

The University of Pennsylvania's  
CENTER FOR NEURODEGENERATIVE DISEASE RESEARCH

25  
of groundbreaking  
research  
*Years*

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Center for Neurodegenerative Disease Research  
UNIVERSITY OF PENNSYLVANIA

## VIRGINIA M.-Y. LEE, PHD, MBA & JOHN Q. TROJANOWSKI, MD, PHD



*As we celebrate this 25th anniversary of the University of Pennsylvania's Perelman School of Medicine Center for Neurodegenerative Disease Research (CNDR), we would like to take this opportunity to recognize and thank all our supporters, research partners, and research participants for helping make the CNDR what it is today – one of the world's leading centers dedicated to curing Alzheimer's (AD) and Parkinson's (PD) disease, Frontotemporal degeneration (FTD), amyotrophic lateral sclerosis (ALS) and related neurodegenerative brain diseases.*

*You will see from the feature stories throughout this special edition newsletter that this is an exciting time for the field of neurodegenerative disease research, and that the CNDR team is poised to lead the way towards more effective cures and treatments for AD, PD, Lewy body dementia (LBD), FTD, ALS and other related disorders.*

*When we founded the CNDR 25 years ago, we could not have imagined the journey that lay ahead. But we knew we could not do this alone. We needed to create a partnership of talented investigators, generous donors, and families who had experienced the challenges of living with these diseases. That we have achieved this is a testament to your dedication and resiliency, and we are truly grateful.*

*Finally, we would be remiss were we not to recognize our incredible staff who have supported us all along the way. They are the glue that holds us together as we navigate the path forward. We would also like to extend our gratitude to Lisa Bain, our science writer for this special edition newsletter, who enthusiastically took on the task of telling CNDR's story through the following articles and interviews.*

**Virginia M.-Y. Lee, PhD, MBA**  
Director and Co-founder, CNDR

**John Q. Trojanowski, MD, PhD**  
Co-Director and Co-founder, CNDR

### The **HISTORY & MISSION** of the **CENTER FOR NEURODEGENERATIVE DISEASE RESEARCH**

When the Center for Neurodegenerative Disease Research (CNDR) was founded twenty-five years ago, a flurry of research had just begun to elucidate the molecular underpinnings of Alzheimer's disease. Three major discoveries had been made in the preceding seven years: first the identification of beta-amyloid as the protein deposited as plaques in the Alzheimer's brain, followed by evidence suggesting that tau was the protein component in tangles; and then in 1987, demonstration that a gene coding for the amyloid precursor protein (APP) was associated with a rare, inherited form of the disease.

Virginia Lee, PhD, and John Trojanowski, MD, PhD, working in their labs to better understand the link between tau and tangles recognized that progress in the field would require more than researchers working in isolation in their laboratories. Thus, with funding from the National Institute on Aging (NIA) of the National Institutes of Health (NIH) that launched the Penn Alzheimer's Disease Core Center (ADCC), they also conceived of and established the CNDR, a "center without walls," where investigators with different types of expertise and from multiple labs and departments could collaborate toward the common goal of increasing understanding of the causes and mechanisms leading to neurodegeneration and developing new and effective therapies.

Since that time, under the leadership of Lee and Trojanowski and with their team of over 60 University of Pennsylvania researchers,

CNDR has fueled an explosion of research into the mechanisms underlying Alzheimer's disease, Parkinson's disease, Lewy Body Dementia, Frontotemporal Lobar Degeneration, Amyotrophic Lateral Sclerosis, and other neurodegenerative diseases.

The Center is housed in the Maloney Building, in 6500 square feet of research space at the Hospital of the University of Pennsylvania in the heart of the Penn campus. From this central location, it fosters multidisciplinary collaborations between basic and clinical scientists at Penn and beyond, and provides training and pilot grants as well as a wide variety of resources to support research projects. These resources include a brain and biosample bank, a drug discovery program (*for more, see p. 4*), data management and biostatistics support, and expertise in biochemistry, histology, molecular biology, microscopy, tissue culture, and genetics.

Even as brain science and the technologies to study the brain have advanced, the mission of the CNDR remains the same – to increase understanding of the causes and mechanisms that lead to brain dysfunction and degeneration in Alzheimer's disease, Parkinson's disease, motor neuron disease, and other less common neurodegenerative diseases that occur more frequently with advancing age. Through the pursuit of these goals, CNDR investigators hope to hasten the arrival of a time when these diseases can be treated effectively and no longer devastate the lives of people as they age, said Dr. Lee.

## a conversation with **DRS. LEE & TROJANOWSKI**

Some twenty-five years ago, when John Trojanowski, MD, PhD, first envisioned a Center for Neurodegenerative Disease Research (CNDR), Virginia Lee, PhD, saw only the additional paperwork that would be required. Since they were both already well established in the field, she thought, “what do we need a center for?” But he convinced her that branding and identifying CNDR as a common locus for studies of Alzheimer’s (AD) and Parkinson’s (PD) disease as well as frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) or Lou Gehrig’s disease was very important to pursue; and they both knew that the mission – to find cures for these neurodegenerative diseases – was not something that they alone could solve. They would need a team, infrastructure, an environment that would be welcoming to a multidisciplinary group of collaborators, and of course, funding. “And that is the dream for CNDR that has come true,” said Trojanowski.

Thus, the Center for Neurodegenerative Disease Research or CNDR was created, with Trojanowski and Lee as co-directors. Later, when Trojanowski became director of the Institute on Aging, Lee took over as director of CNDR with Trojanowski as Co-director.

Today, about 60 scientists with a range of skills and expertise have joined the CNDR team, many of them working at the Center for more than ten years, providing stability and institutional memory, said Lee. Other Penn scientists – such as Viviana Van Deerlin, MD, PhD, Gerard Schellenberg, PhD, and Li-San Wang, PhD -- partner with CNDR, further broadening the research scope. The Center also boasts a Neuropathology, Biomarker, and Genetics biobank – including over 1700 brains from patients with AD, PD, FTLD, ALS, and other less common neurodegenerative diseases, who were followed longitudinally as their diseases progressed – supported by National Institutes of Health grants and philanthropy. The biobank also collects DNA, plasma, and cerebrospinal fluid (CSF) specimens. An Integrated Neurodegenerative Disease Database (INDD), under the direction of Sharon Xie, PhD, professor of biostatistics, captures information from the biobank with clinical and demographic data, generating a platform for discovery research that is accessible to research teams across disease areas, specialties, and institutions.

“CNDR may be the only, or one of very few sites, that cut across all the neurodegenerative diseases in one location, with information from living patients all the way to the analysis of postmortem tissue,” said Lee. “In the last few years, we and others have begun to recognize the fact that there is a lot of cross-over among these different diseases, so that puts us in a unique situation to be able to look at all of them together.”

“What we set out to do from the get-go was to identify the protein building blocks of pathology in the neurodegenerative-diseased brain, and we systematically did that,” said Lee. First, they identified tau as the main component of the “tangles” in the AD brain (Lee et al, Science, 1991); then they showed that alpha-synuclein (a-syn) is the protein that forms clumps called Lewy bodies in the brains of people with PD and dementia with Lewy bodies or DLB (Spillantini et al, Nature 1997).

Later, they showed that a protein called TDP-43 forms the pathological lesions in ALS and some forms of FTD (Neumann et al, Science, 2006). (See p. 5 “Groundbreaking Discoveries” for more).

After identifying these proteins, Lee and colleagues generated mouse and cellular disease models that mimic the disease pathologies in humans. These models, particularly those generated more recently using material from diseased human brains to induce disease in mice, have allowed CNDR scientists and others to study disease mechanisms and formulate different hypotheses: First, they have proposed the “transmission hypothesis” that helps explain how pathology spreads throughout the brain; and more recently the “strain hypothesis” that may explain how the same protein can produce different diseases by taking on different conformations (Guo and Lee, Nat Med, 2014; Brettschneider et al, Nat Rev Neurosci, 2015).

“Think of the proteins as a ball of silly putty, which you can make into a ball, a square, or a snake,” said Trojanowski. “We think these different shapes or conformations impart different clinical and pathological features in the brains of people affected by these diseases.”

“This is a very exciting phase, perhaps the most exciting phase of our careers,” said Trojanowski.

The mouse and cell models developed at CNDR are being used not only for discovery research but to translate these discoveries into new therapies. “Pharmaceutical companies want the latest models coming from CNDR, and we now have three partnerships with them,” said Lee. (See article on p. 4 for more on the CNDR Drug Discovery Program).

Trojanowski added, “The reason pharmaceutical companies knock on CNDR’s door is because they see that this team understands these neurodegenerative diseases and the basic science related to them. I am a neuropathologist, neuroanatomist, and have a clinical understanding; Virginia is a phenomenal biochemist, cell biologist, and neuroscientist who is amazing at coming up with new assays and model systems to interrogate and screen drugs in these neurodegenerative diseases – so working with her is a magical combination of skill sets.”

Just as importantly for the long-term sustainability of the Center, CNDR provides an extraordinary training ground for the next generation of scientists. (See article on p. 8 for more). Over the last 25 years they have trained hundreds of scientists, from high school students to college level undergraduates, graduate students, and post-doctoral fellows. Some of the best among these trainees have subsequently been hired as Penn faculty, including Eddie Lee, MD, PhD, and Kelvin Luk, PhD (Department of Pathology and Laboratory Medicine); and Alice Chen-Plotkin, MD (Department of Neurology).

As pioneers in neurodegenerative disease research, Lee and Trojanowski also take seriously their role as advocates, communicating with the public about the importance of these diseases and the impact they are having and will have in the future on millions of Americans who will develop them. “It’s not just our voice alone, but our efforts to educate leaders of our country about the cost and pain of these diseases has had the positive consequence of increased funding,” said Trojanowski.

Photo credit: Scott H. Spitzer, University of Pennsylvania, Office of University Communications

# The CNDR DRUG DISCOVERY PROGRAM

A central goal of CNDR - developing effective treatments for neurodegenerative diseases – received a major boost in 2004 when the Marian S. Ware Alzheimer Program was established, with one of its four components focused on drug discovery for Alzheimer’s disease. Since then, CNDR’s drug discovery program has expanded its scope to include Parkinson’s and other neurodegenerative diseases, with Kurt Brunden, PhD, recruited in 2007 to lead this joint program. Funding comes from the National Institutes of Health, Marian S. Ware and Woods Foundations, several pharmaceutical companies, and grants from other philanthropic organizations, including BrightFocus, COINS for Alzheimer’s Research Trust, CurePSP, and the Michael J. Fox Foundation for Parkinson’s Research.

The Program enables the seamless translation of basic science discoveries to preclinical and clinical studies, said Brunden. For example, building on research showing that the neurofibrillary tangles seen in the AD brain are composed of misfolded forms of the protein tau (see “Groundbreaking Discoveries” p. 5), Brunden and colleagues have investigated various compounds that target tau. The normal job of tau is to stabilize cellular structures in neurons called microtubules, which carry information through the nerves similarly to how train tracks shuttle cargo. In AD, it seems, misfolding prevents tau from doing its job, resulting in faulty microtubule “tracks” and poor cargo delivery.

**“In the AD brain, it’s clear that there are multiple pathological features.”**

CNDR researchers reasoned that cancer drugs that stabilize microtubules might also be useful in treating AD, said Brunden. Most of these cancer drugs are unable to get into the brain, but in 2010, they identified one drug, epothilone D (EpoD), which can cross the blood-brain barrier and appeared to both reduce the number of tangles and improve cognition in mice. Subsequent studies at CNDR extended this research, showing that the compound had the pharmacological properties of a useful drug.

It was time to hand the project off to a pharmaceutical company with the resources necessary to conduct clinical trials. In this case, the data were sufficiently compelling that Bristol Myers Squibb, which owns the drug and further validated the potential of EpoD, started a 9-week Phase 1b trial in humans with AD. Phase 1 studies are small and short, designed to evaluate safety, not effectiveness.



**KURT BRUNDEN, PHD**

*Research Professor and Director of Drug Discovery, CNDR*

“I think 9 weeks is too short to see any significant improvement in cognitive outcomes,” said Brunden. Thus, he was not surprised when the trial showed no improvement in efficacy endpoints, although the drug appeared to be well tolerated by AD patients. At about that time, BMS disbanded their AD research group and the epothilone D development program was halted.

But Brunden and colleagues were not ready to throw in the towel. “We continue to pursue second generation microtubule stabilizing agents with funding from the NIH,” he said. EpoD is a derivative of a natural product and difficult to synthesize in the lab. “We wanted to make simpler molecules and a classical drug that could be made in four or five steps, so we have been focusing on a new series of compounds known as pyrimidines, which seem to have the right stuff.” A few months ago they published a paper showing that these drugs get into the brain, stabilize microtubules, and appear to be safe. The next step: testing for effectiveness in mouse models.

Meanwhile, Brunden’s team is also investigating other potential therapies that target different pathologies.

“In the AD brain, it’s clear that there are multiple pathological features,” he said. Many of the current AD drugs in clinical trials target amyloid plaques in the brain, but Brunden said that these drugs alone may provide only partial benefits. “Even if you treat a patient who has early AD with one of those drugs, the train has already started rolling down the track, so you may also need a drug that specifically targets tau to get the full benefit,” he said.

For now, Brunden thinks it makes more sense for pharmaceutical companies to focus on single therapies. “But I think all of us recognize that ultimately, combination therapies are going to be required for Alzheimer’s and other neurodegenerative diseases.”

## GROUNDBREAKING DISCOVERIES

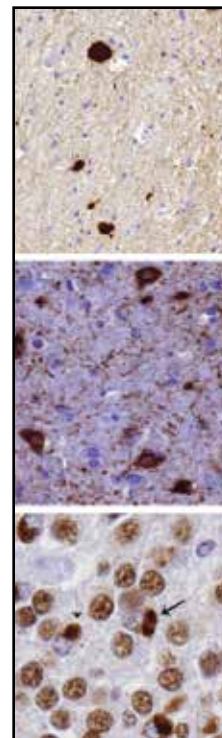
Since its early days, the CNDR Research Program has been driven by the hypothesis that diverse neurodegenerative diseases arise from the ‘fatal attraction’ of brain proteins. In 1991, John Trojanowski, MD, PhD, and Virginia Lee, PhD, demonstrated conclusively for the first time that the filaments that form the characteristic neurofibrillary tangles seen at autopsy in the brains of people with Alzheimer’s disease were composed of aggregated tau protein. This finding was controversial, since although scientists had suspected for some time that tau played some role in AD, the prevailing theory was that the major pathology was the amyloid plaque. Today there is widespread agreement in the field that both plaques and tangles are necessary in AD, and that aggregation of misfolded tau is responsible for a wide spectrum of neurodegenerative diseases collectively called “tauopathies”.

Subsequently, in 1997, CNDR researchers made another groundbreaking discovery when they showed that the Lewy bodies that characterize Parkinson’s disease (PD) and Dementia with Lewy Bodies (DLB) are made up of another aggregated misfolded protein, in this case  $\alpha$ -synuclein. Then in 2006, the CNDR team hit the trifecta when Manuela Neumann, a post-doctoral fellow in Lee’s lab, identified another protein – TDP-43 – that forms aggregates in the brains of individuals with frontotemporal lobar degeneration and amyotrophic lateral sclerosis. As summed up by Trojanowski in a 2011 story in Science Watch, the team “put a molecular face on these pathological structures” – tau in tangles, alpha-synuclein in Lewy bodies, and TDP-43 in ALS and FTLD. It is now believed that accumulation of aggregated misfolded proteins is a feature of most, if not all, neurodegenerative diseases, which has given the field many ideas for designing therapies, for example, by inhibiting aggregation or eliminating the aggregates.

At CNDR and elsewhere, investigators also began pursuing another idea: what if these misfolded proteins are also responsible for spreading the pathology from one cell to another. This “transmission hypothesis” for neurodegenerative diseases would help explain not only why these diseases spread throughout the brain in very predictable patterns, but also suggests other possible therapeutic approaches.

In 2011, Dr. Lee and post-doctoral fellow Jing Guo (now with Denali Therapeutics) showed that they could induce cells to form aggregates that looked like tangles by “seeding” the cells with minute quantities of misfolded tau fibrils. The impact of this discovery, combined with related research from scientists at other institutions, has been enormous, with a rapidly expanding body of literature supporting the transmission hypothesis. The CNDR team went on to show that this same phenomenon could be induced in mouse models, and in the most recent major discovery to emerge from Lee’s lab, her team showed that using tau fibrils purified from AD brains caused tau inclusions to form and spread in anatomically connected brain regions.

These new findings are especially important in terms of moving forward with developing potential treatments for AD. “It is essential for us to have animal models to test the efficacy of potential treatments before they go into humans,” explained Lee.



Misfolded Proteins, top to bottom: Lewy bodies, tau, and TDP-43

## SOLVING THE PARKINSON’S PUZZLE

More than 10 million people worldwide experience the chronic, disabling, progressive symptoms of Parkinson’s disease (PD): motor problems such as tremors, rigidity, poor balance, and incoordination; as well as non-motor problems that can be even more debilitating than the motor issues, including cognitive impairment and mood disorders. Yet although it has been some 60 years since scientists identified the root cause of the motor symptoms of PD – degeneration of neurons that produce dopamine – and developed treatments that provide some relief of those symptoms, there remains no cure and few treatments for non-motor symptoms. Moreover, for many people these treatments lose effectiveness over time and cause substantial side effects.

CNDR has been home to a pioneering research program on PD since its inception. In 2005, it was strengthened further when Kelvin Luk, PhD, began a postdoctoral fellowship with the intention of studying how the basal ganglia is “deconstructed” in PD. Four years later, Luk was hired as a research assistant professor to pursue his interest in exploring the role of the protein  $\alpha$ -synuclein in this process. It was already known that  $\alpha$ -synuclein is the major component of the Lewy bodies that are a key distinguishing feature in PD brains, but Luk wanted to know how those clumps form and how they cause neurodegeneration. It had only been several years since the idea that misfolded proteins could be responsible for neurodegenerative disease had begun to gain traction in the scientific community, he said.

First, he needed to find a way to get the protein to aggregate in the cells he was working with. “We had the idea that if we introduced a small amount of protein that was already aggregated, it would serve as a seed,” he said. After testing this idea in a test tube, where it worked “tremendously well,” Luk showed that the same phenomenon happened in cultured neurons and then in living mice. That’s when the idea of seeding and transmission really began to take off, he said. Not only had they replicated the aggregation phenomenon in a living animal, but they also showed that the patterns of spread in the brain, and the behaviors in the mice, were consistent with what is known about the disease in humans.



But there were many more questions to answer: How does the initial seeding even take place? Why does the neuron take up the seed? How does it spread to the next cell? And how does the cell respond to the presence of the aggregated protein?

Luk said his team has focused on the last part of the puzzle: why is aggregated  $\alpha$ -synuclein so bad for neurons. “We’ve recently found that it’s more toxic to some neurons than to others and we’re beginning to figure out some of the pathways involved,” he said. For example, they have shown that aggregation induces oxidative stress in vulnerable neurons. Although how that occurs is still a mystery, it offers a clue for treatment development, he said.

They also found that it is not only dopamine-producing neurons that are vulnerable in the human disease, but other types of neurons as well. The mouse models they developed have been a powerful tool for teasing out this and other aspects of the disease in a single experiment. “We can address the initial triggering of the aggregation, the spread, cell death, and then what happens after that in terms of neurochemical changes, behavioral changes, etc.,” he said. “And the in vivo models also have the advantage of being a good tool for us to test treatment strategies.”

One of the treatment strategies being tested in collaboration with Drs. Trojanowski and Lee and Kurt Brunden, Director of the Drug Discovery Program, is to try to halt the cell-to-cell spreading of misfolded proteins with antibodies or other molecules, but there is a lot more going on in Luk’s lab. “We’re trying to tackle the basic science of this disease from a number of angles.” This includes understanding the mechanisms of each step: what triggers  $\alpha$ -synuclein aggregation, toxicity, and cell-to-cell transmission. “I think that any of these represents a potential treatment target if we can have a handle on the mechanism,” he said.



**KELVIN LUK, PHD**

Research Assistant Professor, Center for Neurodegenerative Disease Research, Perelman School of Medicine, University of Pennsylvania

# Celebrating 25 Years

with the supporters and friends who make it all possible

In honor of CNDR's 25 years of groundbreaking research, Penn Medicine organized an intimate anniversary event generously hosted by longtime supporters and friends of CNDR, Bob Lane, who is also an Institute on Aging (IOA) External Advisory Board (EAB) member, and his wife Randi Zemsky, at their home in the Rittenhouse Square section of Philadelphia.

The event celebrated the work of CNDR over the past 25 years and highlighted research breakthroughs still on the horizon. It was also an opportunity to bring together and thank many of the Center's supporters. The event was attended by David B. Roth, MD, PhD, Chair of the Department of Pathology and Laboratory Medicine, CNDR researchers, IOA EAB members, supporters of the Center and close friends of the hosts.



Left to right: David Roth, MD, PhD, Kurt Brunden, PhD, Virginia Lee, PhD, John Trojanowski, MD, PhD, and Bob Lane.



Event hosts, Bob Lane and his wife, Randi Zemsky, with Drs. Lee and Trojanowski.

## GIVING TO CNDR

### a donor story with Arthur Peck, MD

As a geriatric psychiatrist for more than four decades, **Arthur Peck, MD**, has intimate knowledge of the challenges faced by people with Alzheimer's disease and other neurodegenerative diseases. Now retired, Peck said working with patients made him acutely aware of the lack of treatments for people with dementia. "We could nibble at the edges with support or with symptomatic treatments for accompanying episodes of depression or anxiety, but we had nothing to offer that changed the basic process," he said. "I was waiting and waiting while money was going for everything else to find an organization that was centering their efforts on neurodegenerative diseases, and finally I found it!"

The organization was CNDR, and Peck has become one of its treasured supporters. He recently signed a five-year commitment to the Center to signal his intent to continue his support until at least 2020. He also bequeathed a portion of his IRA to CNDR at the time of his death and established four charitable gift annuities at the Perelman School of Medicine (he obtained his medical degree from Penn in 1952) with instructions that the proceeds be used to support CNDR.

**"My feeling was that if I'm going to give my money for research, I'd like to do it where it will be most helpful."**

In appreciation of Peck's generosity, Drs. Lee and Trojanowski meet with Peck every year. "They set time aside and prepare a presentation for an audience of one -- that's me," he said. "And they have the patience to try to answer whatever questions I can muster up." These meetings give Peck a sense of what is happening at the CNDR and in the broader world of dementia research, he said. "And in the process, it gives me a chance to get to know them on a first-hand basis."

Peck's support of the Center does not stop with his checkbook. "Even though I am long since retired, the subject of dementia comes up frequently when I'm out socially or with people I barely know who hear that I was a geriatric psychiatrist," he said. "I make sure to tell them that there is a center that is devoted to research on just those problems, and point out that compared to where things were 25 years ago, we have come a long, long way."

He compared the progress made to that seen in the cancer field. "We're beginning to see that what is required is not a single magic bullet, but understanding the molecular basis of these diseases. That's where I found the Center doing exceptional work."



Center for Neurodegenerative Disease Research (CNDR) lab members. *Not all members are pictured.*

# TRAINING *the* NEXT GENERATION of SCIENTISTS

*Keeping CNDR relevant as knowledge about neurodegenerative diseases evolves requires the constant infusion of new blood, new technologies, and new ways of thinking. From its inception, one of the Center's key missions has been training the next generation of scientists, beginning at the undergraduate level and continuing through graduate and post-doctoral fellowship experiences.*



**Edward (Eddie) Lee, MD, PhD**, first arrived on the Penn campus as an MD-PhD student in 1997. As part of the PhD program, he rotated through several different laboratories, ultimately choosing to do his thesis in Virginia Lee's lab. He graduated in 2005 with an MD-PhD, then did a residency and fellowship

in neuropathology, followed by a postdoctoral fellowship. In 2011, he received a faculty appointment to the Department of Pathology and Laboratory Medicine at Penn. Dr. Lee was supported by an NIH/NIA-funded training grant, now in its 20th year at Penn which supports the education and mentoring of young investigators conducting research in age-related neurodegenerative diseases.

Now, he is a trainer of other budding scientists: two of the graduate students working in his lab are supported by the same grant program. "I think I'm the only person who's been a pre-doc, postdoc, and trainer on that grant," he said with a laugh.

Completing a PhD, medical degree, fellowship, and post-doctoral program all at the same institution, and then joining the faculty is somewhat uncommon, but made sense for Lee. "I thought Penn had the best blend of clinical neuropathology and research," he said. "And there's such an infrastructure here – the brain bank and a lot of great collaborators I've worked with over many years. It's difficult for other places to match that level."

Clinicians, geneticists, and basic researchers all work together at CNDR, sharing data, reagents, and whatever else is needed, he said. "The center has been built up with that kind of ethos, which really helps everybody – junior people and senior people alike."

"I think it's one of the few places – there are probably less than three or four in the world – where a researcher can go from a patient level – meaning MRI studies and neuropsychology tests – down through genetics and human tissue to mice, drosophila, and yeast, and anywhere in between those levels," said Lee.

"We're very good at crossing those different boundaries because the Center allows us to share whatever we are doing," he said.

While not everyone who trains at CNDR ends up pursuing a research path, the CNDR experience can nevertheless be transformative. Bryan Zoll, for example, currently a second-year medical student at Temple University was a biology major at Penn when he began working with Jing Guo, PhD, a postdoctoral fellow in Virginia Lee's lab studying the molecular mechanisms of tau spreading. In a gap year between his undergraduate degree and medical school, he returned to CNDR to work as a research technician.

**"I thought Penn had the best blend of clinical neuropathology and research."**

"My work at CNDR was something that allowed me to continue my passion for biology while aiming for the ultimate goal of medical school," he said. With plans to pursue a specialty in internal medicine, Zoll thinks his experiences at CNDR will prove valuable.

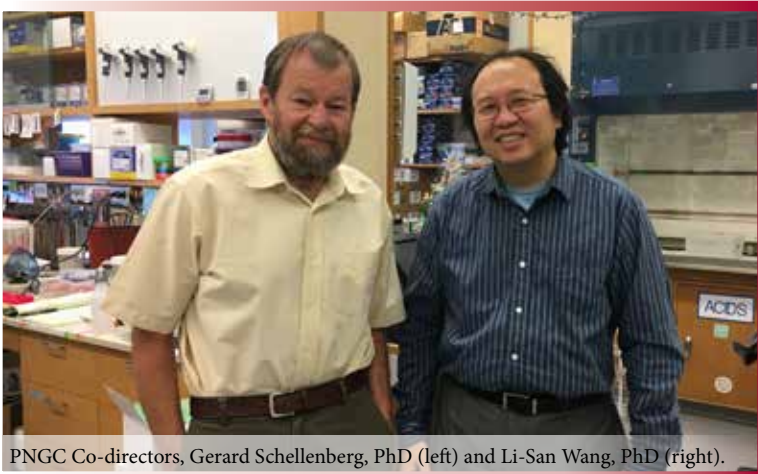
"I'm going to be seeing a lot of neurodegenerative disease and a lot of the sequelae of neurodegenerative diseases, so it will both inform my decision making and give me an idea of what's happening molecularly," he predicted.



### A National Hub for Genetic Research

During the past decade, an explosion of research on the genetics of Alzheimer's disease has provided important insight into disease mechanisms and led to the identification of many potential treatment targets. At the same time, genetics has become an increasingly important part of the CNDR framework; and in July 2016, the Department of Pathology and Laboratory Medicine at Penn established the Penn Neurodegeneration Genomics Center (PNGC) to serve as a national hub for genetics research on AD and other neurodegenerative diseases. Directed by Gerard Schellenberg, PhD, and Li-San Wang, PhD, PNGC brings together under one umbrella several national genomics projects funded by the National Institutes of Health (NIH) and based at Penn – The AD Genetics Consortium (ADGC), the AD Sequencing Project, the Consortium for AD Sequence Analysis, the Coordinating Center for Genetics/Genomics of AD, and the National Institute on Aging's Genetics of AD Storage Facility.

Why create another center? According to Wang, PNGC will streamline all the genomics resources that have been developed at Penn, enabling investigators to more efficiently translate genetic findings into a deeper understanding of biology and new treatment targets. Schellenberg added that it will also increase visibility across the Penn campus for the platform and resources he and Wang have built. "We collaborate with scientists both nationally and internationally, but very few here at Penn," he said. Yet the resources they have amassed, including large amounts of sequence data as well as the technical ability to process and interpret these data, could provide researchers from many different fields with tools not previously available in their individual labs, extending the technical capabilities and expertise of the center beyond Alzheimer's disease and neurodegeneration.



PNGC Co-directors, Gerard Schellenberg, PhD (left) and Li-San Wang, PhD (right).

Schellenberg said that the first step is to assemble large amounts of genetic data; then to make it available to other researchers and devise tools to aid in its analysis. Wang said the enormous size of the data set presents many challenges in terms of storing, sharing, and processing extremely large datasets, and ensuring the quality of data.

"This is a rapidly changing world in terms of analysis," said Schellenberg. Not only are methods changing, but the reference genome, which was originally produced as part of the Human Genome Project and is meant to represent all human genes, is constantly being improved as scientists fill in gaps and correct errors. "Every time it's improved we have to go back and redo a fair amount of analysis. It's a moving target, and when the data are so big, it's a really difficult target to move on," he said.

**"The field has moved to thinking about how to prevent Alzheimer's disease, and to do that you need to be able to predict who is going to get it ten or fifteen years before hand."**

Schellenberg said that despite the advances of the past 10 years, the genetics of Alzheimer's disease is still largely unknown and that consequently, the drug targets being pursued today are based on genetics done in the 1990s. "But I would say within five years, or ten at the most, we'll have a complete understanding of how genetic variations contribute to whether or not you get AD," he predicted. Moreover, "pharmaceutical companies recognize that if there is a genetic basis for a target, the chance that it will be successful in terms of developing a drug that works goes up by a factor of two," he said.

"We're also going to develop new tools, new knowledge, and new systems to understand the biology behind a genetic signal associated with Alzheimer's and why it increases the risk of disease," said Wang.

Schellenberg agreed.

"In the long run, the field has moved to thinking about how to prevent Alzheimer's disease, and to do that you need to be able to predict who is going to get it ten or fifteen years before hand, before any biomarker kicks in that you can measure. That's where genetics fits in in terms of prediction," said Schellenberg.

# Acknowledgements

across the

## THE IMPACT OF CNDR // an interview with David Roth, MD, PhD

In his two roles as chair of the Department of Pathology and Laboratory Medicine -- the departmental home of the CNDR -- and director the Penn Center for Precision Medicine, David Roth, MD, PhD, views Drs. Lee and Trojanowski, as key players. "They are really good scientists and relentless in the pursuit of their ideas," he said. They also excel at getting funding from multiple sources and have made some incredible hires and recruited excellent trainees, he added.

Many pathology departments at other research universities focus heavily on clinical diagnostics, said Roth, but CNDR has brought a very strong research orientation to the neuropathology division. Indeed, he said that Penn's Department of Pathology and Laboratory Medicine is consistently one of the top three departments of pathology in terms of NIH research funding, which he attributes in large part to the efforts of Lee and Trojanowski. They submit very targeted, very strategic grants to NIH, almost all of which get funded, said Roth.

Roth said the Department has also invested heavily in human capital and building infrastructure over the past 20 years to support research on both neurodegenerative diseases and cancer. "We have a cadre of really amazing scientists," he said. In 2007, Penn's Institute on Aging (IOA), CNDR and the Department jointly recruited Li-San Wang, PhD, a bioinformatician who had recently completed a postdoctoral fellowship at Penn; and shortly thereafter hired Gerard Schellenberg, PhD, a cell biologist and expert in the genetics of AD. Not all the exemplary CNDR hires have been in the Pathology and Laboratory Medicine, said Roth, noting especially Alice Chen-Plotkin, MD, a joint hire by IOA, CNDR and the Department of Neurology, who Roth called "pretty spectacular."



Moving forward, Roth said his strategic plan for his Department includes a heavy focus on bioinformatics. Hiring Wang and Schellenberg was a huge step in that direction, said Roth.

"In essence, the CNDR brought in these guys, which spawned a new center," -- the Penn Neurodegeneration Genomics Center (PNGC - see article on pg. 9).

Roth thinks the work of CNDR will also be reflected in new precision medicine initiatives, particularly because of the PNGC's work in identifying genetic targets for neurodegenerative diseases, as well as advances made by CNDR scientists in identifying biomarkers for Alzheimer's disease and other neurodegenerative diseases. "What works in one person is not going to work in another, so the more specific we can be with biomarkers and diagnostics, the better," said Roth.

**"They are really good scientists  
and relentless in the pursuit  
of their ideas."**

Roth added that on a personal level, the multidisciplinary nature of CNDR has broadened his research vision. "It's been kind of wonderful to get to know people in the movement disorders' clinic, and inspired me to fund a precision medicine project on Parkinson's disease," he said. Movement disorders are not typically on the radar screen of pathologists since they rarely see tissue specimens from these patients, said Roth, but because of the PNGC and CNDR, he was brought in proximity with Chen-Plotkin and others. "That has been really enriching for me."

# UNIVERSITY OF PENNSYLVANIA

*a message from* **DEAN JAMESON**



I want to congratulate the Center for Neurodegenerative Disease Research on achieving this 25th anniversary milestone. CNDR exemplifies the ethos that has fueled Penn Medicine's long history of transforming scientific discoveries into better care of patients -- cross-disciplinary collaboration, technological innovation, and a strong focus on translation into clinical practice.

None of this would have been possible without the pioneering leadership of Virginia Lee and John Trojanowski. Their vision of advancing our understanding of neurodegeneration by bringing together expertise across multiple disease areas has proven prescient as we now see the field converging on a common mechanism for most of these diseases.

In the United States and around the world, we are facing the looming challenge of caring for an aging population and the increasing prevalence of chronic disabling diseases, especially Alzheimer's and other progressive neurodegenerative diseases. Here at Penn we are well-positioned to meet these challenges, in large part because of the impactful work of the scientists at CNDR, the Institute on Aging, the Alzheimer's Disease Core Center, and the Udall Parkinson's Research Center of Excellence.

We have also recently established a research program on the genetics of neurodegenerative disease that is unmatched in the world. At the same time, we are expanding our clinical programs to ensure that patients with these diseases receive the most advanced care options available.

To all the scientists, staff, and supporters of CNDR, I want to express my gratitude for your dedication and innovation. I am confident that as we move forward, the CNDR will continue to lead the way in discovering solutions to alleviate the suffering of people with neurodegenerative diseases.

A handwritten signature in black ink that reads "Larry".

**J. Larry Jameson, MD, PhD**  
Executive Vice President, University of Pennsylvania for the Health System  
Dean, Perelman School of Medicine

## CNDR | Celebrating 25 Years of Groundbreaking Research



**University of Pennsylvania**  
**Perelman School of Medicine**  
**Center for Neurodegenerative Disease Research**

**Director**

Virginia M.-Y. Lee, PhD, MBA

**Co-Director**

John Q. Trojanowski, MD, PhD

*The mission of the Center for Neurodegenerative Disease Research (CNDR) is to promote and conduct multidisciplinary clinical and basic research to increase understanding of the causes and mechanisms leading to brain dysfunction and degeneration in AD, PD, LBD, FTD, ALS, PLS, MND, and related disorders that occur increasingly with advancing age. The overarching goal is to find better ways to diagnose and treat these disorders. Implicit in this mission is a commitment to training the next generation of researchers.*

**25th Anniversary Special Edition Newsletter**

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