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Lily and Yuh Nung Jan's collaboration started with the identification of *Shaker* as the first known potassium channel gene and has flourished to produce over 100 former students and postdocs who are now leading their own research groups. In an interview with *Neuron*, they reflect on their scientific discoveries, serendipity in science, and the value of curiosity-driven basic research.

Lily and Yuh Nung Jan were both born in China and raised in Taiwan. They received their undergrad degrees in physics from National Taiwan University. In 1968, they went to Caltech to study physics, but after 2 years, they switched to biology under the tutelage of their PhD advisor Max Delbrück. They began their long-term collaboration after finishing graduate study in 1974. Following their postdoctoral training with Seymour Benzer at Caltech and Steve Kuffler at Harvard Medical School, the Jans joined the faculty of the University of California, San Francisco in 1979 and became investigators of the Howard Hughes Medical Institute in 1984. Their interest in ion channel functions—how a channel works and what it does in the nervous system—can be traced back to their first collaboration, which led to the identification of the *Drosophila Shaker* gene as the first known potassium channel gene. Their interest in neural development—how certain cells in an embryo become neural progenitors that give rise to specific types of neurons with characteristic dendritic morphology—became tractable in *Drosophila* as the question was approached in stages, starting with studies of cell fate specification and asymmetric cell division and progressing to investigation of dendrite morphogenesis. Questions concerning functions befitting a neuron's dendrite morphology then led to their recent studies of mechanosensitive ion channels. Both Lily and Yuh Nung Jan are members of the National Academy of Sciences and the Academia Sinica. They have been recognized with several awards, including the Spencer Award, the Distinguished Alumni Award from Caltech, the Gerard Prize, the Wiley Prize, the Scolnick Prize, and the Gruber Prize in Neuroscience.

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Who were your key early influences?

As we reminisced (a sure sign of becoming old geezers) in a recent autobiographic chapter in the *History of Neuroscience in Autobiography* series edited by Larry R. Squire and published by the Society for Neuroscience (https://www.sfn.org/~/media/SfN/Documents/TheHistoryofNeuroscience/Volume%208/YuhNungJan_LilyJan.ashx), we learned a great deal from our mentors Max Delbrück, Seymour Benzer, and Steve Kuffler. In a "Preparing Future Faculty" type of talk aimed for senior postdocs and starting faculty, we have tried to convey what we learned from our mentors:

> We have been fortunate to have inspiring mentors with tremendous scientific curiosity and a sheer delight in doing science. Having made important scientific contributions, our mentors also exerted strong influence by being open and supportive, rendering the field attractive to newcomers, thus ensuring it'll thrive. Surrounded by circles of friends and collaborators, they exemplified the best practice in advancing the careers of their former lab members. Success of their trainees further boosted the standing of our mentors as leaders. It was also inspiring to witness how they enjoyed life with family and friends.

To tackle your favorite research question, is there a tool that either needs to be developed or is currently available that could be implemented in a novel way?

A vivid memory we share with our compatriots of the Benzer lab is a list of big questions we jointly came up with in one of those extended lunch gatherings four decades ago. Seymour jotted down these questions in neuroscience under the headings of behavior, physiology, anatomy, embryology, molecular biology, and evolution. The topics ranged from behaviors in the realms of psychology and ethology (inborn versus learned, adaptive significance to survival…), functions of various nervous system regions (processing of sensory information for each modality, what changes in synapses correspond to memory…), circuitry of the nervous system and muscles (map all neurons and connections…), development (positional information, inertial guidance versus lick-and-stick for neurospecificity, program for cell division, differentiation…), and genome structure and control (packaging of genes, coordinated repression and derepression…) to

evolution (role of behavior, how can complex behavioral patterns evolve, where is it headed...)—a Polaroid record taken by Seymour of that blackboard reminds us how unabashedly dreamy we all used to be as Seymour's disciples, given that most of the tools required for probing these big questions were inconceivable at that time.

It has been amazing to witness the emergence of so many powerful tools and new concepts over the years, thanks to many dedicated colleagues and thanks to serendipity. Besides developing and repurposing tools, it may also help to keep nurturing those favorite research questions, even though they appear to be beyond reach, as one way to entice chance to favor a prepared mind; with some luck, a totally unexpected emergence of a new tool might just turn a dreamy musing into realistic projects. While this may seem like wishful thinking to young scientists, the fast pace our field has been moving [at] for decades encourages an optimistic outlook. As a case in point, although many of the questions jotted down by Seymour Benzer four decades ago still remain unanswered, it is reassuring to see how much progress has been made.

Which aspect of science would you wish the general public knew more about?

How important "serendipity" has been for making scientific discovery. It will probably help to remind the general public of the circuitous paths leading to scientific discoveries that often were prompted by simple curiosity.

Do you have a favorite anecdote from doing science that you'd like to share (perhaps a key discovery moment)?

In 1980, shortly after we started our lab at UCSF, one Saturday, we did an immunocytochemistry experiment to test whether the fruit fly may have substance P-like peptides, because at the time we were interested in neuropeptides. We were very surprised to see the entirely fly nervous system lit up. This was odd because we knew peptides tend to have very restricted distributions in the nervous system. We retraced our steps and figured out that Lily took a wrong vial of antibody. We meant to use an antibody coupled to HRP, but she took an antibody raised against HRP. It turns out that this antibody against HRP is a highly specific marker for all *Drosophila* neurons (as well as neurons in other insects such as grasshopper), a marker still useful to this day. This lucky mistake (or serendipity) led to identification of the first general neuronal marker in *Drosophila* that provided us with an entry point to plunge into the study of neural development.

What has been the highlight of your career?

There were several, including, for example:

In 1978, while in Steve Kuffler's lab, we were trying to identify the transmitter that mediates a mysterious "late slow excitatory postsynaptic potential" (late slow EPSP) in the bullfrog sympathetic ganglia. We were attracted to the late slow EPSP because it lasts unusually long (several minutes), unlike typical synaptic potentials that last for milliseconds. We tried all kinds of candidate transmitters to see if any could mimic or affect the late slow EPSP. After we exhausted the list of classical transmitters, we tested Steve's collection of peptides. To save time, we tested pools of three at a time. One pool yielded a mild effect and the culprit turned out to be a peptide called luteinizing hormone releasing hormone (LHRH). Since the effect of LHRH was quite modest, we didn't know if it is a real candidate. Fortunately, there were potent agonists and antagonists of LHRH already developed. When we saw that a potent LHRH agonist could elicit a robust slow depolarization and the LHRH antagonist could block the late slow EPSP, we knew we were on the right track. Follow-up studies revealed some interesting features of this peptide transmitter. For example, the LHRH-like peptide is co-released with acetylcholine from nerve terminals that make classical synapses with a subset of sympathetic neurons, but the peptide can diffuse and act on its true target—another subset of sympathetic neurons—tens of microns away. In this case, the wiring diagram based on anatomically defined synapses is actually misleading for identifying the real target of the peptide transmitter.

In 1986, together with three postdocs, Diane Papazian, Tom Schwarz, and Bruce Tempel, we had been struggling for several years to clone the *Shaker* gene by taking a chromosome walk. Even though the genetic and electrophysiological evidences strongly supported the hypothesis that the *Shaker* gene codes for a potassium channel, we could not be absolutely sure until we actually cloned it. Since no potassium channel sequence had been identified then, we didn't know if we could tell from the sequence whether it is for a potassium channel. Finally, one day we saw that part of the *Shaker* coding sequence could be lined up with the S4 sequence of the voltage-gated sodium channel; we knew this part of the sequence is likely to be part of the voltage sensor and went on to show that *Shaker* indeed encodes a voltage-gated potassium channel.

In 1993, we were studying a gene called *numb*. From the phenotype, we knew it is a regulator of cell fate. Tadashi Uemura had cloned the gene in 1989 for his postdoctoral research, but the sequence did not provide us with a clue as to how the Numb protein might function. As Michelle Rhyu continued with the project for her thesis research, she made a good antibody against Numb and the staining pattern was quite stunning. Numb is localized to the cell cortex at one pole of a neuroblast (like a yarmulke worn on a head). When the neuroblast divides, Numb is segregated into one of the two daughter cells. Numb was the first example of a cell fate determinant that is unequally segregated during asymmetric cell division of a neural progenitor, thereby allowing its two daughter cells to take on distinct cell fates.

In each case, the project was at an uncertain stage, and those experimental results convinced us that we were on the right track. The moments when we saw such revealing and unexpected results were particularly thrilling.

What do you think are the biggest problems/challenges science as a whole is facing today?

One big problem is the excessive amount of time and effort that scientists spend nowadays on grant writing and getting papers published. This problem seems to be getting progressively worse and is

especially serious for scientists in their early career when they should have as much time as possible set aside for creative endeavors. We think part of the problem is the micromanaging tendency of some reviewers (of grant applications or papers).

Another big problem for biomedical science is how it is envisioned in a way that may discourage curiosity-driven basic research and the use of "lower" model systems or non-traditional organisms. While well intentioned to focus on dedicating resources for improving human health, we need to continue to sustain basic science as the engine for driving truly groundbreaking discoveries. One would hope that the fact that time and again the most transformative and widely used tools, such as GFP, RNAi, channelrhodopsins, and CRISPR/Cas9, all came from studies of some esoteric non-vertebrate organisms should have made this point amply clear.

What is your view on big data-gathering collaborations as opposed to hypothesis-driven research by small groups?

Both are valuable. We would like to add that there is a third type of research: serendipity-driven research by small groups. Many studies from our lab were initiated by serendipity, as is the case for research of many of our colleagues and forebears. We felt there is an overemphasis of hypothesis-driven research by some funding agencies. It devalues efforts to follow surprising and totally unexpected observations with an open mind, which can lead to breakthroughs.

As a corollary of the current emphasis for hypothesis-driven research, the type of mutant screens such as the ones carried out by Nüsslein-Volhard and Wieschaus in the early 1980s to identify genes affecting *Drosophila* larval body patterning, which led to many important insights not just about development but also about signaling mechanisms, would fall into the "fishing expedition" category that is difficult to garner support. Alas, mutant screens are not deemed to be hypothesis-driven research, notwithstanding their track records in generating interesting hypotheses.

From our own experience, when we started working on a poorly understood problem such as dendrite morphogenesis, initially, we didn't know enough to formulate any very specific or useful hypothesis. Our approach was to first try to characterize the experimental system well by gathering and using markers, and to start probing the system to get a feel about the problem by identifying and studying mutations that affect dendrite morphogenesis. As we learned more, then we can start to formulate progressively more precise hypotheses for testing.

What inspiration have you drawn from working with your students and postdocs?

We have had the good fortune to work with a number of truly talented students and postdocs over the years. They would work on research projects that suit their interest and draw from the experience in our lab as they move on to build their own scientific careers. Precisely 10 years after our first lab reunion, this summer we had a second reunion with 145 former and current lab members getting together for one weekend in San Francisco. It has been great fun to reminisce and to learn about the latest in their lives as well as their science, which has taken on new and interesting twists and turns remarkably characteristic of their individual styles and scientific inclinations. The ways each of them used to talk about science and their own interests in the lab lent us the vantage point to appreciate the creative new directions they are charting out, which have made us feel so proud and excited. With over 150 lab alumni, we are happy to see that more than 100 former students and postdocs are now leading their own research groups while recent graduates are moving along the academic track. We maintain their current contact information on our lab website (http://physio.ucsf.edu/Jan/FormerPersonnel.html) and enjoy opportunities we have to catch up with our lab alums when they return for a visit and when we meet up at conferences.

What do you do when you're not in the lab?

We first met during a hiking trip in Taiwan, and hiking remains one of our favorite activities. Local hikes in the Bay area are part of our family tradition that our children remember fondly and try to work into their schedule whenever they return to San Francisco. Our family hiking trips over the years have taken us to trails in many National Parks and far-flung places like Wadi Rum. Going to the opera is another favorite activity of ours for decades. We took our daughter to Wagner's Ring Cycle when she was barely 6 years old. Some might view this as child abuse, but fortunately she actually liked the experience. With our children on the east coast for now, we would occasionally include an opera on the agenda for a family reunion in New York. In recent years, as empty nesters we managed to go for some memorable hikes, including ones in the Swiss Alps, on the Milford Track, and in Patagonia, where our photo was taken.

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