Chapter 1
The Penn ADCC: Integrating Neurodegenerative Disease Research Across Disciplines, Conditions, and Population Groups

John Q. Trojanowski, Steven E. Arnold, Jason H. Karlawish, Sharon X. Xie, and Vivianna Van Deerlin

Abstract Around the world, countries are experiencing seismic demographic changes due to rapid increases in the "oldest old", those over 85 years of age, and the young old "Baby Boomers" now aged 60–70 years (2014). While Americans are living longer and disability rates are declining, some 77 million began turning 60 in 2006, the time at which age-related early onset dementias begin. This, therefore, means that Alzheimer's Dementia (AD) and other dementias will increase with ominous consequences if we do not develop therapies to treat/prevent them. Thus, the number of Americans with AD will increase to over 13 million and delaying the onset of AD by just 5 years would reduce the number of AD patients and the cost of their care about 50 % by 2050. Intense efforts are urgently needed to develop disease modifying therapies for AD. AD is the most common but by no means the only type of dementia seen in older adults. In one U.S. study, AD accounted for 69.9 % of all cases of dementias, followed by vascular dementia (VaD) in 17.4 %. The remaining 12.7 % of cases were attributed to Parkinson's dementia (PD),

J.Q. Trojanowski, MD, PhD (✉)
Department of Pathology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA
e-mail: trojanow@mail.med.upenn.edu

S.E. Arnold, MD
Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

J.H. Karlawish, MD
Department of Geriatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

S.X. Xie, PhD
Department of Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

V.V. Deerlin, MD, PhD
Department of Pathology and Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

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normal-pressure hydrocephalus, frontal lobe dementia, alcoholic dementia, traumatic brain injury, and Lewy body dementia. Since there are shared mechanisms underlying many of these neurodegenerative diseases, there is much to be gained through joint research and clinical efforts and the sharing of data across disciplines, disease areas, and institutions.

Keywords Dementia • Amyotrophic lateral sclerosis (ALS) • Parkinson disease (PD) • Alzheimer's disease (AD) • Vascular dementia (VaD) • Institute on Aging

Introduction

Around the world, countries are experiencing seismic demographic changes due to rapid increases in the "oldest old", those over 85 years of age, and the young old "Baby Boomers" now aged 60–70 years (2014) [1–4]. While Americans are living longer and disability rates are declining [5], some 77 million began turning 60 in 2006, the time at which age-related early onset dementias begin. This, therefore, means that Alzheimer's Dementia (AD) and other dementias will increase with ominous consequences if we do not develop therapies to treat/prevent them. Thus, the number of Americans with AD will increase to over 13 million and Medicare costs for their care will increase to about $1 trillion by 2050 [6–10]. Since demography is the history of the future written now, the solvency of Medicare is in jeopardy. But, this future is malleable. Delaying the onset of AD by just 5 years would reduce the number of AD patients and the cost of their care about 50 % by 2050 [6]. Thus, intense efforts are urgently needed to develop disease modifying therapies for AD.

AD is the most common but by no means the only type of dementia seen in older adults. In one U.S. study [11], AD accounted for 69.9 % of all cases of dementias, followed by vascular dementia (VaD) in 17.4 %. The remaining 12.7 % of cases were attributed to Parkinson's dementia (PD), normal-pressure hydrocephalus, frontal lobe dementia, alcoholic dementia, traumatic brain injury, and Lewy body dementia. Since there are shared mechanisms underlying many of these neurodegenerative diseases, there is much to be gained through joint research and clinical efforts and the sharing of data across disciplines, disease areas, and institutions.

In anticipation of the "silver tsunami", the National Institutes on Aging (NIA) at the National Institutes of Health (NIH) launched initiatives to stimulate and support research and education on AD and related disorders in the mid-1980s [12, 13]. This resulted in landmark advances in the understanding, diagnosis and treatment of AD, related disorders, Mild Cognitive Impairment (MCI) and normal aging [14–19]. The Alzheimer's Disease Center (ADC) program was established by the NIA in 1984 as a means of promoting collaborations and building multi-site projects through a nationwide network of clinical and research programs. Today (2014) there are 28 ADCs throughout the country, including both AD Research Centers (ADRCs) and AD Core Centers (ADCCs). The ADCs have been instrumental in

promoting research and education on Alzheimer's disease (AD), related dementias, normal brain aging and mild cognitive impairment (MCI), as well as supporting development of better diagnostics and preventions/treatments for AD and related disorders and training researchers and care providers.

The University of Pennsylvania ADCC

The University of Pennsylvania established an ADCC in 1991, with the aim of advancing research by developing an infrastructure that could be leveraged across multiple disciplines and applied to the understanding of a broad range of neurodegenerative diseases. Today, the Penn ADCC has evolved into a highly interdisciplinary and seamlessly integrated Center with five Cores that collaborate extensively with other investigators at and beyond Penn, including other ADCs, the Alzheimer's Disease Cooperative Study (ADCS), the Alzheimer's Disease Education and Referral Center (ADEAR), the Alzheimer's Disease Neuroimaging Initiative (ADNI), The Alzheimer's Disease Genetics Consortium (ADGC), the National Cell Repository for Alzheimer's Disease (NCRAD), and the National Alzheimer's Coordinating Center (NACC). The Penn ADCC has been particularly active in two key areas: (1) expanding and integrating research on related dementias including fronto-temporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Parkinson disease (PD); and (2) developing novel techniques to address the challenges of conducting research on these disorders.

Penn has a long history of leadership in the field of aging. In 1979 the Center for the Study of Aging was established under the leadership of Vincent J. Cristofalo, a cell biologist internationally recognized for his work on understanding the mechanisms of cellular aging. In 1989, the Center was renamed the Institute on Aging (IOA), signifying a structure that cuts across schools, departments, and disciplines. While the IOA is centered in the University of Pennsylvania Perelman School of Medicine (UPPSOM), the approximately 200 IOA fellows and associate fellows represent researchers from Penn's Schools of Nursing, Veterinary Medicine, Dentistry, and Arts and Sciences, the Wharton School, The Children's Hospital of Philadelphia, The Wistar Institute, The Monell Chemical Senses Center, The Richard Stockton College of New Jersey, Widener University, Temple University, the Polisher Research Institute, and the Philadelphia Corporation for Aging.

Today, the IOA and the ADCC are two parts of larger network of resources at Penn focused on aging and age-related diseases (Fig. 1.1). These include the Center for Neurodegenerative Disease Research (CNDR), the Division of Geriatric Medicine, the Morris K. Udall Parkinson's Disease Center of Excellence, and the Marian S. Ware Alzheimer Program, a unique multidisciplinary program that supports drug discovery and clinical trial design, as well as studies focused on biomarkers of stress in AD and continuity of AD care. Penn is also home to the Biomarker Core of the ADNI and the ADGC; and has had/currently has three related Program Projects funded by the NIA: In Vitro and In Vivo Models of AD;

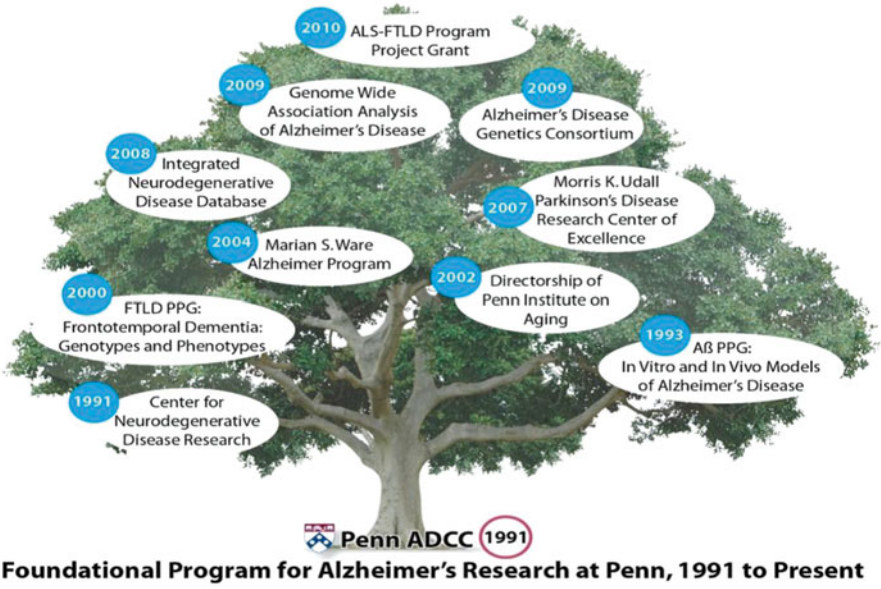

Fig. 1.1 The Penn ADCC is the foundation (*roots and trunk*) for all programs on aging, AD, and related disorders at Penn (*branches*) as depicted for representative programs

Frontotemporal Dementia: Genotypes and Phenotypes; and most recently TDP-43 Proteinopathies in ALS Dementia. These program projects reflect Penn's focus on dementias other than AD as well as comorbid conditions that impact on the manifestation of disease; and the fact that over the past several decades, Penn has been at the vanguard of molecular biological research on neurodegenerative disease.

The goals of the Penn ADCC are implemented through five cores as well as a pilot grant program and collaborations within and beyond the Penn campus. Working together, the five Cores advance an aggressive, integrated research program that has resulted in major discoveries about the mechanisms underlying neurodegenerative diseases and contributed to the development of new diagnostic and treatment approaches. The integration of research among the Cores begins with the Clinical Core, which assesses and follows patients with cognitive impairments due to AD or other dementias through its recently expanded Penn Memory Center. While clinical evaluations are important, the primary mission of the Core is to advance clinical research, both by conducting clinical trials and acquiring biofluids, tissues, DNA, and imaging studies that can be used in a research studies conducted by investigators in the Neuropathology, Biomarkers, and Genetics Core as well as international collaborative studies such as NACC, ADNI and ADGC. Through participation in ADNI, Penn ADCC investigators have developed promising new technologies, including florbetapir (18 F-AV-45), an amyloid imaging agent for use with positron emission tomography (PET) to detect plaques in the brain of living persons [20]; and a cerebrospinal fluid (CSF) biomarker signature defined by Abeta1-42 and

total tau (t-tau) that identifies individuals with mild AD and predicts conversion from MCI to AD [21]. Enrollment of subjects in these studies is dependent on the efforts of the Education, Recruitment and Retention Core; and analysis of data collected in these studies is conducted by the Data Management and Biostatistics Core. Meanwhile, the Administrative Core provides administrative oversight for the entire program and administers the pilot grant program.

Integration Across the Spectrum of Neurodegenerative Diseases

Through collaborations with other Penn-based programs on aging and age-related diseases, the Penn ADCC has integrated research and clinical care across the spectrum of neurodegenerative diseases. Collaborations with the CNDR, in particular, have contributed to a dramatic expansion in basic and clinical research on AD and related disorders as well as investigations into the etiology, pathogenesis, diagnosis, treatment and prevention of these neurodegenerative diseases. The CNDR functions as a "center without walls," wherein investigators collaborate in multidisciplinary clinical and basic research to increase understanding of the causes and mechanisms leading to brain dysfunction and degeneration in AD, PD, FTD, ALS and related disorders that occur increasingly with advancing age. CNDR promotes a number of important research initiatives such as the development of new and effective therapies and finding a cure for devastating aging related neurodegenerative diseases through a number of mechanisms.

For example, there has been considerable excitement at Penn with regard to the discovery of TDP-43 (the ubiquitinated TAR DNA-binding protein 43) as the disease protein that provides a molecular link between ALS and a subtype of FTD called FTLD-U (Frontotemporal lobar dementia with ubiquitinated inclusions). Using postmortem brain tissue collected through the ADCC's Neuropathology, Genetics, and Biomarker Core, CNDR investigators showed in late 2006 that mutated TDP-43 accumulated as a misfolded protein in the hippocampus, neocortex, and spinal cord of individuals diagnosed with FTLD-TDP and ALS [22]. Subsequently, multiple pathogenic mutations in TDP-43 were found to be associated with ALS [23] and a number of other studies identified additional TDP-43 mutations associated with ALS and FTLD. An international collaboration led by researchers at the Penn ADCC and involving 13 countries resulted in the identification of a protein called TMEM106B, which represents a risk factor for FTLD-TDP [24].

The Penn ADCC also works closely with the NINDS Morris K. Udall Parkinson's Disease Center of Excellence at Penn to study the molecular mechanisms underlying movement and cognitive impairments in PD, as well as the care and treatment of patients and training of physicians. Penn is one of only six institutions that have both a Udall Center and an ADC. The theme of the Penn Udall Center is cognitive impairment, a very understudied aspect of PD. Areas of shared research interest between these two Centers is exemplified by recent biomarker collaborations which

showed that the same low CSF Aβ42 levels that are signatures of AD also predict cognitive decline in PD [25], while plasma EGF levels correlate with cognitive performance and predict cognitive impairment in PD, but not in AD [26].

All of these biomarker and genetics studies accumulate massive amounts of data, and rely on resources provided by the Data Management and Biostatistics Core for data analysis. The Core recently launched an Integrated Neuro-Degenerative Disease (INDD) database inspired by NACC. This relational database includes data on AD, PD, ALS, FTLD and related diseases studied by ADCC and affiliated Penn investigator groups. A recent study compared the INDD database against a more traditional database approach where each center operates its own separate database, and concluded that the integrated database excelled in easing the process of querying and extracting data, thus producing results more quickly and with fewer errors [27].

Integrating Across Population Groups

Another unique feature of the Penn ADCC is its focus on dementia among Latino and African Americans. Latinos are at least one and one-half times more likely than whites to develop dementia [28], and African-Americans two times as likely [29], yet these population groups are less likely to participate in research. Consequently, the reasons for their increased risk are unclear. The Penn ADCC received a supplemental ADC grant in 1993 to develop a Latino cohort. In a collaborative study with four other ADCs, they found that after adjusting for education, Latinos in the United States develop AD almost 7 years earlier than Whites [30]. Subsequent research by the Penn ADCC showed that elderly Latinos in Philadelphia, who are primarily immigrants from Puerto Rico, not only have an earlier age of onset but more severe cognitive impairment [31].

Genetic studies on patients in the Latino cohort led to the identification of three families in whom a PSEN1 G201A mutation was found. This mutation was reported previously in Caribbean-Hispanics [32], prompting Penn geneticists to test all available Latino samples in the Penn ADCC DNA bank (n = 282) for the mutation. Remarkably, the mutation was found in ~12 % (12/103) of AD cases in the Latino cohort who were *unselected* for family history. This suggests that the mutation may be more prevalent than previously recognized in this population.

Another study identified the first reported case in an African American of a mutation in the microtubule-associated protein tau (MAPT) gene, which is associated with a rapidly progressive form of familial FTD [33]. Imaging, CSF biomarker, and clinical studies of this patient, as well as post-mortem examination of her brain provided additional clues about the neuropathology underlying this disease. Yet none of these studies would be possible without the participation of individuals in minority communities. This is where the Education, Recruitment, and Retention Core comes into play. For example, the Penn ADCC is also increasingly reaching out to the African American community in West Philadelphia, where the University is located.

New Directions

To achieve the goal of preventing or ameliorating AD and related diseases as well as to promote successful aging, the Penn ADCC has also developed novel partnerships with philanthropic organizations to take its research, education and outreach programs in new directions. One such initiative is the Marian S. Ware Alzheimer Program, which was launched with generous multi-million dollar philanthropic support from the Ware family in January 2004 to comprehensively attack the problem of AD [34]. The Ware Program includes four key components: (1) AD Drug Discovery; (2) AD Clinical Trial Design; (3) Biomarkers of Stress in Normal Aging and AD; and (4) Continuity of AD Care, a project of the University of Pennsylvania School of Nursing. This Program enables the ADCC to expand its role in drug discovery neurodegenerative diseases by bridging the gap between drug target identification, validation and proof of concept studies, and to hasten efforts to bring new therapies out of laboratories into the clinic.

Partnerships are also being forged between the Penn ADCC and pharmaceutical companies. For example, an ADCC-linked AD drug discovery partnership with Johnson and Johnson, Inc. and a cooperative agreement between the Penn Chemistry Department and the NIA is pursuing chemical synthesis of different classes of microtubule stabilization drugs to identify the best class of compounds that enter the brain to stabilize microtubules for the treatment of AD and related tauopathies [35].

The Penn ADCC and IOA also support 1-year pilot grants designed to encourage researchers from disparate fields to turn their attention and expertise toward investigations of dementia. In 2011–2012, 10 pilot grants with were supported. Two of these, funded by the ADCC, will focus on Alzheimer's disease (AD) and related neurodegenerative disorders. The remaining pilots, supported by funding from Penn's School of Medicine and The Bingham Trust, focused on aging and aging related diseases.

The Penn ADCC has also been working with other Penn faculty and the Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020) to convert the Penn ADCC into a prototype model of a Comprehensive Alzheimer's Disease Center (CADC) modeled on the National Cancer Institute's Comprehensive Cancer Centers [36]. 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. The CADC concept was introduced at a symposium in 2008 [37] and incorporated into the Alzheimer's Study Group report that was presented to the U.S. Senate Committee on Aging in 2009 [38]. The Penn CADC would comprise a number of interacting teams, each of which would include both research and clinical components. With an executive/administrative committee as its hub, the teams would address issues related to: training; clinical care; healthy brain aging; genetics; biomarkers; neuropathology; neuroimaging; data management, computational modeling, and biostatistics; drug discovery; integration of care; health policy, comparative, and cost effectiveness; and outreach, education, and dissemination.

Spreading the Message

A final important mission of the Penn ADCC is to increase scientific and public awareness of AD and healthy brain aging in order to advance the research mandate. This is exemplified by the production of two public education films – *Shining a Light on AD* and *Taking Steps to Healthy Brain Aging* – funded by the MetLife Foundation in collaboration with three other ADCs and Penn's IOA and CNDR. MetLife then supported "re-purposing" these two films into a single film for PBS called *Alzheimer Disease – Facing the Facts,* which aired on more than 90 % of PBS outlets in 2009–2010, won the 2008 CINE Golden Eagle Award, and won a 2009 Emmy Award for documentary program (for more details, see http://www.alzheimersfacingthefacts.org/). In addition to spearheading production of these films, the Education, Recruitment and Retention Core provides other educational materials for patients and caregivers and provides.

Conclusion

In summary, the Penn ADCC forms partnerships at and beyond Penn to meet the global challenges of rapidly aging populations and the epidemic of AD and related disorders. These partnerships have enabled the Penn ADCC to accomplish its mission through research on AD and related disorders as well as normal aging, and through education to increase understanding of these disorders and accelerate the pace of developing better diagnostics and therapies for AD and related dementias.

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