenes KIT and PDGFRA. These can be treated by therapies Demetri helped develop. But one GIST subtype lacked any discernable oncogenic mutation. Its genome, however, was known to be aberrantly methylated.

Bernstein, Demetri and their colleagues reported in *Nature* in 2019 that the DNA



Photo by Flynn Larsen

methylation dissolved an insulator in the genomes of these GIST cells and allowed a potent enhancer to move in three-dimensional space such that it could access the gene for FGF4, a known activator of oncogenic signaling. A second disruption of an insulator in these tumors had a similar effect on KIT. Mouse models of such GISTs showed that a new class of drugs that inhibit FGF signaling caused significant tumor regression, an effect amplified when existing KIT inhibitors were added to the mix. The researchers are now planning clinical trials to evaluate FGF inhibitors as a therapy for this subtype of GIST.

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understand some biological phenomenon, you said, ‘it must be epigenetic’,” says Bernstein. “What’s so exciting now is that I can show you with great precision how epigenetic mechanisms are driving certain cancers, and we can generate ideas about how to treat it.”

Malignant hierarchies

Another study led by Bernstein and reported in *Cell* in 2019, done in collaboration with Ludwig Harvard’s John Aster and Andrew Lane and colleagues at the Broad Institute, MGH and the Dana Farber Institute, echoed Bernstein’s 2014 profiling of GBM tumors. In this case, the researchers profiled the cellular constituents of acute myeloid leukemia (AML), a blood cancer that originates in the bone marrow.

AML tumors are highly complex. They harbor a variety of normal and malignant cell types, including primitive cancer cells that closely resemble healthy blood stem cells and others that parallel various stages of normal blood cell formation. They also mutate frequently, forming lineages derived from “subclones.”

Bernstein and his colleagues harnessed a bank of AML tissue established by Ludwig Harvard, applying technologies used in the GBM study as well as a new method of DNA sequencing and machine learning software to profile nearly 40,000 individual bone

marrow cells from 16 AML patients and five healthy donors. The result was a revealing hierarchical atlas of AML cells, their gene expression programs and the relationship of those programs to patient prognoses.

The analysis also revealed one likely reason AML has so far thwarted immunotherapies. Many tumors draw in normal immune cells called ‘monocytes’ and coerce them to suppress immune responses against the tumor. AML takes a different tack to the same end. “While some AML cells rapidly divide and fuel the tumor,” says Bernstein, “others differentiate into monocyte-like cells that prevent an immune response.” The finding, says Bernstein, offers a clue to devising immunotherapies for AML and should be valuable to an interdisciplinary group starting up at Ludwig Harvard focused on immunosuppressive monocytes in a variety of cancers.

“A lot of my path over the years has been figuring out how to bring my interests in basic science and medicine together, and I think the Ludwig Center at Harvard is helping me to do that,” says Bernstein. “It is building bridges, connecting labs with diverse expertise and resources and bringing people together to do science. It has drawn together so many pieces of the Harvard scientific community and hospitals. The benefits were abundantly clear in both the GIST and the AML study.” 