Sydney Kustu

1943–2014

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

SYDNEY GOVONS **KUSTU**

March 18, 1943–March 18, 2014

Elected to the NAS, 1993

Sydney Govons Kustu was an eminent microbiologist, a driving force behind the development of microbiology on the University of California, Berkeley, campus, and a trailblazer for women in science.

Born in Baltimore, MD, her family moved to Lansing, MI, when she was 12. She proved to be a child prodigy, skipping three grades in school and receiving a multitude of honors during her youth. These honors included attending the Peabody Conservatory summer music camp for music composition, playing a piano concerto with the Lansing Symphony Orchestra at a very young age, winning the State of Michigan Detroit Free Press debate contest, for which she was not only the youngest but also the first female to do so, and being awarded a National Merit Scholarship.

At the early age of 15, Kustu began her undergraduate studies at Radcliffe College, still considered Harvard's "coordinate institution for female students" at the time of her matriculation. The institutions soon merged, and when Kustu received her B.A. in General Studies in 1963 she was among the first females to earn a baccalaureate degree from Harvard University.

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After graduating from Harvard, Kustu spent two years as a technician in the laboratory of Saul Roseman at the University of Michigan, where she was trained in the purification and kinetic characterization of enzymes (Roseman was elected to the National Academy of Sciences in 1972). She earned her doctorate in biochemistry with Professor Jack Preiss at UC Davis in 1970. He considered her "one of the brightest if not the brightest of the over 100 researchers (postdoctoral scholars, sabbatical professors and 30 graduate students) present in my laboratory in my 45 years as an active faculty member."

Kustu joined the laboratory of Professor Giovanna Ames at UC Berkeley after completing her doctoral thesis. Ames found Kustu to be "a superb experimentalist with

golden hands." She observed that Kustu's "intuition and expansive view of scientific matters turned all experiments into a perfectionist's game of foreseeing all possibilities and complications, addressing them in advance, and composing an experiment somewhat like a piece of music."

Sydney Kustu as a freshman at Radcliffe College, 1959. (Photo used by permission, Harvard University and Radcliffe College Archives.)

Beginning her career at Davis: discovery of the Ntr system

In 1973, Kustu was hired as an assistant professor of bacteriology at UC Davis, and in 1984 she became a full professor. It was during her time at Davis that Kustu began her pioneering studies of nitrogen metabolism. In addition to launching her research and teaching career, she assumed a prominent role in promoting and co-organizing the West Coast Bacterial Physiologists annual meeting held at the Asilomar Conference Center in Pacific Grove, CA. Kustu continued in this capacity for the greater part of the next two decades. In 2011, these efforts were recognized by a special symposium organized to honor Kustu and her many contributions to microbial physiology.

"While at Davis, Sydney established herself as a skilled, articulate, admired teacher," said professor emeritus John Ingraham, speaking on behalf of the university's Department of Microbiology and Molecular Genetics. This perception was confirmed by former students, who applauded Kustu's high standards and dedication to science—her "higher calling." She was also known for her insistence on clear and concise writing.

After establishing her own laboratory as a faculty member, Kustu consistently worked with a small research group. This arrangement was successful and enabled her to make lasting contributions to microbiology such that her work is now part of the fabric of knowledge of bacterial genetics, metabolism and nutrition.

From the outset of her career Kustu applied the power of a genetic approach to answer biochemical questions. Her major research achievement was unraveling the complex

Sydney Kustu at the UC Davis graduation of an early student, Nancy McFarland, 1981. (Photo courtesy Nancy McFarland.)

interconnected mechanisms that regulate nitrogen utilization by bacteria. She had found that strains of *Salmonella typhimurium* selected for their being able to utilize D-histidine in place of the L isomer frequently resulted from mutations affecting the activity of glutamine synthetase, a central enzyme in the pathways of nitrogen utilization. This genetic tool led her to investigate the regulation of nitrogen utilization, then an active area of research led by Boris Magasanik at the Massachusetts Institute of Technology (Magasanik was elected to the National Academy of Sciences in 1969).

Magasanik held that glutamine synthetase was its own transcriptional regulator as well as the key enzyme of ammonia assimilation. But, in a series of paradigm-altering papers, Kustu and her students showed that this hypothesis was not correct. Rather, as the Kustu team discovered, regulation of the synthesis of glutamine synthetase and utilization of the various sources of nitrogen available to a bacterium is mediated by a consortium of three regulatory proteins. These proteins interact to activate or repress the synthesis of enzymes that catalyze the various routes of nitrogen utilization appropriate to extant environmental conditions. Kustu named the three proteins NtrA, NtrB and NtrC (for nitrogen regulatory), and with her discovery of the so-called Ntr system she had solved a fundamental puzzle of nitrogen regulation. Shortly before leaving Davis, Kustu reported that NtrA was one of the first examples of an alternative sigma factor. In later work this protein was often referred to as RpoN or sigma 54.

Discovery of the Ntr system naturally brought Kustu into competition with Magasanik, who did not appreciate being shown to have misinterpreted some of his findings. The competition was fierce, and it pushed both of them. Although Magasanik's initial response to Kustu's intrusion on his territory was unkind, he grew to appreciate the high quality of her research, and ultimately the two became friends. Magasanik addressed his

relationship with Kustu in a memoir. Coincidentally, they died within three months of each other, Magasanik at the age of 94.

Move to Berkeley: developing NtrB and NtrC into a paradigm for two-component systems

Kustu's move to UC Berkeley in 1986 coincided with two important discoveries concerning NtrB and NtrC. Analyzing the sequences of bacterial regulatory proteins, Frederick M. Ausubel and coworkers discovered the existence of "two-component systems," and NtrB and NtrC were among the founding members of this family of protein-pairs. Simultaneously, Magasanik and Alexander Ninfa found that NtrB activates NtrC by phosphorylating it. Because this finding revealed the basic mechanism of signal transduction by which two-component systems operate, virtually overnight the Ntr system became a paradigm for understanding a huge swath of bacterial signal transduction.

Following up on these reports, Kustu showed that the phosphorylation site in NtrC is within its conserved amino-terminal domain—the domain shared with other so-called "response regulator" proteins of two-component systems. She also made the unexpected discovery that phosphorylated NtrC is subject to dephosphorylation by two pathways. One of them, termed the autophosphatase, had a half-time of about four minutes; the other, called the regulated phosphatase, required several additional factors, including NtrB, and was about 10 times faster. Subsequent characterization of other two-component systems in many labs would reveal that phosphatase activities are the rule rather than the exception. Dephosphorylation is important for turning off a response that is no longer needed, and for preventing different two-component systems from interfering with each other through a process called crosstalk.

Kustu's interests then turned to the mechanism by which NtrC activates transcription by RNA polymerase containing the *ntrA* product, sigma 54. Dissection of this mechanism presented a huge technical challenge. On the one hand, NtrC must be phosphorylated to activate transcription. On the other hand, the autophosphatase activity made it essentially impossible to purify the phosphorylated protein or to control its amount after purification. Kustu circumvented this problem, in her typical fashion, by using a mutant form of NtrC that is capable of activating transcription in the absence of phosphorylation. Constitutively active NtrC variants could be selected for by challenging a strain that lacks NtrB (and thus cannot phosphorylate NtrC) to grow on a poor nitrogen source.

In a series of elegant papers, several produced with colleagues at UC Berkeley, Kustu answered a number of fundamental questions related to transcriptional activation by phosphorylated NtrC. Collectively, these findings helped to make NtrC one of the best-understood transcription factors in all of biology. Kustu showed that NtrC catalyzes the isomerization of closed "recognition" complexes between RNA polymerase and a promoter to open complexes in which a short region of DNA at the transcriptional start site is denatured and thus available to serve as a template for mRNA synthesis. To catalyze open-complex formation, NtrC must hydrolyze ATP, something very unusual for a transcriptional activator. ATP hydrolysis is needed because open-complex formation by RNA polymerase containing sigma 54 is thermodynamically unfavorable even at 37°C. At least one explanation for why NtrC must be phosphorylated before it can activate transcription is that phosphorylation enables the protein to assemble into a large oligomer that is capable of ATP hydrolysis.

The Magasanik group discovered that the DNA binding sites for NtrC at the promoter for *glnA* (which encodes glutamine synthetase) are enhancer-like in that they still facilitate transcriptional activation when moved over a kilobase from the promoter. The question of how NtrC communicates with RNA polymerase over such a large distance intrigued Kustu. The answer, as she soon found out, is that NtrC bound to its DNA sites interacts directly with RNA polymerase bound to the promoter; this interaction takes place by means of a DNA loop that brings these two proteins together. The activation loop forms spontaneously at the *glnA* promoter, but Kustu discovered that loop formation requires a DNA-bending protein that binds to a site located between the enhancer and the promoter in a related system (transcriptional activation by NifA at the *nifHDK* promoter.) Although we now take the idea of DNA looping for granted, it was a relatively new concept at the time. Thus, both Magasanik's discovery that the binding sites for NtrC behave like eukaryotic enhancer elements and Kustu's unambiguous demonstration of DNA looping, garnered a lot of attention.

Kustu had a long-standing and highly productive collaboration with David Wemmer, a structural biologist in UC Berkeley's Department of Chemistry. Together they determined the structures of various domains of the transcriptional activator NtrC. But one structure that for many years eluded them, and indeed the entire field, was a high-resolution picture of a receiver domain of a response regulator in its phosphorylated (activated) state. The underlying difficulty, as alluded to above, is that the phospho-aspartate linkage in these proteins is labile. Kustu's lab broke the impasse with the discovery that

beryllofluoride binds to the phosphorylation site in NtrC and other response regulators in a manner that mimics phosphorylation. This discovery led directly to the high-resolution structures of several receiver domains in their phosphorylated conformation, including NtrC's.

Kustu's interest in the Ntr system naturally segued into an interest in regulation of genes required for biological nitrogen fixation (*nif*). In many bacteria, NtrC activates transcription of the *nifLA* operon, which encodes a transcriptional activator (NifA) and a negative regulator (NifL) that inactivates NifA in response to O_2 and combined nitrogen. Little was known about the details of NifA and NifL functions when Kustu and her colleagues took up this problem. Making headway required overcoming the solubility issues that had bedeviled previous attempts to purify NifA for biochemical studies. Initially, Kustu circumvented the purification requirement by generating and assaying NifA in situ, using a coupled transcription-translation system. It was subsequently discovered that NifA (or its domains) could be purified in an active form if it was fused to the maltose-binding protein, which improved solubility and provided an affinity handle for purification. These approaches led to a number of insights into the mechanism by which NifA activates transcription of *nif* genes and the means by which NifL antagonizes NifA activity in response to oxygen and combined nitrogen.

Later years at Berkeley: the Rut pathway and ammonium transport

Although Kustu is perhaps best remembered for her molecular dissection of the Ntr system, she was first and foremost a bacterial physiologist. She made elegant use of chemostats to demonstrate that enteric bacteria perceive nitrogen limitation as a decrease in the pool of cytoplasmic glutamine. These studies also led her to the realization that an accumulation of potassium in response to high external osmolarity requires that the bacteria be able to synthesize sufficient glutamate as counter ion. Kustu eventually turned to questions of how bacteria obtain and metabolize various nitrogen-containing compounds.

An early adopter of DNA microarray technology, Kustu used this technique to determine the full extent of the Ntr regulon. Hers was a "textbook" study for its use of mutant strains, rather than different growth media, to manipulate the activity of a regulatory system. Two operons under NtrC control that were found to be highly induced in response to nitrogen limitation—the *glnK-amtB* operon and a cluster of seven open reading frames now known as the *rut* operon—became the focal points of Kustu's research during her final decade at Berkeley.

It is rare to discover a major metabolic pathway in present times, particularly in *Escherichia coli*. The presence of the aforementioned NtrC-controlled operon containing seven genes of unknown function caught Kustu's attention. Her research group showed that this operon encoded a new pathway for pyrimidine degradation, and named the genes of the operon *rutA–rutG* for pyrimidine utilization. This same study also identified a divergently transcribed regulatory gene, *rutR*, whose protein product represses *rut* operon expression in the absence of pyrimidines. Kustu would next collaborate with her longtime associate David Wemmer to explore the functions of the Rut proteins. Their work revealed a pathway that employs novel chemistry to degrade pyrimidines, and it highlighted the toxicity problems caused by this unusual catabolic process.

Kustu also devoted considerable research effort in her later years to addressing how bacteria acquire ammonium. Because this compound is the preferred nitrogen source of many microorganisms, the manner by which it crosses cell membranes is of great physiological importance. Whereas the protonated form of ammonium (NH_4^+) is membrane-impermeant, the uncharged species (NH_3) readily diffuses across cell membranes. The rate of NH_3 diffusion provides sufficient nitrogen for optimal growth when the ambient ammonium concentration is high. In low ammonium environments, where such diffusion becomes growth-limiting, protein-mediated ammonium transport by members of the Amt family of channels is required to sustain cell growth. Both the transport mechanism of Amt proteins and the form of ammonium they carry, NH_3 or NH_4^+, were unknown when Kustu began her studies of ammonium acquisition in enteric bacteria.

Working with the *S. typhimurium* and *E. coli* AmtB proteins, which are encoded by the second gene of their respective *glnK-amtB* operons, Kustu gained important insights into how Amt ammonium channels function. Her research group's initial findings demonstrated that the absence of AmtB results in a pronounced growth defect when the ambient ammonium level is low. This phenotype was then exploited as the basis for a genetic selection to isolate suppressors that restored function to inactive AmtB mutants. Kustu used one such suppressor to show that AmtB concentrates the ionic form of its substrates in response to the electrical potential across the cell membrane—a pivotal finding, as it helped settle debate about whether Amt proteins transport NH_3 or NH_4^+. Following this discovery, the genetic selection was used successfully to examine the roles that key amino acid residues and domains play in Amt protein function.

Sydney Kustu with former students and postdoctoral scholars at the 2011 West Coast Bacterial Physiologists Conference held in her honor at the Asilomar Conference Center Asilomar, CA.

Recognition

Kustu garnered a large number of awards during her career. She was elected a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences, the American Association for the Advancement of Science, and the American Academy of Microbiology. She was awarded a prestigious Gauss Professorship by the Göttingen Academy of Sciences and a Miller Professorship by UC Berkeley. She also was honored with a MERIT (Method to Extend Research in Time) award from the National Institutes of Health (NIH), which recognizes researchers who have demonstrated superior competence and outstanding productivity and which guarantees funding for 10 years. Less than five percent of NIH-funded investigators are selected to receive MERIT awards.

An advocate for microbiology, students, and women in science

Kustu arrived at UC Berkeley during a major reorganization of the biological sciences. The department she joined, Microbiology and Immunology, was soon disbanded and its faculty scattered to various other departments. Kustu found a temporary adminis-

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trative home in the Department of Plant Pathology while also holding a decade-long (1989-1999) appointment in the Department of Molecular and Cell Biology, which was the focus of her scientific life. When the Department of Plant Pathology disbanded in 1994, Kustu joined the Department of Plant Biology. From 1989 to 1997, she helped lead the effort to revive and strengthen microbiology on campus. Her contributions culminated in the establishment of a division of microbiology within the Department of Plant Biology in 1997, and the department's name was changed to Plant & Microbial Biology (PMB) to indicate this.

Kustu continued her teaching and mentoring contributions after moving to Berkeley. N. Louise Glass, a Berkeley colleague who took Kustu's microbiology course at Davis, recalls that "Sydney Kustu was particularly beloved by undergraduates. Throughout her career, she was an effective and dedicated teacher at both the undergraduate and graduate levels. Her use of the Socratic method for teaching concepts in microbiology was particularly effective and inspiring." Madeline Ferwerda, who took a genetics class from Kustu as an undergraduate, recalls that "she was inspiring because she was aware of the social undercurrents in science, and was willing to speak about them."

Kustu was a strong proponent for young scientists and mentored numerous students and postdoctoral scholars, many of whom went on to productive careers in the United States and abroad. They often spoke of the lasting effect that Kustu had on their lives and of how her enthusiasm for science made working in her laboratory an exhilarating experience. One former graduate student, Linda McCarter, recalled that "[Kustu's] fierce intelligence unfailingly led her to the crux of every problem, her expectation for excellence was always inspiring, and her keen joy in science and the world was a great pleasure and privilege to share."

In 1993 Kustu and six other women were elected to the National Academy of Sciences, which heralds one of the highest levels of achievement for a scientist. Kustu was particularly proud of her inclusion in the Academy because, in her own words, "at one time it was forbidden fruit for women to do science." At that time, females accounted

for less than five percent of Academy membership. Since then, female representation in the Academy has more than tripled.

Likewise, when Kustu was recruited to Berkeley in 1986, only 15 percent of the campus's faculty in the biological sciences were female. The ensuing years have witnessed striking changes, and women now represent an impressive one-third of the biology faculty. Informed by her own early career experience of female scientists not always being treated as equals of their male counterparts, Kustu made a point of reaching out and mentoring every woman who joined the faculty of her home department of PMB. This led to the instituting of a mentorship program in PMB, in which all new faculty (male or female) were paired with an appropriate and supportive senior faculty member. PMB has recognized Kustu's contributions and accomplishments by establishing an endowed lecture in microbial physiology in her honor.

Sydney Kustu with post-retirement collaborator John Hayes (left) and one of the authors (Bob Buchanan) at the last seminar held in the Calvin Laboratory on the Berkeley campus, July 27, 2012. Buchanan showed a video he had filmed that highlighted the contributions of Andrew Benson and his role in the discovery of the Calvin-Benson cycle of photosynthesis. (Benson and Hayes were elected to the National Academy of Sciences in 1973 and 1998, respectively.) To view the video please visit: "A Conversation with Andrew Benson: Reflections on the Discovery of the Calvin-Benson Cycle" (online at https://www.youtube.com/watch?v=GfQQJ2vR_xE).

Personal life

In addition to her academic interests, Kustu was passionate about the arts and nature. She organized outings with friends and colleagues to Zellerbach Hall (a multi-venue performance facility) on the Berkeley campus and to museums in San Francisco, and often attended movies played at the Pacific Film Archives. She read widely. A favorite author was Grace Paley, whose short stories about the complexities of life resonated with Kustu's personal experiences. She was also attracted to Southern literature and especially favored Walker Percy and Shelby Foote. Her interest in the arts and literature was

reflected in her service on Berkeley's Library Committee of the Academic Senate. An avid hiker, Kustu made a point of taking daily long walks in and around Berkeley, especially to the UC Botanical Garden. Always gracious and likable upon first interaction, she was very supportive of those in need of comfort and assistance. She also had particularly strong feelings for the infirm and the down-and-out.

But some aspects of her personal life were less than rosy. She was a divorced mother, and loved her son, Saul, dearly. Balancing her desires to be a good parent and good scientist was a challenge. It did not help that she suffered from depression, which worsened as the years passed. This unfortunately sometimes led to angry outbursts that ended up alienating some of her colleagues. By the late 1990s it was difficult for her to attract new graduate students to her lab, a sad state of affairs for a mentor with so much to offer. Those who stuck with Kustu found that it was not always easy to deal with her, but it was always rewarding.

Last years

Kustu retired from the University of California in March 2010 after serving 37 years on its faculty (24 years at UC Berkeley, 13 years at UC Davis) and was appointed Professor Emerita. She remained active in science in the first two years after retiring, and published several papers during this time. However, in the fall of 2012 she ceased her scientific activities because of declining health and moved to Los Angeles to be close to her sisters. On March 17, 2014, Kustu made a final trip to Berkeley, where she checked into the Berkeley City Club. The following day, her 71st birthday, she took her own life. She is survived by her son, Saul Kustu of Aptos, CA, and two sisters, Roberta Glassman of Calabasas, CA and Marica Govons of Belmont Shores, CA.

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