Howard Chang, MD, PhD

Virginia and D.K. Ludwig Professor of Cancer and Genetics
Director, NIH Center for Dynamic and Personal Regulomes

Summary of Work

Every cell in a person's body has the same DNA and yet, different cells look and act differently: skin cells are not the same as brain cells, which are not the same as bone cells or blood cells. The reason is that each cell is making choices about which genes to turn on and off.

Howard Chang, MD, PhD, and the Virginia and D.K. Ludwig Professor of Cancer and Genomics, has dedicated his career to understanding the system of switches that controls when and where a gene will turn on. To gather more detailed information about these switches, he developed cutting-edge technology that allows him and scientists around the world to see the molecular differences that drive gene regulation on a cell by cell basis.

"The focus of our research has implications for how different diseases arise and how different experiences change the way your genes are turned on and off," Dr. Chang said. "It even has implications for aging."

Dr. Chang discovered that the part of the human genome, often called "junk DNA" because it does not trigger the production of proteins, has important and previously unknown functions. He pioneered technologies to study these long non-coding RNAs (lncRNAs) and has shown that they are master regulators of cellular development, aging, and cancer progression. His groundbreaking work promises to open a new world of RNA-based strategies against disease.

"LncRNAs are choreographed to dictate cell type, like a recipe," Dr. Chang said. They fold into complex 3D shapes that bind DNA and recruit protein complexes to alter gene expression. When lncRNAs malfunction, cells go haywire. Dr. Chang discovered one lncRNA that drives cancer metastasis.

"Cancer cells reprogram themselves to think they belong elsewhere, accessing a genetic mechanism to spread," he said, adding that the lncRNA he discovered is a biomarker for poor prognosis in more than 25 different cancers. His research has yielded a powerful diagnostic tool for high-risk patients and could generate treatments against deadly metastatic disease. His work may also point to new therapies for infectious and autoimmune diseases as LncRNAs also control immune activation programs.

Scientists in the Chang Lab were able to advance our understanding of LncRNA because of technologies that Dr. Chang created. ATAC-seq or Assay for Transposase Accessible Chromatin using sequencing, which Dr. Chang developed with Professor of Genetics William Greanleaf,

PhD, allows researchers to observe living cells' behavior so they can study molecules that regulate switching in real time. Previously, researchers needed to collect more cells than a living person could offer, so they compensated by growing cells in labs. By the time they had enough cells to study though, the originals were long gone. Only copies of copies remained, which changed cell behavior. "How the laboratory cells behave has nothing to do with what the person just ate, whether they had a fight with their girlfriend, or whether they had an infection," said Dr. Chang. Lab-grown cells don't experience any of those things, which can all alter the regulation of individual genes.

ATAC-seq is one million times more sensitive than previous technology and one hundred times faster. Because of this, scientists can take a smaller sample from patients and establish a baseline measure of how much gene switching varies among healthy people. Dr. Chang's team reported that more than a third of the variation in gene activity was not connected to a genetic difference, which suggests that gene regulation trumps genetics.

Biography

Dr. Chang directs the NIH Center of Excellence in Genomic Science: Center for Personal Dynamic Regulome at Stanford University, which aims to map the "regulome"—the complete set of all switches that turn genes on and off in real time. He was elected to the National Academy of Medicine in 2017, received the prestigious NAS Award in Molecular Biology for creating new technologies, and earned the Outstanding Investigator Award from the National Cancer Institute. He is currently working to democratize science by using Eterna, an online gaming platform that invites independent video game players to design molecules to be used in gene editing.

Dr. Chang holds undergraduate and medical degrees from Harvard University and a doctorate in biology from the Massachusetts Institute of Technology. He completed his internship at Santa Clara Valley Medical Center and residency and fellowship at Stanford University School of Medicine. He is board certified by the American Board of Dermatology.

Stanford MEDICINE

Kathrin Walsch, MBA
Senior Associate Director, Major Gifts
650.785.4511 | kwalsch@stanford.edu