**1993**

## Keith Yamamoto

It was at home in Des Moines, Iowa, as a junior high school student, that Keith Yamamoto recalls happening upon Frances Crick's article in Scientific American about the messenger RNA hypothesis, and "first thinking that this biology stuff seemed exciting, perhaps something I might want to try." Try it he did, and Yamamoto, now Professor and Vice Chair of Biochemistry and Biophysics at the University of California, San Francisco, says that his scientific training was a "charmed life, guided and nurtured by really remarkable mentors" that instilled in him a keen devotion to science and scientists that has benefited everyone who has worked with him.

By the time he ventured off to college at Iowa State ("thirty five miles north of my high school, about the limit of my pioneering spirit") Yamamoto declared himself a Biochemistry and Biophysics major, but less than whole-heartedly at first. "I didn't really have a clue about what a professional biologist would do all day. I was afflicted with a stereotyped image of the solitary scientist, hunched over his work in the corner of some laboratory, never encountering another person. This worried me so much that in my sophomore year I almost changed my major to English, with fantasies of becoming a writer." Only later did he learn that science is in fact a very social endeavor—"that interaction and communication with others is a constant and crucial part of the scientific process at every level."

A strong influence on his development while an undergraduate was Jack Horowitz, with whom Yamamoto worked studying the role of transfer RNA base modifications in protein synthesis. Yamamoto chose Princeton for graduate school, hoping to study with a well-known geneticist there. Arriving the summer before his first year of course work, he was assigned to a ten-week rotation with Bruce Alberts, then a third-year Assistant Professor with a technician and one grad student in his lab.

During that summer, Yamamoto "helped Bruce to develop a method he had devised for bacteriophage isolation. Things went well, and we submitted an abstract to the Cold Spring Harbor Phage Meeting in August. So with Bruce's encouragement and coaching, I found myself presenting a talk at Cold Spring Harbor even before my first official day in grad school." For Yamamoto, this typified Alberts' support of young people. Eventually, Yamamoto returned to Alberts' lab for thesis research, and through the years, working with Alberts has proved to be one of the most energizing and influential experiences of his life.

Yamamoto's graduate school years straddled the late sixties and early seventies, and the war in Vietnam was raging. In 1970, he became actively involved in the anti-war movement and in 1971 joined the McGovern Campaign for President. With Alberts' support, Yamamoto took a leave of absence to become a political organizer for McGovern in New Jersey. "That period of total immersion in regular party politics was quite an education for me, although the election result was a bit reminiscent of my lab results at the time," Yamamoto recalls.

After the McGovern debacle, Yamamoto returned to Alberts' lab, where he had for the first time demonstrated hormone-dependent DNA binding by a steroid hormone receptor, and had been laboring unsuccessfully to detect specific binding to mammalian versus bacterial DNA. "Fortunately, a wonderful paper on the lac repressor-DNA interaction, published by Arthur Riggs during my leave of absence, revealed a conceptual flaw in my thinking that had doomed my experiments. Riggs saved me a year, and McGovern saved Bruce's supply budget." Crafting victory from defeat, Yamamoto and Alberts published a paper showing why specific DNA binding sites could exist undetected in mammalian DNA. "The only hope was a small viral genome carrying a steroid responsive gene, or a DNA clone—and DNA cloning hadn't yet been invented."

Yamamoto earned his Ph.D. in 1973 and moved to UCSF for postdoctoral work with Gordon Tomkins, a pioneer in the study of gene expression and cellular growth control, especially as governed by steroids and cyclic nucleotides. Yamamoto recalls Tomkins' "boundless imagination, his incredible zany wit, his remarkable talent as a musician, and his enthusiastic support for his large group of students and postdocs." He considers himself personally and professionally blessed to have worked with both Tomkins and Alberts.

As a postdoc, Yamamoto contributed to efforts to isolate and characterize mouse somatic cell mutants with defects in the glucocorticoid receptor. In addition, he collaborated with Gordon Ringold, then a student with Harold Varmus, to demonstrate that mouse mammary tumor virus gene transcription was glucocorticoid responsive. This was the hormone responsive viral genome that would be used six years later in Yamamoto's own lab to identify the first sequence-specific DNA binding sites for steroid receptors, and the first "response element", a DNA sequence that confers on nearby genes a specific transcriptional response to a particular physiologic or environmental signal. "In a way," says Yamamoto, "I'm still trying to finish my thesis. But this time around, I have had an outstanding collection of colleagues in my lab that are actually getting the job done."

In the early seventies, the UCSF Biochemistry department had less than ten faculty members, including several beginning assistant professors attracted there in no small part by Tomkins' brilliance and charm. Tomkins' unexpected death in 1975 shocked and saddened the community, and left the future of Biochemistry at UCSF uncertain and uneasy. Yamamoto had just accepted a faculty position on the East coast, but William Rutter, the Department Chairman at UCSF, encouraged him to stay, and was also recruiting Bruce Alberts from Princeton. They both accepted in 1976 and have remained ever since (Alberts is presently on leave to serve as President of the National Academy of Sciences).

Yamamoto's lab still remains focused on the mechanism of action of steroid receptors, with particular emphasis on signal transduction and transcriptional control by the glucocorticoid receptor. The binding of the hormone to the receptor causes the receptor to change its shape and to migrate from the cytoplasm into the nucleus, where it associates with specific response elements and turns up or down the expression of nearby genes. As

the receptor is made in virtually all cell types, it enables the circulating hormone, somehow triggering cell-specific gene responses.

Yamamoto and his colleagues are trying to answer in molecular detail three fundamental questions: How is the receptor converted between its inactive and active states? How does the receptor choose to bind or act at certain of its potential response elements and not others? How does the receptor change the level of activity of its target genes? Using the receptor as a "biological probe," they have uncovered a broad range of cellular factors with which the receptor functionally interacts — heat shock proteins, kinases, other transcriptional regulators, factors that may alter chromatin structure — in order to signal and regulate. Their studies have led to the view that at least one heat shock protein, Hsp90, is required for signaling, that other signals reach the receptor through particular kinases and phosphatases, that the receptor commonly integrates signaling information from other regulators by interacting at particular DNA sites with factors from distinct factor families, and that chromatin components may participate in certain modes of regulation by the receptor.

"One of the most exciting things about modern biological research," says Yamamoto, "is that a problem can be attacked with multiple experimental approaches, and can generally be examined in the context of a biological species that is particularly advantageous for asking the question or applying a technique." Hence, on any given day, Yamamoto lab members may apply experimental tools from cell and developmental biology, molecular biology, genetics, biochemistry, microscopy, crystallography and spectroscopy, to material from cultured mammalian cells, yeast, Drosophila, or transgenic mice.

Although Yamamoto is not an old-time member of the ASCB—he joined in 1988—he is one of the Society's most active members, serving on Council and two committees, as well as editing the Society's journal. He says he is certainly not a classical cell biologist, but he "discovered that the activities of the ASCB, scientific, political, and educational, encompassed many of my own interests and concerns," much in the same manner that cell biology as a discipline has come to impact all phases of biology. Thankfully, the McGovern defeat did not irreversibly stifle Yamamoto's interest in politics or public policy: he serves on the ASCB Public Policy Committee and is responsible for science policy issues for the Society, including some of the most complicated issues of peer review, conflict of interest, and scientific misconduct. Yamamoto feels that ASCB's public policy efforts have been instrumental in helping the basic research community frame the debate and define critical policy questions. Specifically, Yamamoto cites the ASCB Congressional Liaison Committee initiative and the Congressional Biomedical Research Caucus.

Yamamoto, who is a regular on the Red Eye to Washington so he can represent the Society on the Hill and in key policy meetings, strongly believes that all scientists should take an active role educating the public and our elected representatives on the importance of basic biological research. He says that "scientists have a genuine responsibility to the public that supports our efforts, and it is critical that we communicate clearly what we do,

and how the knowledge that we generate serves as a building block within our field and can also find practical application outside of it."

ASCB public policy activities have taught Yamamoto much about the power and limits of government. He is hopeful that Harold Varmus' impending appointment as Director of the NIH will "signal new vigor and rigor in the leadership at NIH, and a clear appreciation of the relationship of basic research to clinical advances that results in fuller and wiser funding, and in more effective long-term education, not just lobbying, of Congress and the Executive Branch."

Among the many advisory boards that he has served on, Yamamoto feels that the most important may be those of federal agencies and private foundations that make decisions about the support and funding of individual scientists and their research. But he also makes special mention of the National Academy of Sciences Panel on Scientific Responsibility and the Conduct of Research (1990-1991). That panel reviewed issues related to scientific integrity and fraud, "but it was at least as notable for the issues it did not tackle, as for those it did," Yamamoto points out. As a next step, Yamamoto would like to see the ASCB begin to explore how it can better prepare young people to manage the "practice of science."

Since 1991, Yamamoto has served as Editor of Molecular Biology of the Cell. His goals for MBC, shared by Editor-in-Chief David Botstein and an outstanding group that comprises the Associate Editors, Editorial Board and staff, are ambitious. Yamamoto says that he finds it "distressing that we have ceded to others management of the way that we report our science to each other. We are allowing science journalists to set trends, to define what's hot and what's not. In doing so, we risk losing sight of what's interesting and informative, and what's not." He hopes that MBC can help to change the way that scientists present their work in print, and "that it can make a real contribution to the integration of knowledge across traditional boundaries."

Yamamoto enjoys climbing San Francisco's hills on his bicycle ("actually, I guess I enjoy going down the other side"), whether riding to and from work each day or for recreation. He appreciates the beauty and diversity and cultural attractions of the city, and frequents its symphony, ballet, dance clubs, and "don't forget the restaurants!" He is proud of his small home with its view of the city and the Bay. It was originally built in 1916, but Yamamoto says that it is gradually being taken apart and put back together, and that reconfiguring the interior seems a constant ongoing process. "A little like trying to finish my thesis, I guess."