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A model for improving the treatment and care of Alzheimer's disease patients through interdisciplinary research

John Q. Trojanowski^{a,b,c,*}, Steven E. Arnold^{a,d,e}, Jason H. Karlawish^{a,f,g}, Mary Naylor^{a,h,i}, Kurt R. Brunden^{a,b,c}, and Virginia M.-Y. Lee^{a,b,c}

^aInstitute on Aging, University of Pennsylvania, Philadelphia, PA, USA

^bCenter for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA, USA

^cDepartment of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^dDepartment of Psychiatry (Section of Geriatric Psychiatry), Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^eDepartment of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^fCenter for Bioethics, University of Pennsylvania, Philadelphia, PA, USA

^gDepartment of Medicine (Division of Geriatric Medicine), Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

^hPerelman School of Medicine and School of Nursing, University of Pennsylvania, Philadelphia, PA, USA

ⁱNewCourtland Center for Transitions and Health, University of Pennsylvania, Philadelphia, PA, USA

Abstract

The emerging global epidemic of Alzheimer's disease (AD) demands novel paradigms to address the two unmet needs of the field: (a) cost-effective health care delivery programs/services, and (b) clinical and basic research to accelerate therapy discovery/development. This report outlines a model demonstration project, the Marian S. Ware Alzheimer Program at the University of Pennsylvania, which was designed to achieve four specific aims: (1) improve the integration and continuity of AD care; (2) identify biomarkers that detect the earliest presence of AD and related neurodegenerative cognitive disorders; (3) enhance both the design and conduct of clinical trials as well as review their results to more effectively test new AD therapies and translate valuable therapies into clinical practice; and (4) discover and develop novel disease-modifying small molecule treatments for AD.

The "Ware-UPenn" program has been presented in this report as a useful prototype for partnerships between private philanthropy and academia in planning and developing programs to address a major national public health problem.

Keywords

Drug discovery; Biomarkers; Clinical trial design; Continuity of care; Alzheimer's disease

1. A growing crisis

The aging of populations globally has precipitated a demographic “sea change” that is having a profound impact on societies worldwide, and is the most powerful driver for aging-related disorders. For example, as of January 1, 2011, the first of the estimated 75 million members of the American “baby boom” generation (i.e., those born between 1946 and 1964) turned 65 years, and over the next 20 years, a baby boomer will turn 65 years every 7 seconds [1–6]. This has important implications in terms of health, health care, and health care policy because after age 65, the incidence of Alzheimer's disease (AD) rises exponentially, doubling every 5 years. Thus, only 20 years from now, baby boomers will begin to turn 85 years, and about half of them will have AD, unless interventions are developed to prevent or delay the onset of the disease [1–6]. Hence, the epidemic of aging-related neurodegenerative diseases is upon us now, and an international plan is urgently needed to combat this epidemic before it becomes the most socially, economically, and medically transformative natural disaster experienced to date.

The arguments for global action to prevent the AD epidemic and to reduce the impact of AD on societies worldwide are illustrated by dramatic demographic changes in the United States. For example, although the prevalence of chronic disability is decreasing at a rate of just >2% per year for those aged >65 years since 1999 [7], which suggests that aging-related disabilities can be delayed [7], there are increasing concerns about the impact of aging-related neuro-degenerative disorders such as AD on the growing number of individuals entering the seventh decade of life and beyond [5]. In the United States alone, it is estimated that approximately 5.3 million Americans have AD [6], and as populations age in the United States, Europe, Africa, Australia, Asia, and elsewhere, the number of people with AD will explode, unless ways to prevent or treat the disease are found very soon [6]. Indeed, someone develops AD in the United States every 70 seconds, and AD has displaced diabetes as the sixth leading cause of death in the United States [6]. By 2030, as many as 7.7 million Americans could have AD, and by 2050, this number could rise to 11 to 16 million people [1–6]. The annual cost of AD in the United States is >\$150 billion, and AD will affect the economies of other countries to a similar extent, including developing nations [6]. For example, the London-based Alzheimer's Disease International (ADI) has determined that in the next 30 years, the number of AD patients will more than quadruple in India, China, other countries in Asia, Australasia, and Oceania, from approximately 16 million in 2010 to approximately 61 million by 2050 [6]. Further, in Africa, there are expected to be >8 million AD patients by 2050, when the worldwide burden of AD will be >115 million people [6]. Although the global explosion of AD may seem too overwhelming a challenge to overcome by 2050, a “cure” for AD is not essential, as delaying the onset of AD by just 5 years could have a profound impact on this disorder by reducing the incidence and cost of AD by 50% between now and 2050 [8].

The total worldwide costs of dementia in 2010 were estimated to be US\$604 billion (~70% of which occur in Europe and North America), and these expenditures are approximately 1% of the global gross domestic product [6]. Accordingly, if dementia care was a country, it would be the world's 18th largest economy; if it were a company, it would be the world's largest, exceeding Walmart (US\$414 billion) and Exxon Mobil (US\$311 billion) in expenditures [6]. Given these economic realities, ADI has called for governments and other research funders to act now to increase dementia research funding (including research into

prevention) to a level more proportionate to the economic burden of AD and related disorders [6]. To that end, ADI points to data suggesting that a 15-fold increase in funding for dementia is required to reach parity with heart disease, and a 30-fold increase is needed to achieve parity with cancer research [6].

Although there are many causes of dementia, AD is the most common cause of dementia [1–6]. The hallmark lesions of AD are deposits of fibrillar β -amyloid ($A\beta$) in neuritic plaques and neurofibrillary tangles (NFTs) formed by abnormal tau [4,9–13]. Clinical symptoms in AD patients relate more closely to NFTs, neurodegeneration, and synapse loss than to $A\beta$ deposits [9,11,12,14,15]. AD can be divided into a presymptomatic phase in which subjects are cognitively normal but have AD pathology, a prodromal phase known as mild cognitive impairment (MCI), and a third phase when patients show evidence of clinical dementia with impairments in multiple domains and loss of the ability to carry out customary activities of daily living [4,10,16–19]. It has been suggested that diagnostic criteria for early AD should be redefined by the presence of memory impairments plus biomarker evidence of AD pathology, although the diagnosis of definite AD still requires an autopsy [17]. However, it is critical to identify the beginning stages of AD before symptom onset to optimize efficacy of disease-modifying therapies when they become available, as well as to enable drug development aimed at AD prevention [9,16,20]. Indeed, data emerging from the North American Alzheimer's Disease Neuroimaging Initiative (ADNI) suggest that success in accomplishing this may be close at hand [16,18,21,22].

To address the pending public health crisis due to AD, a unique alliance between academia and philanthropy was formed. The Marian S. Ware Alzheimer Program at the University of Pennsylvania (Figure 1) was designed as a highly integrated, multidisciplinary initiative with a converging focus on advancing patient care, clinical research, and drug discovery for AD patients now and in the future. The Ware Program comprises four interrelated programs that take a research approach to address critical unmet needs, as described later in the text. Although structured like a National Institute on Aging (NIA) P01 or P50 Center grant, with funding at an annual level like that of NIA P01s/P50s, the components of this program are uniquely integrated in a way that we are unaware exists at this time for any current grant in the NIA portfolio.

2. Care Coordination Program: A focus on transitional care

Improving health care quality and reducing costs for the growing group of chronically ill older Americans whose care is complicated by cognitive impairment is a significant challenge, but one that Dr. Mary Naylor, the leader of this component of the Ware Program, has effectively implemented [23]. Episodes of acute illness resulting in hospitalizations among this population are frequent, disruptive, costly, and often associated with poor outcomes resulting from accelerated cognitive, physical, and functional decline and high rates of adverse events and rehospitalization [1,24].

The Ware Program brings together a multidisciplinary team of scholars from nursing, medicine, health care economics, and biostatistics to advance knowledge regarding care management strategies designed to better address the complex care needs of this high-risk group of individuals and their family caregivers, while increasing the efficiency of the health care system. Importantly, the Program also uses its findings to influence health care policy and clinical practice [25].

One promising strategy to achieve higher value care among cognitively impaired older adults is an adaptation of the Transitional Care Model (TCM). The TCM emphasizes identification of older adults' health goals; coordination and continuity of care throughout episodes of acute illness; development of a rational, streamlined plan-of-care to prevent

future hospitalizations; and preparation of the older adults and their family caregivers to implement this care plan [25]. The TCM is applied in collaboration with physicians and other health team members. In multiple National Institutes of Health (NIH)-funded randomized controlled trials, the TCM has consistently demonstrated improved health outcomes and decreased all-cause hospitalizations and health care costs among high-risk, cognitively intact, chronically ill older adults [26–28].

The Care Coordination team has made the case for large-scale, NIH-funded studies related to the TCM and has implemented a unique private–public partnership to conduct these studies. A summary of accomplishments of the Care Coordination Program to date is presented in the following text.

2.1. Hospital to home: Cognitively impaired elderly individuals and their caregivers

Building on the results of three NIH-funded randomized controlled trials [27–29], we enrolled and collected data from 407 cognitively impaired older adults and 407 family caregivers to assess the clinical and economic outcomes achieved by nursing innovations of varying intensities. This large-scale study tested the effects of the following three interventions [30]:

1. Comprehensive screening for cognitive impairment among hospitalized older adults, with reports of screening results distributed to all health professionals involved in these patients' care (*low dose*).
2. Comprehensive screening plus the use of Web-based education modules to prepare hospital nurses to address the unique needs of cognitively impaired older adults and their family caregivers (*medium dose*).
3. Comprehensive screening plus the implementation of the TCM, led by master's-prepared nurses using an evidence-based protocol initiated at hospital admission and continuing through an average of 2 months postdischarge (*high dose*).

Preliminary findings reveal a significant reduction in costly health resource utilization among older adults who received the TCM intervention when compared with those in lower-dose intervention groups.

We anticipate that findings from this study will contribute substantially to our understanding of the unique needs of cognitively impaired elderly individuals and their caregivers across episodes of acute illness, as well as offer evidence-based solutions to enhance their care and outcomes. Further, these data position our team to make the case for improving the standards of care for these vulnerable groups. Several manuscripts are under review and one is in press on screening older adults for cognitive impairment in the emergency department [31].

2.2. Health-related quality of life: Elderly individuals in long-term care

A second large-scale effort co-funded by the Ware Program and the NIH is a longitudinal study assessing changes in health and quality of life over time among older adults newly transitioned to long-term services and supports (LTSS). In this study, we compare changes in multiple domains (e.g., cognition, function, quality of life) among older adults who receive LTSS in their homes, assisted-living facilities, or nursing homes, and assess the impact of transitions between LTSS and hospitals for this group. Cognitively impaired older adults, who comprise approximately 50% of this study sample, are arguably the most vulnerable of this frail population. Currently, these older adults experience frequent, often avoidable transitions between the acute and long-term sectors of the health care system that have vastly different goals and few bridges to connect them.

The health-related quality of life study represents the first attempt to capture and document the experiences of frail older adults as they navigate challenging care transitions in health and health care. To date, we successfully completed enrollment of 470 English- and Spanish-speaking older adults in the Philadelphia and New York areas from 12 major LTSS organizations and 57 individual sites. Completion rates for quarterly follow-up interviews are excellent, with rates consistently more than 80%.

Findings generated from this study will position our team to test innovative care management strategies, including adaptation of the TCM, which are designed to enhance health and quality of life outcomes, foster use of more effective services such as palliative care, and reduce health care costs among older adults coping with frailty and cognitive impairment. A manuscript is in press on advance care planning among LTSS recipients [32].

2.3. Pilot studies on transitions of elderly long-term care recipients to and from hospitals

The Ware Program has also supported two pilot studies designed to describe the major facilitators and barriers to high-quality care associated with the transitions of elderly recipients of LTSS who are transferred to and from hospitals for episodes of acute illness based on the perspectives of the older adults, their family caregivers, and health care clinicians from acute hospitals and LTSS.

Through semistructured interviews with LTSS recipients and staff, these studies have revealed the following common barriers to person-centered care: lack of staff communication; substantial delays in receiving care in the emergency department; perceived inaccessibility and responsiveness of health care staff; inadequate transfer of information about individualized needs, goals, and plan of care; limited preparation and time for staff in both LTSS and hospital settings to respond to residents' acute and long-term needs; and lack of mutual respect between acute and long-term care staff. These findings will enable the design of interventions to enhance the transition of frail older adults with cognitive impairment to and from hospitals and improve their care throughout these transitions.

Another pilot study is underway to assess the feasibility of and response to a transitional care intervention for elderly long-term care recipients transitioning to and from hospitals. The purpose of this study is to determine whether interventions designed to address the barriers to care previously identified can improve the transitions of frail older adults to and from hospitals, enhance the health and quality of life outcomes, and decrease health care costs. Findings from this study will be used to make the case for rigorous, large-scale testing of the proposed interventions.

2.4. Potential impact of the Care Coordination Program

Findings from our studies will contribute to our nation's efforts to redesign the care system for this vulnerable population and their family caregivers, as well as to achieve cost savings and other efficiencies. This body of work has clinical and health policy implications for all older adults, but especially for those whose care is complicated by cognitive impairment. To position findings from our studies to have a more immediate impact, partnerships have been formed with national and local advisory groups comprising leading health care purchasers, providers, clinicians, and policy-makers. These partnerships offer a strong dissemination network and the ability to incorporate complementing perspectives at the policy table, and therefore will enhance the care of chronically ill older adults who also are coping with cognitive impairment and provide better support to those who are responsible for their care during common and challenging transitions.

3. Developing and validating novel biomarkers to detect the earliest presence of AD

A second major goal of the Ware Program is to develop, implement, and validate cognitive and biological assessment tools (i.e., biomarker assays) to efficiently and reliably categorize the cognitive and neurodegenerative disease status of older adults. The settings for this work are the University of Pennsylvania Geriatric Practice in West Philadelphia and community primary care practices in North Philadelphia, as well as the Penn Memory Center (PMC) and the Penn AD Core Center (ADCC) as the research-based validation clinic.

As a first step, we designed a brief, 7-minute paper and pencil cognitive test and administered it to more than 2000 subjects whose cognitive abilities ranged from normal to severe dementia. The Penn Brief Cognitive Test diagnosis was then validated by a research-level PMC evaluation, consisting of neuropsychological testing, clinical interview, and neurological examination by specially trained clinicians. Ongoing analyses of the results show that this brief assessment reliably distinguishes individuals who are aging successfully from those who are failing due to AD or related cognitive disorders. In secondary analyses, however, we noted that this brief test cannot reliably distinguish the cognitive failure of AD from cognitive failure due to other neurodegenerative conditions such as Lewy body diseases or frontotemporal degeneration. Thus, the major utility of this test is as a brief screening instrument for dementia. In addition, we found that screening diagnoses of MCI in general clinical practice are unstable. Many people revert to normal or do not change at all over time, whereas for others, MCI is a way station to AD. This emphasized the need for better chemical and brain imaging biomarkers to identify which people with MCI will go on to develop AD.

A significant accomplishment of this study was the successful implementation of screening and clinical characterization in underserved Spanish-speaking communities of North Philadelphia followed by the Penn ADCC. We have demonstrated the utility of our Penn Brief Cognitive Test and learned important information about differences in the presentation of AD in this rapidly growing minority group compared with non-Hispanic white and African-American English-speaking groups. Two particularly noteworthy differences were that the age of onset of cognitive failure was significantly younger, and that levels of depression were significantly higher in the Latino group and to a lesser degree in the African-American group [33]. Understanding these differences in biological, psychological, and socioeconomic contexts will provide important clues to AD.

This component of the Ware Program also played a lead role in cerebrospinal fluid (CSF) studies conducted at the University of Pennsylvania and in partnership with the ADNI. These studies have already led to important recognition of the increasing clinical utility of CSF measurements of A β and tau for the differential diagnosis of AD and for predicting the progression of MCI to AD [34–37].

Although abnormal tau and A β are presumed to be the principal pathological causes of brain cell degeneration in AD, we and others have observed that people vary in their vulnerability or resistance to the cognitive failure associated with tau, A β , and neurodegeneration [38]. Cerebral and cognitive “reserve” or “resilience” based on education, hereditary endowment, or many lifestyle factors are important concepts for interpreting such variability. In this regard, we observed that people who tend to experience higher levels of stress and depression in their lives are at greater risk of dementia and have a worse progression, whereas those who manage stress well are at lower risk for AD [33].

The biological effects of stress have been well characterized in animal models and young people; however, their importance in older people and individuals with AD and other dementias has not been meaningfully examined. Thus, we have initiated a new longitudinal cohort of older adults with normal cognition in whom we investigate psychological distress, coping skills, and biomarkers of stress and how they are related to more established biomarkers of AD, such as CSF A β and tau, and cognition. To date, >100 subjects have had their baseline assessments, including clinical rating scales of stress, distress, anxiety, depression, and coping skills; paper and pencil and computerized cognitive testing; and collection of plasma, DNA, saliva, and hair for molecular and biochemical analyses.

We seek to establish clinically predictive biomarker profiles of healthy and pathological aging by combining CSF and brain imaging measures of neurodegeneration, including tau and amyloid pathology, with novel, stress-related biomarkers of cognitive vulnerability. Examples of newer imaging modalities we are evaluating include computational recognition of AD-specific patterns of cortical atrophy with volumetric magnetic resonance imaging (MRI) [39], arterial spin-labeled MRI of AD-specific hemodynamic patterns [40], identification of either aggregated mis-folded protein (T₁ ρ MRI) [41] or the accumulation of sodium associated with AD pathology (3-T sodium MRI) [26], as well as positron emission tomography scanning with novel ¹⁸F ligands to A β [42]. We exploit data from ADNI to determine how well these biomarkers detect resilience, vulnerability, and pathology indicative of AD as well as impending cognitive decline at the earliest stage possible. To maximize the efficient use of resources supporting this project, our evaluation protocols will be harmonized with the NIA-funded public/private ADNI studies wherein Penn is an active participant.

Our future plans are to (1) elucidate the contributions and pathophysiological mechanisms of chronic stress for the onset and course of AD dementia, and (2) refine and develop novel biomarker profiles for AD that encompass vulnerability and resilience risk factors. We hypothesize that chronic psychological distress weakens some of the same memory areas of the brain that tend to accumulate amyloid and tau pathology, thereby rendering the “toxicity” of these lesions more potent. We further hypothesize that this effect of distress continues to affect the course of AD, increasing the rapidity of cognitive and functional decline and decreasing the quality of life at all stages of dementia.

We expect that these efforts will further improve the accuracy and clinical effectiveness of clinical and biomarker tools to detect the earliest stages of AD and predict which normal individuals or those with MCI as well as very mild MCI will remain healthy and free of AD versus those who will progress to AD. In the process, we will lay down fundamental new knowledge about how the biological effects of chronic stress contribute to the vulnerability of individuals to develop AD.

4. Improving participant recruitment and retention and the outcomes of clinical research in patients with AD

Progress in therapeutics for AD relies on studies that enroll, recruit, and retain participants, and measure outcomes that adequately reflect the patient’s quality of life. These studies are essential to show that an intervention is safe and effective, and to meaningfully disseminate these interventions to patients. Unfortunately, clinical research for AD as well as other diseases faces a number of challenges. These include concerns about the risks, stresses, and uncertainties of research participation; lack of trust; and ineffective messaging about the value of and need for patient-oriented clinical research. In addition, as definitions of AD begin to incorporate biomarker measures that predict who is at risk to suffer cognitive decline, clinicians, patients, and the public will face the challenge of incorporating this

concept of AD risk into their understanding of healthy brain aging. Taken together, these challenges affect the ability to conduct clinical trials with meaningful outcomes and then translate these outcomes into practice, and it is the goal of Dr. Karlawish to meet these challenges in this component of the Ware Program.

4.1. Redesigning clinical trials to maximize enrollment

We examined ways to redesign an AD clinical trial to maximize caregivers' willingness to enroll their relative with AD. This study assessed the relative value of changes to the standard clinical trial design: home visits, car transport to the study site, the risk of the study drug, and the chance of receiving the study drug. Briefly, we pursued a creative strategy to address this issue by using "conjoint analysis," a multiattribute utility assessment method developed in marketing research to assess the relative value of a product's attributes. Although this strategy had never been used in AD research before, we successfully used it to answer our research questions.

Among a sample of 102 caregivers, we found that home visits substantially increased caregivers' willingness to allow their relative to participate in a clinical trial of a potential new AD therapy. In fact, the value of home visits was significantly large enough to offset the negative impact on enrollment associated with an increased risk of the study drug. In addition, home visits had particular value to care-givers of more severe-stage AD patients, thereby expanding the range of AD severity studied in clinical trials. This, in turn, improved the clinical value of a study's results. Finally, we did not find that burdened caregivers were more willing than nonburdened caregivers to subject their relative to research risks. This is a result with considerable ethical and policy significance.

4.2. Using memory and organizational aids for informed consent

In a randomized trial, we demonstrated that a memory and organizational aid provided early-stage AD patients with sufficient support to overcome the clinical impact of their cognitive impairments. Compared with the patients who did not receive the aid, nearly half of those who received the aid could provide their own informed consent to participate in a clinical trial. In contrast, only 20% of patients who did not receive the aid were judged capable of consent. This result has substantial promise for investigators who are conducting early-phase AD clinical trials in which the informed consent of the patient, instead of proxy consent, may be a requirement.

4.3. Support for proxy consent

We also discovered that older adults generally support proxy consent to enroll noncompetent patients into AD research that does not benefit the subjects. Using a cross-sectional, face-to-face interview with 538 persons aged 65 years who resided in the southeastern Pennsylvania region, we found that 96% of persons interviewed were willing to identify a proxy for research decision making and most were willing to grant their proxy leeway over their advance consent to the biomarker studies involving blood draw (81% [434/538]) and blood draw plus lumbar puncture (70% [375/538]). Combining the preferences for advance consent and leeway, we found that the proportion who would permit being enrolled in the blood and CSF studies were 92% (497/538) and 75% (404/538), respectively. These results show that older adults generally support enrolling noncompetent persons with AD into research that does not present a benefit to the subjects directly, but does advance our understanding of AD. These results thus support the development of research policies and guidelines that allow the use of proxy informed consent [43–45].

4.4. Future plans

These studies have laid the groundwork for projects aimed at better understanding how to assess quality of life in persons with AD, including its prodromal state, that is, MCI. Quality of life is a core outcome to show that a patient has benefitted from an intervention, such as a symptomatic or disease-modifying drug. Our approach recognizes that quality of life is an important outcome for a number of stakeholders. Clinicians, patients, and their families value it to make decisions about the care of individual patients. Policy-makers value it to make decisions about how best to allocate resources and justify the risks of an intervention.

Thus, the program to improve participant recruitment and retention and the outcomes of clinical research in patients with AD will examine a critical issue in quality of life in persons with AD: the impact of awareness of cognitive problems on quality of life. These studies will examine the following questions:

- a. How does patient awareness of cognitive problems impact patient self-reported quality of life?
- b. Can AD clinical trials be improved to encourage patient participation?
- c. What are the policy implications of developing better ways to diagnose and treat AD?

To address these questions, we will combine unique approaches involving social history, ethical analysis, patient and physician narratives, interviews with key informants, and critical analyses of primary sources to support a study of the policy implications of advances in AD research. Key foci of this project are biomarkers of AD, MCI, and healthy brain aging.

5. Marian S. Ware Alzheimer Drug Discovery Program

The fourth component of the Ware Program focuses on drug discovery, particularly on identifying novel AD drug targets and developing therapeutics directed to these targets. Accordingly, as illustrated in Figure 2, the intention and goal of this component of the Ware Program has been to create the equivalent of an academic “biotechnology company” within the Penn Center for Neurodegenerative Disease Research (CNDP) to pursue novel avenues of AD drug discovery. Notably, there now are multiple ongoing Ware AD Drug Discovery projects that are making rapid progress in identifying potential therapeutics, as summarized in the following text.

An important strength of this program is its ability to exploit basic research findings developed at the CNDP with NIH funding, and translate these findings into drug discovery opportunities. For example, the transition from basic to applied research has been significantly aided by the creation of novel transgenic (Tg) mouse models of AD that were developed and characterized in CNDP with NIH funding. Another important tool in the Drug Discovery toolbox is high-throughput screening (HTS), which allows investigators to screen hundreds of thousands of compounds to identify those with potentially therapeutic potential.

Molecules identified through HTS must then be further developed through chemical modifications to yield compounds that have greater potency and other desirable drug-like properties for use in AD patients, including an absence of toxicity, good oral absorption, adequate stability in the bloodstream, and, importantly for AD drugs, an ability to gain access to the brain [9]. To do this, we collaborate with medicinal chemists at Penn and have recruited a senior-level scientist from the private sector, who provides expertise in orchestrating the drug discovery process and understanding the various dimensionalities of

drug optimization. Through this team approach, we have made substantial progress, as summarized later in the text.

5.1. Inhibition of NFT formation

One of the hallmarks of AD is NFTs, which are composed of tau fibrils that lead to neuronal damage in AD [9]. Thus, we developed a novel robotic HTS assay that allows us to survey for molecules that prevent tau fibrillization, and we conducted an HTS campaign with our compound library for inhibitors of tau fibril formation [46]. A number of compounds were identified that effectively prevented tau fibrillization [9]. However, because none of these molecules had other characteristics needed for a drug to treat patients, we collaborated with the NIH Chemical Genomics Center to screen their 290,000 compound library in our tau fibrillization assay [47]. A number of interesting and unique chemical structures were identified from this HTS campaign, and the aminothienopyridazine class of inhibitors seems most promising for further development [46].

5.2. Microtubule stabilization in AD

Another serious consequence of tau deposition into AD NFTs is a loss of the normal ability of tau to stabilize micro-tubules (MTs), which are critical for the transport of cellular cargo in nerve cells [9,48–50]. The destabilization of MTs as a result of tau sequestration into NFTs damages neurons, but this loss of function could be overcome by substituting another MT stabilizer to replace tau, as exemplified by our studies showing that the Food and Drug Administration (FDA)-approved drug paclitaxel improves nerve cell function in a Tg mouse model with AD-like tau tangles [50]. We also identified members of the epothilone family of MT stabilizers as compounds that readily gain access to the brain and ameliorate the disease phenotype in tau Tg mice [9,46]. Thus, this program continues to be a major focus of our efforts.

5.3. Thromboxane receptor blockers as AD therapeutics

Research from our group demonstrated that oxidized lipids known as isoprostanes are elevated in the AD brain and activate neuronal thromboxane receptors that cause increased formation of amyloid plaques in a Tg AD mouse model [51]. Although a number of thromboxane receptor blockers are being developed as antithrombotics, we have found that the existing compounds do not penetrate the blood–brain barrier and are not suitable for treating brain disorders like AD. We therefore initiated a drug discovery program to identify thromboxane receptor blockers that penetrate the blood–brain barrier for the treatment of AD, and this program has obtained NIH funding to augment Ware support.

5.4. Future plans

Over the next 3 years, we plan to build on the progress and accomplishments to date by bringing existing/ongoing projects to fruition and identifying additional AD drug discovery targets based on research conducted in our Drug Discovery Program. These objectives will be achieved by identifying small-molecule compounds that ameliorate Alzheimer brain degeneration at multiple steps in the disease process and then testing the most promising drugs in preclinical studies using Tg mouse models of AD.

In parallel with these activities, we will undertake biological and medicinal chemistry studies to establish that lead compounds have required drug-like properties (i.e., lack of toxic effects, good oral absorption, good brain penetration, and suitable stability within the body). We expect these studies will lead to partnerships with NIH/pharmaceutical/bio-technology companies to bring the most promising compounds closer to clinical trial in AD patients.

6. Conclusion

The Marian S. Ware Alzheimer Program is unique in concept, design, and funding strategy. Although proposals have been made [52] to create comprehensive AD centers that significantly enhance or extend programs currently supported by NIA-funded AD centers [53], there is no other program like the Ware Program in the United States or abroad. However, the importance of this program goes beyond its uniqueness because it brings together key disciplines and individuals needed to solve the major puzzle to society that AD represents nationally and globally. Indeed, as shown in Figure 1, by working together as a team, Ware investigators will develop disease-modifying interventions for AD and apply them to real patients in clinical trials that are more effective and efficient because they use novel biomarkers, as well as develop better methods to recruit and retain subjects. Significantly, this program is more than a collection of projects; it is a highly integrated program designed to meet the challenge of creating a world without AD.

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Fig. 1. Schematic illustration of the Marian S. Ware Alzheimer Program and its four components. The leaders of each component in the Ware Program are listed, including Dr. Christopher Clark, who led the biomarker project from 2004 to 2009, and Dr. Steven Arnold, the current leader of this project.

Fig. 2.

The Ware Drug Discovery Program has created a new model for Alzheimer disease (AD) drug discovery that seamlessly extends from target identification through to human clinical trials and Food and Drug Administration approval of potential new AD therapies. Previously, academia focused on drug target and biomarker discovery and validation (brown text), whereas industry uses this information to develop new compounds and advance them through clinical trials to Food and Drug Administration approval for treating patients (blue text). The novel concept underlying the Ware Alzheimer Drug Discovery Program is to bring these two critical components into a unified program (orange arrow). Finally, the Ware Program can pursue compounds that industry is not interested in because of lack of patent protection, but that nonetheless have the potential to become therapies for the benefit of AD patients.