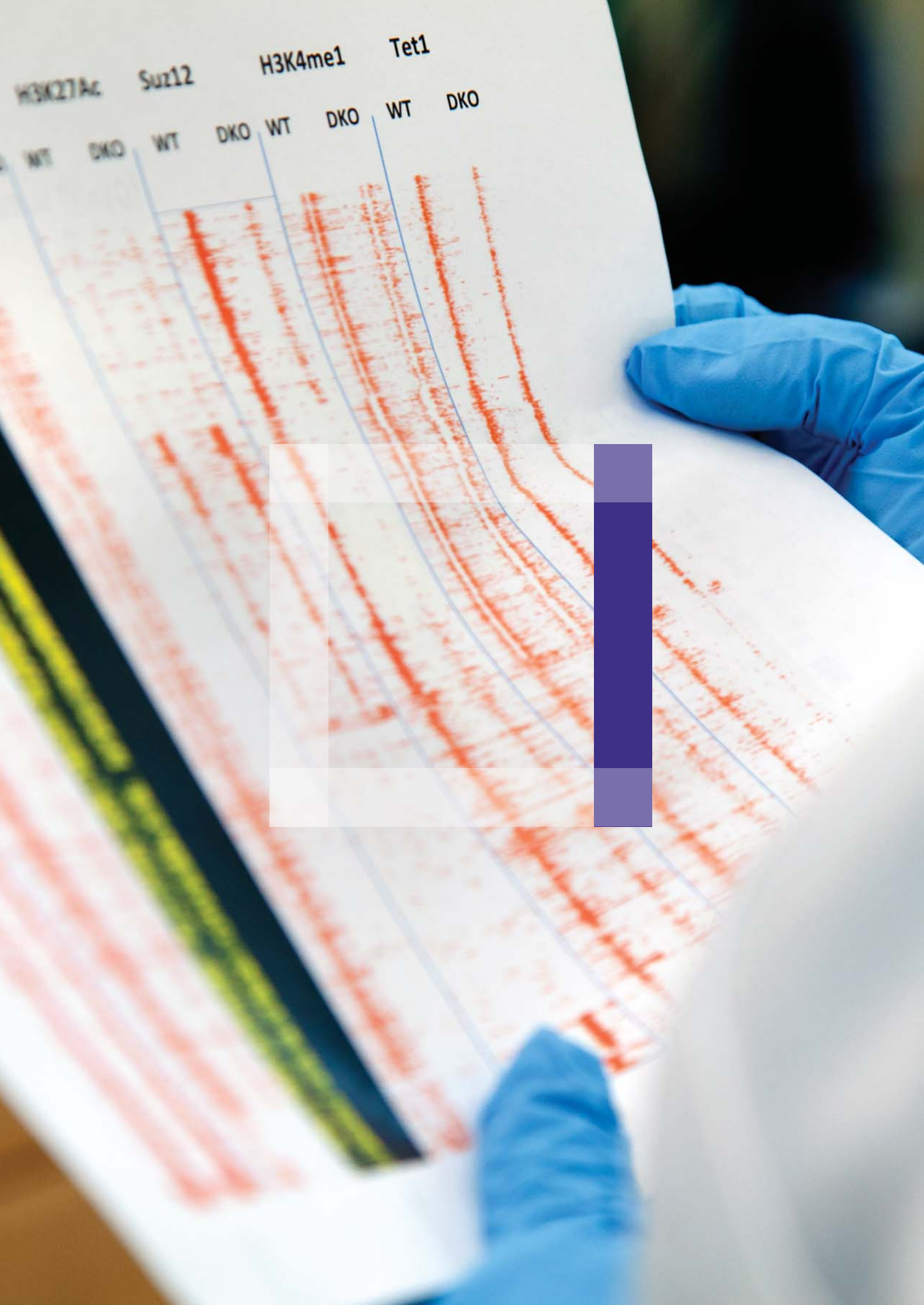
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TECHNOLOGY

New scientific technologies are the wellspring for major research discoveries, and they often lead to new diagnostic and therapeutic tools. Such connections are coming alive in the laboratories of innovative Ludwig researchers.

DECODING THE HUMAN GENOME

When Bing Ren interviewed for a position at Ludwig San Diego in 2001, his scientific discipline was just emerging. Researchers were beginning to explore how chemical modifications to DNA, or the proteins that bind to it, could change how genes are regulated.

They were looking at these modifications throughout the genome. This area of study, called epigenomics, was about to take off, “Biology was set for a major conceptual shift,” recalls Web Cavenee, Ludwig San Diego director.

At the time, much research in cancer biology focused on how a single gene or molecular process affects a tumor cell. But Ren was thinking bigger. He was examining the genome of a cell as a unit, and assessing how entire sets of genes are turned on or off. He was particularly good at this approach, having developed a key technology called ChIP-on-chip. This technique identifies regions of DNA bound by proteins that help determine whether a gene is active or silent. By illuminating where on DNA such epigenetic changes occur, Ren’s approach could help researchers understand how genes are regulated, cells proliferate and disease progresses.

“His work struck me as intellectually daring and was coupled with flawless experimental controls,” recalls Cavenee. But there was a flip side. “I knew that work like this, taking him beyond the edge of knowledge, was also likely to have a hard time being funded.” Cavenee decided to take a leap and hire Ren. Neither researcher has been disappointed.

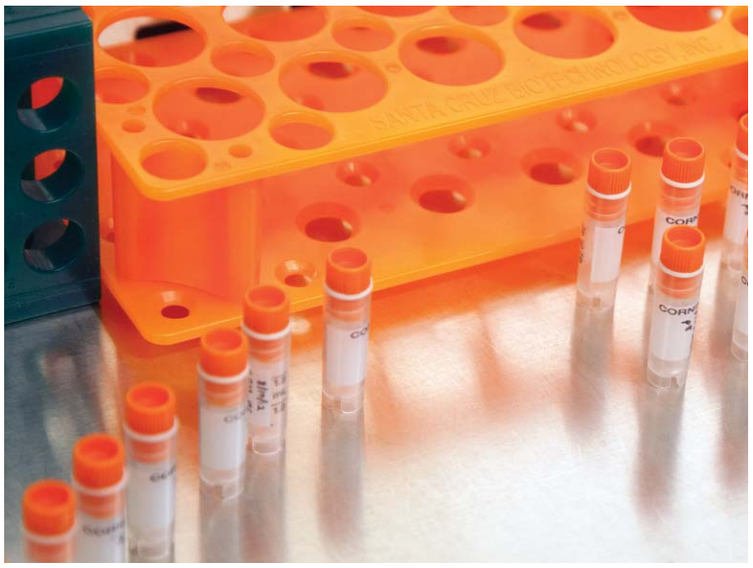
“Joining Ludwig was the best decision I have ever made in my career,” says Ren. He has since become a leader in epigenomics. In 2012 his laboratory produced four major studies revealing how cells manage the activity of their genes, for instance turning them on or off depending on cell type or signals from the environment. In the long term, the research could lead to new technologies to diagnose and assess tumor types. Ludwig’s initial investment

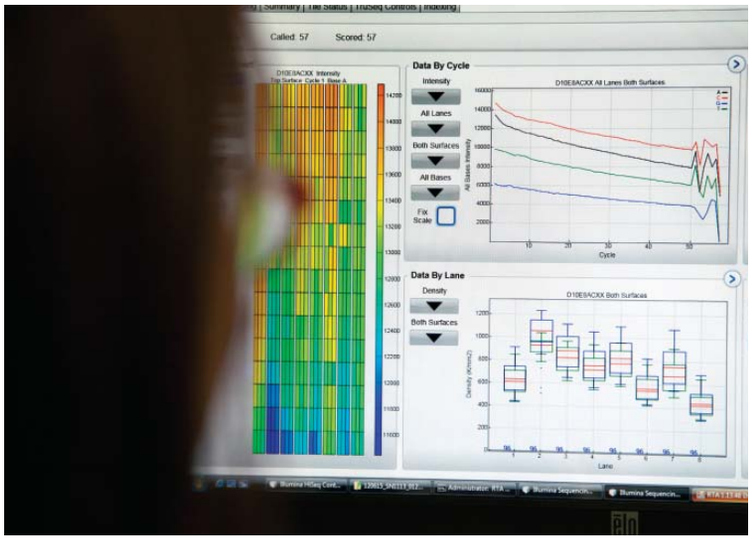
Bing Ren

has snowballed: Ren's lab is now a center for two large international research initiatives, patterned after the human genome project, to assess gene regulation in normal and diseased cells.

Ren's laboratory is one of seven centers for the ENCyclopedia of DNA Elements (ENCODE) Project, which is funded partly by the US National Institutes of Health. The project aims to catalog DNA sequences that regulate whether genes are expressed. And another major initiative, the NIH Roadmap Epigenomics Project, has tapped Ren's laboratory to run one of its four centers. His focus is analyzing the epigenomes of embryonic stem cells to map key modifications to DNA and histones, proteins that bind to DNA.

Ren traces his bounty of recent data to a moment in 2007 when he realized that his lab might be falling behind. He had just learned of new DNA sequencing technology that could fast-track ChIP-on-chip, enabling the technique to examine DNA faster and more comprehensively. The "next generation" DNA sequencing machines had the potential to accelerate Ren's research dramatically, but they cost a hefty $750,000 each.





"Joining Ludwig was the best decision I have ever made in my career." **BING REN**

Such a big purchase would normally require its own grant, which could take a year to work its way through most institutions.

But Ludwig was able to corral the resources. Within a week, the funding was secured, and Ren had his machine. "These four studies are a direct result of our early access to next-generation sequencing technologies," says Ren.

Each of the studies focuses on a different aspect of gene regulation. But they all stem from the same fundamental idea—that cancer and other human diseases can arise not only from mutated genes, but also from defects in how those genes are turned on and off.

Two of the studies emerged as part of the ENCODE Project. In one of last year's international scientific triumphs, the project coordinated the release of almost 100 studies. Ren and his colleagues contributed a study showing how DNA is organized into domains that tend to fold together, promoting interactions between genes and their regulatory sequences. In a second study, they identified the location of nearly 300,000 DNA regulatory sequences, covering about 11 percent of the bases of the mouse genome. A third study, which was part of the NIH Epigenome Project, deployed a new technique to identify the locations of a key type of DNA modification, 5-hydroxymethylcytosine, which abounds in human and mouse brains and in embryonic stem cells.

Ren is already applying his technique to understand the epigenomics of cancer. In a fourth study in 2012, he teamed up with Ludwig researchers in Baltimore, Lausanne, New York and São Paulo. The researchers examined the cancer epigenome, the sum of modifications to DNA or histones that may affect the expression of cancer-related genes. They released a study of breast cancer showing how low levels of a DNA modification called methylation lead to DNA silencing.

“How does a normal cell become metastatic by acquiring the ability to grow indefinitely, or evade the immune system, or become impervious to dying?” asks Cavenee, who is now teaming up with Ren to study the epigenome of glioblastoma, a deadly brain cancer.

Ren’s work on fundamental aspects of gene regulation in normal and cancerous cells is already beginning the journey to the clinic. His research also may one day complement the work of other Ludwig researchers, such as Bert Vogelstein, who design tools to detect and evaluate tumors at their earliest stages, when cancer is easiest to cure. Ren’s research could eventually lead to new, affordable diagnostic tools for tumor assessment.

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