Bradley Bernstein, MD, PhD

The Bernstein laboratory studies how the DNA in the human genome is packaged by a structure called chromatin. A central question in human biology is how the one genome we inherit at birth can give rise to the hundreds of cell types in the body. The genome consists of genes that code for the protein machines in our cells as well as regulatory elements that control those genes. A liver cell is different from an immune cell or a neuron because it makes different proteins. The way a gene is organized into chromatin predicts whether it will be turned on or off—and thus make protein—in a particular cell type. Our lab has identified specific types of chromatin that help determine when certain genes are on or off or that keep a gene poised to be turned on later in development. We leverage emerging technologies in genomics and computation to study chromatin organization across the genome. We use this information to better understand chromatin regulatory processes and how their failure contributes to cancer.

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A central question in human biology is how a single genome sequence can give rise to the hundreds of different cell types in the body. Scientists understand that differential patterns of gene expression underlie the many different cellular phenotypes seen in multicellular organisms. However, our understanding of how these gene expression patterns arise during development and how they are subsequently maintained in the adult organism remains poor. A number of studies have indicated that these different expression patterns and phenotypes are intimately related to the way in which genomic DNA is organized into chromatin in the cell. This organizational structure of proteins and DNA, sometimes referred to as the epigenome, helps control which genes are expressed in a given cell type and is critical to the function of normal cells. Moreover, a large body of evidence suggests that the epigenome is inappropriately altered in most—if not all—human cancers.

The long-term goal of our research is to achieve a comprehensive understanding of how the human genome is organized into chromatin. Our group is further focused on understanding how dynamic alterations in chromatin structure contribute to mammalian development and how aberrant chromatin regulation contributes to cancer progression, heterogeneity and therapeutic resistance. We are taking a multifaceted approach involving stem cell biology, biochemistry genetics, genomics and computational biology. The specific areas of research activity in the lab are explained below.

Technologies for mapping histone modifications and chromatin proteins

We are combining tools in cell biology, biochemistry and molecular biology with next-generation sequencing to achieve increasingly precise, genome-wide views of chromatin structure, chromatin regulator

The machinery of chromatin regulation

The Bernstein group is focused on understanding the genome-wide regulation and control of chromatin — DNA and its associated proteins. Studies in this group provide views into the 'machinery' that regulates chromatin in mammalian cells, demonstrating that Chromatin Regulators (CRs) act in a similar manner to the way gears function in a machine. In the illustration, the gears represent CRs that may act in concert or alone to control different genomic environments.

Artwork by Lauren Solomon, Alon Goren and Leslie Gaffney, MGH and The Broad Institute. Original photograph from iStockphoto (Maksim Toome, photographer).

binding and genome organization. Integrative analysis of such chromatin state maps yields detailed annotations of the locations and dynamics of functional elements in the human genome, including promoters, transcripts, silencers, insulators and enhancers. Ongoing projects are applying these annotations to understanding cell circuits and how they vary across cell types during development and in cancer.

Epigenetic regulation of stem cell differentiation

Chromatin regulators, such as the Polycomb and trithorax complexes, play critical roles in controlling the expression and potential of genes during development. We identified a novel chromatin structure, termed bivalent domains, that is subject to simultaneous regulation by Polycomb repressors and trithorax activators. Bivalent domains appear to keep developmental regulator genes poised in pluripotent embryonic stem cells and may also serve similar functions in multipotent progenitor cells. Current studies are leveraging a new generation of experimental assays to characterize the functions of bivalent domains and to understand the mechanisms that underlie their establishment and function.

Chromatin regulation in cancer cells

Genes encoding chromatin regulators are frequently mutated in human cancer. In specific cases, these alterations appear to be major drivers of the malignant state. Ongoing studies in the lab seek to apply epigenomic technologies to characterize the transcriptional and epigenetic landscapes of cancer stem cells and to identify mechanisms by which epigenetic changes contribute to therapeutic resistance.

Selected Publications:

Flavahan WA, Drier Y, Liau BB, Gillespie SM, Venteicher AS, Stemmer-Rachamimov AO, Suva ML, **Bernstein BE**. Insulator dysfunction and oncogene activation in IDH mutant gliomas. *Nature* 2016; 529:110-4.

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Knoechel B, Roderick JE, Williamson KE, Zhu J, Lohr JG, Cotton MJ, Gillespie SM, Fernandez D, Ku M, Wang H, Piccioni F, Silver SJ, Jain M, Pearson D, Kluk MJ, Ott CJ, Shultz LD, Brehm MA, Greiner DL, Gutierrez A, Stegmaier K, Kung AL, Root DE, Bradner JE, Aster JC, Kelliher MA, **Bernstein BE**. An epigenetic mechanism of resistance to targeted therapy in T-cell acute lymphoblastic leukemia. *Nat Genet*. 46: 364-70, 2014.

Suva ML, Riggi N, **Bernstein BE**. Epigenetic reprogramming in cancer. *Science*. 339:1567-70, 2013.