Profile of Lily and Yuh Nung Jan, winners of the 2017 Vilcek Prize in Biomedical Science

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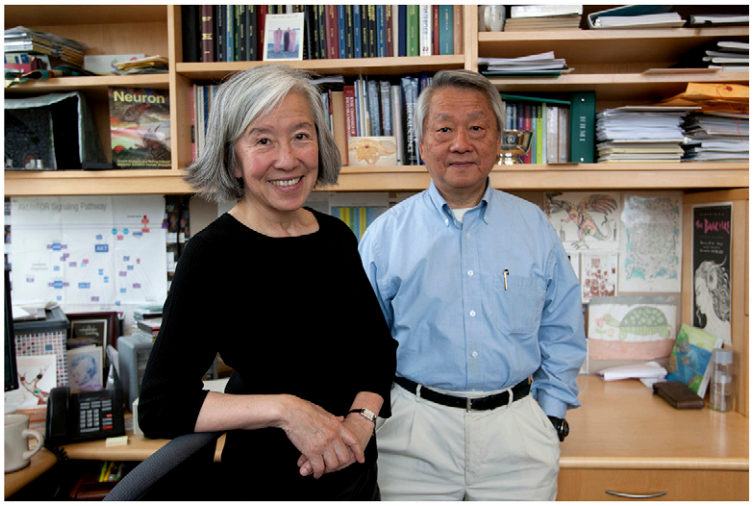
The 2017 Vilcek Prize in Biomedical Science has been awarded to Lily Y. Jan and Yuh Nung Jan, professors in the department of physiology at the University of California, San Francisco (UCSF), and Howard Hughes Medical Institute Investigators. The Jans are being recognized for demonstrating how ion channels contribute to neuronal signaling and how neurons acquire their cell fates and morphologies.

Vilcek Prizes—accompanied by an unrestricted cash award of $100,000 each—have been awarded annually since 2006 to prominent foreign-born biomedical scientists and artists. To recognize a younger generation of distinguished immigrant scientists, in 2009 the Vilcek Foundation also established annual Prizes for Creative Promise in Biomedical Science. Currently, three scientists, 38 years of age or younger, are selected for the latter awards, each carrying a cash prize of $50,000.

The Jans are the first Chinese-born scientists to receive the main biomedical prize awarded by the Foundation. Today, numerous Chinese American scientists play invaluable roles in science and technology in the United States. By contrast, when the Jans arrived in this country in 1968 to pursue graduate studies, there were few scientists of Chinese origin in laboratories in this country. Perhaps even more significantly, the 2017 Vilcek Prizes reflect the fact that the proportion of foreign-born researchers among highly accomplished American scientists greatly exceeds the fraction of foreign-born people living in the United States. The remarkable achievements of these scientists attest to the vital and well-documented role of immigrants in sustaining the American economy.



Lily and Yuh Nung Jan. Image courtesy of Cindy Chew (photographer).

Lily and Yuh-Ning Jan: Winners of the 2017 Vilcek Prize in Biomedical Science

Beginning in 1979, neurologist John Nutt and his colleagues at Oregon Health Sciences University in Portland examined a series of patients with a strange mix of symptoms. The patients complained of crippling tremors triggered by stress, exercise, and fatigue that lasted minutes to hours. One patient recalled a mortifying attack at the precise moment she was introduced to her fiancé's parents; another described a fateful episode in the final lap of a high-school swim meet. "The symptoms varied, but the core feature was walking and talking as though they were drunk. They simply couldn't coordinate movements," recalls Nutt. Before long, Nutt and his team cataloged more than five dozen cases, all diagnosed with a disorder called autosomal dominantly inherited episodic ataxia (1). Some patients were afflicted with a form of the disorder that struck in childhood or adolescence and was marked by bouts of muscle twitching, flailing movements, and uncoordinated gait.

Premising from the case histories that the disease runs in families, Nutt partnered with molecular geneticist Michael Litt to pinpoint a genetic basis. Together, the researchers scoured through patients' cells and found mutations in a gene called *KCNA1* in four of the seven afflicted families. The gene, it turned out, encodes a channel that shuttles potassium ions across membranes enclosing nerve cells (2). Litt, working with molecular biologist John Adelman, found that the mutations disrupted the function of the channel (3). Isolated and described only 6 years earlier by a pair of mild-mannered neuroscientists working with fruit flies as experimental models, potassium ion channels are now implicated in an array of genetic disorders.

Thanks to the work of Lily and Yuh Nung Jan, now at UCSF, the genetic basis of a rare but debilitating human movement disorder was brought to light. "Lily and

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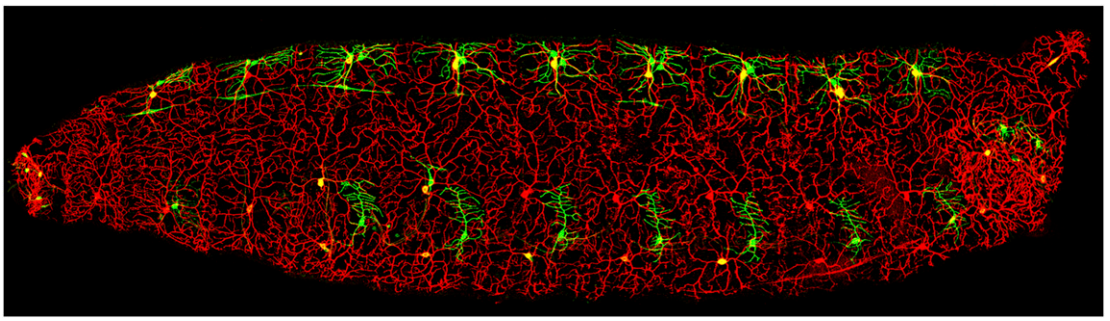


Side view of a *Drosophila* larva, with body wall innervated by two types of sensory neurons (green and red). Image courtesy of Chun Han (Cornell University, Ithaca, NY).

Yuh Nung broke open the field by publishing the potassium channel. It was groundbreaking work that allowed us to undertake functional studies of the channels essentially by copying their techniques," says Adelman.

Imbued with exploratory zeal, the Jans' work has elaborated the role of ion-transporting channels in nervous system function. Moreover, they have described in pointillist detail processes that shape the formation, identity, and structure of neurons. The contemporaneity of their decades-long work in neuroscience is evident in its clinical implications, for which the Jans have earned well-merited accolades, including membership in the United States National Academy of Sciences, Howard Hughes Medical Institute Investigator awards, and the 2017 Vilcek Prize in Biomedical Science.

"Don't Do Fashionable Science"

So intertwined are the Jans' life histories, their companionship might be traced back to their moment of conception without stretching the imagination. "Because Yuh Nung was born slightly ahead of his due date, we might have started our embryonic development at the same time," notes Lily in their autobiography. Born in China mere days apart, the Jans were raised by doting parents in Taiwan, where they attended prestigious public schools. A standout whose intelligence and industry presaged a career in science, Lily resolved to study physics at university, inspired in part by a 1957 Nobel Prize awarded to Chinese theoretical physicists. In contrast, Yuh Nung's talent remained largely undiscovered until he excelled in a nationwide college entrance exam, finishing among the top 10 of 30,000 high school students. Soon, he too gravitated to physics, focusing his restless energy on his chosen field.

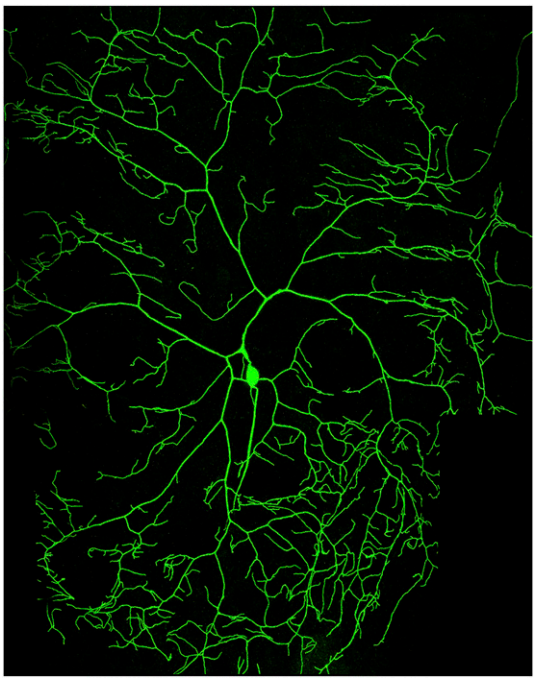
Thus, in the mid-1960s, their separate paths converged in the physics department at National Taiwan University, which was then a coveted enclave to which few won entry. Years later, as they approached graduation, a weeklong hiking trip to a nature reserve in central Taiwan proved formative, forging a romantic alliance between them that led to a lifelong partnership. Before long, the Jans set their cap for the United States and gained admission as graduate students to the California Institute of Technology's hallowed physics department in 1968, when luminaries like Richard Feynman and Murray Gell-Mann were formulating theories now enshrined in the physics canon. Feynman's classic 1960s collection of undergraduate lectures and Caltech's reputation helped cement their choice, recalls Yuh Nung.

But after only 2 years at Caltech as hopeful physicists, the Jans abandoned their well-laid plans, braving tentative forays into biology. Inspired by renowned Caltech molecular biologist Max Delbrück, himself a convert from physics, the Jans began doctoral work in biology, with Delbrück as mentor and exemplar. While Yuh Nung attempted to unravel a stubborn mystery surrounding the perception of sensory signals by a single-celled fungus, Lily embarked on a project aimed at localizing the visual pigment rhodopsin in photoreceptor cells in the retinas of mice. Despite their inexperience, the Jans' intrepid efforts and Delbrück's unstinting support helped them master biology's intricacies, culminating in a pair of reports in the *Journal of Biological Chemistry* and the *Journal of Cell Biology* that launched their careers (4, 5). Since those early days, Delbrück, who won a share of the 1969 Nobel Prize in physiology or medicine for unraveling the genetic structure of viruses, has remained an abiding presence in their lives, in spirit if not in person. "Max always said, 'Don't do fashionable science,' and that [maxim] is still on our lab's website," says Yuh Nung, hastening to add that the maxim by no means forbids researchers to embrace the latest methods. Years later, the Jans would name their second child after their lodestar.

Six Years to Shaker

Toward the end of 1973, the Jans began angling for postdoctoral positions when they chanced upon a report in *Nature* by Caltech molecular biologist Seymour Benzer. The report articulated a method for mapping behavioral defects in fruit flies to particular sites in the anatomy of fly embryos (6). Captivated by the promise of fruit fly genetics for studying animal behavior, the Jans joined Benzer for postdoctoral apprenticeship, but before they could strike out on their own they needed a crash course in neuroscience. The training came in the form of immersive summer courses at Cold Spring Harbor Laboratory in New York, a well-known crucible of revolutionary methods in molecular biology. There, the Jans absorbed an exhilarating mix of lectures and laboratory training that steeled the duo for stimulating challenges in Benzer's laboratory, which they entered in 1974.

Fresh from Cold Spring Harbor, where they became agile in experimental neuroscience, the Jans developed a technique in Benzer's lab for recording the transmission



Dendritic arbor of *Drosophila* larval neuron. Image courtesy of Lily and Yuh Nung Jan.

of nerve impulses at the junction between nerves and muscles in fruit flies, in hopes of uncovering the basis of defects in synaptic transmission. While combing through a collection of mutant fly larvae using the technique, the Jans stumbled upon Shaker, a mutant marked by spontaneous leg trembling. Working together with UCSF neuroscientist Michael Dennis, whom they had befriended at Cold Spring Harbor, the Jans soon found that the defect in the aptly named Shaker flies could be traced to the repeated firing of action potentials at nerve terminals. The relentless neuronal firing results in off-kilter ion transport, sustained neurotransmitter release, and unchecked leg muscle contractions that lend the mutant flies their name. Further studies revealed that the flies' condition could be traced to a defective potassium ion channel, setting the stage for the pair's career-defining work.

Around this time, molecular biologists began to isolate fruit fly genes that encoded proteins through a method called positional cloning: scientific vernacular for cloning genes by mapping traits on chromosomes through strategically arranged matings between flies. The Jans hoped to use the method to snag the *Shaker* gene, but isolating a gene without a purified form of its protein product to provide DNA sequence-related clues was no mean task, especially in the era preceding genome sequencing. So the Jans briefly shelved the project as cumbersome, choosing instead to hone their skills in neurophysiology through a second postdoctoral stint, this time with Harvard Medical School neuroscientist Stephen Kuffler. By then, the Jans were married, and they set off on a road trip, their 7-week-old infant in hand, leaving sun-drenched California for Boston's gunmetal-gray skies.

In Kuffler's lab, the Jans became adept at neurophysiology, uncovering along the way the role of a molecule inelegantly named lutenizing hormone-releasing hormone-like peptide in mediating a kind of nontraditional nerve impulse transmission. They soon demonstrated that the peptide that powers the transmission is released from nerve terminals into synapses but can act on distant neurons, as far as tens of microns away and lacking direct connections to the source. By then a growing area of interest among neuroscientists, such remote action of peptide neurotransmitters suggested that wiring diagrams based solely on anatomically deduced synaptic connections between neurons may not reflect the full range of neuronal cross-talk. "And this is a serious problem for connectome work," says Yuh Nung, prefiguring an anomaly that could plague neuroscientists' ongoing efforts to build comprehensive brain network maps. Published in PNAS in 1979, the findings announced the Jans' arrival on the world neuroscience stage and assured a handful of attractive job offers (7). Driven by a deep-seated westering instinct, the Jans chose to return to California, whose undimmed allure has since kept them rooted in the state.

At UCSF, where the pair accepted faculty positions in 1979, the Jans renewed efforts to isolate the *Shaker* gene, unabashed by the earlier, failed attempt. Armed with improved tools to dissect and clone genes in fruit flies, the Jans and their postdoctoral associates, Diane Papazian, Bruce Tempel, and Tom Schwarz, succeeded after 6 painstaking years in isolating the gene for the Shaker potassium channel (8, 9). Shortly thereafter, they repeated the feat with the mammalian version of the gene, named *KCNA1*, reporting the findings in a string of papers published over 9 months (10–12). More than a decade later, the mammalian voltage-gated potassium channel Kv1.1 became a focus of intense clinical interest when it was shown to underlie the runaway muscle contractions of patients with a type of episodic ataxia. Today, potassium channels are implicated in an ever-growing array of conditions, including hypertension, arrhythmia, sudden death in epilepsy, deafness, appetite control, and neonatal diabetes.

Bounty of Clinical Benefits

Since the isolation of the first voltage-gated potassium channel, the Jans have enriched researchers' appreciation of ion channels and shown in fine detail how their dysfunction can trigger disease. To wit, the Jans and their postdoctoral associates isolated the founding member of a novel family of potassium channels, called inwardly rectifying potassium channels, which control heart rate and insulin release (13). Before long, the Jans demonstrated that blocking an overactive potassium channel, called EAG2, in mouse brain cancer cells shrinks medulloblastoma, a brain tumor that affects up to 500 children in the United States alone each year (14).

With the forward momentum from their work on potassium channels, the Jans set forth to isolate the genes for a different family of channels: calcium-activated chloride channels, whose role in regulating the surge of salt and water across cell membranes renders them crucial to functions like smooth muscle contraction and mucus secretion in lung airways. "People tried but just couldn't identify these channels. And that was the case even after [the advent of] genome sequencing,"

says Lily. After 6 years of steadfast efforts, using axolotls as experimental models, the Jans and their postdoctoral fellow, Björn Schroeder, isolated the genes for the chloride channels TMEM16A and TMEM16B (15); simultaneously, Korean and Italian research groups reported the same findings using different strategies. Five years later, the Jans and colleagues reported that a fruit fly version of a TMEM16 channel, called *subdued*, plays an unexpected role in innate immunity. Fruit flies lacking the *subdued* gene were more likely to succumb to bacterial infection than wild-type flies, suggesting that the channel is required for defense against pathogens (16). The same year, the Jans found that a different member of the TMEM16 family, TMEM16C, works together with a potassium channel to control pain processing in rat sensory neurons (17).

Genes and Neurogenesis

Medical gains notwithstanding, the Jans' studies of ion channels stem from a shared predilection for basic research, one that is exemplified by the other major focus of their career. At UCSF, influenced by Delbrück's distrust of fashionable science, the Jans were drawn to the elemental problem of how the dazzlingly complex nervous system of animals is built, their interest sparked by a pair of advances in biology. In the mid-1970s, with the advent of hybridoma technology to generate monoclonal antibodies, which can serve as tools to follow the fates of individual cell types in embryos, tracing neural development was rendered a realizable goal. And when in 1980 embryologists Christiane Nüsslein-Volhard and Eric Wieschaus (who each earned a share of the 1995 Nobel Prize in physiology or medicine) reported in *Nature* that only a handful of genes control the segmented body plan of fruit fly embryos (18), the stage for the Jans' work had been set, and Yuh Nung led the charge on developmental studies.

The Jans fastened on the peripheral nervous system—a collection of sensory neurons that help the larvae of fruit flies perceive touch, heat, and chemical signals—as the favored model to probe the genetic underpinnings of the origins and course of neural development. The simplicity of the fruit fly system, which is similar in wiring and function to the vertebrate nervous system, proved appealing, says Yuh Nung. Over the next decade, through a string of reports that assembled the key genetic players, the Jans and their colleagues helped establish the timeline of nervous system development, a tightly orchestrated arabesque whose smooth execution depends on the synchronized and stepwise action of several genes. For example, the Jans found that the genes *daughterless* and *cut* help control neuronal cell identity and type (19, 20), that the gene *numb* determines how the progeny of dividing cells are earmarked for distinct fates in developing sense organs (21), and that the gene *atonal* is required for the development of sensory neurons involved in vision and hearing (22, 23). Many of the genes implicated in fruit fly nervous system development are conserved—and sometimes improvised—in mammals, says Yuh Nung. "In mice, for example, the fruit fly gene *atonal* splits into two different genes, *Math1* (hearing) and *Math5* (vision)," he explains (Years later, Baylor College neuroscientist Huda Zoghbi would demonstrate *Math1*'s role in human hearing).

Form and Function

Like many neuroscientists of his generation, Yuh Nung was smitten with Santiago Ramon y Cajal's famous painterly depictions of interlacing forests of neurons, rendered by the Spanish anatomist as sepia-toned abstractions gleaned from brain slices more than a century ago. So Yuh Nung decided to delve into the long-standing mystery of the development of dendrites, the slender branches of neurons whose rococo flourishes recall the masterworks of mid-18th century virtuosos. "I have always been intrigued by dendrites. Both for their importance in neuron function and also just aesthetically," he says.

Studying how dendrites of distinct sizes and shapes establish stunningly precise links with their targets can lead to insights into human mental disorders, such as autism and schizophrenia. Beginning in the late 1990s, the Jans and their colleagues uncovered genes that govern the size, shape, and branching patterns of dendrites. Along the way, they ferreted out principles underlying dendrite development. For example, the Jans found that different types of sensory neurons differ in their capacity for developing elaborate dendritic bouquets, that repulsion between encroaching dendrites prevents their cross-over and constrains their growth, and that the dendritic bouquets of individual neurons of a particular class are arrayed along the fly's body wall like nonoverlapping tiles on a floor. "Before this, there hadn't been any systematic study of dendrite development," says Yuh Nung.

Systematic studies soon led to clinically relevant findings. The Jans and their postdoctoral associates showed, for example, that activating a biochemical signaling pathway mediated by the Akt protein enhances neuron regeneration in the fruit fly central nervous system, raising the possibility that fruit flies can be used to identify boosters and blockers of nerve regeneration to help treat spinal cord injury and neurodegenerative disorders (24). Equally, the Jans pinpointed key proteins—minibrain and TAO2 kinase—in cellular signaling pathways that influence the maturation of the mushroom-shaped spines that adorn dendrites (25, 26). Some of these players, it turns out, are implicated in disorders such as Down's syndrome, autism, and schizophrenia. "Whether there would be a possibility of pharmacologically interfering with them, that's [a question] for the future," says Yuh Nung.

Over a career spanning more than four decades, the Jans have explored an array of topics in neuroscience with assuredly long-term clinical implications. Yet they reject the dubious but common notion that all scientific enterprise must ultimately strive for human betterment as surely as they resist the lure of fashionable science. Thanks to the unalloyed sense of wonder that has driven their collective pursuits, the Jans' continuing efforts to penetrate basic mysteries in neuroscience might prove to be their claim to posterity.

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