# Joshua Lederberg: The Stanford Years (1958–1978)

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As the 1950s gave way to the 1960s, recent Nobel prize winner Joshua Lederberg established and implemented his unique concept of a Department of Genetics. Having helped to re-invent the Stanford Medical School as it moved from its long-term San Francisco home to the University campus in Palo Alto, Lederberg joined Henry Kaplan, Arthur Kornberg, Avram Goldstein, and other visionary colleagues in laying the interdisciplinary groundwork for what is now called Translational Medicine. But in his own department, he went further: He brought together world-class geneticists, immunologists, biochemists, physicians, engineers, and computer specialists whose interaction on a daily basis spawned many of the concepts, tools, and instrumentation that today sit at the heart of modern science and medicine.

Since Lederberg's death earlier this year, a spate of articles has appeared lauding his many direct contributions to science and medicine. However, while these highly central contributions are more than sufficient to establish his place as a leader among leaders, they are in a sense the trees that obscure the woods. For Lederberg's greatest contribution, if greatness can be measured in terms of impact on thinking and practice in science and medicine, may indeed be the diverse and apparently unrelated discoveries and engineering accomplishments that emerged from the intellectual stew he created in his nascent department—or, equally important, the diverse and apparently unrelated scientific and engineering lineages rooted in the intellectual interchange occurring daily in the Lederberg Genetics Department.

Of course, the way that Lederberg staffed the Department was neither random nor accidental. The people he chose reflected his encyclopedic interests and his talent for finding creative colleagues with whom he could interact to further the implementation of ideas that he or they had generated. Thus, in the early 1960s, the department included: a bacterial genetics group whose work proceeded from that for which Lederberg won the Nobel Prize; an immunology group exploring the clonal selec-

tion of antibody-producing cells postulated by Lederberg and Sir MacFarlane Burnet; a series of groups and collaborators focused on tissue and organ transplantation and other areas of importance in medicine; a somatic cell genetics and immunogenetics group that morphed (partly) into an engineering group intent on identifying and sorting mammalian cells; an exobiology group that began by developing technology to probe life forms on Mars but that ultimately made major contributions to cell-sorter technology; and several computer science groups that collectively pioneered artificial intelligence (AI) approaches to determination of chemical structures; instrument automation systems; network-based computing technologies leading to the development of the first Internet routers; and the establishment of two widely shared computing resources that became central to these and many other projects.

There were critics at the time, and later, who openly wondered how all of this could be considered genetics and why it should be given a home in a genetics department. However, Lederberg was acutely aware that progress in genetics over the years would depend as much on the development of enabling technologies—tools that would make it possible to understand the genome and its expression—as it would on the development of enabling ideas. Indeed, he saw the two as marching hand in hand, and the development of a diverse department as the ferment within which such tools and ideas could be conceived and explored. Certainly, considered in retrospect, the concepts on which the Lederberg Genetics Department was based have clearly been validated, both by the tangible output of the department and by the productivity of the people who were educated in this extraordinary milieu.

We reflect here on three of the many areas in which work in the early years of the department was formative for concepts and capabilities of importance today in genetics and medical science. Tom Rindfleisch, former director of the national SUMEX-AIM computer resource, focuses on Lederberg's vision of the central role of network-based computing in the conduct of

science and the augmentation of human intellect. Len and Lee Herzenberg draw together the ways in which Lederberg's catholic interests created an environment where forefront ideas about the importance of genetic mechanisms in the immune system flourished and, not incidentally, nourished the development of Fluorescence Activated Cell Sorter (FACS), which Herzenberg built (in collaboration with Lederberg's hardware and software engineers) to meet the needs of this newly emerging science.

Josh Lederberg's deep recognition of the importance and synergistic role of computing and instrumentation in human scientific endeavors led to a most unusual assemblage of computer science equipment and talent in his Genetics Department. Over the course of his 15 years as chair, he developed groups that experimented with the first laboratory computer, the LINC, that invented a novel time-sharing system that made interactive computing available broadly through the Stanford Medical School, and that built a networked computing resource that served as the home for a national community of researchers studying artificial intelligence in medicine.

Josh's interest in computing began early with an exposure to automatic tabulating equipment in high school. This interest took on new dimensions, however, when he established the Stanford Genetics Department and its Instrumentation Research Laboratory under Elliott Levinthal for the design of special purpose instruments for biological research and life detection systems on a microbial level in remote Martian exploration missions. In addition to the electrical, mechanical, and optical design issues for such instruments, computer systems were essential for the acquisition and analysis of the data produced. In the summer of 1963, Lederberg was awarded 1 of 12 experimental Laboratory Instrument Computers (LINC) developed by Clark and Molnar at MIT—the predecessor to the DEC LINC/8 and PDP-12 commercial computers. At Stanford, the LINC was used to interface with a variety of instruments for physical measurements such as low- and high-resolution mass spectrometry,

radioactive and fluorescent tagging, fluorescent decay time measurements, particle counting, and the interpretation of Raman spectra. In order to pursue these goals, Lederberg assembled a group that developed machine-level and scientific software for the LINC. The detailed analysis of these instrument data, for example the interpretation of biomolecular fragments in terms of their elemental composition, was done in batch mode on a campus computer.

This work continued well into the 1970s, with successive versions of DEC's PDP-11 computers replacing the LINC. Powerful programs were developed to automate and make ever more precise the analysis of (low- and high-resolution) gas chromatography/mass spectrometry data to facilitate studies of biological fluids, meteorite composition in search of extraterrestrial organic molecules, and other applications (under Tom Rindfleisch, Mark Stefik, Bill Yeager, Alan Duffield, Willie Periera, and Dennis Smith). These programs had the distinction of being adopted by the U.S. Environmental Protection Agency as a standard for their own laboratory analyses.

As this work progressed, Lederberg's attention turned to facilitating the broader analysis and interpretation of scientific data. His own interests centered on biomolecular structure determination and the representation and manipulation of molecular structures as graphs, but many other Medical School faculty needed statistical tools, database tools, graphical display tools, and text processing tools. In the fall of 1966, under a grant from NIH to Lederberg in the Genetics Department, the Stanford Medical School obtained an IBM 360 Model 50 computer in an unusual configuration that supported systems for medical laboratories. The Advanced Computer for MEdical Research (ACME), as it was called, provided a unique time-shared computing environment as well as real-time data acquisition and control interface for laboratory equipment. Interfaces were available for various laboratory computers and a locally built network for terminals was developed for access throughout the Medical School.

To create ACME, Lederberg enlisted the collaboration of computer scientists Ed Feigenbaum and Gio Wiederhold. The system included a time-share monitor and an incremental compiler for PL/1, called PL/ACME, designed by Gio Wiederhold. Extensive software was developed for statistical work and for a time-oriented database that was an early instance of a tool that could be used as a medical record system. ACME promoted the use of computers widely in Stanford medical research and resulted in innovative computing applications such as for cardiology angiography research, for Jim Fries's ARAMIS rheumatology database and for Stan Cohen's pioneering drug-interaction system, MEDIPHOR. Such an advanced facility was unique for medical schools of that time, and it is a credit to the vision of Josh Lederberg that it was centered in the Department of Genetics.

In parallel with the ACME work, Lederberg's own interests focused increasingly on the frontiers of symbolic studies of molecular structures. Starting in the mid-1960s, an extensive series of papers appeared on the topic of mechanizing inductive inference in organic chemistry—centered on the DENDRAL project. Under unusually close and productive interdisciplinary collaborations with computer scientists Ed Feigenbaum and Bruce Buchanan, and with chemist Carl Djerassi, an unprecedented line of work was begun, based on an initial concept Lederberg himself developed starting in 1963, to completely and non-redundantly enumerate and label graphs representing possible isomeric structures for arbitrary molecules. As Josh himself reflected in 1987, "My interest in AI has little to do with my background as a biologist, a great deal with curiosity about complex systems that follow rules of their own, and which have great potentialities in preserving the fruits of human labor, of sharing hard-won traditions with the entire community. In that sense, the knowledge based system on the computer is above all a remarkable social device, the ultimate form of publication." (**http://profiles. nlm.nih.gov/BB/A/L/Y/P/_/bbalyp.pdf**)

Out of this extraordinary vision of computing applied to discovery in real-world science came still another generation of computer systems centered in the Lederberg Department of Genetics—the national SUMEX-AIM resource, under computer scientist Tom Rindfleisch. The beginnings of wide-area computer networks around 1970 under DARPA, along with NIH's promotion of nationally shared resources under their Research Resources Program, led Lederberg and his colleagues to imagine communities of scientists, and not just computer scientists, collaborating on research by means of these new tools. The SUMEX-AIM resource that he created in the early 1970s focused on developing symbolic computing tools for artificial intelligence research and network communications to facilitate remote collaborations based on shared interests rather than the happenstance of shared geography. SUMEX was the first non-DOD node on the ARPANET and forged new technologies as the Internet and local area networks took hold and changed forever the way computing systems are organized. This community, spanning 20 projects at 6 universities, produced many of the best-known early AI systems in biochemistry, molecular biology, and clinical medicine, as well as fundamental distributed computing tools for Internet routing, email and network interest group services, personal computing, information retrieval, multiprocessor systems, and tools for open, machine-independent software development.

Part of the great influence of SUMEX-AIM derived from its intrinsically interdisciplinary and collaborative character and its being imbedded in a fully functional Genetics Department, where Lederberg's continued interest in microbial and mammalian genetic mechanisms drew together a highly interactive group of fellows and faculty located both within the Department and in the Stanford Medical School as a whole. As he arrived at Stanford at the end of the 1950s, Lederberg and other medical school luminaries pressed the school to establish mechanisms that would increase collaborations between

basic science and clinical faculty members. This belief that the future of medicine and medical teaching lay in such collaborative interactions, and his continued work in fostering such interactions, laid key groundwork for the development of what is now known as translational medicine.

In his own department, Lederberg was similarly eclectic. Although he had just recently won a Nobel Prize (1958) for his work in microbial genetics, he established only a small laboratory dedicated to work in this area. Instead, he made his first appointment in the nascent field of somatic cell genetics, choosing a peripatetic investigator (Len Herzenberg) who had worked with Neurospora at Caltech, E. coli at the Pasteur Institute, and mammalian cell cultures at the NIH, to head a laboratory in which this new technology would be exploited in genetic studies.

Lederberg made his next faculty appointment several years later, choosing Walter Bodmer, who had trained with human genetics and statistics giant R.A. Fisher. Population geneticist Luca Cavalli-Sforza visited in the department about this time, and returned later to join as a permanent faculty member. Lederberg later enlarged the department further by appointing Stanley Cohen of Cohen-Boyer fame, mitochondrial expert Doug Wallace, and Lawrence Korn (later a PBL co-founder). But in the very early years, he restricted the permanent Genetics faculty to two members (Herzenberg and himself) and filled the space allotted to the Department with an outstanding series of visiting scientists who worked more or less directly with him. This was a deliberate strategy on Lederberg's part, emphasizing the "flow-through" of excellent young researchers with their excellent new ideas. He tried to duplicate this approach later, when he became president of The Rockefeller University in 1978, for the various departments there but with only limited success because of faculty resistance.

Walking through the department corridors at this time, one would find people doing computer science and knowledge engineering research juxtaposed with engineers building prototypes of exobiology gadgets that could be used to detect life on Mars. Right next door, or in the same ping-pong and lunch room, one would find wet lab biologists studying cancer cells or transplantation immunology or microbial genetics. It was "an amazing environment," as Len Herzenberg describes it. "Everything was integrated through and around Lederberg, who seemed to know everything that was going on."

Among the very early research paths, Lederberg recruited several immunologists to focus on testing the validity of clonal selection as the underlying mechanism determining the specificity of the antibodies produced in response to pathogen invasion. In the late 1950s, he had gone to Australia to work with Sir MacFarlane Burnett, a well-known immunologist who was at the time the head of the Hall Institute in Melbourne. Although B cells and T cells were yet to be recognized and distinguished functionally from one another (in part by "Sir Mac's" students and fellows), Sir Mac had already formulated the idea that an individual (B) cell becomes committed to the production of a single antibody molecule that specifically binds a particular antigenic structure. He and Lederberg expanded this idea, considering it in the context of bacterial selection, to emerge with the concepts of antigen-mediated clonal selection that still govern our basic ideas about how antibody responses are organized.

The competing hypothesis at the time viewed individual antibody-producing cells as more plastic and able to produce antibodies that recognize several distinct antigenic structures. To determine which hypothesis was correct, Lederberg brought Gus Nossal from Melbourne and Olli Makela from Finland to Stanford to do a series of difficult but definitive micromanipulation studies that ultimately validated the clonal selection premise by showing that individual antibody-producing cells from animals immunized with a mixture of antigens each produce antibodies that react with only one of the immunizing antigens. These findings, which provided the first indication that the

structure of the antibodies produced by an individual antibody-producing cell is inherently defined, introduced genetic mechanisms into concepts of how immunity develops and hence opened the way to the modern molecular understanding of how antibody and T cell receptor structures are generated.

In addition to Nossal and Makela, Lederberg attracted immunologist N.A. (Avrion) Mitchison and cancer biologists and immunologists George and Eva Klein to the department in its early years, creating an environment where genetic approaches to working with, and thinking about, the cells and processes in the immune system became commonplace. Clinicians like radiologist Henry Kaplan of Hodgkin's disease fame, cardiac transplantation surgeon Norman Schumway, lupus specialist Halsted Holman were drawn into the arena and regularly attended a weekly tissue and organ transplantation seminar that Lederberg asked Herzenberg to run. Caught up in the immunology cum genetics excitement, Herzenberg switched his research focus from selecting drug mutants in neoplastic cell lines to exploring naturally expressed mammalian cell surface markers (H-2, now aka MHC Class I) that could be detected and selected, as his first fellow pediatrician and geneticist (Howard Cann) showed, with antisera raised in one mouse strain against cells derived from another.

Joined at this time by his wife, Lee, Herzenberg rapidly completed several MHC-related projects, beginning with the demonstration that H-2 antigens are cell surface proteins rather than adherent DNA, as had been thought at the time. However, he and Lee soon extended their immunological explorations to include mouse immunoglobulin polymorphisms (allotypes), with which they defined the series of closely linked loci that individually encode immunoglobulin heavy chain (IgH) structures expressed, respectively, in each of the IgH isotypes (e.g., IgM, IgG, IgA). Similar findings by Henry Kunkel working with human immunoglobulin polymorphisms soon led to the recognition that the IgH chromosome region is highly con-

served and thus laid the groundwork for today's molecular understanding of how IgH structures are defined.

Lederberg's decision to place the Herzenbergs in a laboratory right next door to Nossal and Makela, and to locate Avrion Mitchison in the immediate neighborhood a year later, likely reflected his belief that these young people would do well to collaborate in the development of genetic concepts in immunology. His decision to locate his exobiology engineers in the same corridor was perhaps more fortuitous and fateful, both in terms of the Herzenbergs' future and the future of immunological sciences. As Len Herzenberg watched the painfully slow separation and functional testing of individual antibody-producing cells in the Nossal and Makela laboratory, and as he and others in his own laboratory struggled to work with immunoglobulins and other cell surface antigens expressed on subsets of cells in the immune system, he began to formulate the idea of developing a cell-sorting device that would let him use these surface antigens to isolate and study cells. However, this idea might have suffered a premature death were it not for his daily contact with Lederberg's engineers and computer scientists working "down the hall," and with whom Herzenberg ultimately collaborated to develop the Fluorescence Activated Cell Sorter (FACS).

The physicians and scientists who gravitated to the immunology group Lederberg built in the Genetics Department also encouraged the development of this key instrument, which has been used for years in basic studies and has more recently become central to medical practice in a variety of areas, ranging from HIV disease monitoring to bone marrow and stem cell transplantation. The initial instrument was based on the addition of fluorescence detection to a sorting device developed by Mack Fulwyler and colleagues at Los Alamos National Laboratory. Hugh McDevitt, Sam Strober, Garry Fathman, and Irving Weissman were among the early users. Lederberg blessed this collaborative effort, which continued for many years as the immunologists and geneticists devised new

needs and uses for the instrument and Herzenberg, with the engineers and computer scientists in Lederberg's group, devised new ways to meet these needs.

Although the FACS is often discussed in terms of its importance to immunology, cell biology, and medicine, it is arguably the first biotech instrument and well predates the development of other technologies focused on detecting gene expression in a variety of contexts. In its infancy, it suffered from a paucity of reagents that were specific for individual gene products. However, with the introduction of monoclonal antibodies as FACS reagents and the coincident beginning of the molecular era, it came into its own. It is no accident that this instrument was developed in a department that fostered interactive, interdisciplinary research and put a high value on creative, out-of-the-box thinking.

The breadth of Lederberg's interests, the ways in which he encouraged collaborations among the people who shared aspects of those interests, and the ways in which he challenged us all to go further and do more generated a legacy of achievement that far exceeds his credited accomplishments. It is to this legacy that we pay homage today. The work discussed above barely begins to touch upon his interests in biology and medicine, many of which found a place in the Department he created. Lederberg similarly had an intense interest in and made extraordinary contributions to the development of U.S. government science policies and strategies related to major disease epidemics and biological attacks. His interests in information technology were equally broad and visionary.

Josh's scientific approach to computing and his emphasis on methodological development, together with his creation of successive environments in which great theoretical and experimental computer science work could be done, exemplify this legacy. In his early years he helped to create this field, and in his later years he continued to challenge it. In his comments for an oral history interview collected by the U.S. National Library of Medicine (NLM), he notes, "One principle I'd like to have my name attached to, Lederberg's Principle, is that machines will become really smart only when they can directly read the literature and spend some time living in the real world, where the survival of the fittest is what will determine who's out there. As long as we have to spoon feed them, datum by datum, they're going to be evolving in a very cumbersome and costly way indeed."

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**Errata**

An online log of corrections to *Annual Review of Genetics* articles may be found at http://
genet.annualreviews.org/errata.shtml