

Passing the Torch

BY JEAN SUZUKI

City of Hope's diabetes research program has been shaped by visionaries such as Rachmiel Levine, M.D., who in 1949 discovered the action of insulin at the cell membrane, and the team of Arthur Riggs, Ph.D., the Samuel Rahbar Chair in Diabetes & Drug Discovery, and Keiichi Itakura, Ph.D., who in the 1970s were the first to create technology that led to the development of synthetic human insulin.

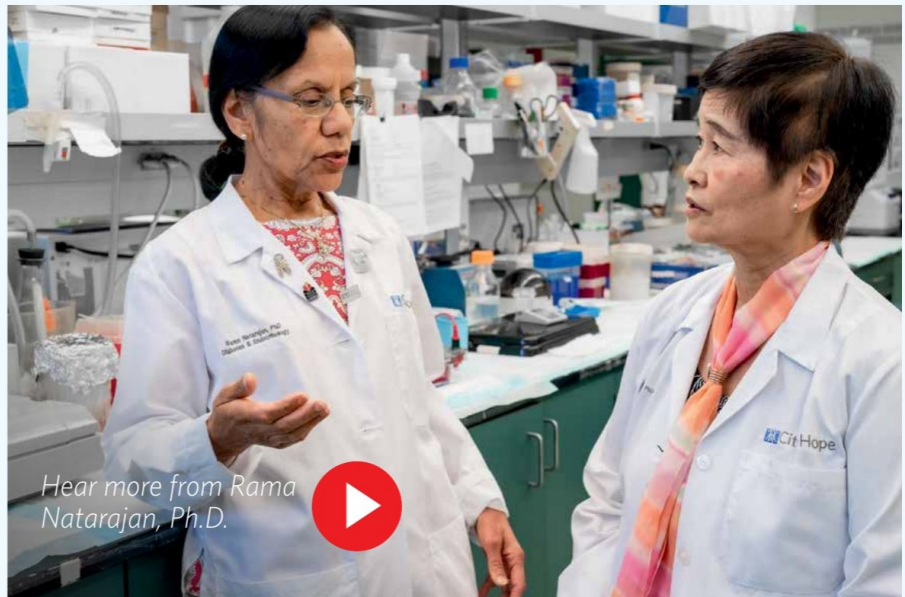
Their achievements inspired others, including two researchers who, early in their careers, made important discoveries that launched groundbreaking new areas of diabetes research: Yoko Fujita-Yamaguchi, Ph.D., professor emerita of the Diabetes & Metabolism Research Institute at City of Hope, and Rama Natarajan, Ph.D., the National Business Products Industry Professor in Diabetes Research and chair of the Department of Diabetes Complications & Metabolism.

In 1980, Fujita-Yamaguchi was a young protein chemist who received her first National Institutes of Health grant as a principal investigator. Her research hoped to understand how insulin binding to its cell surface receptor stimulated molecular mechanisms within the cell.

At that time, the insulin receptor's specific function at the cell surface remained a mystery, but Fujita-Yamaguchi was able to confirm what had eluded others before her — that insulin bound to its cell receptor stimulated the activity of a type of enzyme called tyrosine kinase inside of the cell.

Fujita-Yamaguchi's discovery was a breakthrough in understanding how insulin functions in cells. Her work inspired new research that led to the identification of cell-signaling pathways, such as those that mediate the process of bringing glucose into a cell. Soon after, she successfully cloned the insulin growth factor-1 (IGF-1) receptor, which has been found to play a key role in cell survival and, importantly, cancer.

As a result of Fujita-Yamaguchi's contributions, interest in diabetes research continued to grow at City of Hope. In the 1980s, the Department of Diabetes, Endocrinology & Metabolism was



Rama Natarajan, Ph.D. (left), with Yoko Fujita-Yamaguchi, Ph.D.

“To see the success of the next generation gives me the greatest pleasure.”

Rama Natarajan, Ph.D.

established. Talented diabetes researchers were soon attracted to the program, including Natarajan, who joined City of Hope in 1990 and was pivotal in expanding the field of diabetes research into new and exciting areas.

In the early 1990s, Natarajan identified the role of inflammation in diabetes complications. She was able to link high glucose levels with increased vascular inflammation — a hallmark of diabetic complications such as kidney and heart disease.

This early work sparked her interest in epigenetics.

Epigenetics is the study of heritable changes in gene expression that occur without changes in the underlying DNA sequence of the gene. What can

change is whether certain genes get switched on (expressed) or switched off (inhibited) as a result of external factors. In this way, external factors can alter epigenetics to influence the development of human diseases.

“With epigenetics, we ask the question, ‘What about the environment and lifestyle, and how do they affect the onset and severity of diabetes and its complications?’” Natarajan explained.

Natarajan was the first to demonstrate the role of epigenetics in diabetic vascular inflammation and the first to characterize the epigenetic mechanisms involved in diabetic kidney disease. She was also one of the first to show the involvement of epigenetic mechanisms in the phenomenon of metabolic memory, in which periods of prior high blood sugar levels predispose patients with diabetes to long-term persistent complications, despite normalized blood sugar levels.

The connections she identified between epigenetics, inflammation, diabetic complications and metabolic memory have transformed the field. But she acknowledges that there is more work to be done.

“There are excellent drugs now to treat diabetes itself, but people still continue to suffer from complications,” Natarajan said.

Her pioneering studies are driving the development of novel therapeutic approaches. Unlike genetics, epigenetics is reversible and yields opportunities for therapeutic intervention.

For Fujita-Yamaguchi and Natarajan, their legacy extends beyond the lab, as both are actively involved in mentoring the next generation of scientists — Fujita-Yamaguchi as the director of the City of Hope — Japan Scientific and Educational Exchange Program and Natarajan as chair of the Women's Leadership Committee.

“To see the success of the next generation gives me the greatest pleasure,” Natarajan said.