



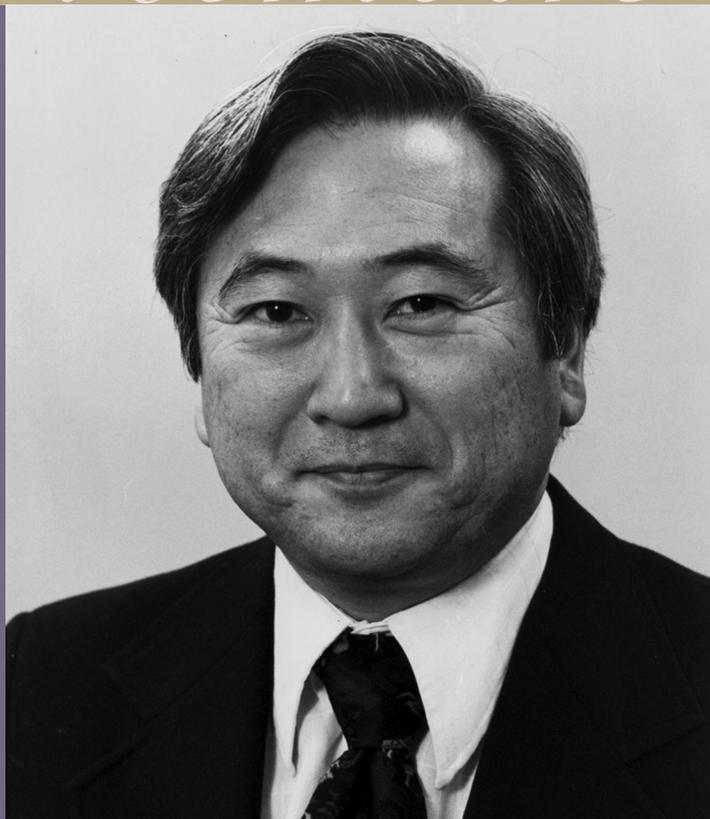
Roy H. Doi  
1933–2017

BIOGRAPHICAL

*Memoirs*

*A Biographical Memoir by  
Martina Newell-McGloughlin*

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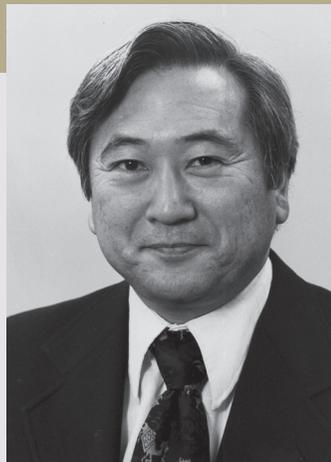
NATIONAL ACADEMY OF SCIENCES

# ROY HIROSHI DOI

March 26, 1933–October 9, 2017

Elected to the NAS, 2006

Roy H. Doi was one of those rare individuals who packed many lives into one lifetime. Over a long career in microbiological research he attained some of the pinnacles of achievement in his field. Through decades of studying gene activity in *Bacillus subtilis*, Doi made pioneering advances in the understanding of the mechanisms of RNA polymerase, sigma factors, ribosomes, transfer RNA, and other elements of bacterial gene expression. In mid-career he turned his focus to a second type of bacterial machinery, the cellulosome, a complex of enzymes and anchoring proteins secreted by several bacteria that breaks down cellulose and other components of the plant cell wall into sugars. Later he made a final career shift, toward biotechnology, an area in which he engendered a broad array of programs to promote this relatively new field. Doi began his undergraduate study at Placer Junior College in Auburn, California, then transferred to UC-Berkeley, where he took a bachelor's degree in physiology in 1953. After army service from 1953 to 1955, he returned to Berkeley and earned a second bachelor's in bacteriology in 1957. He followed these with an M.S. (1958) and a Ph.D. (1960), both in bacteriology, from the University of Wisconsin. After a three-year post-doctoral stint at the University of Illinois, he got his first faculty position at Syracuse. In 1965 he became an assistant professor at UC-Davis, where he spent the rest of his career.



*Roy H. Doi*

By Martina  
Newell-McGloughlin

While we are all shaped to varying degrees by our life experiences, it could be said that Roy H. Doi's life experiences were richer and more impactful than most. He grew up just a few miles from where he spent most of his career, in the town of Loomis, California, near Sacramento, but he travelled a lifetime of experiences over those few miles. Roy was the son of Japanese immigrants and began his working life by helping out his migrant-farm-worker father, mother, and five siblings in the fruit fields of the Sacramento valley. As tough as that life was, it got immensely more challenging when Roy

was nine years old and the family, along with over 100,000 other citizens of Japanese descent, become the victims of the U.S. government's post-Pearl Harbor internment policy. Japanese Americans on the West Coast were forced to sell their businesses and belongings, removed from their homes, and interned in remote and inhospitable camps. In Roy's family's case the camp was initially Tule Lake, California, and, subsequently, Heart Mountain, Wyoming. His father had to abandon everything, even selling the family car for \$50, as they were allowed to only take what they could carry.

Ever the stoic, Roy was not bitter about this treatment, even when life did not get much better after the family was released more than three years later. The hostility towards his ancestry persisted, and he took refuge in the library, reading over 100 books the first year after his return home. One of those books, "*Microbe Hunters*" by Paul de Kruif, spurred an interest that shaped his future career. Studying bugs, however, did not have the familiarity or stature of being prestigious, like a medical profession, in his family's eyes. So he began college as a pre-med student. After two years at Placer Junior College, in Auburn, Roy transferred to the University of California, Berkeley, where he completed a degree in physiology in 1953.

In another nod to the hand of fate, the country was in the midst of another war, this time in Korea, and Roy was drafted into the army upon his graduation from Berkeley. Fortuitously, this second career detour also contributed to his ultimate life's direction. While stationed in North Carolina he was assigned to a genito-urethral research project ward where GIs returning from Korea with STIs were treated. During a discussion with a colonel as to whether some soldiers were faking symptoms to gain a discharge, Roy deduced that the symptoms were most probably due to an infectious agent or agents, which, of course, was subsequently proven with over 30 bacterial, viral and parasitic agents shown to be responsible for STIs. This observation piqued his interest in microbial research.

As yet more Charons of fate carried him along, he was transferred to Japan and assigned to a medical unit studying viral Japanese encephalitis. He became part of a team searching for virus-harboring mosquitoes, aiding researchers studying their life cycle. He was pretty clear by then, having been banged over the head by the fates, that he should become a microbiology researcher. But when enquiring as to how, exactly, one accomplished this and was told he had to go to graduate school, he wondered—what was graduate school.

After getting the answer, he returned to Berkeley to garner another undergraduate degree, this time in bacteriology, and from there he proceeded to grad school at the University of Wisconsin—supplier of much of the UC-Davis Biochemistry and Biophysics Department’s faculty in the 1960s. His research, under the supervision of noted professor Harlyn Halvorson, focused on the metabolism of bacterial spores, and he earned his Ph.D. in this subject in 1960. This focus on bacterial spores would define the first half of Roy’s career and would bring him professional recognition around the world.

Roy’s next career move was to a postdoctoral position with the eminent microbiologist Sol Spiegelman at the University of Illinois. Spiegelman worked on the replication of the small RNA bacteriophage  $\phi\beta$ , particularly in vitro replication of  $\phi\beta$  RNA and deletion mutants thereof, which came to be termed Spiegelman’s monsters. This is where Roy learned his first molecular biology techniques, especially mastering some of the early applications of DNA/RNA hybridization. Roy always claimed that working with Sol is where he learned his real work ethic, with anecdotes of Sol calling him on Thanksgiving or Christmas checking for updates! He was thankful to Sol for exposing him to many others in the pantheon of pioneers in the emerging field of molecular biology, and he was especially grateful for being able to accompany Sol to the 1961 meeting at Cold Spring Harbor on Cellular Regulatory Mechanisms, where many of this pantheon were present, including the “fathers” of the Operon, François Jacob and Jacques Monod.

When Roy founded his own laboratory at Syracuse University in 1963, he reverted to his Wisconsin focus on sporulation—spore production—but adopted and adapted many of the techniques learned in the Spiegelman laboratory. He realized that *Bacterium subtilis* provided a prokaryotic—that is, typically one-celled and having no nucleus or membrane-bound organelles—developmental biology model. Applying some of those newly learned techniques, especially DNA/RNA hybridization, he made a number of seminal discoveries on the appearance of new families of messenger RNA during sporulation. That is, he demonstrated that differential gene expression was an essential ingredient in spore formation. In achieving this, he was one of the first to demonstrate the phenomenon of differential gene expression, and, indeed, he presaged the recognition that a plethora of RNA family players are involved in gene expression, although none of this was recognized for the breakthrough it was at that time.

In 1965 Roy got the opportunity to return to the familiar locale of his childhood when he was appointed as an assistant professor at the University of California, Davis. There he built on his Syracuse discoveries on bacterial sporulation, becoming a shaper of the entire



Roy Doi received a lifetime achievement award at the UC Davis Biochemistry and Molecular Biology Colloquium in 2008.

field. Among his many contributions was his finding that sporulating bacilli contain multiple forms of RNA polymerase. This finding led to his discovery that, contrary to contemporary thinking, multiple protein factors, designated sigma factors, direct RNA polymerase to synthesize different sets of messenger RNAs. He was also one of the first to demonstrate that the ribosomal RNA sequence of different bacillus species was conserved, a concept later exploited by the team that used 16s ribosomal RNA conservation as the basis for establishing Archaea as a completely separate kingdom of life!

Although Roy had been at the forefront of research in bacterial expression systems during the course of the evolution of molecular biology, his own interests and research pivoted directly to biotechnology in 1989. That year Roy was appointed chair of a committee tasked with assessing the biotechnology programs at Davis. He had just taken over as Director for Biotechnology for the College of Agriculture and Environmental Sciences following the passing of plant pathologist and founding director Tsune Kosuge. This is when I first met Roy in person, having known him by reputation for many years, when he recruited me to help run the program as the associate director.

The biotechnology program was embryonic at the time but had grand ambitions. We came up with the motto “Biotechnology: The Tools to Forge a Better Tomorrow.” With this in mind and under Roy’s able leadership, we created a system that went on to become a major influence and programmatic trailblazer on the Davis campus and, ultimately across the UC system, since the training and leadership skills that I learned from Roy enabled me to pursue and win the University of California Systemwide Biotechnology Program (which covered all ten UC campuses and the three national labs) for UC Davis, taking it away from UC Berkeley!

One of our first activities was applying to the newly created NIH pre-doctoral Training Grant Program, designated a T32 program and created to “produce broadly trained investigators who have the facility and orientation to combine basic and applied research.” We successfully gained one of those highly competitive awards in 1991, being, at the time, one of only three in California, and 11 in the whole country.

We went a step further than normal T32-type training in partnering with the local biotechnology industry, obtaining industry fellowships for the trainees and requiring that the trainees do internships with the industry partners. This ensured that the students were exposed to the culture and rigors of working in an industrial setting. Some students, at first, went reluctantly to their company internships. Whatever the initial perspective of the faculty trainer and the student, however, virtually all students returned extolling the value of their training experience. They learned how to work in teams towards a common goal. They shared the new approaches and new techniques they had learned in industry with their Davis colleagues.

For this, among other reasons, even the faculty mentors saw the industry sojourn of their students as a net gain, although some trainees returned spoiled by the experience of using fabulous instruments not available at Davis and of having media and other solutions provided for them and expecting the same on their return to college! Some unexpected hurdles arose. For example, following one particular incident when a student presented her thesis committee with a non-disclosure agreement, some faculty were rather nonplussed at what they saw as contravening the notion of academic freedom and collegial sharing of knowledge. We solved that problem by having students work on non-proprietary projects to avoid intellectual property issues and allow freedom to publish.

From the successful outcome of this training we decided that we should formalize the program, and we purloined an idea from the humanities to create a “Designated Emphasis in Biotechnology” (DEB), which would allow students to have an official designation on their degree indicating that they had received interdisciplinary training and had industrial research experience, giving many an advantage in pursuing their careers.

Roy was a dedicated mentor to graduate students. He was well-tuned to each student’s stage of development and provided supervision appropriately. His greatest impact on graduate education at UC-Davis, however, was probably through his leadership of the Biotechnology Program. Under the more recent able leadership of Bruce Hammock and Judy Kjelstrom, the DEB program now trains students from 29 affiliated Ph.D. programs across the campus. As of 2017, the DEB has approximately 230 students enrolled and about 250 alumni. Each year, approximately 40 DEB students are placed in internships, with between 15 and 20 percent of them getting jobs with their industry partners upon graduation. Since that first NIH grant in the early ’90s, the Biotechnology Program has won federally funded doctoral training grants benefitting more than 80 graduate

students. Additionally, an undergraduate biotechnology major was created within the College of Agricultural and Environmental Sciences. So the seeds planted by Roy have blossomed into a mighty forest.

Roy's leadership of the Biotechnology Program also greatly benefitted UC-Davis faculty members, as well as instructors at area community colleges and high schools. The program created courses in proteomics, bioinformatics, and other current research areas to serve UC-Davis faculty members and researchers at local companies. Many courses anticipated future trends and were offered before the techniques became mainstream. For example, at the first offering of a bioinformatics course in the early 1990s, one feedback form noted that, before taking the course, the individual thought that Phred and Phrap—DNA-base calling and sequence assembly programs—were characters from Sesame Street!

Roy emphasized the importance of public outreach to the local community college and high schools. Given his own start at Placer Junior College, he understood that community colleges can provide opportunities for young people who may be interested in a career in science but have no notion as to what graduate school might be! Grants from the National Science Foundation supported a number of “train the trainer” programs with local community colleges and high schools. Many teachers and lecturers have taken their training back to their home institutions and incorporated what they learned into their curricula, inspiring the startup of many biotechnology initiatives around the state. Roy thus influenced generations of students, and some have been inspired to follow in his footsteps.

While directing the Biotechnology Program, Roy was motivated to switch his own research to a more applied-biotechnology focus. He learned that the California legislature was about to outlaw rice-straw burning by 2001. Roy proposed that enzymatic degradation could replace burning and that he could develop a system to accomplish this objective. He chose the then recently discovered sporulating bacterium *Clostridium cellu-*



George Breuning, Don Carlson, Martina McGloughlin, Roy Doi, Judy Kjelstrom, and Alan Bennett.

*lovorans* as his model, as it produces copious amounts of extracellular cellulolytic enzymes that assemble into a large complex. This complex of enzymes and anchoring proteins is secreted by several bacteria, which enables them to degrade cellulose and other components of the plant cell wall into sugars. Over the next decade, Roy was largely responsible for building a comprehensive picture of a scaffolding protein, called CbpA, and of the multitude of cellulases that dock with it, together known as the cellulosome. His contribution in this area also spurred the interest of the local enzyme company Novozymes, and he developed a strong working relationship with them, even working with their research scientists to help create a course for the DEB.

Toward the end of his research career Roy brought all the pieces together, demonstrating that *C. cellulovorans* genes can be expressed in *B. subtilis* and that the proteins will still be secreted into the medium. That finding led him to wonder whether expressing genes in multiple bacteria would also produce a functional cellulosome. Roy found that if two different *B. subtilis* strains, one expressing the CbpA docking protein and the other an enzyme component, are co-cultured, the components assemble to create a functional unit; this cooperation worked for both glucanase and xylanase enzymes. This was the first demonstrated example of bacteria cooperating to form an active enzyme, and he coined the term “intercellular complementation” to represent this phenomenon.

While seeing the obvious potential to exploit this system in the midst of the biofuel craze at that time, Roy was well aware that the focus on biofuels as sole alternatives may have been somewhat misguided. Even using all of the components of a putative biofuel plant such as corn, the cost in terms of land, fertilizer, and input energy made the energy garnered neither cost effective nor sustainable without considerable improvement in the efficiencies of the conversion process. In fact, he considered the land would be better used to grow food, given the need to sustain a burgeoning world population. However, he did have a rather interesting take on an alternative source—using the ocean as a farm to grow and harvest marine plants as a source of fuel.

Roy was ever the optimist and had a great belief that by using a collaborative approach, with experts from many complementary disciplines bringing different perspectives to the challenge, the problem could eventually be solved. Irrespective of whether such ocean farming is ever fully realized, there is no question that this understated pioneer’s contribution to the problem of low-cost degradation of cellulose and other plant components has contributed to the underpinnings of that biotechnology application.

Apart from the science itself, Roy also believed in using science to enhance public education and to inform policy development. In the '90s he was appointed a member of the influential Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health, where he often expressed some amusement that a bacteriologist was providing input on gene therapy research, but he took his assignment seriously and always provided well-thought-out opinions. He encouraged colleagues to take every opportunity to advocate for science at the local, state, national, and international levels, which resulted in his contributing, over many years, effective work with state and federal government agencies, including the USDA, USAID, DOE, DOD, and, especially, the State Department. Around the world he made the case for the value of using sound scientific principles to advance sustainable systems for the betterment of humanity. He was elected to the National Academy of Sciences in 2006.



Roy Doi. Final Days in Lab MCB UC-Davis.

In addition to his contribution to science and policy during his 40-plus years of service to UC-Davis, Roy personally mentored hundreds of students from undergraduates to postdocs, including students from many countries. Four members of the current UC-Davis faculty are products of his training, Valerie Williamson (Nematology/Plant Pathology), Chet Price (Food Science and Technology), Ronald Chuang (Med School), and even a student who began in his lab as an undergraduate, Ken Burtis, who rose to become Dean of the College of Biological Sciences and Interim Provost of UC-Davis under Roy's mentorship.

Ever the humanitarian, with compassion for the underserved or the exploited forged in the furnace of his traumatic childhood, Roy always looked out for his fellow human beings. As a young man in his first faculty position at Syracuse he demonstrated against the destruction of low-income housing. He received many plaudits for such activities over the years; in one that held special meaning for him, the UC-Davis Asian American Studies Program recognized him, in 2004, for outstanding commitment, generosity, and service to the community. And one of the most positive outcomes of his time at Heart Mountain was meeting his future wife Joan in the midst of the harrowing experience of living in an internment camp.

One sentence in Roy's memorial truly captured his spirit: "[H]e will be remembered for his intellectual curiosity, his humility, his compassion, his avid support for the Cal football team, the 49ers, and the Dodgers, his love of the arts, and his love of travel."

From my almost 30 years of knowing Roy I can attest to all of that—well, except maybe his love for the Dodgers(!)—and I remember one memorable occasion at a conference when he confessed that under his very formal suit and shirt he was wearing a Joe Montana T-shirt to honor the 49ers' last Super Bowl win! He was a true friend and colleague and, even many years after he left UC-Davis, I would invariably get a message from him every St. Patrick's Day with some interesting titbit and piece of advice (don't go to the Middle East!) and a comment about the Aran sweater I had given him many years before. To paraphrase, and conflate, Shakespeare and the translation of an old Irish saying—He was a man, take him for all that, we shall not soon see his like again.

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