

# INSTITUTE ON AGING

Special Edition 2011

Penn Alzheimer's Disease Core Center

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Basic Science  
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21  
years

## Two Decades of Progress and Counting: The Penn Alzheimer's Disease Core Center

The Penn Alzheimer's Disease Center (ADC) was not the first of the 29 ADCs established nationwide, but throughout its 21 years it has been in the vanguard of progress toward a treatment, cure, or prevention strategy against AD and other types of dementia.

Originally conceived in the late '70s by the eminent physician, scientist, and author Lewis Thomas, who was then president of Memorial Sloan-Kettering Institute and had experience with the National Cancer Institute (NCI) Cancer Centers program, the ADCs were envisioned as a means of developing a broad-based research effort at a time when aging and AD languished behind more established scientific disciplines.

The task of creating the ADC program was handed over to Zaven Khachaturian, PhD, the Associate Director for the Neuroscience and Neuropsychology of Aging Program at the National Institute on Aging (NIA). The first ADCs were launched in 1984, and in 1990, a congressional mandate

expanded the program. Penn's ADCC was funded in 1991 and "has been a very productive center ever since," said Creighton (Tony) Phelps, PhD, who has directed the ADC Program at the NIA for the past 20 years.

According to Dr. Khachaturian, establishing the Centers gave the field recognition and visibility at a time when few academic medical centers had established programs in aging or Alzheimer's disease. From a scientific perspective, the Centers also created a vehicle for conducting systematic longitudinal studies and for integrating basic research with clinical care. Thus, the Centers were required to have clinical, neuropathology, and education cores, and they provided funds for pilot studies in order to attract new investigators to the field.

The Centers also provided a network on which to build multi-site projects, including the AD Clinical Studies (ADCS) and the AD Neuroimaging Initiative (ADNI) projects. "That's been one of the biggest strengths of the ADCs,"

*Continued on page 2*



Research in brain aging at Penn

MESSAGE FROM THE DIRECTOR



*Congratulations to all involved with the Penn Alzheimer's Disease Core Center (ADCC)! This August, we received a renewal grant from the NIA to fund research efforts here at Penn through the Penn ADCC's 25th year of operation in 2015. In this incredibly competitive grant process, the renewal comes as strong encouragement and support for the research path we have been pursuing at the Penn ADCC.*

*For the next five years, the Penn ADCC will concentrate on plasma, CSF, and genetic biomarker studies of AD; we will further explore related dementias like FTL and DLB/PPD and will work to characterize AD and related disorders in urban Latinos. It's a tall order, but one, with the addition of the new facilities at Perelman and the new staff, that I believe wholeheartedly we will meet with great success. The need to know more is great and increasing with each day. One has only to look at*

*the growing numbers of those affected by AD, Parkinson's, and related neurodegenerative diseases. Together, as a team, we at Penn will continue to work to decipher the mystery of Alzheimer's. Please read on for more information on our efforts and our progress.*

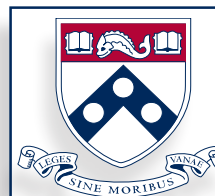
History of the Penn ADCC

Continued from front cover

said Dr. Phelps. "Now we're doing the AD Genetics Consortium (ADGC), based at Penn, with all the Centers contributing samples and patients for genome-wide association studies (GWAS)." Data from the ADGC, as well as from the National Cell Repository for Alzheimer's Disease (NCRAD) based at Indiana University, is all collected at the National Alzheimer's Coordinating Center (NACC), which is based at the University of Washington School of Public Health.

Aging had long been an area of active research at Penn when the ADCC was created - the Center for the Study of Aging had been established in 1979 - but AD research was just getting started. Dr. Trojanowski and colleagues had just been awarded their first program project grant from the NIA on Molecular Substrates of Aging and Neuron Death. This grant set the stage for what was to come at the Penn ADCC, and indeed, from the field in general.

The Penn team decided to structure their center as an Alzheimer's Disease Core Center (ADCC), which meant that the funds were used primarily to support the development of infrastructure that could be leveraged to get other grants by researchers from multiple disciplines across the University. In contrast, some ADCs are structured as research centers (ADRCs) and use the funds to support research projects as well as infrastructure. "My view was that we could always get money to do research from outside the center, but our priority was to support clinicians and build the infrastructure," said Dr. Trojanowski. Indeed, the ADCC has proved to be a "huge driver of research," he said, enabling the recruitment of research cohorts needed to conduct studies, supporting the collection of biofluids and



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## History of the Penn ADCC



DNA, supporting the establishment of a “brain bank” to collect autopsy tissue for neuropathologic studies, and eventually, facilitating the development of a data management and biostatistics core that could manage the massive amounts of data collected in these various studies. The Penn ADCC also includes an education core that disseminates information both within the ADCC community and to the public at large.

Said Nina Silverberg, PhD, Program Officer for the ADCCs, “The infrastructure as well as the network provided by Alzheimer’s Disease Centers has helped to shape the major advances in understanding AD. The centers provide a unique environment where basic and clinical research come together to advance the science. We hope that the information gained from this research will lead to opportunities to prevent or treat AD in diverse populations in the near future.”

While the focus is on the Cores, the Penn ADCC supports a pilot grant program that is designed to encourage researchers from disparate fields to turn their attention and expertise toward investigations of dementia. “The ADCC has been a great generator for collaborations and an incubator for new ideas,” said Dr. Trojanowski. Here too, the judgment of the ADCC leadership has been prescient. Among the first pilot projects funded was one by then Assistant Professor Jim Eberwine, PhD, to study what happens at a molecular level in an area of the brain called the hippocampus when a person has AD. Dr. Eberwine and the other initial pilot grant awardees have all gone on to become leaders in their respective fields and have made important discoveries about AD and

other dementias.

Dr. Eberwine used his pilot grant to gather data from single cell studies, which showed that there was genetic material in the plaques and tangles found in AD brains, and also to get some baseline gene expression data from individual hippocampal neurons in a rat model. These data were eventually used in successful applications for multiple NIH grants that have demonstrated the importance of understanding disease processes at the level of a single cell.

“When people look for disease genes, they try to find SNPs [single nucleotide polymorphisms, which are tiny changes in the normal DNA sequence] or mutations that are associated with the disease state,” said Dr. Eberwine. “These genetically identified disease-related genes impact the normal cellular environment and our data suggest that multiple genes and coordinated changes in gene expression underlie the disease process. So to look at those coordinated changes in disease cells versus normal cells we hope will provide fundamental and therapeutic insight into the disease process.” In the process of studying this phenomenon, Dr. Eberwine and colleagues also developed more precise techniques to measure changes in gene expression - techniques that “laid the foundation for doing a whole host of other work in understanding single-cell disease processes.” He has applied these approaches to studies of Parkinson’s and Huntington disease, the neurodegeneration associated with traumatic brain injury, as well as to studies of normal brain processes and normal development.

Dr. Eberwine’s is just one of dozens of pilot grants awarded over the years that have confirmed the approach taken by the Penn ADCC. “One of the themes from the very beginning was how neurodegenerative diseases can overlap – how people with memory impairment can also have parkinsonism and vice versa,” said Dr. Trojanowski. “This was a vision we had that was upheld and has since been confirmed and extended.”

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## Clinical Research the Key to Better Treatment: The Penn ADCC Clinical Core at Work

The Penn Memory Center, which recently moved to a gleaming new facility at the Perelman Center for Advanced Medicine (see back cover), is the clinical home of the ADCC, where people come when they are having memory problems, or when mom is having memory problems, or maybe when their grandparent had dementia and they want to know their risk

of also developing Alzheimer's disease (AD). They come because Penn is where many of the most advanced diagnostic tests have been developed, and because Penn has a long history of caring for and conducting research with people with age-related diseases. They also



Penn ADCC Clinical Core is led by Steven Arnold, MD.

come because they want to participate in testing an experimental treatment for AD or another dementia and know Penn is likely to be a research site.

In addition to participating in ongoing clinical trials, the Penn ADCC is also an incubator for new approaches to treating AD and other dementias. "We're looking for the most promising opportunities to build a clinical trial," said Steven Arnold, MD, Director of the Penn Memory Center and Associate Director of the ADCC. Most of the agents currently being tested in clinical trials target two proteins called amyloid and tau, which form the plaques and tangles that are characteristic of the AD brain. "As we learn more and more about Alzheimer's disease, while

amyloid and tau seem to play a central role in the pathophysiology of the disease, what we're finding is that there are many influences on tau and amyloid," said Dr. Arnold. "For example, one of the things we have discovered is that insulin resistance in the brain seems to be a very potent factor in terms of the degree of cognitive impairment that someone has."

This discovery may help explain why diabetes is a strong risk factor for AD, but it could also point to a new treatment approach. Perhaps drugs that have been safely used to treat diabetes for many years might be repurposed to treat AD. Indeed, said Dr. Arnold, there is epidemiological evidence indicating that people who take these drugs for diabetes have a lower risk of developing dementia than they normally would have. "How can we translate this finding into a pilot clinical trial and ultimately, if there are signs of success, into a multicenter clinical trial?"

Another interesting pathway being investigated by Penn ADCC researchers is the role of the hormone leptin, which is produced by fat cells and is thought to regulate hunger and weight gain. Research led by Edward B. Lee, MD, PhD, one of the Penn ADCC's rising stars and head of the Translational Neuropathology Research Laboratory, is using an array of methods to try to understand how hormones like leptin influence brain health. Dr. Lee's work is just one example of the kind of innovations that can arise out of an approach that couples basic science with clinical research, said Dr. Arnold. "It's just an incredibly rich environment in which to translate things going on in laboratories into clinical science."

Whether or not they choose to participate in clinical trials, patients at the Penn Memory Center get a thorough evaluation, including imaging tests and



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## New Docs Moving Research Forward

biomarker studies that were developed here at Penn by investigators who are part of the ADCC. Penn is the site of the biomarker core of the Alzheimer's Disease Neuroimaging Initiative (ADNI), a public-private partnership that began in 2003 with the goal of validating imaging as a reliable and valid biomarker for AD as a means of speeding drug development. In 2010, Penn researchers identified a cerebrospinal fluid "signature" that predicts who is at higher risk to go on to develop AD. Penn investigators also helped develop a novel contrast agent called florbetapir, which when used in conjunction with positron emission tomography (PET) scanning, can identify amyloid plaques in the brains of people developing symptoms of AD.

"These imaging and biofluid analyses are still primarily research tools, but we anticipate they will soon also be used to enhance clinical diagnosis and management," said Dr. Arnold. "The added benefit of having spinal fluid testing here is that we also use the fluid in research tests and will share the research findings with patients and family members."

Despite the added space and resources at the new facility, new patients sometimes still have to wait two or three months to get an evaluation appointment. Jason Karlawish, MD, Associate Director and a practicing clinician at the Penn Memory Center, said that more efficiencies are coming. "We will continue to strike a balance between our research, clinical care, and education missions. We do clinical evaluations, and we will increase that; an important reason we are here is to be at the vanguard of research. We also want to be able to inform the Delaware Valley about how to better take care of memory problems. So it's a bit of a tension, and we know that, but our expertise, our time, our sweat equity is to advance all these missions."



The success of the Penn ADCC in moving neurodegenerative disease research forward has been sustained by the continuous infusion of new clinicians and investigators, supported by the Institute on Aging and the Perelman School of Medicine at the University of Pennsylvania. In the last few years, five new faculty have joined the ADCC: three new clinicians along with two other researchers.

New physicians at the Penn Memory Center (PMC) have expanded the Center's ability to enroll new patients, while at the same time broadening the scope of clinical research. Steven Huege, MD, came to Penn in 2008 as an Assistant Clinical Professor of Psychiatry and PMC physician. He specializes in diagnosing and treating older adults with AD, other dementias, and other chronic psychiatric disorders; he also evaluates novel experimental treatments for dementia, including natural/herbal compounds, with a special emphasis on biomarkers.

David Wolk, MD, joined Penn in 2009, as an Assistant Professor of Neurology in the Cognitive Neurology Division and co-leader of the Clinical Core, after having completed his internship and neurology residency at Penn in 2002. His research focuses on early detection of AD through the use of a variety of new technologies and novel psychometric measures. On the treatment front, Dr. Wolk has also been studying a technique called transcranial direct current stimulation (tDCS), which stimulates the brain with tiny electrical currents to enhance brain function.

Mitchel Kling, MD, came to Penn in 2010 as an Associate Professor of Psychiatry (although he also did his residency at Penn in the early '80s), and sees patients at the PMC as well as at HUP and the Philadelphia VA Medical Center.

## Three Perspectives Are Better Than One: The Penn ADCC Neuropathology, Biomarker, and Genetics Core

Since 1906, when Alois Alzheimer first described to his colleagues the disease that would come to bear his name, scientists have been trying to understand how and why brain cells degenerate and die, not only in Alzheimer's disease (AD), but in other types of dementia as well. For many years, this search was conducted mainly by neuropathologists like Dr. Alzheimer, who had examined his patient's brain under the microscope and saw tangled fibers and unusual clumps of protein – the same plaques and tangles that are used today to diagnose AD. While neuropathologists remain at the center of dementia research, they have been joined by geneticists and biomarker specialists in trying to understand the factors that influence not only whether a person gets AD or another form of dementia and also when, how severely, and with what constellation of symptoms.

While plaques and tangles are still considered the primary pathological features of AD, recent research, much of it done here at Penn with the benefit of having access to biological samples provided by the Penn ADCC and other NIH grants, has revealed that the brains of people with AD as well as other neurodegenerative diseases are littered with other abnormal protein deposits, especially spherical deposits called Lewy bodies and aggregates of a protein called TDP-43.

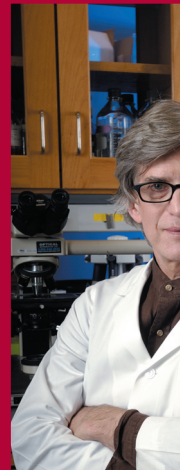
The TDP-43 story exemplifies the power of multidisciplinary research. A Penn research team led by Virginia Lee, PhD, first identified TDP-43 as the characteristic pathological protein signature of Frontotemporal Lobar Degeneration (FTLD) and Amyotrophic Lateral Sclerosis (ALS) through studies of the brains of people with these disorders in 2006, after a 5 year campaign taking on this challenge. FTLD is the second most common cause of presenile dementia, after AD, and a family history is present in as many as half of all cases, which suggests a genetic predisposition. Thus, geneticists began searching

for the genetic factors that play a role in this disease. By the time Dr. Lee and colleagues discovered that TDP-43 pathology is also found in patients with AD, Down's syndrome, and other dementias, biomarker studies had found characteristic patterns of biochemical markers in the cerebrospinal fluid of people with the disease.

At the Penn ADCC, this broader way of looking at the fundamental mechanisms underlying AD is reflected in the renaming of the Neuropathology Core to the Neuropathology, Biomarker, and Genetics Core. The Core acquires and stores the raw materials – brain tissue, biofluids including cerebrospinal fluid (CSF) and DNA – that scientists will use in their discovery research that moves the field forward.

Leading the Genetics effort at the Core is Vivianna Van Deerlin, MD, PhD. Working with the Clinical Core, she and her staff collect samples from individuals with neurodegenerative diseases and their family members. “We do all the genetic analysis, including genetic studies that can track a disease in a family by identifying specific genetic abnormalities; we also do large genome-wide studies focused on gene discovery and looking for risk factors.”

Dr. Van Deerlin has been interested in understanding genetic factors that play a role in FTLN and ALS. Her group and others recently identified mutations in TDP-43 in patients with ALS and correlated the mutations with TDP-43 pathology. Dr. Van Deerlin also led a genome-wide study to identify genetic risk factors associated with FTLN. This study showed that genome-wide association studies (known as GWAS among the cognoscenti) could be conducted with smaller sample sizes than typically required



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by limiting the analysis to a homogeneous group of subjects - in this case, those with TDP-43 pathology proven at postmortem examination of the patient's brain and spinal cord. Even with this limitation, she had to set up a large collaborative group of researchers from 13 countries in order to collect the 500 or so cases she needed. A new risk

factor for FTLD called TMEM106B was identified in the study. Now, investigators at Penn's Center for Neurodegenerative Disease Research (CNDR), the ADCC, and others are trying to figure out what the risk factor gene they discovered actually does. "The jury is still out as to what role it plays in the pathway to FTLD, but I think it is a significant discovery because other groups are confirming the result," said Dr. Van Deerlin.

Meanwhile, scientists are using CSF samples to identify biomarkers that can distinguish FTLD from AD or other neurodegenerative diseases. Les Shaw, PhD, along with Dr. Trojanowski, leads the Biomarker Core of the Alzheimer's Disease Neuroimaging Initiative (ADNI) as well as the Bioanalytics Core for the Parkinson's Progression Marker Initiative (PPMI), sponsored by the Michael J. Fox Foundation.

"We apply the same methodology across all Alzheimer's studies, ADNI studies, PPMI studies, and Penn studies," said Dr. Shaw. "The biomarker data show that the distinction between Alzheimer's and FTLD can be made with a lot more confidence using biomarkers than with clinical judgment alone."

The gold standard against which all of these new technologies are measured remains pathological diagnosis of autopsy-derived tissue. Edward (Eddie) Lee, MD, PhD, a new Penn neuropathology faculty member with expertise in neurodegenerative disease research, recently joined the



Neuropathology led by John Q. Trojanowski, MD, PhD, pictured with Virginia M.-Y. Lee, PhD.

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**Director**  
 John Q. Trojanowski, MD, PhD

**Associate Director**  
 Steven E. Arnold, MD

**Deputy Director**  
 Kathryn Jedrzewski, PhD

**MISSION:**

The mission of the Institute on Aging (IOA) at the University of Pennsylvania is to improve the health of older adults by increasing the quality and quantity of clinical and basic research as well as educational programs focusing on normal aging and age-related diseases at the Perelman School of Medicine at the University of Pennsylvania and across the entire Penn campus.

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## Making Sense of the Data: Penn's Integrated Neurodegenerative Disease Database (INDD)

An individual who takes part in clinical research at the Penn ADCC goes through what undoubtedly seems like an endless number of evaluations, ranging from a simple cognitive assessment through, in many cases, a neuro-

pathological study of his or her brain after death. Along the way, psychometricians perform neuropsychological testing; radiologists perform magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, as well as other imaging studies. Blood and cerebrospinal fluid are collected for biomarker and genetic testing,

and clinicians gather data about symptoms and other conditions. The result is a lot of data, and the question facing investigators is how to make sense of it all.

The creation of huge databases to manage the enormous amounts of data gathered in medical research, such as that conducted at the Penn ADCC, got its start shortly after the launch of the ADCC network. With the funding of National Alzheimer's Coordination Center (NACC), today they have grown to be powerful research tools for AD and related disorders. The Penn ADCC first added a Data Management and

Biostatistics Core in 2004 with a supplemental grant from the NIA; before that, data were managed in the Clinical Core. The Data Core provides database, biostatistics, and bioinformatics support to the ADCC. The Core's most recent innovation is an Integrated NeuroDegenerative Disease (INDD) database, which includes data from the Penn ADCC as well as from the Frontotemporal Degeneration (FTD) Clinic, the Amyotrophic Lateral Sclerosis (ALS) Clinic, and the Penn Udall Center for Parkinson's Research. The INDD database, by incorporating biomarker, imaging, neuropathological and genetic data across multiple neurodegenerative diseases, allows investigators to conduct comparative studies to look for common and distinct clinical and pathological features of these diseases.

"We are more aware now of the power in performing comparative studies across these diseases, but without an integrated database, this kind of comparative study could not be done," said Sharon Xie, PhD, Director of the Data Management and Biostatistics Core, who created the INDD with Mr. Young Baek, the ADCC Senior Data Manager. Moreover, the INDD database was a natural outgrowth of the collaborative climate at Penn. "Penn has the unique feature that everyone has been collaborating for many years, so we can take advantage of the long time collaborations of investigators across several diseases," said Dr. Xie.

Dr. Xie pointed to a recent collaborative biomarker study between Penn and Pfizer as an example of how the INDD database facilitates and enhances cross-disciplinary research. In this study, 1500 plasma and cerebrospinal fluid (CSF) samples from several hundred patients seen at multiple sites were tested for more than 150 dif-



The 'architects' of the INDD project are Data Core Director Sharon X. Xie, PhD, and Young Baek.



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ferent chemical constituents each. The INDD database was pitted against a more traditional database approach where each center operates its own separate database. While results of the two approaches were identical, the INDD database excelled in easing the process of querying and extracting data and thus produced results more quickly and with fewer errors. These data were thus able to demonstrate the association of different biomarker profiles with different diseases and clinical characteristics, information that can be used to improve diagnostic accuracy, identify underlying pathological features that may suggest new treatment strategies, aid in prognosis, and even elucidate the underlying mechanisms of the diseases. The potential power of the database is no surprise to Dr. Xie. “All scientific findings rely on the data so it’s absolutely crucial to have a reliable and efficient database, and we give special thanks to Young Baek for his heroic efforts in creating the INDD database,” she said.

In dealing with large data sets, particularly those from biomarker and genetic studies, the Core also

provides bioinformatics assistance under the direction of Li-San Wang, PhD. Bioinformaticians like Dr. Wang convert raw data into a form that can be understood by and shared with researchers across disciplines. Through the use of different computational processes, they can illuminate relationships that may be hard to detect in one dataset, let alone the combination of many datasets, and thus increase understanding of the pathologic processes that underlie changes in a particular biomarker, gene, or clinical characteristic.

For example, Dr. Wang and colleagues used gene expression data from large datasets obtained from postmortem human brain samples to develop a computational method for determining an individual’s “physiological brain age.” When applied to brain samples from individuals with AD or FTD/FTLD, they showed that some of the physiological mechanisms associated with normal aging are accelerated in people with these diseases, suggesting a link between normal aging and different neurodegenerative diseases.

## Three Perspectives

*Continued from page 7*

ADCC Neuropathology, Biomarker, and Genetics Core to conduct neuropathology studies on brain and spinal cord tissues collected by the Core. This entails examination of slides made from these samples for microscopic analysis and diagnostic assessment. “Our clinicians are excellent at diagnosing Alzheimer’s disease, but sometimes we see other things like Lewy body pathology, vascular disease, or other pathologies. So we see what they suspected, but now we realize that each patient has a unique pattern of pathology,” he said. FTLN cases are particularly varied, split almost equally between those with AD, tau, and TDP-43 pathology. In addition, many people

with AD also have TDP-43 pathology. “We don’t know exactly what that means and if we need to treat people somewhat differently, so understanding this diversity is important.”

Dr. Van Deerlin added, “The important thing is tying it all together with biomarkers, genetics, clinical, and pathology. The neuropathology core provides us with tissue from which we extract DNA and can make correlations to what’s seen, to the genetics, and to the biomarkers. Because we’re a large team it enables us to do powerful studies, whereas any one group or small number of people alone wouldn’t be able to do all the things that we do.”



### What's In a Name? The Penn ADCC Education, Recruitment & Retention Core

When the Penn ADCC was first established in 1991, the Education and Information Transfer Core took on the task of educating not only researchers

and health care professionals, but also the general public about what Alzheimer's disease is and how it differs from normal aging. Today, however, thanks in part to attention in the media and the work of the Alzheimer's Association and other advocacy

organizations, Alzheimer's disease is widely recognized and feared as a dementing disease that affects millions of people in the United States and worldwide. As a result, the mission of the education core changed, and with that change came a new name: the Education, Recruitment and Retention Core.

mission of the Core. For example, he led a study that examined how people make the decision to enroll or not enroll in a clinical trial and discovered that clinical investigators often fail in communicating to participants the results of the study. "People in the study used terms like, 'we know we're the guinea pig,' or 'we know we're the lab rat', but they also said that a little more information would be nice. So after that we instituted several different policies and procedures to better convey to people what we have learned from their participation in research." Now, at the end of a clinical trial, each participant receives a personalized letter describing how they did in the study, whether they got placebo or study drug, and what the overall results of the study were. The Core also invites all research participants to an annual "thank you" breakfast, where the study team explains the research results and opens up the floor to questions from participants.

Has the increased information provided to study participants helped? Dr. Karlawish thinks it has. "We went from sort of struggling to fill our clinical trials to finding that in the last five or six years it has been much more efficient. Some trials are harder to get filled than others, but overall we have noticed that enrollment and retention rates are good. We don't have a lot of dropouts, I think, because we are making the research experience satisfying."

The team has also discovered that a positive attitude about research is more important than even perception of risk or the expectation of benefit in determining whether a person will volunteer for a research study. "So we make a lot of effort to develop materials that foster a deep appreciation and understanding of what the value of research is and why we do it," said Dr. Karlawish.



Penn ADCC Education Core is guided by Jason H.T. Karlawish, MD, and Carol Edwards.

organizations, Alzheimer's disease is widely recognized and feared as a dementing disease that affects millions of people in the United States and worldwide. As a result, the mission of the education core changed, and with that change came a new name: the Education, Recruitment and Retention Core.

"We don't need to do that general kind of raising awareness anymore," said Jason Karlawish, MD, Director of the Core. "Now what we need to do is really aggressively push the research mandate, informing people about what we have learned, what we need to learn, and how we are going to get there." Getting there, he said, involves maximizing recruitment and retention in trials.

Dr. Karlawish's long-standing academic interest in what makes people volunteer for and continue participating in research studies melds well with the

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The Core also goes even further in its recruitment and retention efforts. For example, another study they conducted showed that the best way to improve enrollment in a clinical trial was a home visit. So whenever resources permit, Dr. Karlawish sends his study team to patients' homes to collect data from cognitive tests, surveys, and other quality-of-life measures. "Sometimes they want to come here, which is fine, but our default is that we'll go to their home." Home visits have been especially important in recruiting subjects for a study that requires infusions. The first few infusions have to be done at Penn's Clinical Trials Research Center on campus, but patients who are stable and show they can tolerate the drug are able to have subsequent infusions done at home. "We knew from our data that people would like that. We filled that study without any problem, and I think one of the reasons was because people knew if they tolerated the drug they would be able to get it at home, which is very convenient."

The team has even expanded the definition of "home," by starting what Dr. Karlawish calls a "very successful, promising, and what we think is a model for future collaborations with a continuing care retirement community." Ann's Choice is a large lifecare community in Delaware County. Dr. Steven Arnold leads a study there. "It was a slam dunk success in terms of recruitment," said Dr. Karlawish. "The response has been overwhelming, and we're now booked up for months for cognitive assessments to enroll people in the memory center research cohort and recruit them for studies."

Involved in research.

Penn ADCC study to  
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[www.pennadc.org](http://www.pennadc.org)



## New Docs Moving Research Forward

He is working with Drs. Arnold, Trojanowski, and Virginia Lee to search for biomarkers that might signal a higher risk of dementia associated with long term stress or depression, as well as to tease out the role of cerebral vascular disease (CVD) on the risk for AD and how CVD may contribute to disease processes in AD.

In addition to new clinical researchers, the Penn ADCC has recently welcomed two other investigators as new Assistant Professors in the Department of Pathology and Laboratory Medicine: Edward B. Lee, MD, PhD, and Li-San Wang, PhD. Neither of them are exactly "new kids on the block." Dr. Lee earned his MD and PhD at Penn and followed that with a residency, fellowship, and postdoctoral fellowship here; Dr. Wang first came to Penn as a postdoctoral fellow in 2003.

Dr. Lee leads the Translational Neuro-pathology Research Laboratory, which seeks to understand how certain risk factors affect Alzheimer's pathogenesis (see page 4) and to understand what is happening with TDP-43 at the neuro-pathological level (see page 6).

Dr. Wang, an expert in bioinformatics, has been instrumental in developing the Integrated NeuroDegenerative Disease (INDD) database (see page 8) and leveraging it to form a partnership with Johnson & Johnson, Inc. This resulted in a \$1.5 million grant from Johnson & Johnson to improve the database and make it a tool for data mining to develop various AD algorithms for diagnosis and progression.



## Penn Centro Para La Memoria: Meeting the Needs of Our Latino Neighbors

Latinos are the fastest growing minority group in the United States, and the proportion of elderly Latinos is expected to triple between 2005 and 2050. Since advanced age is the greatest risk factor for AD, it stands to reason that the prevalence of AD is likely to skyrocket among Latinos. Moreover, according to the Alzheimer's Association, Latinos are at least one and one-half times more likely than whites to have dementia, and African Americans two times as likely. Yet since these minority population groups are less likely to participate in research, understanding the reasons for their higher risk has been difficult to study.

Recognizing the need to be more inclusive of minority populations, the NIH began funding minority supplemental projects early in the ADC program that reached out beyond the confines of academic medical centers into the communities where these populations live. Researchers at Penn, led by Chris Clark, MD, received one of these supplemental grants in 1993, and since that time the "Latino Cohort" has been an important part of the Penn ADCC.

Dr. Clark said that, at the time, there was little known about the differences between Latinos and whites with regard to AD and other dementias. He began seeing patients at Episcopal Hospital in North Philadelphia, which at the time was an independent hospital not affiliated with Temple, as it is now. "I would go out and work in that clinic one day a week, and I was surprised at the age of the individuals we

were seeing there in that they were younger (often in their 50s or 60s) than the patients we saw at Penn. I thought we must be doing something wrong, not understanding them and thus not able to separate out Alzheimer's disease from non-Alzheimer's disease." Dr. Clark contacted colleagues at other ADCs with

Latino cohorts to find out if others were seeing similar age disparities. "We thought it might be an education issue, since we knew the average education level was 4 years, very different from the white population, which was closer to 12 years."

The results of this informal survey stunned him: everyone got back to him and said that indeed, the average age of Latino patients being diagnosed with AD was younger than that of the general population. "It wasn't just a Philly phenomenon or me not knowing what I was doing," said Dr. Clark. He

and his colleagues at the Penn ADCC and four other ADCs went on to publish a study in 2005 which documented that, even after adjusting for education, Latinos in the United States develop AD an average of almost 7 years earlier than whites. The reason for this disparity, however, remains unclear. Education appears to explain only a small part of the difference in age of onset. Other factors like hypertension and diabetes, both of which occur more frequently among Latinos than whites, also appeared to play only a small role in lowering the age of onset. The strongest risk factor appeared to be immigration status, since the immigrant population tends to be younger.

**Latinos in the United States develop AD an average of almost 7 years earlier than Caucasians.**

# Basic Science Clinical Education & Policy Translational

Subsequent research conducted by the Penn ADCC showed that elderly Latinos in Philadelphia, who are primarily immigrants from Puerto Rico, not only had an earlier age of onset but more severe cognitive impairment. Another study, conducted by the Penn Frontotemporal Lobar Degeneration (FTLD) Center Genetics Core, which is led by Dr. Vivianna Van Deerlin, has looked at all the Latino samples in the Penn ADCC DNA bank for a particular mutation that is associated with FTLD. Interestingly, the mutation was found in 12% of all Latino AD patients, suggesting that it is more prevalent in this population than in non-Latinos.

These studies highlight the value of reaching out to the Latino community both to provide care and conduct research. “We have engaged this cohort of older Spanish-speaking adults in our research for nearly 20 years,” said Steven Arnold, MD, who now directs the Latino project. “They are engaged in biomarker research, in DNA genetic studies, and some have even donated their brains to science when they die.” In an effort to better understand whether the earlier onset seen in Latinos living in the United States is also

seen in those who remain in their native countries, the Penn ADCC has also de-

veloped a collaboration with the University of Puerto Rico, bringing faculty and research coordinators from Puerto Rico to Penn to learn research protocols and give talks in the Philadelphia community.

The Penn ADCC is also increasingly reaching out to the African American community in West Philadelphia. In its efforts to serve these communities, the Penn ADCC is cognizant of the need to provide care that is both culturally and linguistically appropriate. However, said Dr. Arnold, “There is a manpower issue to get minority people into physician/researcher roles. What we hope is that our ADCC can serve as an engine to attract and recruit younger physicians who are interested in these issues.”



Among the staff of the Penn ADCC Latino Cohort are Mirna Negrón and Jessica Nuñez.

## Celebrating 21 Years of Working Together in the Fight Against Alzheimer’s Disease

*“I think [Alzheimer’s] is the defining challenge of our era and certainly of the baby boom era. The numbers are staggering. The costs to the nation are staggering. The costs to individual families are staggering...I call it a mind-blowing disease because not only does it blow the mind of the person who gets it, but it blows the mind of everybody who loves that person.”*

- Maria Shriver on CNN’s Larry King Special, “Unthinkable: The Alzheimer’s Epidemic”

The IOA, the Penn ADCC, and their research partners are leading the charge against Alzheimer’s and related brain and movement disorders. Penn Medicine’s world-renowned scientists, collaborative research philosophy, and sophisticated technology give us the edge. But, we need your financial support to accelerate progress. **You can make a difference by giving generously. Please contact Irene I. Lukoff, Sr. Director of Development, at 215-573-0187 or via email at [ilukoff@upenn.edu](mailto:ilukoff@upenn.edu).**



## The Next Decades: Ideas on How to Tackle Alzheimer's

In 1984 when the first Alzheimer's Disease Centers (ADCs) were established, the field was at a crossroads. Nearly ten years of planning and strategizing by leaders at the National Institutes of Health (NIH), advocacy organizations such as the Alzheimer's Association, academic institutions, and the pharmaceutical industry had finally yielded the legislation and funding necessary to build a national network of research facilities focused on AD. Now the field is at another critical juncture, as around the world, countries are bracing for the "silver tsunami," a perfect storm created by a disease that primarily affects older people, the exponential growth in the aging population, and a worldwide financial slow-down that threatens existing funding streams.

"Penn is uniquely qualified to confront the challenge of cognitive impairments that will become epidemic as our population ages," said J. Larry Jameson, MD, PhD, Executive Vice President for the Health System and Dean of the Perelman School of Medicine. "Penn has built leading clinical and research programs in aging that have successfully leveraged the uniquely integrated culture of this institution. The Penn Alzheimer's Disease Core Center is an outstanding example of how faculty from different disciplines can work together to address complex health related issues. We are committed to bringing together all of the resources Penn has to offer, as well as collaborating with other institutions, to confront the enormous challenge that Alzheimer's presents."

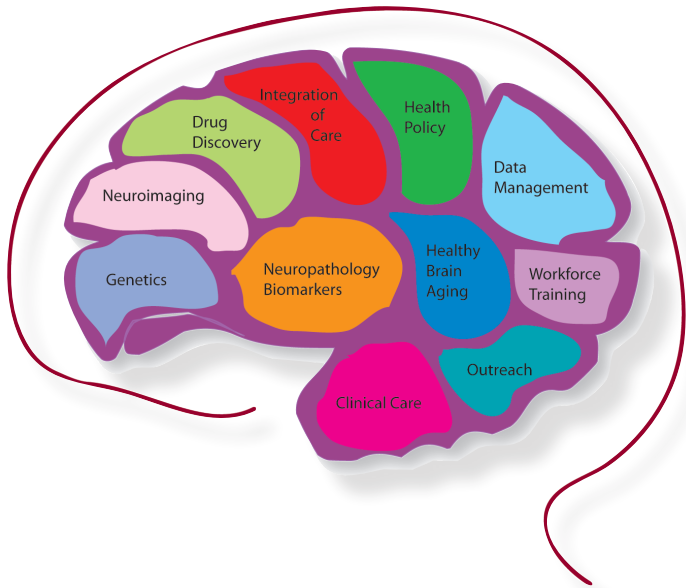
Penn ADCC Director Dr. John Trojanowski has worked with his ADCC colleagues and other Penn faculty from across the Schools of Medicine and Nursing, as well as the Wharton School, the Office of the Executive Vice Dean for Research, and the Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020) to develop a plan that comprehensively addresses these challenges. Their plan proposes to convert the Penn ADCC to a prototype model of a Comprehensive Alzheimer's Disease Center (CADC)

modeled on the National Cancer Institute's Comprehensive Cancer Centers. CADCs would serve as coordinating hubs of existing ADCs, facilitating expanded multidisciplinary and multisite collaborative research studies and integrating active programs in clinical care and clinical trials.

Glen Gaulton, PhD, Executive Vice Dean for Research and Chief Scientific Officer at the Perelman School of Medicine at Penn, said that a national program such as this is essential to bridge the national imperative to address the pending Alzheimer's crisis with broad-band discovery efforts. "We are among a handful of institutions, in part because of the leadership of John and Virginia Lee, that have been able to morph a focal effort into a broad program encompassing all neurodegenerative disease, tissue banking, imaging, clinical care, and so on. A program of national centers would first, raise the overall priority of Alzheimer's disease to the highest possible level; second, position institutions such as Penn to develop even more comprehensive programs, and third, hold institutions accountable for the quality of research and care, and the juxtaposition of those two."

The CADC concept was introduced at a symposium in 2008 and incorporated into the Alzheimer's Study Group report that was presented to the U.S. Senate Committee on Aging in 2009. The Centers would provide both clinical and basic neurodegenerative disease research programs as well as research on health care policy, health services, and the economics of health care financing. With its existing ADCC, Institute on Aging, Center for Neurodegenerative Disease Research (CNDR), Marian S. Ware Alzheimer Program for Drug Discovery, and strong collaborations with the School of Nursing and the Wharton School, Penn has all of the components in place. By proposing that Penn serve as a model for this type of Center, Dr. Trojanowski hopes to expedite implementation of a nationwide network of CADCs.

"I think this a reasonable next step to escalate the



## Comprehensive Alzheimer's Disease Center (CADC)

*Schematic illustrating the various teams that would comprise a CADC.*

science,” he said. “The CADCs could take on much more in drug discovery, biomarker research, genetics research, neuroimaging, and clinical care, which, in the long run, would result in significant cost savings.” The cost of establishing 5 CADCs would be some \$500 million over 5 years - less than 1% of the \$150 billion per year that AD costs the U.S. economy. If successful in developing treatments that slow or prevent dementia, the health care cost savings could be substantial. “The CADCs would put under one roof all the essential tools and people to have a major impact in finding better ways to diagnose and treat AD and related disorders,” according to Virginia M.-Y. Lee, PhD, Director of CNDR, who has been involved with the Penn ADCC since it was founded.

Dr. Trojanowski envisions the Penn CADC as a comprehensive neurodegenerative disease center that would continue to integrate programs in AD, frontotemporal lobar degeneration (FTLD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and vascular dementia (VaD). “The whole heterogeneity theme that was in an embryonic stage in 1991 when we first started the Penn ADCC has now fully blossomed,” he said. Common mechanisms and overlapping pathologies among these diseases support the wisdom of integrating these diseases. For example, neuropathological studies suggest that half of all AD patients also have the Lewy bodies that are indicative of PD, and half also have the TDP-43 pathology that suggests FTLD or ALS. “There may be an upstream mechanism that could be shut down to block progression of all of these neurodegenerative pathologies,” said Dr. Trojanowski. If such a master switch is not found, these patients are likely to need multiple drugs that target these different pathways.

This integrated vision of neurodegenerative disease has also been recognized at the NIA. Creighton (Tony) Phelps, PhD, Director of the ADC Program, said that about ten years ago he polled the Centers to “take stock of where we were and where we needed to go.” Out of that came the recognition that an increased focus was needed on co-morbid conditions, other forms of dementia, and the relationships between them both mechanistically and clinically. As a result, many of the Centers specialize in one form of dementia or another; Penn is one of the few ADCs with the expertise across all of these disease groups.

Penn’s CADC would be structured as a number of interacting “teams,” each of which would include both research and clinical components (see above left). In addition, the training team would focus on developing a stronger workforce of clinicians, researchers, and other health care workers. The healthy brain aging team would explore how lifestyle interventions, such as exercise, diet, cognitive training, and improved social interactions influence the likelihood of developing dementia and/or the ability to cope with the effects of the disease.

Dr. Phelps said the quandary is how to pay for such an ambitious program when even existing programs are contracting due to federal budget cuts. Zaven Khachaturian, PhD, the former Director of the Office of Alzheimer’s Research and the person who spearheaded the symposium that conceived of the CADCs, is more optimistic. “The NIA centers program was conceived and developed as a tool to address the particular research needs of the field in 1984. Now in 2011 the needs of the field are totally different, whereby more collaborations across disciplines and institutions is required in the effort to discover and validate new effective treatments. The concept of a ‘Comprehensive Center’ as described by Dr. Trojanowski is one prototype model for such new center. After nearly 30 years, it is time to re-think and re-structure NIA programs.”



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### A NEW HOME TO BETTER SERVE PATIENTS

how to find us

The Penn Alzheimer's Disease Center and Penn Memory Center moved to a state-of-the-science space at the Perelman Center for Advanced Medicine on July 27, 2011, providing more comfortable waiting areas and double the number of exam and testing rooms. The new location also provides easier access for patients to all of the facilities they may visit for a full evaluation or for participation in research studies. Moving from Ralston House where they had resided since 1991 raised some concerns among the staff. "We weren't sure patients would like coming here," said Felicia Greenfield, MSW, LSW, Associate Director for Clinical and Research Operations at the Center. An informal survey found the vast majority of patients liked the beautiful new space and the cutting-edge feel of the facilities.

**2 South Pavilion  
Perelman Center for Advanced Medicine  
3200 Civic Center Boulevard**

**To make an appointment, please call 215-662-7810.**

Driving directions and information on taking public transportation and parking can be found online at [www.pennmedicine.org/perelman/visitor\\_info/directions.html](http://www.pennmedicine.org/perelman/visitor_info/directions.html).