ASPB Pioneer Member

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How did your career get started?

When I was born, my father came to the hospital to visit my mother and me with a giant-sized apple as a gift. It seems my fate of becoming a teacher was sealed! Dad was an economics professor whose mentorship is still celebrated by his many Ph.D. students 20 years after his passing. He was also my first mentor, suggesting I take microbiology as my major in college, because he read that molecular engineering would be a driving force for economic development. As an undergraduate student at Wuhan University in China, "Molecular Genetics: An Introductory Narrative" by Gunther Stent and Richard Calendar1 sparked my passion for microbial genetics. In 1982, I was among the first group of mainland Chinese students to come to the US to pursue my Ph.D. in microbial genetics with Dr. Robert H. Rownd at Northwestern University in Chicago. China had just opened her doors to the West and pursuing this research direction was a dream-come-true experience for me. After my Ph.D. training, during which I determined how an antisense RNA controls the replication of a multidrug-resistance plasmid in pathogenic bacteria2, I decided to switch fields to study multicellular eukaryotic organisms. Dr. Fred M. Ausubel at Harvard Medical School offered me a postdoctoral project that allowed me to pursue my other interest, immunology, which didn't involve the need for animal sacrifice. I published one of the first papers using Arabidopsis thaliana-Pseudomonas syringae as a host-pathogen system to elucidate plant immune mechanisms3. My training in molecular biology led me to generate transgenic Arabidopsis reporter lines (via tissue-regeneration), one of which turned out to be responsive to the plant immune signal, salicylic acid (SA).

What do you consider your most important research contributions?

After becoming an Assistant Professor at Duke University in 1992, my lab, which started with my first graduate students Hui Cao, Scott Bowling, Joe Clarke (two years later) and my technician Susan ("Susu") Gordon, used the reporter line I generated during my postdoctoral work to perform genetic screens for mutants lacking SA-induced reporter expression (nprs)4 and mutants with constitutive reporter expression (cprs)5. While only a few in-depth studies have been done in my lab on CPRs by Shui Wang, Sophie Zebell, and Yangnan Gu, NPR1, which was cloned by Hui Cao in 19976, has become a focus of my and many other labs' research programs due to its central role in the plant defense network. Many of my lab members, including Mark Kinkema, Xin Li, Yuelin Zhang, Weihua Fan, Zhonglin Mou, Andrew Heidel, Dong Wang, Meenu Kesarwani, Steven Spoel, Yasuomi Tada, Rajinikanth Mohan, Abdelaty Saleh and John Withers, have made major contributions to our current understanding of the activation mechanisms and the nuclear function of NPR1 using genetic and genomic approaches. More recently, Raul Zavaliev discovered that NPR1 also controls defense protein homeostasis in the cytoplasm through biomolecular condensate formation to promote cell survival under biotic and abiotic stress7.

In all these years, one question that remained was how NPR1 senses SA. Based on the genetic data, it should be an SA receptor. The turning point for us was a study performed by Zhengqing Fu, who showed that compared to the low SA-binding activity of NPR1, its paralogs, NPR3 and NPR4, could bind to SA at Kd values in the nanomolar range8. This information encouraged us (John Withers, Raul Zavaliev, and Jordan Powers) to collaborate with Drs. Ning Zheng's and Pei Zhou's labs to solve the structures of the NPR4 SA-binding core and the full-length NPR1, in apo and SA-bound forms and in complex with TGA transcription factor (TF), respectively. The active NPR1 dimer turns out to be a bird-shaped beauty and explains how NPR1 reprograms the defense transcriptome by cross-linking two TGA TFs to form an enhanceosome9. Understanding

how NPR1 forms the nuclear and cytoplasmic complexes with distinct functions will keep us busy for the foreseeable future.

As all good geneticists would have done, we performed multiple rounds of genetic screens for suppressors of npr1. These screens, spearheaded by Xin Li, opened two different new research directions: (1) The suppressor of npr1 constitutive 1 (snc1), an autoactivated immune receptor mutant, has been used by Xin Li in her own lab as a background to identify many new components in immune receptor signaling pathways. (2) The suppressor of npr1 inducible 1 (sni1) was the parent of another round of suppressor screens that elucidated the role of DNA damage repair machinery in regulation of defense gene expression in plants. After several years of investigation on the project by Wendy Durrant, Becky Mosher, Junqi Song, Shui Wang, Sophie Zebell, Jorge Marques, and Shunping Yan, the torch has been passed on to Shunping Yan's lab where they have been making strides in recent years.

Besides SA-mediated defense through NPR1, Steven Spoel initiated a study of the crosstalk between SA/NPR1 and another plant defense hormone, jasmonic acid (JA), in collaboration with his MS advisor Dr. Corné M. J Pieterse10. This study indicated that plants can adjust the type of immune response based on the pathogens encountered (i.e., biotrophic vs. necrotrophic) and opened an active research area in understanding the interplay between plant defense hormones and growth hormones with additional members from my group, Dong Wang, Karolina Pajerowska-Mukhtar, Xiaoyu Zheng, Natalie Spivey, and Lijing Liu participating in the project.

For over 10 years, my lab's research was supported by the NSF2010 project, in collaboration with the labs of Dr. Fred M. Ausubel and Dr. Sauna Somerville. Through this project, which aimed to profile transcriptomic changes during plant immune responses, we made a few unexpected discoveries. The most exciting one was made by Wei Wang and Jinyoung Y. Barnaby, who discovered that plants use the circadian clock to directly regulate defense gene expression, allowing them to anticipate infection by pathogens whose life cycles are dictated by the earth's day-night cycle11. Members from our lab, Wei Wang, Musoki Mwimba, Mian Zhou, and Sargis Karapetyan from that of our collaborator, Dr. Nick Buchler in Physics, were enthralled by this new research direction, and we immediately started our crash courses on the circadian clock as well as custom-building automated imaging chambers. We were fortunate to have colleagues in the circadian clock field, Drs. Steven Kay, Rob McClung, Jose L Pruneda-Paz, and Stacy Harmer, lend us helping hands with great suggestions and experimental materials. Of course, we had to pay our dues for venturing into this new field. Our paper demonstrating that relative air humidity is the third zeitgeber of the plant circadian clock, besides light and temperature, took three years of intense revisions to get published12. But my student Musoki Mwimba, who insisted on doing everything right, is the proud first author of this groundbreaking paper.

Another serendipitous finding that came from our transcriptomic study, after we failed to obtain viable transgenic Arabidopsis over-expressing TBF1 using only the coding sequence of the gene, was the discovery that translation of the defense TF is tightly controlled. To understand how endogenous TBF1 gene expression is managed in planta to avoid the deleterious effect of overexpression, Karolina Pajerowska-Mukhtar discovered the 5' leader sequence of the TBF1 mRNA (5'LSTBF1) to have two upstream open reading frames (uORFs) that normally inhibit TBF1 translation by sequestering ribosomes from the main ORF. This inhibition is alleviated upon immune induction. This finding once again made us scramble for information through literature studies. The scarcity of information on how translation is regulated during an immune response in both plants and animals suggested a brand-new research direction. Translational regulation is a convoluted process involving many possible layers of control. Our timing was right once again, because various global analytical tools, such as ribosome-profiling (Ribo-Seq) for estimating mRNA translational activities and SHAPE-MaP for probing RNA secondary structural changes in vivo, were becoming available. The decision to launch a new research project on translational regulation of plant immune responses was reaffirmed by Guoyong Xu, in

collaboration with Meng Yuan of Dr. Shiping Wang's lab, through their demonstration that the 5'LSTBF1 can be used for engineering broad-spectrum resistance without a yield penalty in both Arabidopsis and rice13. In the past several years, my "translation team" (Guoyong Xu, George Greene, Heejin Yoo, Tianyuan Chen, Jinlong Wang, Yexi Xiang, and Yang He) have discovered and characterized several translation regulatory modules that are conserved in all eukaryotes14-17. With these toolkits in hand, we will be able to rationally design stress-responsive broad-spectrum resistance to biotic and abiotic stress to make translation translatable for improving agriculture without a yield penalty.

From my father and my postdoctoral mentor, Dr. Fred Ausubel, I learned that our scholarly contributions are also measured by our trainees. Though they must experience ups and downs in their careers, I hope their time in my lab prepared them well to face these challenges. I am saving acknowledgement of those who are currently working in my lab for a later time, because we still have a lot of fun research to do together.

What advice would you offer a young person considering a career in plant biology?

I do not believe academic life is for everyone. But if you are a curious person who is always excited about learning new things, it is a great profession. You will need this intrinsic drive to sustain you through hard times. All successful scientists I have had the privilege of knowing experienced hard times in their careers. It is an unavoidable part of the journey. Persistence is a key ingredient for success. Having someone(s) to help release your frustration and tell you that based on their experience things will get better, makes a big difference. For me, my husband Dr. Xiaofan Wang, has been my sounding board since our college days. My lab manager, Mindy Sponsel, has made my life so much easier by taking many details of the work off my shoulders.

Being a plant biologist has extra challenges. I do not have to list them, because they are well known. This means that we have to try harder to educate our students, our colleagues, the public, funding agencies, and policy makers about the unique importance of understanding the plant world. There is much more to it than feeding the world. Just ask people to imagine a world without plants and whether they could live in such a world. Tell them about the fascinating plant biology you are studying. I have never regretted my decision to switch from microbiology to plant science. The smaller number of scientists means the field is more available for us to explore. I do not mind being the only plant biologist at a conference, because it makes my talk even more special. Although we study plant-specific phenomena, the underlying mechanisms can be conserved, giving us opportunities to make fundamental discoveries14-17.

Though many of our discoveries were made serendipitously, to quote Louis Pasteur, "Chance favors the prepared mind." Our success came from a bit of luck and vast amounts of hard work. Moreover, finding mentors and mentees with a similar passion for science made my journey more exciting and enjoyable. A question frequently asked of me is how to pick the right person for the lab. I answer that the person picks the lab instead of the other way around. What I can provide is a supportive environment for mentees to explore their passion for science. Along the way, they become my teachers. I can recall many occasions when, after papers got rejected or my anxiety grew pending grant applications, my students and postdocs were my source of consolation. A collegial relationship, instead of an employer-employee one, makes being the PI less of a lonely job. However, group brainstorming cannot substitute for solitary time for thinking and procrastination. Our lives can get too busy too quickly, but thinking is still a solitary act. There needs to be a fine rhythm between stimulation and relaxation. One thing with which I am still struggling is how to define "enjoying life". I have concluded enjoyment cannot be stereotyped. I wish you success finding your own enjoyment as a plant scientist.

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