Profile of Robert B. Goldberg

Over the next 50 years, as Earth's population races toward 9 billion inhabitants, we will need to produce more food than we have produced since the advent of agriculture 10,000 years ago (1). This challenge, warns National Academy of Sciences member Robert Goldberg, is particularly daunting given the finite and shrinking amount of arable land on which food crops can be grown. Increasing the yields of crop plants is therefore critical. With that goal in mind, Goldberg, a professor of molecular, cell, and developmental biology at the University of California at Los Angeles, has devoted his career to understanding the processes that program the life cycle of plants, with a particular focus on the genes required to make a seed. He envisions harvesting this information to engineer crops that produce more seeds, bigger seeds, and seeds with enhanced nutritional content, which could significantly enhance our food supply because the majority of the calories that people consume worldwide are either directly or indirectly obtained from seeds.

Since the early 1970s, Goldberg has kept pace with the rapid discovery, development, and application of plant genetic engineering technologies. His pioneering work may lead to solutions to some of the most pressing problems that our society faces. His findings have changed the face of agriculture by enabling the production of new hybrids, such as the widely grown canola plants that produce at least 30% more oil than their conventional inbred parents. And Ceres—the plant biotech company that Goldberg cofounded—promises to change the way we produce fuel and electricity.

A Seed Is Planted

A career in science was not on the horizon for the young Goldberg, born in 1944 and raised in an idyllic suburb of Cleveland, Ohio. "I wasn't really motivated much as a student when I was a kid," Goldberg recalls. "I was much more interested in playing baseball." When he took his SATs, he filled in his examination at random, marking the start of a life-long rebellious streak.

Uncertain of his future, Goldberg set off in 1962 for college at Ohio University in Athens, Ohio. "I thought that maybe I might go into teaching or maybe I'd go into law, because I was really interested in those [subjects] in high school," he says. Goldberg chalks these interests up to his "gift of gab." "My political science teacher used to call me the Philadelphia

Courtesy of Ann Amores.

Bob Goldberg in his office.

lawyer, because I was good at debating," he remembers.

However, upon his arrival at college, a series of serendipitous events changed everything. For one, it was the Sputnik era, a time of tremendous funding and excitement for science. However, more importantly, because Ohio University freshmen were required to take standard curricula, Goldberg enrolled in a biology class taught by botany professor Norman Cohn, who turned out to be "a phenomenal, engaging, brilliant young biology professor." What's more, Goldberg's dorm assistant, Jim Frank, was a botany major. "[Frank] lived next door to me in the dorm, and he just kept saying how exciting it was to study plants, and he took me into the field."

Goldberg soon found the intellectual stimulation he had been longing for through Cohn, who had just started an exciting new research program at Ohio University, and by spending his free time making leaf collections. What really interested him was not really plants—although he loves plants—but rather genetics, which at that time was predominantly taught in the Ohio University botany department. Goldberg had witnessed the birth of molecular genetics, with less than a decade since the discovery of the structure and semiconservative replication of DNA, and he realized that by joining the field he could address a lot of exciting questions and potentially enjoy an exciting career. So he decided to pursue a dual major in political science and botany. "From the time I was a freshman, I got serious," Goldberg says. "Instead of getting Cs, I was able to get all As because I spent 90% of my time studying."

His undergraduate experience, along with thesis research on the mechanisms by which mutagens affect genes, coalesced in his decision to earn a PhD in genetics. Not wanting to spend hours studying for and taking the GRE, Goldberg rebelled and again marked his examination at random, causing many graduate programs to overlook his application despite his excellent grades and strong letters of recommendation. The University of Arizona recognized his potential, however, and offered him full funding under a National Defense Education Act fellowship. Goldberg readily accepted the offer, intrigued by the work of University of Arizona professor Albert Siegel, who had just started his laboratory after obtaining his PhD at California Institute of Technology under the direction of Nobel laureate and molecular genetics pioneer, Max Delbrück.

Goldberg joined Siegel's laboratory in 1966 and began pursuing a PhD in plant genetics. "You could count on one hand the number of labs in the world that were actually interested in plant DNA, because of technical problems and all kinds of things," Goldberg recalls. "I decided I was going to tackle that problem." Goldberg used nucleic acid hybridization techniques to compare the differences between the genomes of different species of cucurbits—a plant family that consists of various melons, squashes, and gourds—to better understand their genome structures and evolution (2).

Getting Organized

As Goldberg's comparative analysis of the genomes of cucurbits was unfolding, two seminal papers were published that would later shape his postdoctoral research focus and ultimately his contemporary interest in gene regulatory networks. The first reported the discovery of repetitive sequences in eukaryotic genomes by Roy Britten's laboratory (3), which opened an exciting area of research into unraveling the function of these sequences. The second paper, by Britten and developmental biologist Eric Davidson, put forth a theoretical model for how repetitive sequences and other genomic elements might help regulate gene expression in eukaryotic cells (4).

Together, these papers inspired Goldberg to study not only the structure of eukaryotic genomes, but also their regulatory circuits. So he decided to pursue a postdoctorate with Davidson, a young professor who was in the process of moving his laboratory to California Institute of Technology. Soon thereafter, Britten also moved to California Institute of Tech-

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's inaugural article on page 8063 in issue 18 of volume 107.

nology. "So now I'm working with, as a postdoc, the two most important forces of understanding gene regulation and genome structure, organization, and evolution, in the world," Goldberg says. "It was probably the most important major influence on my entire scientific career. And in terms of mentorship, Eric had more influence on my scientific thinking than anybody, because he is brilliant."

At California Institute of Technology, Goldberg moved away from plants to study gene regulation in sea urchins, one of the model systems Davidson's laboratory was using. The laboratory had recently discovered that repeated DNA sequences were typically adjacent to nonrepeated sequences, in an alternating pattern (5), but the roles of the different sequences had not yet been experimentally established. Goldberg helped to solve this mystery by discovering that the genes that are active during the early development of sea urchins are transcribed almost exclusively from nonrepetitive DNA sequences (6).

Establishing Roots

At age 28, Goldberg started his own laboratory as an assistant professor at Wayne State University in Detroit, Michigan. He was recruited there by his PhD advisor, Albert Siegel, who was developing a biology department. Goldberg returned his attention to plants, applying the tools and concepts he gleaned from Davidson's laboratory. He started out studying the organization of plant genomes and found that plant genomes have repetitive sequences that are organized in a pattern similar to that in animal genomes (7, 8). "Then I started working on something that no one was working on at the time, in plants," says Goldberg: gene expression. "I knew all the procedures and how to do it, so I brought all these elegant tools of animal molecular biology, of the time, into the plant kingdom."

Goldberg also had free reign to experiment in the classroom, and it was then that he honed his teaching style. Recalling his own lack of challenge in primary school, Goldberg decided that he wanted to do something different for his students. "If I had to say what were the most creative things I've ever done in my career, it's absolutely been in the classroom," he says. "I always believed in trying to interest students. My job was really to stimulate them and make science exciting, relevant, and fun, yet still rigorous. And if that meant that I had to work 7 days a week and go without sleep, then that was the way it was going to be."

Going to Seed

Like his early path into science, Goldberg's foray into seeds was also seren-

Courtesy of Reed Hutchinson.

Bob Goldberg in the classroom teaching his class "Genetic Engineering in Medicine, Agriculture, and Law".

dipitous. By 1976, Goldberg had returned to California as an assistant professor at University of California at Los Angeles and was studying the soybean genome when he received a call from Bill Breidenbach at University of California, Davis. Breidenbach also studied soybeans, but his research focused on the storage proteins in soybean seeds. Breidenbach had read Goldberg's recent paper on the organization of the soybean genome (8) and suggested that the two collaborate to analyze the regulation of the genes encoding the seed storage proteins. Goldberg was intrigued, because at that time it was difficult to study individual plant genes unless they produced highly abundant mRNAs that could be cloned using the relatively inefficient techniques of the day. Breidenbach's storage proteins, however, composed up to 30% of the dry mass of the seed and were made from mRNAs that were about as abundant as one could find in plants. These attributes helped to ensure the success of the project (9, 10), and the fruitful collaboration marked the beginning of Goldberg's nearly 40-year journey in trying to understand gene activity in the development of seeds.

As Goldberg's early soybean studies were ongoing, his laboratory was also studying the organization of the tobacco genome, using the tobacco plant as a tool to characterize the temporal and spatial regulation of gene activity throughout the entire life cycle of the plant. His group pioneered some of the first plant genomics experiments and identified genes that were specifically expressed in the male and female reproductive organs, as well as the leaves, roots, and stems. In the mid-1980s, his laboratory identified genes that were expressed only in the male reproductive organ of the plant, the anthers (11–14).

Goldberg presented his data at a meeting in Belgium, and his work caught the attention of two scientists, Jans Leemans and Celestina Mariani, from the former biotech company Plant Genetic Sciences. The pair invited Goldberg to collaborate on a practical project to use these anther-specific genes to engineer plants for male fertility control. Male fertility control promised to facilitate the breeding of hybrid crops, which have been one of the major contributors to increased crop yields throughout the 20th century. Many plants are hermaphroditic and self-pollinate; therefore, to generate hybrids, traditionally plant breeders have manually castrated the male organs on each flower of a plant so that the remaining female organ could undergo a directed cross. Painstaking and expensive as it was, such an approach works for plants such as corn, which have large anthers, but is virtually impossible for plants such as rice and canola, which have miniscule flowers. Therefore, if Goldberg and Plant Genetic Sciences succeeded, they might be able to make hybrids in crops that never had hybrids before and to make cost-effective hybrids.

The team set out to engineer male sterility in tobacco, the plant in which Goldberg first discovered the anther-specific genes. Goldberg's laboratory cloned the promoter of one of those genes, *TA29*, and Mariani fused it to a self-defense gene from the soil bacterium *Bacillus amyloliquefaciens* called *barnase*, which encodes a ribonuclease. The researchers inserted the construct into the tobacco plant, where the cytotoxic RNase specifically destroyed the anther cells during development. The engineered plants were identical to controls except they failed to shed pollen, resulting in male sterility. The team then demonstrated the transferability of the *TA29*–*barnase* system to other plants by using it to engineer sterility in canola (15).

Goldberg and his collaborators were not content to rest after this feat of genetic engineering, because although a male-sterile line is extraordinarily useful for breeding desired characteristics into hybrid plants, it is difficult to maintain such hybrids, because they are sterile. Restoration of fertility is therefore very important to agriculture. In a Eureka moment, Mariani learned that the barnase-producing bacterium protects itself from the lethal effects of its own RNase by producing a corresponding inhibitor, called barstar. The team fused the barstar gene to the *TA29* promoter and inserted it into plants. Then they then crossed the male-fertile, barstar-producing plants with the male-sterile plants, and fertility was restored to their progeny (16). The team had succeeded in creating a method to regularly produce hybrid seed.

The male-sterile canola plants went on to be a commercial success, and hybrid canola plants derived from the fertility control system created by Goldberg and

Plant Genetic Sciences have been grown in Canada for more than a decade. "It was one of the most satisfying things that I've ever done in my scientific career," Goldberg says. University of California at Los Angeles placed Goldberg's work on genetic engineering for male fertility control in crop plants among the "top 15 discoveries in UCLA history." While this work was ongoing, Goldberg founded the preeminent plant molecular biology journal, *The Plant Cell*, where he served as editor-in-chief from 1988 to 1993 (17).

Goldberg's most recent work is an extension of the soybean studies he began in the late 1970s. As part of his quest to understand how genes are active during the development of a seed, Goldberg's team recently identified DNA sequences that regulate gene transcription in a specific region of scarlet runner bean during a specific stage of development (18). In his Inaugural Article, Goldberg used genome-wide transcriptional profiling to identify genes—with a particular focus on transcription factors—expressed in different compartments and tissues of *Arabidopsis* seeds at unique times during development (19).

However, despite his trailblazing scientific accomplishments, Goldberg insists that he is first and foremost a teacher. The tireless Goldberg has received numerous accolades for teaching, including being named one of America's "Top Professors" by *Newsweek Magazine* in 2009. His courses reflect his interests in political science and genetics and convey the excitement and relevance of science through provocative debates and discussions of intellectual property and the societal and legal implications of scientific advances (20). He particularly enjoys teaching nonscience majors, because "they are the decision makers of the future—the people that will be the senators, the congress people, the city council people, the people that are going to be having kids," Goldberg says. "We're in a genetics era, where everything that we do is influenced by science and genetics in some way, and there's a tremendous amount of misinformation out there, a lot of anti-science. I'm on a mission to counteract that."

Nicholette Zeliadt, *Science Writer*

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