FACES OF MASS SPECTROMETRY / Hee-Yong Kim

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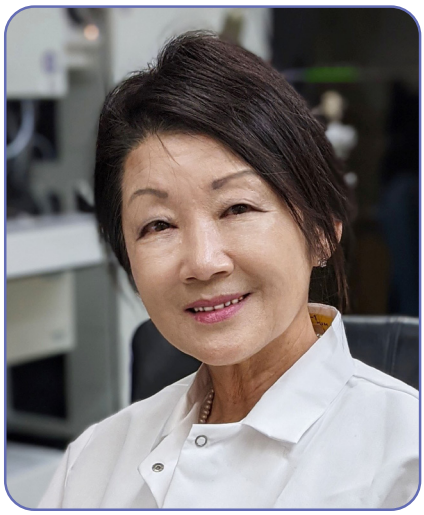

A Leap of Faith

When Hee-Yong Kim decided to leave South Korea and relocate to Texas where her husband was studying, she took a leap of faith that it would also be a forward move for her career in biomedical research. Planning to continue her own studies, Hee-Yong was interested in accessing instruments useful for her analysis of biomolecules, but she did not know that mass spectrometry would become a major component of her research.

Trailblazing work was happening at the University of Houston when Hee-Yong enrolled in the chemistry graduate program there. Exciting advancements were taking place, making direct analysis of biological samples more convenient and comprehensive. Liquid chromatography–mass spectrometry was being developed by a team at the university, and it caught the attention of Hee-Yong, who had always hoped for a tool sensitive enough to detect biomedical components that she first began to study in pharmacy school.

Proving to be an ambitious researcher, Hee-Yong earned a PhD and started a career at the NIH in the challenging area of lipid research. Tracing her start at the NIH back to an act of trust that she would find her niche, Hee-Yong recounts how overcoming hurdles early on paved the way to a rewarding career. Her long research career at the NIH led her to become a laboratory chief in 2006. She is now Chief of the Laboratory of Molecular Signaling at the Intramural Research Program of National Institute of Alcohol Abuse and Alcoholism.

While English is Hee-Yong's second language, she describes mass spectrometry applications and the study of biochemical mechanisms with outstanding clarity. Her ability to explain challenging concepts and the motivation behind her research is captivating.

Simultaneously distinguished and relaxed, Hee-Yong smiles with her eyes. Her advancements in the fields of neurodevelopment and neuroprotection give Hee-Yong a lot to smile about. She has developed and applied mass spectrometry to make pioneering advances in the area of brain health. A long-standing member of the ASMS, Hee-Yong has become an impressive role model for scientists interested in mass spectrometry–based novel approaches and those in the Asian scientist community.

How did you get your start in mass spectrometry?

It's an interesting story. I received my master's degree from my country, South Korea, at Seoul National University. I then got married and moved to Texas, following my husband who was studying in Houston. When I came to the United States, I wanted to go to graduate school, and I went into the chemistry department at the University of Houston. There, I found Marvin Vestal who was developing LC-MS, which later became an essential tool for biomedical research, and I was fascinated by the possibility of the emerging technique at that point. Ever since I was working for my master's thesis in South Korea, my interest was always on biomedical research. I felt that biomedical research was facing significant challenge because there was no tool sensitive enough to detect the physiologic or even pathophysiologic levels of metabolites or essential biological components. So, that was the start of my interest in the mass spectrometry, along with the coincidental presence of Marvin Vestal in the Houston area.

How did you start your career with the National Institutes of Health? How did you ascend to the role of laboratory chief?

My husband Gil-Jong Kang waited for a year after completing his PhD, so that I also could finish my PhD degree. Therefore, when he wanted to get trained further in cancer research at the NIH, it was my turn to go along with him. Since I had studied LC-MS which was a developing technique at that point, I did not have much option but to join a relatively new lipid laboratory, where the first and only LC-MS prototype was recently installed at NIH. When I first started, I really disliked the lipid research, because lipids were very difficult to handle. But after about two years, I had overcome some of the hurdles of lipid research, gradually understood the

The Kim lab team at a holiday luncheon. (From left, Bill Huang, Hee-Yong Kim, Hope Shapiro, Yoosun Kim, Arthur Spector, Karl Kevala, Taeyeop Park, Huazhen Chen, and Abhishek Desai).

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importance of lipids, and eventually fell in love with it. With the successful outcome in a difficult field, the NIH persuaded me to stay and fast-tracked me for tenure in only 7 years. After tenure, I was naturally given my own laboratory as a principal investigator (PI) and a Section Chief. In 2006, I was promoted to Laboratory Chief as our research had expanded and grown into the level with a broader scope and goals. During this progression, mass spectrometry played an essential role by providing an indispensible tool in tackling biomedical problems.

What are the backgrounds of your colleagues in your lab team at the NIH?

Of course, our laboratory definitely has mass spectrometry expertise. We also have scientists with expertise in cell biology, molecular biology and biochemistry which are as important in our research. In addition, we have a behavioral scientist along with physiology experts, and we collaborate with computational biologists, geneticists, and medicinal chemistry experts. So, our laboratory is composed of a truly multidisciplinary team.

How has your work in neuroscience contributed to our understanding of alcoholism?

The brain is full of lipids. Once the brain is developed, the lipid composition does not change much. But we found that ethanol is one agent that can change the lipid composition in the brain. As lipids are present as phospholipids in cell membranes, we developed a method to analyze the phospholipid molecular species that can uncover how ethanol changes brain lipid composition, which was the starting point of our alcohol research. I was most interested in a polyunsaturated fatty acid called docosahexaenoic acid, or DHA, which is an omega-3 fatty acid that is unusually enriched in the brain, and can be depleted by ethanol even in the adult stage. I thought there must be some role for such high level of DHA in the brain. That curiosity was the material for my imagination and became the theme of my research: What is the contribution of this particular lipid to the brain function? Over the course of our study, we found that DHA is indeed important for proper brain development and neuroprotection, and ethanol exerts neurotoxicity at least in part by interfering with DHA neurodevelopmental and neuroprotective mechanisms.

What have you learned through mass spectrometry about the relationship between omega-3 fatty acids and traumatic brain injury?

Our body is equipped with the mechanisms to recover by itself, which is called "spontaneous recovery." When an injury occurs, these recovery mechanisms help us to heal. Using lipidomic analysis, we found that a high level of DHA can lead to the expansion of a specific phospholipid class pool in the brain that can protect the neurons to survive under the adverse conditions such as in injury. Furthermore, with the help of mass spectrometric metabolomic approach, we found that DHA is endogenously converted to a potent bioactive metabolite (synaptamide) that prevents inflammation after injury, promotes neurite growth and synapse making, and stimulates neurogenesis. One very important point is that when DHA content in the brain is high, the metabolite production is higher, and therefore, the protective effect is greater.

In humans, the people who do not eat omega-3 fatty acid-containing foods such as fish have lower brain DHA in the brain compared to people who do eat fish, and therefore, have less capacity to produce the protective metabolite needed for spontaneous recovery after brain injury. Even after accidental brain injuries, if your brain is well-prepared with high level of DHA that can be converted to the protective metabolite on demand, you might not suffer from the adverse impacts of the injury as much. So, enriching the brain with DHA is a preventive strategy that we developed for traumatic brain injury. Another strategy is the therapeutic use of a protective metabolite, synaptamide in this case. We make analogs of synaptamide after injury to mitigate the injury effects and improve recovery outcomes. Currently, we are investigating with two major approaches in terms of brain injuries: preventive strategies and therapeutic strategies. These DHA-based strategies are rooted in the physiologic mechanisms that we discovered for which mass spectrometry played an essential role.

Hee-Yong Kim with her husband, Gil-Jong Kang, on the back nine.

What are some of the modern mass spectrometry techniques that your laboratory is developing to characterize protein–protein and protein–membrane interactions?

I started with lipid research and lipid mass spectrometry at the NIH, which, like I mentioned before, I hated at first and missed protein research. During the course of our study, I came back to the protein research by the need to study the lipid protein interaction. Lipids do not work by themselves. Rather, lipids have to interact with a protein or to target a protein such as a receptor to exert biological effects. To figure out how and when they interact, we had to study conformational changes of the protein in relation to the activities of proteins.

We found that the cell membrane very rich in DHA interacts with proteins a bit differently. The interaction with the cell membrane is necessary for certain proteins to get activated. By intramolecular chemical cross-linking of the protein of interest we were able to probe the conformational changes of the protein. By comparing the crosslinking profile with and without membrane interaction using label-free quantitative mass spectrometry, we were able to demonstrate the conformational changes in relation to different activation stages. This approach led us to propose the activation mechanisms of certain kinases. We also developed in-cell cell chemical cross-linking strategy, which allowed the conformational monitoring and protein-protein interaction in living cells. This approach allowed us to unveil physiologic activation mechanisms of a G-protein coupled receptor triggered by the endogenous ligand.

What are some of your interests outside of the lab?

I love reading books of various kinds—history, spirituality, scientific fictions, etc. I also enjoy going to concerts and art museums. Occasionally, I like to play golf with my husband, although I am not good at it. Traveling is something else I enjoy. I just returned from Hawaii. At first I was hesitant about traveling with the COVID situation. However, I was impressed that they enforced the health regulation strictly and people observed the rules very well in Hawaii. In addition, the beach was beautiful and the air was fresh with low humidity. I am glad that we went.

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You were the first Asian to serve on the ASMS Board of Directors from 1996 until 1997. How do you feel about that honor.

To tell the truth, I was very surprised when I was elected. A few people, including Catherine Fenselau, nominated me to run for secretary. Although I was already a tenured scientist at NIH, I did not think I was a recognizable candidate for an elected office of the professional society. As an Asian foreigner, my English was still improving at that point and to make matters worse, I had a very soft-spoken voice.

But I was pleasantly surprised to be elected, and felt really honored. During those years of seving on the Board of Directors, I learned a lot about how the society operates. At that time, we had about 3,000 members, which is far less than the current membership number. It was a busy task for me. I had to work extra to overcome somewhat insufficient language skills and understanding of the American culture. The responsibility took a lot of time and effort with frequent travels for board meetings in addition to my other travels of professional duties, which required the support and sacrifice of my husband and two growing sons, Auggy and Eugene.

But looking back, it was a rewarding experience that made me grow a great deal and led me to many outstanding professional friends and colleagues. I hope that my contribution to the society as the first-generation Asian American board member and mass spectrometrist paved a way for the next generation of women scientists, especially Asian women mass spectrometrists. It was indeed a privilege to have served, and I cherish every moment of the board activity with fond memory.