

Virginia Lee and John Trojanowski

Between lively banter and public debates, Virginia Lee and John Trojanowski have challenged Alzheimer disease researchers to look beyond the usual suspects. What's the secret of their success?

Take one petite, driven, classical pianist turned biochemist. Add one gangly, loquacious, Goethe-loving pathologist. Titrate with insatiable curiosity about demented brains, then stir in love and lab for 30 years.

The result: a duo that runs one of the world's leading teams in Alzheimer disease research.

Virginia Lee and John Trojanowski, who together direct the Center for Neurodegenerative Disease Research at the University of Pennsylvania, may well be the only collaborators who run a lab that produces more than 30 papers a year and—incredibly—remain happily married.

The two have carved out a leading role not only in Alzheimer research but in the broader quest to demystify neurodegenerative diseases. Their contributions to understanding what goes wrong in demented brains, “rank among the most significant of the last century,” says Nigel Cairns, who spent two years in their lab and is now director of the Betty Martz Laboratory for Neurodegenerative Research at Washington University in St. Louis. “Their influence has really been enormous,” Cairns says.

For years, Lee and Trojanowski defied the dominant theory in Alzheimer disease research: that plaques made of a sticky protein called amyloid-beta trigger the damage in demented Alzheimer brains.

They argued instead that tangles of the tau protein, the other pathologic hallmark of Alzheimer disease, cause the telltale symptoms. By elucidating the biology of tau, a protein that is found in a hyperphosphorylated form in the tangles, they opened up a new frontier in the study of the disease and a separate set of targets for drugs to combat it.

Lee has a master's degree in business administration from the Wharton School in Philadelphia. She got the degree in the early 1980s as an exit strategy if the Reagan administration's plans to privatize the US National Institutes of Health were to come to fruition. That background lends her a savvy about the industry that is rare in researchers. “I think [the companies] are realizing that they cannot ignore tau at this point,” she says, “though, to be fair, beta-amyloid is a more tangible target.”

Such open-minded attitudes are hard to come by in the acrimonious Alzheimer field.

Dale Schenk, the chief scientific officer and former head of neurobiology at the drug firm Elan, says he admires the pair for their adaptive approach. “They have been one of the few groups of scientists who have moved with the field and adjusted their research to the question at hand,” Schenk says.

Lee and Trojanowski met exactly 30 years ago in a Boston bar. Lee was born in Chongqing, in southwest China, to a traditional Chinese family, and had abandoned piano studies at the Royal Academy of Music in London when she realized she didn't have the makings of a world-class concert pianist. When they met, she was a postdoctoral fellow at Boston Children's Hospital, and he was getting ready to begin a residency in pathology at Harvard University.

“John walked by and I opened my mouth and said, ‘haven't I met you some place before?’ not knowing that it is a classical pick-up line,” she recalls. “The rest

is history.”

Lee says she had first laid eyes on Trojanowski two years earlier, across a table in a seminar room. “There was this fellow sitting opposite me, and there was something about him that intrigued me,” she says. “My heart skipped a beat. I thought, ‘I just want to get to know this fellow.’”

“I was plaque- and tangle-free,” he quips, laughing.

The two were soon a serious item. When she took a job in Philadelphia, he reluctantly relinquished a plum job at Massachusetts General Hospital to follow her. By 1981, both had become faculty members at the University of Pennsylvania. Before long, they realized they made a formidable combination. The center, which they launched in 1991, employs 50 and collects \$4 million in grants each year.

Both radiate the energy of people 20 years younger. He is an athletic six-foot-three and given to long discourses and historical asides. She is five-foot-seven, rail-thin and intense—and prone to correcting him.

He: “We are excited, 25 years into our careers in Alzheimer disease, to be at the beginning of a phenomenal opportunity for drug discovery.”

She: “We didn't work on it for 25 years. I would say since 1989, 1990.”

He (laughing): “I agree, I agree.”

There's plenty of disagreement too. Their scientific arguments are legendary and public—but productive. “I think they need these fights,” says Manuela Neumann, a neuropathologist at Ludwig Maximilians University in Munich who finished a stint in the lab in April. “Through [the fights], they come to the kind of answer they really want.”

The duo spent many years studying the tau protein. In 1998, Trojanowski and others identified six tau mutations in a group of families with an inherited dementia historically called Pick disease (*Nature* 393, 702–705; 1998). This was the first proof that tau pathology is enough to cause dementia. Proponents of the amyloid hypothesis had until then contended that tau in its pathologic form is merely a byproduct of Alzheimer disease.

“That was the first serious challenge to the amyloid cascade hypothesis,” says Cairns. “It opened a whole new field of research.” Today, more than 30 mutations in the tau gene have been discovered, and Lee and Trojanowski have been at the forefront of exploiting them, developing animal models of different tau mutations with drug discovery never far from their minds. In January 2005, they showed that mice genetically engineered to overproduce humanized tau develop motor weakness, and the drug Taxol corrects the defect (*Proc. Natl. Acad. Sci. USA* 102, 227–231; 2005).

They also continue work on a broad swathe of neurodegenerative diseases, assisted by a highly productive, international coterie of scientists.

Kelvin Luk, a postdoctoral fellow, arrived at the lab 16 months ago. “It just seemed like the mecca of neurodegeneration,” he says. But demands are high, and there is always pressure to produce. “There are definitely lots of stressful moments,” he says. “[Lee] is very performance-oriented.”

She's equally bold about telling Trojanowski when she thinks he's wrong.

He: “From the mid-80s until 1998, tau was always on the last day of any scientific meeting.”

She: “That's not entirely true.”

He: “It was called the ‘other’ session.”

She: “John does have a chip on his shoulder.”

He [laughing]: “Not anymore.”

Meredith Wadman, Washington, DC

