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BING REN

GENOME'S TOPOGRAPHER

Bing Ren took his first real stab at grown-up science in the early 1980s. A strapping middle-schooler in Taiyuan, the capital of China's coal-rich province of Shanxi, Ren got word that NASA was soliciting suggestions for experiments that might usefully be conducted in orbit. Excited by the possibility—his brainchild, in outer space!—Ren in short order mailed out his very first research proposal to the authorities. "It was not selected," he recalls.

If outer space once disappointed, Ren has had much better luck with the inner variety: His scientific forays into the cell's nucleus are illuminating how the genome controls its own expression—and how that control runs awry in diseases such as cancer. Thanks to his experimental virtuosity, Ren has helped launch a revolution in genomics, one that has made him, according to Thomson Reuters, among the most influential researchers in his field.

In a series of papers published in 2015, Ren and his team at Ludwig San Diego captured on a vast scale the variability of the genome's expression through the early stages of development and across an array of cell types, linking that variation to the chemical modification and physical structure of chromosomes; they worked with other Ludwig researchers to profile in vivid detail how aberrant signals from a mutant receptor alter the activation of the genome in cells of the brain cancer glioblastoma multiforme (GBM); and they partnered with another group of scientists to describe how stem cell chromosomes sequentially unfurl as they prepare to generate cells of the pancreas and liver.

First steps

Ren's journey to the frontiers of genomics began at the University of Science and Technology of China, where he majored in biophysics, studying the neurology of visual processing. But soon after he started his doctoral studies at Harvard in 1992, he became fascinated by gene regulation and joined the laboratory of Tom Maniatis, one of the pioneers of modern molecular cloning. "Gene regulation is such a fundamental problem in biology," says Ren. "It explains

how all these different types of cells in the body emerge from the information encoded by the genome."

Ren focused on how specialized proteins called transcription factors control gene expression by recognizing unique DNA sequences. As was the norm at the time, he probed such interactions one at a time, outside the cell, binding the protein factors to their target DNA sequences in a test tube. But Ren was eager to capture such events as they occur inside cells and, a few years into his research, adopted a technique to do so. It involved chemically gluing the proteins to their target DNA inside the cell and then using antibodies to pull the whole scrum down for subsequent analysis.

After obtaining his PhD, Ren joined Richard Young's laboratory in the Whitehead Institute at MIT as a postdoctoral researcher. Young's team was at the time using DNA microarrays—glass slides peppered with short DNA sequences—to fish out the full spectrum of genes expressed by cells in response to various stimuli. Ren wanted to similarly profile the DNA switches that control such gene expression.

To that end, he adapted his antibody-based assay to the DNA chip, developing a technology in 2000 that later came to be known as ChIP-chip. "It was the first technique that permitted the large-scale analysis of the genetic switches responsible for gene expression," says Ren.

As DNA sequencing technology evolved, Ren and other researchers further adapted his ChIP protocol to create ChIP-Seq, which is compatible with modern sequencing machines. This technology, and his laboratory's mastery of computational biology, have since powered Ren's prolific exposition of the genome's regulation and turned his Ludwig-supported laboratory into a technological engine for a new era of genomics.

The layered genome

If the human genome is a recipe book, its chapters are 23 distinct chromosomes, each of which is stuffed, in rough duplicate, into the nucleus of almost all the cells of the human body. But how is that single book read to build the body's diverse constituency of cells? Or, for that matter, to generate such a variety of humans? And how is it read differently by malfunctioning or cancerous cells?

In 2015, Ren made significant contributions to solving each of these problems as leader of two studies and senior author on a third. The papers were part of a package of six papers published in *Nature* summing up the findings of the $300 million Roadmap Epigenomics Program. An initiative of the U.S. National Institutes of Health, the project had explored how chromatin—DNA and its protein scaffolding—is chemically tagged to control gene expression.

Such "epigenetic" tags have long been known to help control gene expression and to be broadly misplaced in cancer cells. Stretches of chromatin that are tagged to be silent are typically bundled up and so sequestered from the cell's gene-reading machinery. Those bearing genes to be expressed are, conversely, held open and available. These patterns give resting chromosomes a subtle and layered structure that is directly related to gene expression.

One of Ren's *Nature* studies employed ChIP-Seq to determine the degree to which the same genes—known as alleles—inherited from each parent are differently expressed across the genome. It tied that difference in expression to the distribution and sequence of "enhancer" DNA sequences, which boost the expression of specific genes. Ren and his

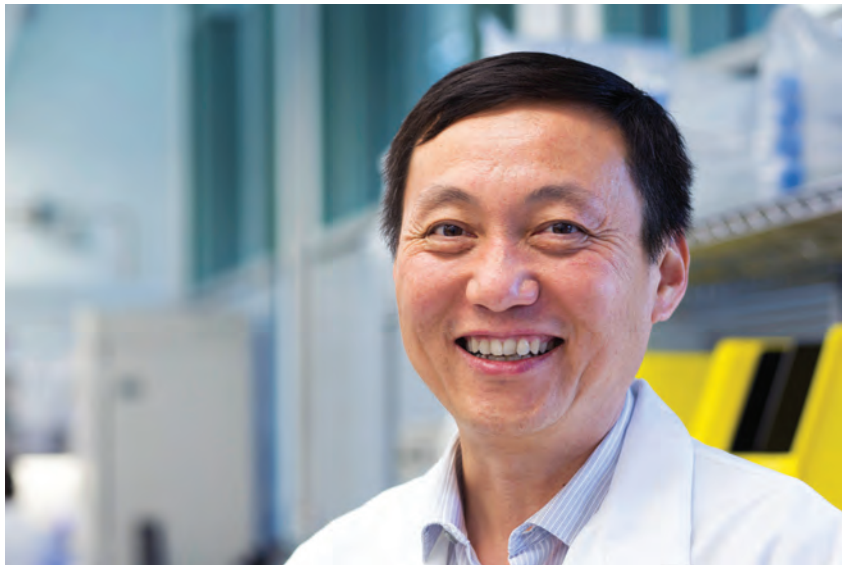
colleagues found that roughly 30 percent of the gene set we carry is expressed variably between the two copies in some of 20 tissues and cell types examined. Much of that variation appears to be due to differences in DNA sequences of enhancers and other regulatory sequences of DNA.

His other *Nature* study examined how the 3D structure of chromosomes and their epigenetic landscapes differ between different types of adult and embryonic cells. It also integrated data from the former paper to reveal how all of these phenomena interact to ensure the appropriate expression of the genome. The ample and freely available data from these studies will for years be mined by researchers studying virtually every subfield of human biology, not least cancer.

Beyond basic biology

In two other studies published in 2015, Ren and his team took on the epigenetics of disease and the biological effects of chromosomal architecture. In one study, published in *Molecular Cell*, Ren partnered with Ludwig's Paul Mischel and Andrew Shiau to examine how a mutant growth factor receptor (EGFRvIII) that drives many GBM tumors alters the epigenetic landscape of the genome (see accompanying story, page 35). The team identified a large set of enhancer sequences that are aberrantly activated by the redistribution of epigenetic tags. The scientists then showed how two of the proteins produced at higher levels by such activation play a critical role in the survival of GBM tumors and used these findings to devise a potentially novel approach to treating GBM.

"This study is proof of principle that by analyzing noncoding, gene-regulating DNA sequences, we can get to the heart of the problem in a given cancer and identify new strategies for its treatment," says Ren.



Bing Ren
Ludwig San Diego

For the other study, published in *Cell Stem Cell*, Ren partnered with a colleague at the University of California, San Diego, to detail how the sequential and fastidiously choreographed unfurling of chromatin is essential to the generation of pancreatic and liver tissues from stem cells. The findings have biomedical relevance because dysfunctions in the choreography of chromosomes might cause diseases like diabetes. The findings could ultimately also help researchers figure out how to make therapeutically useful tissues from stem cells.

Ren, it appears, is only getting started. His lab was recently picked as one of the technological hubs within a potentially $120 million project named the 4D Nucleome Program. The project will chart over the next five years the relationship between the epigenetic control of gene expression and the three-dimensional structure of chromosomes—and how the two change over time, the eponymous 4th dimension.

If history is any guide, this project too will likely be of lasting importance to every subfield of the biomedical sciences.