

THE PENN CENTER FOR NEURODEGENERATIVE DISEASE RESEARCH

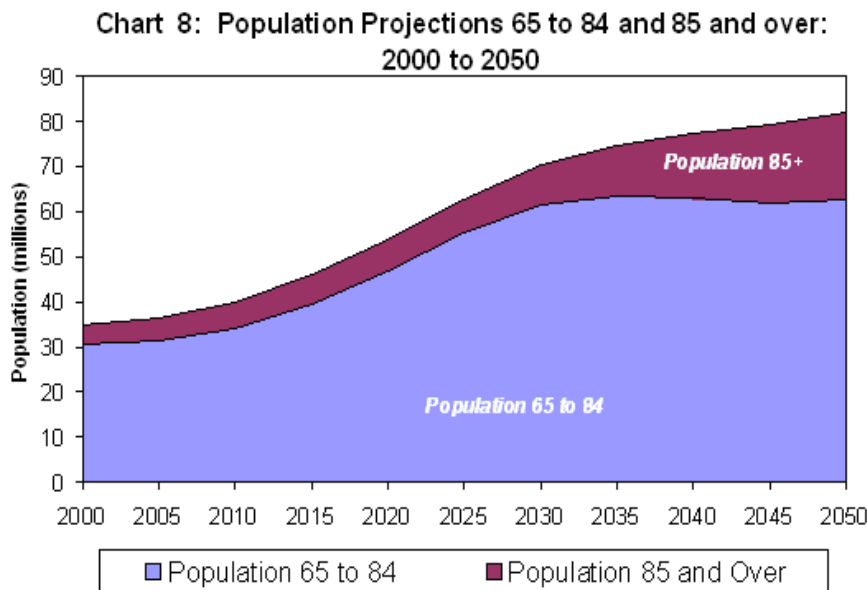
The motivation over 15 years ago to establish a Center for Neurodegenerative Disease Research (CNDR) at the University of Pennsylvania School of Medicine (PENN) was to augment growing collaborations among young and established investigators who conducted research on Alzheimer's disease (AD), Parkinson's disease (PD), other Lewy body disorders (LBD), Frontotemporal Lobar Degeneration (FTLD), Amyotrophic Lateral Sclerosis (ALS), Primary Lateral Sclerosis, other motor neuron diseases (MND) and related neurodegenerative conditions. CNDR also seeks to provide opportunities for other PENN faculty interested in neurodegenerative disease research to develop their interests further. CNDR was co-founded by Drs. Virginia M.-Y. Lee and John Q. Trojanowski in 1991 as a Type I Center in the Department of Pathology & Laboratory Medicine (P&LM), and in 2002 Dr. Lee assumed the role of Director with Dr. Trojanowski as Co-director.

CNDR functions as a "center without walls" wherein PENN investigators collaborate in the study of neurodegenerative diseases (<http://www.uphs.upenn.edu/cndr/>). The mission of the 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, FTLD, 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. Since its founding, CNDR has contributed to a dramatic expansion in basic and clinical research programs on neurodegenerative disorders at PENN, and CNDR continues to provide leadership, training/education and core support to augment and enhance ongoing collaborative studies as well as to stimulate new investigations into the etiology, pathogenesis, diagnosis, treatment and prevention of neurodegenerative disease. Commensurate with the growth of programs related to CNDR, PENN is now recognized as a leading academic center for basic and clinical research on neurodegenerative disorders. CNDR partners and programs are summarized below after a brief summary of the scope of the challenges that the longevity revolution and neurodegenerative disease present to the United States and many other countries across the globe.

THE LONGEVITY REVOLUTION AND NEURODEGENERATIVE DISEASES

The United States, like many countries, is experiencing a seismic shift in its demographics due to two rapidly growing segments of the population: the “oldest old,” >85 years of age, and the “Baby Boomers” born between 1946 and 1964 (1, 2). It is estimated that between 2000 and 2030 this older population will double (see Figure 1) and that by 2050 there will be five times the number of those age 85 and older compared to the year 2000 (3). This rapid growth is due in large part to astonishing increases in life expectancy in the last millennium. For example, estimates suggest that life expectancy increased ~27 years in less than a century from 1900 to 1990, while an increase of about the same number of years occurred in the nearly 5 centuries extending from the Bronze Age to about 1900 (4). Currently, a 65 year-old can anticipate living approximately 18 additional years while an 85 year-old woman can look forward to living about 7 more years, and an 85 year-old man will have 6 additional years (3).

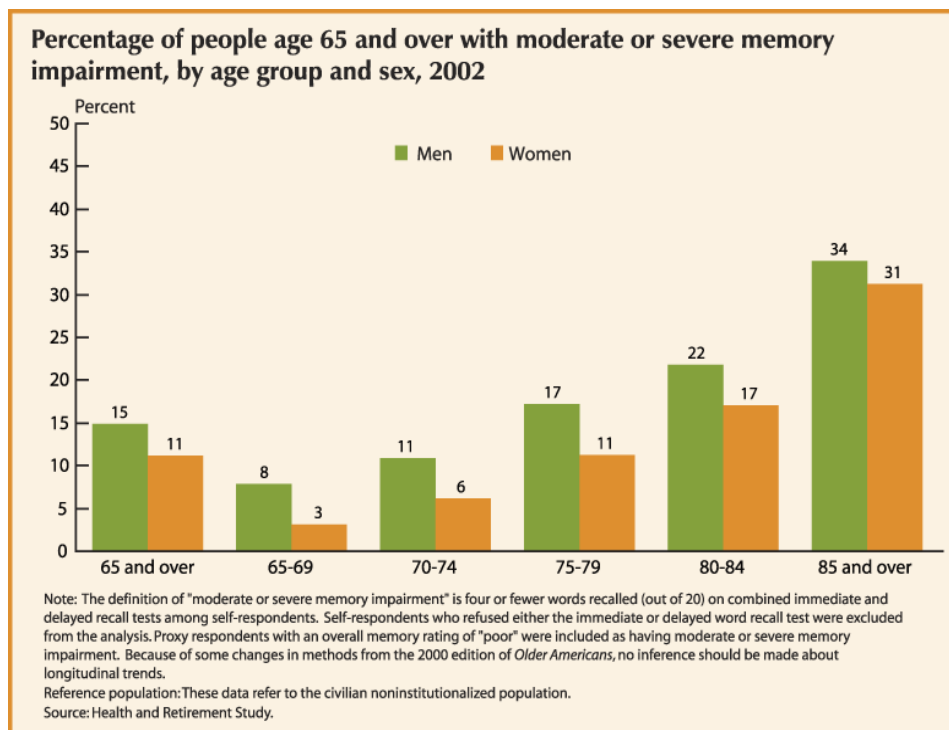
FIGURE 1



The good news about this longevity revolution is that Americans are not only living longer now, but disability rates in the United States continue to decline from the 1980s to the present (5). The changes to date have been dramatic, but even greater transformations will occur in society as the Baby Boomers enter their 7th decade of life

and live well beyond their ancestors to the 9th decade or even longer. Indeed, starting in 2006, the leading edge of ~77 million American Baby Boomers began turning 60! However, the longevity revolution is not all good news, since, if action is not taken now to plan for this demographic “sea change”, aging related disorders like AD may have ominous consequences. In this regard, AD and related disorders provide an excellent example of the deleterious repercussions of societal inaction (see Figure 2). For

FIGURE 2



example, in 2008, there were about 5.5 million AD patients in the United States. Yet, since the prevalence of AD is highest in individuals who are ≥ 85 years old, by 2050, the number of Americans with AD is expected to reach >13 million if nothing is done very soon to delay or prevent the onset of AD (6). Significantly, the costs to Medicare for treating AD patients were estimated to be about \$62 billion in 2000. But, Medicare costs will increase to ~\$1 trillion by 2050 for treating beneficiaries with AD and related dementias if no effective treatments or preventions are developed (7-9). Hence, if demography is the history of the future written now, then the future solvency of Medicare is in jeopardy, but it is important to emphasize that the future is malleable and

that it can be changed now. Indeed, models of the future incidence and prevalence of AD predict that if the onset of AD is delayed by just one year, this will reduce the number of AD patients by ~800,000 over the next 5 decades, while an intervention that delays the onset of AD by 5 years will reduce the incidence of AD by 50% thereby cutting the costs of this devastating dementia by half (8). Thus, preventative and ameliorative strategies will be crucial to avoid the potential detrimental consequences of the current dramatic shift in demographics, and evidence suggests that delaying the onset of AD may well be within our reach. For example, reviews of factors associated with the risk of developing cognitive impairment suggest there may be life styles and activities that show potential as preventative strategies for these impairments (see examples in Figure 3), but more research is needed to elucidate the determinants of

FIGURE 3

Association Data Offer Tips For Healthy Brain Aging & Preventing Cognitive Decline, But These Need To Be Tested In Clinical Trials

- **Cognitively stimulating activities** - Read, do crossword puzzles, play cards or other games that engage your mind.
- **Education** - Take a class, attend lectures, read websites like this one and advise the next generation to stay in school.
- **Exercise** - Talk to your doctor about designing an exercise program, even as simple as walking, geared just for you.
- **Head injury** - Always buckle your seatbelt and wear a helmet when biking or participating in similar activities to avoid traumatic brain injury.
- **Good nutrition** - Eat a heart healthy diet; it may benefit your brain as well.
- **Cholesterol and blood pressure** - Maintain your cholesterol and blood pressure within normal limits.

successful/healthy aging and preventative strategies to reduce aging related functional limitations (10,11). Further, intensified efforts also are needed to develop effective

disease modifying therapies for AD, PD, LBD, FT Mozilla Firefox.Ink LD, ALS, PLS, MND and other aging related neurodegenerative diseases. This challenge is the rationale behind the mission pursued by CNDR at and beyond PENN.

PENN CNDR: ITS PARTNERS AND PROGRAMS

The long predicted “age boom” is upon us, but we as a society are totally unprepared to manage it from medical, public health, education and fiscal perspectives. PENN has made a significant commitment to address this public health issue through research programs that focus on aging and aging related brain diseases, and CNDR’s partners and programs at and beyond PENN are briefly highlighted here. These programs reflect efforts at PENN to fit the pieces of the neurodegenerative disease puzzle together so we are able to understand the mechanisms that underlie them and thereby develop better ways to diagnose, treat and, perhaps, even prevent neurodegenerative diseases, so that we can improve the quality of life for all members of our aging populations (see Figure 4).

FIGURE 4

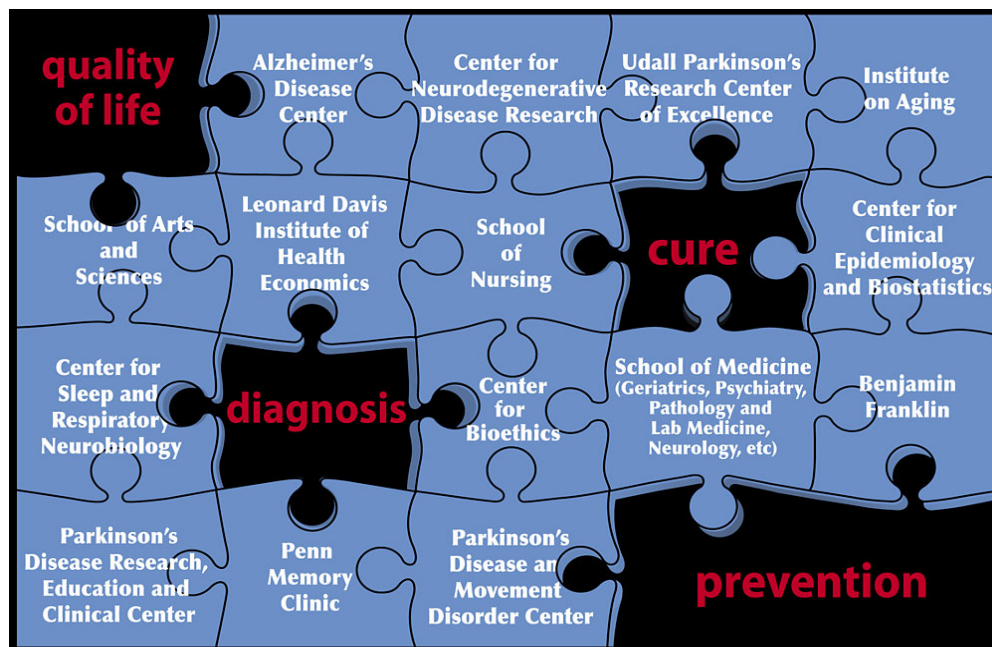


Figure Legend: PENN Neurodegenerative Disease Research – Solving the Puzzle! This figure illustrates synergistic collaborations among PENN investigators and programs to find better diagnostics, cures and preventions for aging related neurodegenerative diseases in order to achieve the shared goal of improving the quality of life for the millions of individuals who are now, or will in the future, be affected by these disorders.

Since its inception in 1991, CNDR has augmented research and education on AD, PD, LBD, FTLD, ALS, PLS, MND and related disorders in several ways. First, as depicted in Figure 4, CNDR fosters collaborative interactions between basic and clinical scientists from Centers, Institutes, Schools and Departments throughout PENN including the: Institute of Medicine and Engineering, Institute on Aging, Institute of Neurological Sciences (INS), Center for Bioethics, BioMedical Informatics Facility, School of Arts and Sciences (Departments of Biology and Chemistry), Smell and Taste Center, Population Center, Center for Environmental Medicine, Nursing School, Wistar Institute, School of Social Work and, in the School of Medicine at PENN, the Departments of Biophysics and Biochemistry, Medicine, Neurology, Neurosurgery, Rehabilitation Medicine, Otorhinolaryngology, Pathology and Laboratory Medicine, Pharmacology and Psychiatry. Second, CNDR enhances the development of multidisciplinary research on neurodegenerative disorders by providing core support and collaboration to investigators through CNDR grants from the National Institutes of Health (NIH), foundations, philanthropies and other agencies or commercial entities. Third, by increasing awareness of neurodegenerative disorders for the public as well as scientists through CNDR sponsored conferences/symposia.

For example, CNDR works closely in partnership with the Institute on Aging, the oldest aging focused organization at PENN, which was founded >25 years ago by the late highly regarded gerontologist, Dr. Vincent Cristofalo. The Institute on Aging is dedicated to improving the health and well being of our aging population through the efforts of ~200 Institute on Aging Fellows in highly collaborative programs on aging research, education and clinical care (<http://www.med.upenn.edu/aging>). The Institute

on Aging is directed by Dr. Trojanowski, and PENN is among the top National Institute on Aging (NIA) funded institutions. PENN faculty/ Institute on Aging Fellows lead many aging-focused grants funded by the NIA and other components of the NIH, the Commonwealth of Pennsylvania, industry, private foundations and other sources.

While the Institute on Aging is centered in the PENN School of Medicine, it seeks to have an impact across the PENN campus and beyond. Thus, Kathy Jedrzejewski, the Deputy Director of the Institute on Aging, recently worked for the past 2 years with the Alzheimer's Association, the Center for Disease Control and experts from around the Nation to formulate "The Healthy Brain Initiative", which is a remarkable "roadmap" for the public on how to maintain cognitive health throughout the life span (for details, see www.cdc.gov/aging and www.alz.org). Moreover, the Institute on Aging Pilot Grant Award Program stimulates new aging research and educational initiatives among PENN faculty by supporting 8 new pilot initiatives per year, for up to \$50,000 per grant. These Institute on Aging Pilot Grants are made possible by funding from a private foundation and PENN School of Medicine resources. Preference for pilot awards is given to junior faculty who seek to obtain pilot data to launch new initiatives that clearly have a high likelihood of garnering sustained extramural support from the NIA, NIH or other external funding agencies.

With respect to AD research, CNDR is the home of the Administrative and Neuropathology Cores of the Alzheimer's Disease Core Center (ADCC; <http://www.pennadc.org>), which is one of 32 NIA funded Alzheimer's Disease Centers (ADCs) in the United States (12). Working with CNDR, the PENN ADCC has contributed to a dramatic expansion in basic and clinical research on AD and related disorders at

PENN over the past 15 years by providing leadership, education and core support to enhance and stimulate investigations into the etiology, pathogenesis, diagnosis, treatment and prevention of these neurodegenerative diseases. The ADCC also funds Pilot Grants and it does so in partnership with the Institute on Aging and the Institute of Medicine and Engineering, which is led by Dr. Peter F. Davies. Commensurate with this growth, PENN is recognized as an international leader in research on AD and related disorders.

The mission of the PENN ADCC complements that of Institute on Aging and CNDR as it focuses on increasing understanding of and research on AD and related disorders at and beyond PENN, fostering interactions between this ADCC and other ADCs and/or institutions, interacting with the National Alzheimer Coordinating Center, participating in National Alzheimer Coordinating Center sponsored ADC collaborative studies, and responding to NIA initiatives on AD and related disorders (12). The Clinical Core of the PENN ADCC is located in the PENN Memory Center in close proximity to Institute on Aging offices in the PENN Ralston House. This ADCC Core is led by Dr. Steve Arnold, Associate Director of the ADCC, and the Clinical Core recruits, assesses and monitors AD and control subjects, including women and minorities.

There also is a Latino Clinic that focuses on recruiting urban Latinos into the ADCC dementia and control study cohorts. The PENN Memory Center, which also is led by Dr. Arnold, works in close partnership with the ADCC and it is dedicated to improving the health, well-being and quality of life of patients and their caregivers. Thus, the PENN Memory Center offers expert comprehensive diagnostic evaluation and a multidisciplinary team approach that provides good medical management, education

and social support. As the home of the ADCC's Clinical Core, the Memory Center is responsible for carefully collecting data on the course of AD and related diseases in patients and providing an environment for the conduct of clinical research to improve the standard of care. Research ranges from the development of new diagnostic methods to the evaluation of new treatments.

The other two key core components of the ADCC are the Data Management/Biostatistics Core led by Dr. Sharon Xie, and the Education and Information Transfer Core led by Dr. Jason Karlawish. Both of these Cores are located in the PENN Ralston House adjacent to Institute on Aging offices. The ADCC Data Management/Biostatistics Core plays an important role in providing biostatistical support for studies conducted by ADCC investigators and their collaborators as well as in data management, which includes sharing PENN ADCC data sets with the other investigators through regularly scheduled data downloads to National Alzheimer Coordinating Center.

Notably, the Education and Information Transfer Core is a unique feature of ADCs that plays a critical role in educating professionals and the public about AD and related dementias. This is critical for increasing the participation of patients and controls in AD research. Moreover, the PENN Education and Information Transfer Core has taken the educational mission to a new level of sophistication by developing educational videos on AD and healthy brain aging to air on PBS for the public with the support of the MetLife Foundation.

Because neurodegenerative diseases are aging related disorders, CNDR also partners with the Division of Geriatric Medicine that is recognized for its outstanding

clinical care program, as well as an exceptional Geriatric Medicine training program, which includes several Fellowship opportunities. The Division is led by Dr. Jerry Johnson, and it is dedicated to enhancing the health of older adults by establishing models of interdisciplinary clinical care that span the array of sites in which elderly receive care; training physicians to provide excellent clinical care of older adults with an emphasis on enhancing functional status, quality of life and survival; conducting and facilitating research on issues of premier importance to the elderly; and sponsoring community-based education and demonstration projects. The Division is located in the PENN Ralston House in close proximity to Institute on Aging and shares clinic space with the PENN Memory Center and the ADCC. Geriatric Psychiatry, led by Dr. Steven Arnold, also is located in PENN Ralston House. Under the leadership of Dr. Arnold, Geriatric Psychiatry develops innovative research programs that enhance and strengthen partnerships between PENN research programs on aging related neurodegenerative and neuropsychiatric diseases.

With respect to PD and LBD, CNDR is the home of the National Institute of Neurological Disorders and Stroke (NINDS) Morris K. Udall Parkinson's Disease Center of Excellence which is funded to study the molecular mechanisms that underlie the movement and cognitive impairments of PD and related LBD, as well as the care and treatment of patients and training of physicians. PD is one of the most common neurodegenerative diseases, second only to AD in the number of people affected. Estimates suggest that approximately 800,000 Americans have PD and this Udall Parkinson's Center will enable PENN to better combine achievements in clinical care for PD patients with basic science studies of PD, LBD and related disorders.

The theme of the Udall Center is cognitive impairment, a very much neglected aspect of PD. Dr. John Trojanowski leads the Center's overall operations and neuropathology studies, while Dr. Vivianna Van Deerlin pursues genetic studies of PD and LBD. Dr. Howard Hurtig investigates potential markers of PD-related neurodegeneration and he leads educational efforts for physicians and the lay community.

Drs. Andrew Siderowf and Murray Grossman each lead projects that will define the nature of cognitive impairments in PD and LBD, while Drs. Virginia Lee and Benoit Giasson each lead projects that study the nature of these impairments in mouse models and Dr. Sharon Xie oversees data management and biostatistics for the Center. This Udall Center builds on over 20 years of basic research on neurodegenerative diseases at PENN that enables psychiatrists, neurologists, geriatricians, pathologists, basic neuroscientists, and biostatisticians to better interact under one virtual roof. Notably, PENN is part of a network of 13 other existing Centers in this NINDS Udall Center Program, but PENN is one of only 9 institutions that have both an NINDS funded Udall Center and a NIA funded Alzheimer Center.

Significantly, this Udall Center partners with the CNDR and the PENN ADCC while also taking advantage of outstanding clinical programs on PD, LBD and related movement disorders at PENN. For example, these disorders are the major clinical focus of the Parkinson's Disease and Movement Disorder Center (PD&MDC) of the PENN Neurological Institute at the Pennsylvania Hospital and the Hospital of the University of Pennsylvania. Indeed, the PD&MDC, which was founded in 1982 and is led by Drs. Matt Stern and Howard Hurtig, has grown over the past 25 years to become the largest

facility of its kind in the Delaware Valley (encompassing Pennsylvania, New Jersey and Delaware) and a National Parkinson Foundation designated Center of Excellence.

Moreover, the PD&MDC is closely allied with the Parkinson's Disease Research, Education and Clinical Center (PADRECC) at the Philadelphia Veterans Hospital. This PADRECC, which is led by Drs. Matt Stern and John Duda, draws patients from the veteran population of the entire Delaware Valley making it a magnet clinical site for underserved minority patients. Exciting research on PD, LBD and related disorders will emerge from the powerful synergies between investigators in the Udall Center, the PD&MDC and the PADRECC.

To prevent or ameliorate aging related neurodegenerative diseases as well as to promote successful aging, PENN CNDR develops novel partnerships to take its research in new directions. This includes the establishment of the Marian S. Ware Alzheimer Program, as well as PD drug discovery programs funded by generous support from the Picower and Benaroya families.

Another novel program is exemplified by the PENN Biomarker Core of the NIA funded Alzheimer's Disease Neuroimaging Initiative that is designed to test imaging and biological markers for measuring the progression of a condition known as mild cognitive impairment, which may be a prodromal or nascent phase of AD, and early AD, as well as for distinguishing normal controls from subjects with mild cognitive impairment or AD.

The PENN Biomarker Core is led by Drs. Les Shaw and John Trojanowski, who, with their colleagues at PENN and the other Alzheimer's Disease Neuroimaging Initiative investigators, will define and standardize biomarkers for the early diagnosis of AD and to identify healthy elderly individuals at great risk for AD. The rationale for

pursuing efforts for the early and reliable diagnosis of AD is because that is the stage at which disease modifying therapies are likely to be most effective, and interventions to prevent AD will be most effective if targeted to populations at greatest risk for AD before they develop cognitive impairments as reviewed in reference 13 and illustrated in Figure 5.

FIGURE 5

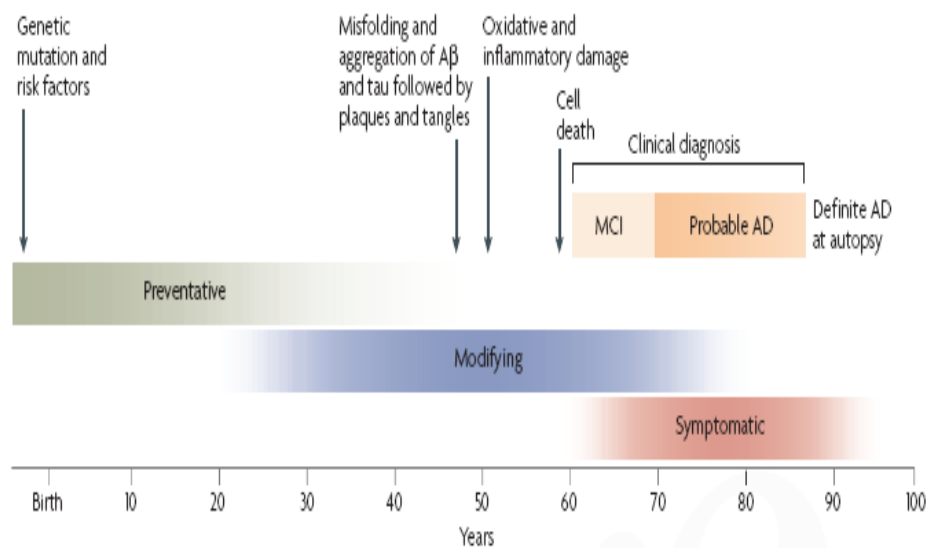


Figure Legend: This is a schematic showing a hypothetical time line for the onset and progression of sporadic as well as familial AD progressing from no cognitive impairment to mild cognitive impairment (MCI) and on to AD. There are few predictive biomarkers for AD except genetic mutations that are pathogenic for familial AD, which could be measured from conception onwards, but the emphasis in the Alzheimer Disease Neuroimaging Initiative is on promising AD biomarkers identified through research. The green, blue and magenta shaded bars indicate the time points at which preventative, disease modifying and symptomatic interventions are likely to be most effective, but AD biomarkers are needed to accelerate efforts to test the efficacy of preventive and disease modifying therapies for AD.

With respect to the Marian S. Ware Alzheimer Program, this was launched with generous philanthropic support from the Ware family in January 2004 to comprehensively attack the problem of AD. This unique multidisciplinary program includes 3 key components: 1) AD Drug Discovery, led by Drs. Lee and Trojanowski; 2)

AD Clinical Trial Design, led by Drs. Chris Clark and Jason Karlawish; and 3) Continuity of AD Care, led by Dr. Mary Naylor of the PENN School of Nursing.

Academic drug discovery programs for neurodegenerative diseases have the potential to bridge the gap between drug target identification, validation and proof of concept studies to hasten efforts to bring new therapies out of laboratories into the clinic. However, the funding opportunities for these programs are limited and it is gratifying that philanthropic sources of support for them are becoming available. For example, CNDR has been able to launch PD drug discovery programs with support from the Picower and Benaroya families.

Notably, Dr. Kurt Brunden was recruited to CNDR to lead these drug discover programs, and while these programs are new, they already are beginning to generate new leads for AD and PD drug discovery (14-20). This program takes advantage of robotic high throughput screening technologies and large compound libraries for neurodegenerative disease drug discovery with the goal of finding drugs that will eliminate misfolded proteins since the accumulation of misfolded proteins is a pathological hallmark of AD, PD, LBD, FTLN, ALS, PLS, MND and almost all other aging related neurodegenerative disorders.

Figure 6 shows a photograph of the CNDR HTS robot work station which is 7 ft wide and 12 ft. long.

FIGURE 6



Significantly, research from CNDR and its affiliated investigators at and beyond PENN has demonstrated that AD and many other neurodegenerative disorders share common disease mechanisms since they are associated with the pathological aggregation of proteins that misfold and accumulate as fibrillar amyloid deposits in the central nervous system (CNS) as shown schematically in Figure 7. Thus, neurofibrillary

FIGURE 7

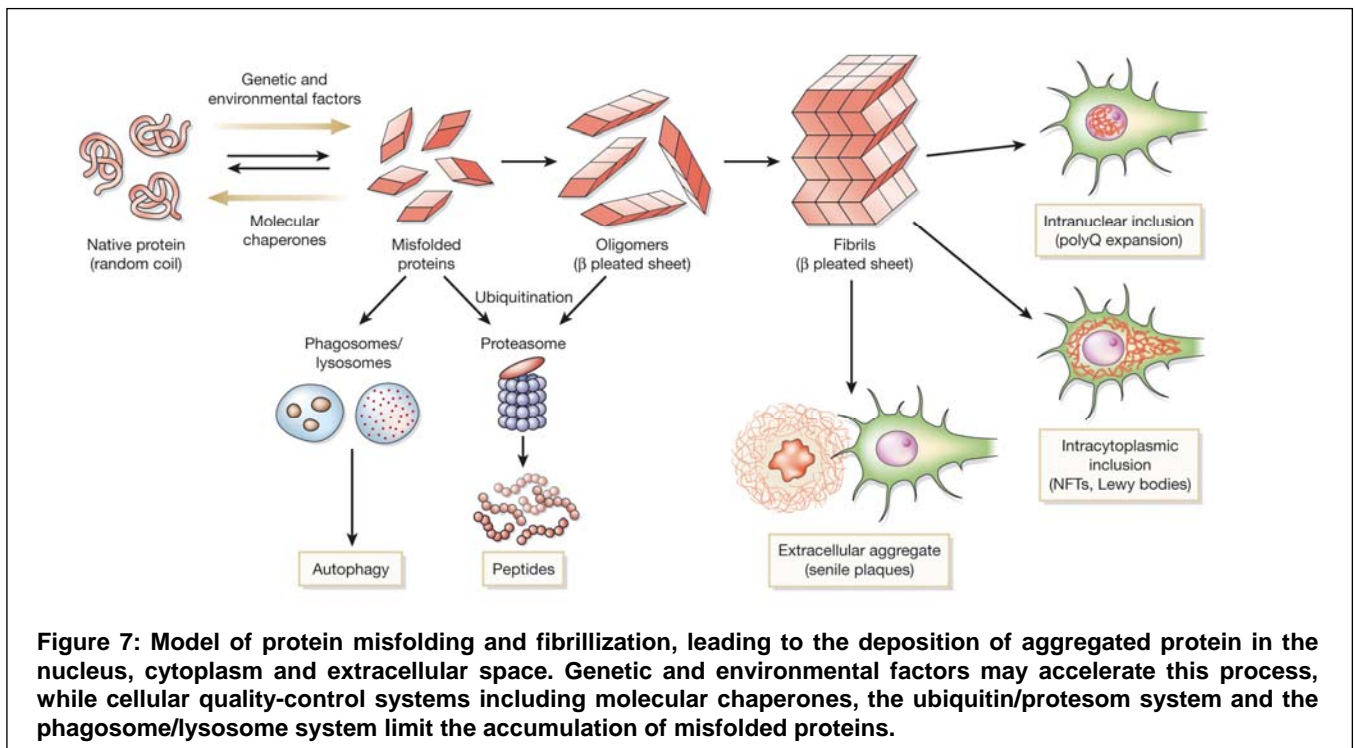


Figure 7: Model of protein misfolding and fibrillization, leading to the deposition of aggregated protein in the nucleus, cytoplasm and extracellular space. Genetic and environmental factors may accelerate this process, while cellular quality-control systems including molecular chaperones, the ubiquitin/proteasome system and the phagosome/lysosome system limit the accumulation of misfolded proteins.

tangles and senile plaques, the two diagnostic hallmarks of AD, are formed by intraneuronal accumulations of abnormal tau filaments and extracellular deposits of A β fibrils, respectively. Moreover, there have been dramatic advances in understanding mechanisms of A β generation and accumulation as well as the cascade of events leading to neurofibrillary tangle formation. Further, a growing body of evidence supports the view that these lesions compromise the function and viability of neurons, but the exact mechanisms whereby brain degeneration results from neurofibrillary tangles and senile plaques remain incompletely understood. Nonetheless, since the misfolding and fibrillization of normal brain proteins results in their accumulation as disease specific fibrillar inclusions in many neurodegenerative disorders, these mechanisms are targets for drug discovery.

A novel example of how research can change approaches to drug discovery is illustrated by the recent discovery by CNDR investigators and the colleagues of a novel disease protein known as TDP-43 that links FTLD and ALS, PLS and related MNDs mechanistically (21,22). This implies that drugs capable of ameliorating the accumulation of TDP-43 aggregates in FTLD also may do the same for ALS, PLS and other MND, which is something that never would have been imagined without the discovery of TDP-43 as the disease protein underlying all of these disorders despite their different clinical manifestations. For these reasons, CNDR has launched new research programs on TDP-43 linked disease to complement the other research programs mentioned above. To that end, Dr. Virginia Les has put together a team of investigators including Drs. Murray Grossman, Lauren Elman, Leo McCluskey, John Trojanowski, Viviana Van Deerlin and Sharon Xie to investigate these new TDP-43

findings in greater detail and these studies will complement another NIA funded FTLD research program involving Drs. Murray Grossman, Jerry Schellenberg, John Trojanowski, Vivianna Van Deerlin and Sharon Xie, that focuses on elucidating tau mediated mechanisms of neurodegeneration. Hence, by studying the two major disease proteins in linking FTDL and MND, the chances of discovering meaningful disease modifying therapies for patients afflicted with these disorders is substantially enhanced.

However, more partnerships with pharmaceutical and biotechnology companies as well as philanthropies, foundations and other entities are needed as well to make these efforts successful, and this also is being actively pursued by CNDR. Thus, through its relentless efforts to understand AD, PD, LBD, FTLD, ALS, PLS, MND and related neurodegenerative diseases, CNDR and its collaborators at and beyond PENN will be able to translate this research into better ways to diagnose and treat these disorders (23).

Selected References

1. Meyer J: Age: 2000, Census Bureau Brief, C2KBR/01-12, Washington, DC: US Census Bureau, 2001.
2. Hetzel L, Smith A: The 65 years and over population: 2000, Census Bureau Brief, C2KBR/01-10, Washington, DC: US Census Bureau, 2001.
3. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2004: Key Indicators of Well-Being. Federal Interagency Forum on Aging-Related Statistics. Washington, DC: US Government Printing Office, 2004.
4. Rowe JW, Kahn, RL: Successful Aging. New York: Pantheon Books, 1998.

5. Manton KG, Gu X, Lamb VL: Changes in chronic disability from 1982 to 2004/2005 as measured by long term changes in function and health in the U.S. elderly population. *Proc Natl Acad Sci USA* 2006;103:18374-18379.
6. Hebert LE, Scherr PA, Bienias JL Bennett DA, Evans DA: Alzheimer disease in the US population: Prevalence estimates using the 2000 census. *Arch Neurol* 2003;60:1119-1122.
7. The Lewin Group. Saving lives, saving money: Dividends for Americans investing in Alzheimer research. Alzheimer's Association Report 2006.
8. Brookmeyer R, Gray S, Kawas C: Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health* 1998;88:1337-1342.
9. Cogan JF, Mitchell OS: Perspectives from the President's Commission on Social Security Reform. *J Econom Perspectives* 2003;7:149-172.
10. Jedrziewski MK, Lee VM-Y, Trojanowski JQ: Lowering the risk of Alzheimer's disease: Evidence-based practices emerge from new research. *Alzheimer's & Dementia* 2005;1:152-160.
11. Jedrziewski MK, Lee VM-Y, Trojanowski JQ: Physical activity and cognitive health. *Alzheimer's & Dementia* 2007;3:98-108.
12. Hodes RJ: Public funding for Alzheimer disease research in the United States. *Nat Med* 2006;12:770-773.
13. Shaw LM, Korecka M, Clark CM, Lee VM-Y, Trojanowski JQ: Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Rev Drug Discovery* 2007; 6:295-303.

14. Ballatore C, Hyde E, Deicher R, Lee VM-Y, Trojanowski JQ, Hurn D, Smith AB, III: Paclitaxel C10 carbamates: Potential candidates for the treatment of neurodegenerative tauopathies. *Bioorg Med Chem Lett* 2007;17:3642-3646.
15. Crowe A, Ballatore C, Hyde E, Trojanowski JQ, Lee VM-Y: High throughput screening for small molecule inhibitors of heparin-induced tau fibril formation. *Biomed Biophys Res Comm* 2007;358:1-6.
16. Lee VM-Y, Trojanowski JQ: Mechanisms of Parkinson's disease linked to pathological alpha-synuclein: New targets for drug discovery. *Neuron* 2006;52:33-38.
17. Skovronsky DM, Lee VM-Y, Trojanowski JQ: Neurodegenerative diseases: New concepts of pathogenesis and their therapeutic implications. *Annu Rev Pathol Mech Dis* 2006;1:151-170.
18. Trojanowski JQ, Duff K, Fillit H, Koroshetz W, Kuret J, Murphy D, Refolo L: New directions for frontotemporal dementia drug discovery. *Alzheimer's & Dementia* 2008; 4:83-93.
19. Yoshiyama Y, Higuchi M, Zhang B, Huang S-M, Iwata N, Saido TC, Maeda J, Suhara T, Trojanowski JQ, Lee VM-Y: Synapse loss and microglial activation precede tangles in a P301S tauopathy mouse model. *Neuron* 2007; 53:337-351.
20. Zhang B, Maiti A, Shively S, Lakhani F, McDonald-Jones G, Bruce J, Lee EB, Xie SX, Joyce S, Li C, Toleikis PM, Lee VM-Y, Trojanowski JQ: Microtubule binding drugs offset tau sequestration by stabilizing microtubules and reversing fast axonal transport deficits in a murine neurodegenerative tauopathy model. *Proc Natl Acad Sci USA* 2005; 102:227-231.

21. Neumann M, Sampathu DM, Kwong LK, Traux A, Misceniyi M, Chou TT, Bruce J, Schuck T, Grossman M, Clark C, McKlusky L, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ, Lee VM-Y: Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006; 314:130-133.
22. Kwong LK, Trojanowski JQ, Lee VM-Y: TDP-43 proteinopathies: Neurodegenerative protein misfolding diseases without amyloidosis. *NeuroSignals* 2008; 16:41-51.
23. Trojanowski JQ: PENN neurodegenerative disease research – In the spirit of Benjamin Franklin. *NeuroSignals* 2008; 16:5-10.