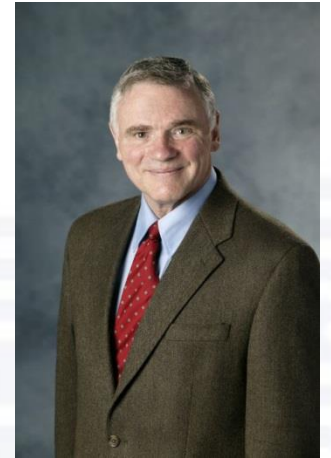


## CASE STUDY: LEROY HOOD

### Introduction

Leroy Hood is an inventor, entrepreneur, and in the vanguard of molecular biotechnology and genomics. He co-founded systems biology: an interdisciplinary, holistic approach to biomedical research that focuses on how molecules operate together. His inventions include the gas liquid phase protein sequencer, protein synthesizer, DNA sequencer, DNA synthesizer, the ink-jet-based DNA synthesizer (large-scale DNA synthesis) and the nanostring technology for single-molecule DNA and RNA analyses. Taken together, these six instruments have formed the technological foundation for much of the research conducted in the biotechnology- and genomics-related fields today. Hood received the Lemelson-MIT Prize in 2003 for his revolutionary innovations, which led to new, comprehensive knowledge of the factors that contribute to human disease and wellness.



Leroy Hood (Photo/Dale DeGabriele)

### Background and Early Life

Born between mountain ranges in Missoula, Montana, Leroy Hood cultivated an early fascination with the natural world and a lifelong affinity for physical fitness. He spent much of his childhood at his grandfather's ranch in the Beartooth Mountains, and his family encouraged exploration, independence and excellence in all endeavors. Hood's interest in biology began with the birth of his younger brother who was diagnosed with Down syndrome. At the time, the scientific community had no way of explaining why some babies were born with this condition, and Hood's curiosity about biological conundrums and the human complexities they dictated began to grow.

Hood's family moved to Shelby, Montana, at the start of his high school career. Several teachers across subjects — from chemistry, to mathematics, to social studies — introduced him to a range of new interests and career possibilities. Summers brought Hood back to the Beartooth Mountains where his grandfather managed a geology camp with students and professors at Columbia, Harvard, Princeton and other prominent universities. Participation in this camp and the projects that came out of it gave Hood a deeper and more varied



Hood, top, as a boy in Montana, and bottom right, with his siblings. (Photos/Leroy Hood)

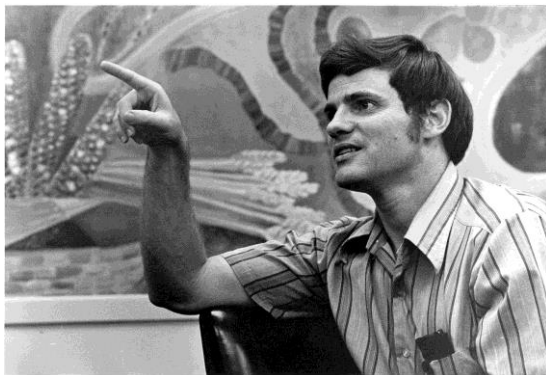
appreciation of scientific work and achievement.

One high school teacher in particular, Cliff Olson, solidified Hood’s primary area of interest when he invited Hood to assist him with a sophomore biology class. Hood was thrilled not only to be sharing his enthusiasm for biology with students, but also to be learning alongside them. Hood found himself reading and teaching from *Scientific American* articles about biology and DNA. One article in particular on the structure of DNA – only three years after its discovery in 1953 – peaked his curiosity. It led to his realization that the DNA molecule held fundamental answers to questions of human biology, genetics and health, and it was determinative in his deciding to pursue biology over geology. Olson encouraged Hood to follow in his own footsteps and pursue a bachelor’s degree at the California Institute of Technology. Hood found mentorship in plant biologist James Bonner and immunologist Ray Owen during his undergraduate years. Their instruction, graciousness, and passions for science would inform Hood’s work for decades to come. He graduated from Caltech with a bachelor’s degree in biology in 1960.

Hood went on to attend the Johns Hopkins University School of Medicine, drawn to the complexity of human biology and driven to understand its relationship to his brother’s experience of Down syndrome. He became fascinated with immunology, researching how the immune system responds to diverse viruses, bacteria and other pathogens. Hood and two of his classmates also taught science classes at a local underserved high school where Hood established a lifelong commitment to K-12 science education.

## Process: From Intent to Impact

Hood broke with tradition when he graduated from medical school in 1963. Instead of taking the expected path of clinical medicine to internship and residency, he affirmed his commitment to a career in basic science. Hood returned to Caltech to pursue a doctorate degree and work with Bill Dreyer, a molecular immunologist conducting research into antibody diversity. Together, they arrived at a revolutionary,



Hood at CalTech. (Photo/Leroy Hood)

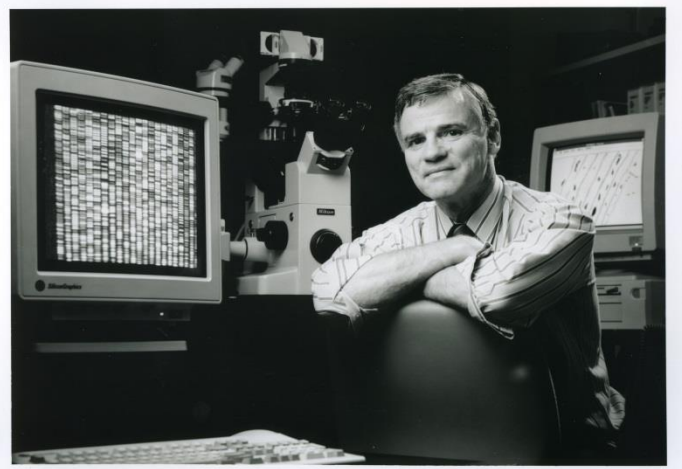
ultimately proven, hypothesis: that antibody-producing cells are encoded by two distinct genes that join together in ways that generate enormous genetic diversity with each cell expressing just a single form of this diversity. This generated a diverse population on immune cells that could either identify potential pathogens or spur an antibody response to kill them. Their theory met immediate skepticism in the scientific community, showing Hood that many scientists felt threatened by new ideas or discoveries.

Still, Hood was not deterred. He credits Dreyer with both facilitating this cutting-edge research and teaching him how to think innovatively: to approach any problem with both creativity and practicality. Dreyer advised him, “If you want to practice biology, do it on the leading edge, and if you want to be on the leading edge, invent new tools for deciphering biological information.” These axioms would guide Hood’s scientific priorities and innovations throughout his career.

In 1967, Hood received his Ph.D. in biochemistry, and the escalating Vietnam War compelled him to join the National Institutes of Health’s Public Health Service. He conducted molecular immunology research at the National Cancer Institute for three years as an independent scientist, and became increasingly interested in using technological development to advance the knowledge and practice of molecular immunology. Once more, he returned to Caltech as an assistant professor. Hood’s laboratory became one of the first to combine biology and engineering, using biological knowledge to determine which technologies should be developed in order to solve specific biological problems.

Hood divided his lab into two domains: technological development and molecular immunology. He and his collaborators began producing technology that could decipher critical pieces of biological information from DNA, proteins and biological systems. They first identified a problem — that many types of proteins were unavailable to study in-depth and efficiently with existing instruments, forming a clear barrier to biological inquiry and its potential positive impacts on society. Consequently, his lab invented a high-speed protein sequencer that used a gas-phase-based detection method, making it approximately 200 times as sensitive as previous sequencers. Their sequencer enabled researchers to examine trace proteins in living beings for the very first time and led to the founding of Applied Molecular Genetics and the production of erythropoietin, the first biotech product to reach \$1 billion in sales. Hood’s lab soon developed a protein synthesizer, allowing scientists to effectively generate small proteins for further research and experimentation. This instrument, among its many applications, would catalyze the creation of a protease inhibitor to treat human immunodeficiency virus and acquired immunodeficiency syndrome.

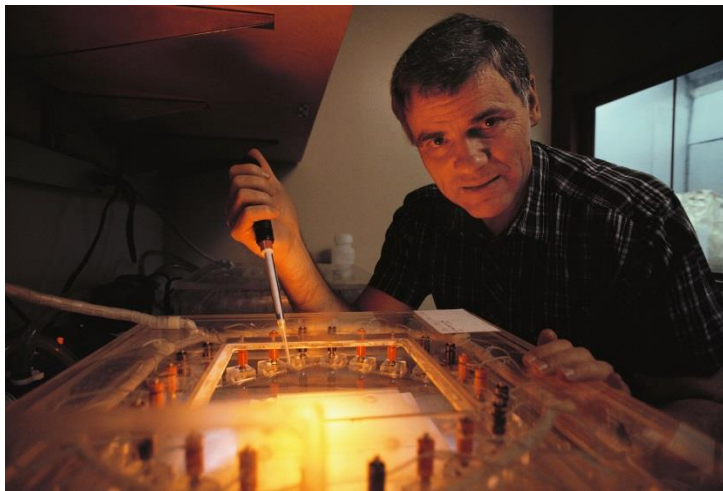
Several of Hood’s related inventions came to fruition in the 1980s, including his most impactful instruments. Building on Fred Sanger’s brilliant discovery of how to manually sequence DNA, Hood’s lab developed an automated DNA sequencer that made possible the rapid sequencing of the structure of DNA. They followed up with the first DNA



*Hood with one of his first-generation DNA sequencers.  
(Photo/Leroy Hood)*

synthesizer, based on the clever chemistry of Marvin Caruthers, which could automatically synthesize DNA structures and reproduce them for initiatives like gene cloning and DNA mapping. The invention of these four instruments formed the technological cornerstone of modern molecular biology; it also demanded expertise and collaboration across basic science and technical fields, including biology, chemistry, computer science and engineering. Hood championed this cross-disciplinary approach to invention which defined and impacted his lab and beyond. He co-founded Applied Biosystems with Caruthers to commercialize their instruments for widespread use and maximum efficacy.

Shortly after its invention, the automated DNA sequencer would make possible the largest collaborative biological research project in biology history. The 23 pairs of chromosomes that reside in each human cell, taken together, are called a “genome”; sequencing the human genome would allow scientists to identify and examine the structure of all human genes. Hood and his many collaborators in this effort hypothesized that obtaining this massive database of genomic information would facilitate the discovery of genetically-defective genes and the ability to correlate their genetic variability with wellness and disease phenotypes – a central feature of 21<sup>st</sup>-century medicine. Hood’s invention and advocacy, together with many others, led



*Hood preparing an electrophoresis gel in an early iteration of his computer-controlled system for DNA sequencing human chromosomes. (Photo/Leroy Hood)*

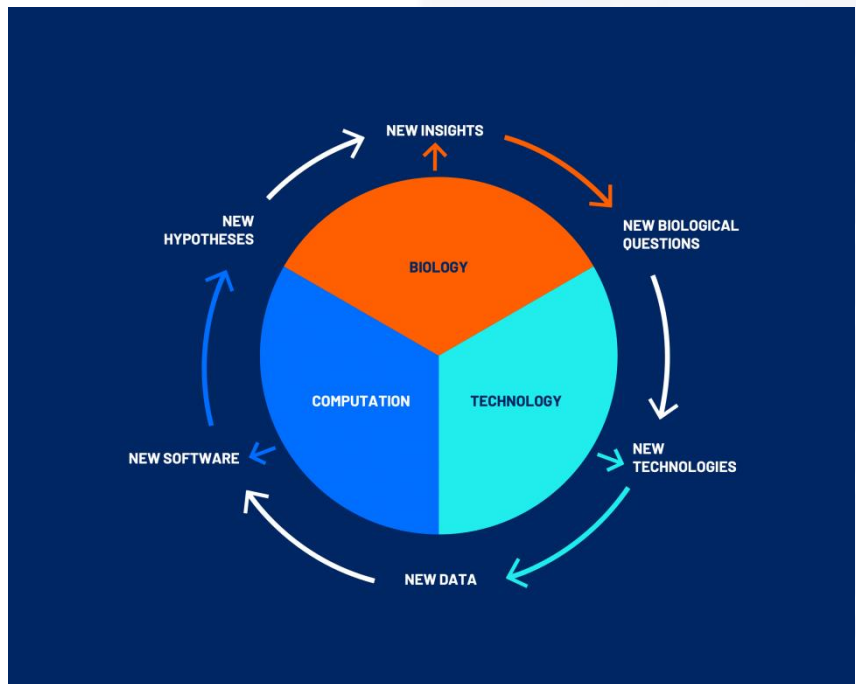
to the Human Genome Project, a 15-year effort that completed mapping and sequencing of the human genome in 2003. This project, sparked by a commitment to biotechnical innovation and impact, has provided a comprehensive global resource on the inheritable blueprints for human development, physiology and aging – as well as understanding the genetic contributions to many different diseases. It has given scientists the instruction manual for beginning to understand different human cell types, and allowed health care providers to predict, prevent, treat, and cure disease with more frequency and effectiveness than ever before.

Hood left Caltech for the University of Washington in the early 1990s and spearheaded the first cross-disciplinary biology department. His collaborators in the department of molecular biology consisted of biologists, chemists, computer scientists and engineers. Hood’s lab invented an ink-jet oligonucleotide printer technology that could synthesize DNA with such accuracy and efficiency that researchers could compare gene expressions of normal and mutated cells and begin to identify the nature of cancerous ones. He and others founded Rosetta Inpharmatics to optimize this ink-jet technology, which was later sold to

Agilent. A host of other inventions came out of the department, including Ger van den Engh’s multidimensional, high-speed cell sorting machine and Phil Green’s two software programs to assemble shorter DNA-sequenced fragments into chromosomes and to assess the quality of each DNA fragment sequenced.

Systems biology soon emerged, in part, as a result of the Human Genome Project. Hood led the charge to shift the paradigm of scientific inquiry from the investigation of one gene or protein at a time to a consideration of the interactions of all the elements in a defined system, thus moving toward another innovative direction to approach biology and disease holistically in order to better understand their complexities. He likened this approach to studying how a car functions: identifying all of its elements, drawing up a model of its functions from prior (experimental) knowledge, and then test-driving it to observe how each element

coordinates with each other to accelerate or brake. In 2000, with immunologist Alan Aderem and protein chemist Ruedi Aebersold, Hood co-founded the Institute for Systems Biology, striving to integrate all levels of data studied within an organic system — from bacteria, to sea urchins, to humans — with the ultimate aim of improving global health. Early on, Hood’s lab developed a novel digital molecular barcoding instrument that examines single molecules of DNA and RNA. It has since become the flagship technology of NanoString, a company that facilitates a range of basic science research and related medical applications.



*ISB’s Innovative Engine. Solving challenging biological problems always requires the development of new technologies in order to explore new dimensions of data space. New data types require novel analytical tools. Biology driving technology driving computation. (Image/ISB/Leroy Hood)*

A major focus area of ISB today is P4 medicine, which encapsulates predictive, preventative, personalized and participatory medicine. P4 medicine’s mission is a radical departure from contemporary medical practices that revolve reactively around treating sick patients. P4 medicine is informed by the Human Genome Project and longitudinal, data-driven phenomic analyses (see below) and prioritizes optimizing

wellness and healthy aging, making it a far more proactive approach to health care than many other treatments. In the 2010s, Hood and his team at ISB explored new, actionable ways to quantify wellness and improve P4 medicine.

One study involved collecting comprehensive data – complete genome sequences and longitudinal phenome data every three months (for nine months) on 108 participants’ blood analytes, gut microbiome, digital self-measurements and assessment of environmental risk measurements – in order to provide them with individualized lists of recommendations (actionable possibilities) for optimizing wellness and avoiding disease. Researchers found, for instance that 91 people in the study had low blood vitamin D and many had one or more of six genetic variations that hindered their ability to absorb vitamin D. They notified these participants of their vitamin D deficiency — which can lead to a range of ailments, from depression to osteoporosis — and advised each of them on how much vitamin D to consume to achieve healthy levels. Another participant learned from a blood test that he had very high iron levels; researchers notified him



An illustration from ISB’s Pioneer 100 Study on the cover of *Nature Biotechnology*. A subset of statistically significant correlations are extruded in three-dimensional space. Nathan D. Price et al. describe the integration of whole genome sequences; clinical tests, metabolomes, proteomes, and microbiomes at three time points; and regular quantified self-measurements for 108 individuals over nine months. Researchers obtained thousands of cross-sectional interomic correlations, each represented by a line in the circular figure, to better understand health and disease. (Image/ISB/Leroy Hood)

and encouraged him to see a doctor. His participation in the study had revealed hemochromatosis, a rare and life-threatening genetic disorder that causes the body to absorb too much iron, damaging organs and elevating the risks of liver fibrosis, diabetes and heart attacks. If caught early, this disease can be completely mitigated by simple blood draws until the blood levels of iron returned to normal and these normal iron levels could be maintained throughout the rest of the patients’ lives by similar blood draws.

Several clinical health markers improved as a result of these innovative, personalized evaluations. Hood termed this process “scientific (quantitative) wellness.” The “wellness pioneers” were so enthusiastic that Hood started a company called Arivale and brought scientific wellness to consumers. Over the four years of its existence, it recruited 5,000 consumers – each with their longitudinal data clouds. This effort reaffirmed the power of scientific wellness in making people healthier and it demonstrated the power of analyzing the 5,000 longitudinal data clouds to provide new insights into human biology and disease. This has led most recently to a

bold new project termed the one million patient genome/longitudinal phenome project with Providence, a large, nonprofit health care system on the West Coast (51 hospitals) where Hood is Chief Scientific Officer. This will catalyze his vision of 21<sup>st</sup>-century medicine, which is to optimize the health trajectory of each individual human and thus focus health care on the uniqueness of each individual and move away from the contemporary medicine of population averages.

Hood envisions this personalized, proactive focus on wellness as the future of medicine, capable of extending human lifespans by decades, facilitating healthy aging and significantly reducing health care system costs. A crucial step in implementing it, however, is encouraging participation by educating the public: providing citizens with a solid foundation in the sciences and keeping them informed on progressive health care initiatives. This commitment to scientific literacy stems from Hood's early, transformative educational experiences in Montana and carried through his graduate school career and beyond. In 1987, his lab at Caltech founded a Science and Technology Center program that trained approximately 60 teachers, who then taught experimental, innovative biological science to thousands of K-12 students. Hood went on to collaborate with the Seattle Public School District to generate programs at all levels of K-12 education to enact curricular reform at a systemic level – bringing “hands on-inquiry-based science” to teachers and students. Instead of traditional science classes in which teachers would generally present established facts, these new curricula emphasized inquiry-based learning. They encouraged students to approach science with curiosity and problem-solving at top of mind, as an inventor would. The elementary school program alone reached approximately 1,100 teachers and 23,000 students. Hood is also a co-author for a variety of textbooks on biochemistry, genetics, immunology and molecular biology to present biological conundrums, medical frontiers and the radical potential of scientific advancement. Like his other educational initiatives, they go beyond conveying established facts, teaching critical thinking and examining the challenges of modern science.

Hood believed from the beginning of his career that scientists had an obligation to bring any useful knowledge that they gain to society – by education, startup companies or by licensing to pre-existing companies. All of Hood's inventions and impacts have involved academic, commercial and societal paradigm shifts, and as a result met immediate skepticism and resistance. Hood has co-founded 17 biotech companies. And this was



*Hood in the ISB lab with one of his lab members. (Photo/ISB/Leroy Hood)*

initiated by the founding of Applied Biosystems, where 19 already-existing companies declined to invest in his revolutionary sequencers and synthesizers, but venture capitalist Bill Bowes was willing to invest. Facing obstacles to creating a program integrating biology and technology at Caltech, he moved to UW, with the help of Bill Gates, to create the country's first cross-disciplinary biology department. And he pursued unconventional, innovative inquiry-based science, despite waves of skepticism, in order to advance the frontiers of scientific knowledge and its positive impacts on the health and wellness of individuals and communities across the globe. Key to such achievements, for Hood and other problem-solving innovators, is an independent mindset he calls "determined optimism": pushing through obstacles, critiques and failures, believing in one's purpose, and never giving up. Another aspect important to Hood's career is that, in a sense, he has changed his science fundamentally every 10-15 years. He argues that the average scientific career is a bell-shaped curve, rising to a level of top achievement and typically declining as one ages. With new careers, one can always be on a continual career ascendancy – and never have to worry about a declining career – as long as one follows the rules of healthy aging.