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Mary S. Easton Center of Alzheimer's Disease Research at UCLA: Advancing the Therapeutic Imperative

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Abstract

The Mary S. Easton Center for Alzheimer's Disease Research (UCLA-Easton Alzheimer's Center) is committed to the "therapeutic imperative" and is devoted to finding new treatments for Alzheimer's disease (AD) and to developing technologies (biomarkers) to advance that goal. The UCLA-Easton Alzheimer's Center has a continuum of research and research-related activities including basic/foundational studies of peptide interactions; translational studies in transgenic animals and other animal models of AD; clinical research to define the phenotype of AD, characterize familial AD, develop biomarkers, and advance clinical trials; health services and outcomes research; and active education, dissemination, and recruitment activities. The UCLA-Easton Alzheimer's Center is supported by the National Institutes on Aging, the State of California, and generous donors who share our commitment to developing new therapies for AD. The naming donor (Jim Easton) provided substantial funds to endow the center and to support projects in AD drug discovery and biomarker development. The Sidell-Kagan Foundation supports the Katherine and Benjamin Kagan Alzheimer's Treatment Development Program, and the Deane F. Johnson Alzheimer's Research Foundation supports the Deane F. Johnson Center for Neurotherapeutics at UCLA. The John Douglas French Alzheimer's Research Foundation provides grants to junior investigators in critical periods of their academic development. The UCLA-Easton Alzheimer's Center partners with community organizations including the Alzheimer's Association California Southland Chapter and the Leeza Gibbons memory Foundation. Collaboration with pharmaceutical companies, biotechnology companies, and device companies is critical to developing new therapeutics for AD and these collaborations are embraced in the mission of the UCLA-Easton Alzheimer's Center. The Center supports excellent senior investigators and serves as an incubator for new scientists, agents, models, technologies and concepts that will significantly influence the future of AD treatment and AD research.

INTRODUCTION

Alzheimer's disease (AD) is an impending public health disaster. Every 70 seconds someone in the United States progresses in their cognitive impairment syndrome to a point where they meet criteria for diagnosis of dementia of the Alzheimer's type (DAT) [1]. Five million U.S. citizens currently have DAT, and the aging "baby boomer" population is expected to add 10 million victims to this number. By 2050, AD will affect 11 to 16 million individuals if the disease frequency progresses unchecked [1]. Medicare costs for individuals with AD are approximately three times higher than those without a dementing disorder. This will

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translate into a staggering Medicare expenditure if attempts to stem the rising tide of AD victims are unsuccessful [1].

The UCLA-Easton Alzheimer's Center comprises a spectrum of research (Fig. 1) from basic science, to T1 translational activities (animal models, drug candidate discovery, biomarker method discovery, facilitative research in biotechnology), clinical research (neuroimaging and other biomarkers, neuropathology, clinical trials, clinical phenotype characterization), T2 translational research (human services research, outcomes assessments), and educational and translational activities [2]. This spectrum model organizes the research into a comprehensive enterprise addressing multiple aspects of AD and related dementias. The organization allows investigators to interact and creates a matrix of human and research resources. The organizational model is multi-disciplinary, facilitates bench-to-bedside approaches, and optimizes the opportunity for trainees and junior faculty to interact with multiple scientists [2-4].

The members of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA (UCLA-Easton Alzheimer's Center) embrace the importance of advancing therapeutics for AD that will prevent the disease, delay its onset, slow its progression, improve the symptoms, or enhance the quality of life of victims and caregivers. The theme of the UCLA-Easton Alzheimer's Center is *the therapeutic imperative* and all basic science, clinical studies, clinical trials, biomarker investigations, educational and recruitment activities, and donor-related functions are organized around this critical translational neuroscience theme. Advancing therapeutics requires improved understanding of the basic mechanisms and pathophysiology of AD, better biomarkers for diagnosis and tracking progression of the disease, a clinical trials program addressing a diversity of disease mechanisms, and recruitment and educational activities to inform practitioners of progress in therapeutics and attract patients to clinical trials and clinical research.

The UCLA-Easton Alzheimer's Center is comprised of interactive cores that enhance the collaboration of individuals with complementary skills necessary to advancing the Center's activities and theme. The cores include an Administrative Core, Data Management and Statistics Core, Clinical Core, Neuropathology Core, Recruitment and Education Core, and Neuroimaging and Biomarkers Core (Fig. 2).

HISTORY OF THE UCLA-EASTON ALZHEIMER'S CENTER

Dementia research has a long history at UCLA, beginning with early studies of familial and genetic influences on the heritability of AD by Lissy Jarvik [5] and studies of the neurobiology and cytoarchitectonics of AD by Arnold Scheibel [6]. Understanding of the clinical phenomenology was advanced by studies of language and behavioral alterations of AD by D. Frank Benson and collaborators [7,8]. Michael Phelps, David Kuhl, and colleagues performed the first studies of fluorodeoxyglucose (FDG) positron emission tomography (PET) at UCLA [9-11]. Funding from the National Institute on Aging (NIA) augmented these research activities through the award of an AD Core Center (ADCC) grant in 1991. Jeffrey Cummings was Principal Investigator. The ADCC was advanced to an AD Research Center (ADRC) award in 1994. Establishment of a California Alzheimer's Disease Center (CADC; one of ten such centers funded by the State of California) occurred in 1998.

Philanthropic support has been critical to the success of the AD research programs at UCLA. In 1998, the Sidell-Kagan Foundation began support of the Katherine and Benjamin Kagan Alzheimer's Disease Treatment Development Program, the AD clinical trials organization of the UCLA-Easton Alzheimer's Center. This relationship has been sustained and has proven to be central to the success of the clinical trials program.

In 2008, Jim Easton, Chairman and President of Jas. D. Easton, Inc. and Chairman of Easton Bell Sports, Inc., made a \$10 million gift to support AD research at UCLA. The Center was re-named to honor his mother who succumbed to AD. The gift provides an endowment to support the Center's efforts in perpetuity as well as research funding to advance therapeutics and biomarkers through the Jim Easton Consortium for Alzheimer's Drug Discovery and Biomarker Development.

The Kagan clinical trials group conducts clinical trials in the Deane F. Johnson Center for Neurotherapeutics at UCLA, the Department of Neurology's Clinical Trials Center, named to honor Deane F. Johnson, a prominent Los Angeles attorney and former president of the board of Time Warner, Inc. Mr. Johnson died of AD in 1999, and Mr. Johnson's widow, Kate Edelman Johnson supports the clinical trials center.

The Lincy Foundation supports basic science studies aimed at understanding the proteomic markers of AD and studying gene expression mapping in AD transgenic mouse models and human AD. Many other donors have provided critical support to AD research at UCLA and philanthropy accounts for a significant portion of the Center's budget. A board of directors, comprised primarily of philanthropists, assists the center leadership in connecting with the community and developing donor relationships.

CLINICAL RESEARCH

The faculty and staff of the UCLA-Easton Alzheimer's Center assess approximately 400 new cognitively impaired and cognitively normal patients annually and approximately 150 persons are followed longitudinally. Every effort is made to align the patient flow with the research objectives of the Center.

The clinical faculty providing clinical services and conducting research include neurologists, psychiatrists, neuropsychologists, and nurses. The research agenda of the UCLA-Easton Alzheimer's Center includes studies of the neuropsychiatric manifestations of AD and other dementias; neuropsychological aspects of AD and dementia prodromal states; features of frontotemporal dementia; characteristics of familial AD (FAD); biomarkers and neuroimaging; clinical trials; and basic neuroscience. Each of these articulates with the center theme of the therapeutic imperative.

Neuropsychiatry of AD

Jeffrey Cummings, M.D., Director of the UCLA-Easton Alzheimer's Center is the author of the Neuropsychiatric Inventory (NPI) [12], an instrument commonly used to characterize the behavioral aspects of AD, non-AD dementias, and AD prodromal states [13]. NPI profiles have been developed for most dementias and neurodegenerative disorders [14-19]; correlations between NPI scores and neuropathological changes identified at postmortem assessment have been established [20,21]; relationships between NPI changes and imaging have revealed anatomic regions critical to behavioral symptoms [22]; and behavioral responses to treatment with cholinesterase inhibitors and memantine have been investigated using the NPI [23-27]. Recent studies have demonstrated that behavioral changes detected by the NPI in patients with mild cognitive impairment (MCI) assist in predicting which patients will develop DAT [13].

Familial AD cohort of the UCLA-Easton Alzheimer's Center

FAD provides a unique opportunity for the study of AD since it is possible to assess through mutation carrier status determination for exactly which persons will develop the illness and which will not. Studies of the FAD cohort recruited and followed by John Ringman, M.D., at the UCLA-Easton Alzheimer's Center have shown biomarker alterations and imaging

changes that precede clinical manifestations in FAD patients [28]. Of particular interest is the discovery that changes in the white matter, measured using diffusion tensor imaging (DTI), are evident very early in the course of this condition [29]. The biochemical studies support the role of oxidative stress in this form of AD and biomarker investigations are yielding insights into the status of amyloid- β (A β)₄₂ measured in plasma, an important molecule in the causative chain leading to AD. The UCLA program is integrated into the Dominantly Inherited Alzheimer's Network (DIAN); J Morris, Principal Investigator).

Neuropsychological Laboratory at the UCLA-Easton Alzheimer's Center

Po Lu, Psy.D., directs the Neuropsychology Laboratory of the UCLA-Easton Alzheimer's Center. The laboratory conducts neuropsychological assessments of adult and geriatric patients with neurological disorders as part of clinical evaluations and research projects. Dr. Lu also investigates longitudinal changes in whole and regional brain volume and white matter integrity using standard structural imaging techniques and Tensor-Based Morphometry (TBM), a novel computational approach. TBM can be used to map the relationship between brain changes with clinical measures (e.g., cognition and behavioral functioning) [30]. Imaging studies show that the presence of the apolipoprotein ϵ 4 allele is associated with increased rate of myelin breakdown and temporal lobe atrophy in healthy cognitively intact elderly individuals [31]. Other research activities include characterizing the neuropsychological and neuropsychiatric changes associated with normal aging and neurodegenerative disorders such as AD and frontotemporal lobar degeneration and identifying risk factors that can predict or modulate the progression of cognitive decline from normal aging to MCI or dementia [13].

Dr. Lu's research has shown that neuropsychiatric symptoms, particularly depression, increase the risk of progression from MCI to DAT and that donepezil treatment can modify this relationship by delaying the time to progression to DAT in depressed MCI patients [32].

The Cognitive Neuropsychology Program of the UCLA-Easton Alzheimer's Center, a Neuropsychology Laboratory component, is led by Ellen Woo, Ph.D. This program bridges basic cognitive science and clinical neuropsychology. The goal of the research is to develop new theories and examine extant models of executive and memory processes in very early AD. Dr. Woo and her colleagues are investigating those processes that are more predictive of changes in higher-order activities of daily living. In addition to utilizing standard neuropsychological measures, her team employs cognitive experimental tasks to parse the particular processes that are impaired in this population. The research is focused on novel, sensitive tests to detect the earliest levels of cognitive decline [33-37].

Frontotemporal Dementia Clinic

Mario Mendez M.D., Ph.D., is director of the Frontotemporal Dementia Clinic of the UCLA-Easton Alzheimer's Center. Dr. Mendez has contributed importantly to understanding the clinical phenomenology of the frontotemporal lobar degenerations as well as to imaging and pathological aspects of these disorders [38,39]. Dr. Mendez has contributed to developing clinical trial methodology for frontotemporal dementia and has pioneered therapeutic concepts for the disorder [40].

KAGAN ALZHEIMER'S DISEASE TREATMENT DEVELOPMENT PROGRAM

The Katherine and Benjamin Kagan Alzheimer's Disease Treatment Development Program conducts the clinical trials of the UCLA-Easton Alzheimer's Center and supports AD Cooperative Study (ADCS) clinical trials, investigator-initiated trials, and industry-sponsored clinical trials. ADCS trials are particularly important as a means of studying

compounds that may not be advanced by industry sponsors and for developing clinical trial methodologies. Josh Grill, Ph.D., is program Director.

Investigator-initiated trials are a means of generating preliminary information on compounds and to determine whether they should be studied in larger trials. Dr. John Ringman led a trial of curcumin demonstrating that in its current formulation the bioavailability of the compound is too low to produce a clinical benefit. New formulations are under development for further testing. Po Lu, Psy.D., led a trial of testosterone in normal aged men and men with mild AD and determined that both groups experienced a measurable and significant improvement in quality of life compared to those receiving placebo [41]. A biomarker based trial OC Axona™ funded by the John Douglas French Alzheimer's Research Foundation and led by Dr. Grill is underway.

The Kagan trials program tests a balanced portfolio of agents targeting several mechanisms of AD and addressing AD in non-overlapping populations. Therapeutic approaches being studied include immunotherapies, secretase inhibitors, inhibitors of receptors for advanced glycation end products, neuroprotective agents and latrepirdine (dimebon). Patients with AD type of dementia and pre-dementia AD are included in trials.

NEUROIMAGING AND BIOMARKER DEVELOPMENT AT THE UCLA-EASTON ALZHEIMER'S CENTER

Identification of patients with AD or those at risk for AD at a time when they have no or minimal symptoms is increasingly important as the field of AD research moves toward development of disease-modifying therapies. Neuroimaging and biomarkers may assist in identifying those at risk or those who are minimally symptomatic. Investigators at the UCLA-Easton Alzheimer's Center are advancing studies using Magnetic Resonance Imaging (MRI), DTI, fluorodeoxyglucose (FDG) positron emission tomography (PET), TBM, FDDNP PET amyloid imaging, and cerebrospinal fluid (CSF) and plasma markers of AD.

Dr. Liana Apostolova's research focuses on developing imaging biomarkers for detection of early and pre-symptomatic AD, specifically those that characterize cortical and hippocampal atrophy [42]. In collaboration with Dr. Paul Thompson and colleagues from the Laboratory of NeuroImaging (LONI) at UCLA, Dr. Apostolova works on the development and validation of cutting-edge MRI techniques that allow increased sensitivity for detecting subtle changes during the initial silent spread of AD pathology [43,44]. Dr. Apostolova and colleagues identified atrophic areas in the hippocampus that place one at risk for MCI and described the hippocampal regions that show changes up to 6 years before diagnosis of dementia and 3 years before the onset of memory loss [44,45]. This research demonstrated that subjects in the mildest stages of DAT have 10–25% greater gray matter atrophy relative to subjects with amnesic MCI (see Fig. 3) [45]. The most important short-term goal of this research is to be able to screen patients and reliably identify AD in the latent asymptomatic stage when introduction of disease-modifying therapies may have the greatest impact.

Amyloid imaging with Pittsburgh Compound B (PIB) identifies individuals in pre-symptomatic stages of AD, persons with MCI whose cognitive impairment is attributable to AD, as well as amyloidosis in patients with DAT [46]. FDDNP PET represents an alternate imaging approach with a ligand that labels both plaques and tangles. FDDNP labeling has been shown to correlate with dementia severity and to progress in intensity with clinical progression from MCI to DAT [47]. Dr. Gary Small, director of the Neuroimaging and Biomarkers Core of the UCLA-Easton Alzheimer's Center, is conducting studies of FDDNP in AD and other dementias.

Plasma and CSF studies in FAD show that amyloid-related abnormalities are demonstrable prior to the onset of clinical symptomatology. Dr. Ringman's research has shown that symptomatic FAD mutation carriers have elevated levels of serum A β relative to non-carriers [28].

Further development of imaging and bio-fluid disease markers may play a role in disease diagnosis, differential diagnosis, staging, response to therapy, and drug – placebo differentiation in randomized clinical trials. Figure 4 shows the interaction of the Neuroimaging and Biomarkers Core with other cores of the UCLA-Easton Alzheimer's Center and the diversity of imaging modalities and biomarkers currently under study.

New studies funded through the UCLA-Easton Alzheimer's Center have been initiated to correlate peripheral markers of central nervous system gene expression with longitudinal studies of brain atrophy demonstrated by MRI and proteomic studies aimed at capturing the link among gene expression, proteomic changes, and neurodegeneration.

PATHOLOGY STUDIES OF THE UCLA-EASTON ALZHEIMER'S CENTER

Neuropathological investigations of biopsy and autopsy material obtained from AD and non-AD dementia patients have been critical to advancing understanding of dementing disorders. Neuropathology has assumed great importance recently in documenting effects of therapeutic interventions such as the AN1792 vaccination trial [48,49] and in documenting congophilic angiopathy that may represent a vulnerability to adverse events in patients receiving immunotherapy.

Harry Vinters, M.D., leads the Neuropathology Core of the UCLA-Easton Alzheimer's Center, performing routine and molecular autopsy procedures to comprehensively characterize the post mortem findings of the patients studied in the Center as well as the post mortem features of brains referred from other sources. Dr. Vinters has described the gross and molecular alterations characteristic of congophilic angiopathy in AD and vascular changes associated with vascular cognitive impairment [50,51] (Fig. 5).

RECRUITMENT AND EDUCATION ACTIVITIES OF THE UCLA-EASTON ALZHEIMER'S CENTER

Recruitment and education represent the bi-directional activities of the Recruitment and Education Core of the UCLA-Easton Alzheimer's Center, led by Josh Grill, Ph.D. Education activities raise awareness of AD and the UCLA-Easton Alzheimer's Center mission and provide an opportunity to recruit patients and controls into clinical trials and clinical research projects. These dual activities are implemented in a variety of activities in the community and at UCLA, including joint activities with advocacy groups such as the Alzheimer's Association California Southland Chapter and the Leeza Gibbons Memory Foundation. An annual conference for community practitioners, community lectures for physicians and caregivers, seminars for UCLA faculty and outreach events for the local Hispanic and African American communities are components of the Core's activities.

MINORITY OUTREACH ACTIVITIES

The UCLA-Easton Alzheimer's Center faculty is actively engaged in recruiting ethnic minority members to participate in AD research. This effort requires an understanding of the sociocultural and educational barriers to research participation present in ethnic minority populations. Studies by Jaime Fitten, M.D., and Fred Ortiz, Ph.D., document barriers to health care and differential behavioral manifestations of Hispanic patients compared to majority population AD patients [52-54].

BASIC SCIENCE RESEARCH OF THE UCLA-EASTON ALZHEIMER'S CENTER

Advancing therapeutics depends on an improved understanding of the molecular biology and pathophysiology of AD. Target identification is a necessary step in developing new treatments. Transgenic models have been particularly informative for understanding disease pathways and signaling cascades and providing preliminary treatment target validation. The predictive validity of mouse models of AD has not been established but compounds that lack effects in these models would usually not be advanced to human testing. Investigators at UCLA have studied transgenic mouse models, transgenic rat models, and tau transgenic *Drosophila* [55]. The latter model is used as a bioassay to discover compounds potentially active in modifying tau pathology [56,57].

Greg Cole, Ph.D., is Associate Director of the UCLA-Easton Alzheimer's Center and Associate Director for Research at the Geriatric Research, Education and Clinical Center for the Greater Los Angeles Veterans Administration System. Dr. Cole conducts research centered on the production and role of $A\beta$ in AD. He worked with Dr. Karen Hsiao to develop the first successful academic transgenic mouse model for AD [58]. Based in part on a series of screens in pre-clinical models from his group, four compounds – ibuprofen [59], R-flurbiprofen [60], curcumin [61], and docosahexaenoic acid (DHA) [62,63] – have advanced to clinical trials for AD. Dr. Cole and colleagues investigate the potential for AD prevention with DHA and their role in preventing amyloid formation and $A\beta$ toxicity, notably through induction of the AD protective gene, SorLA [64]. Dr. Cole is exploring the efficacy of the curry spice extract curcumin to control inflammation and oxidative damage and to act directly on insoluble amyloid fibrils in plaques and on more soluble toxic $A\beta$ species *in vitro* and *in vivo*. Together with his colleague, Dr. Sally Frautschy, he developed a more bioavailable formulation of curcumin that is in current clinical trials for cancer [65], and has planned for trials in AD. Dr. Cole works with Bruce Teter, Ph.D. on the role of apolipoprotein E as a risk factor for AD using transgenic mouse models and with Karen Gyls, R.N., Ph.D. on synaptic $A\beta$ analyzed by flow cytometry. They are currently evaluating agents from a variety of sources including the Easton Drug Discovery Consortium using multiple animal models for AD. Dr. Cole's primary goal is to develop safe and widely available methods for the prevention of AD and possibly other degenerative diseases of aging.

Dr. David Teplow's laboratory uses computational methods to identify structures in $A\beta$ that could be useful targets for therapeutic drugs. In the past, target identification has been problematic because $A\beta$ does not possess a stably folded structure. However, *in silico* approaches allow atomic resolution of conformer structure, and importantly, an assessment of the thermodynamics of the $A\beta$ conformer space [66,67]. This latter achievement enables the targeting of steps in the $A\beta$ assembly process that should be amenable to drug intervention. Using this approach, simulations have revealed important differences between the conformational spaces of the shorter $A\beta_{40}$ peptide and the longer and more pathogenic $A\beta_{42}$ peptide. Multiple conformers have been revealed that may be involved in peptide oligomerization, a process postulated to be the key pathogenetic event in AD [68]. The identification of these conformers provides a starting point both for subsequent simulations of $A\beta$ oligomerization and for experimental studies of the process. Dr. Teplow also has demonstrated that polyphenols derived from grape seed extracts inhibit the oligomerization of $A\beta$ [69] and are promising treatment candidates.

Gal Bitan, Ph.D., currently focuses on the development of aggregation inhibitors using detailed knowledge of the three dimensional structure of the $A\beta$ peptide to develop rational pharmacotherapies that will prevent the aggregation of monomers into oligomers [70,71].

Hong-Wei Dong, Ph.D., has contributed to mapping gene expression in the normal mouse brain [72,73] and is now using these techniques to address gene expression in transgenic AD mouse models. These findings will be compared to gene expression observations in humans to determine the fidelity with which the transgenic model recapitulates the intracellular genetic activity of human AD.

DATA MANAGEMENT AND STATISTICS CORE

Data are the currency of scientific advance. It is through data generation and interpretation that knowledge is advanced and new discoveries made. The data generated in contemporary science is voluminous and complex. Its management is itself a scientific enterprise. Advanced data management is critical to collecting, organizing, and making data available in formats that facilitate analysis and interpretation. Data from the UCLA-Easton Alzheimer's Center are transmitted to the National Alzheimer's Coordinating Center (NACC, Bud Kukull, Principal Investigator) in Seattle, Washington, where they become widely available for study. Both clinical and pathology data are archived in this national data repository.

Analysis and interpretation of large data sets obtained from neuroimaging, microarray studies, genomics, and proteomics require sophisticated understanding and advanced expertise. This skill set is provided by the Data Management and Statistics Core. David Elashoff, Ph.D., leads the core and provides informatics expert guidance. He is assisted in data management by colleagues devoted to data integrity including Cathy Lee, Ph.D., Jenny Kotlerman, and Sun Huang.

TRAINEES AND SCHOLARS

The UCLA-Easton Alzheimer's Center has many trainees and scholars. A 2 year fellowship program in dementia research is available for US Citizens and permanent residents. There have been over 40 fellows trained in this program and many are now leaders of AD research centers.

International Scholars observe clinical assessments and participate in AD-related research. The UCLA-Easton Alzheimer's Center has an international scholars program and accepts up to two individuals at a time for study periods of 1 month to 2 years. International scholars now comprise a global fraternity of AD clinician-scientists.

COLLABORATIVE RESEARCH OF THE UCLA-EASTON ALZHEIMER'S CENTER

There has been a gradual shift in the type of AD research conducted at academic medical centers from single site investigator-centered unique projects to multiple site large-scale studies. This evolution is necessary to generate data sets of sufficient size to allow both negative and positive conclusions to be adequately powered, to facilitate studies of the natural history of AD (critical to designing clinical trials), and to generate a sufficient number of biological samples to allow complex informatics analyses to be implemented (such as genome wide association studies (GWAS)). In this context academic medical centers are shifting towards local incubator functions including culturing new investigators, novel concepts, preliminary data and promising technologies that may be advanced to more large-scale multi-site applications.

Among the multicenter investigations engaged in by UCLA-Easton Alzheimer's Center investigators are the ADCS, NACC, Alzheimer's Disease Neuroimaging Initiative (ADNI) [74], DIAN, Late Onset Alzheimer's Disease (LOAD) study, and the AD GWAS.

COMMUNITY PARTNERSHIPS OF THE UCLA-EASTON ALZHEIMER'S CENTER

Dissemination of information and raising awareness of AD are important functions of the Easton Alzheimer's Center. This is accomplished through a variety of internal and external partnerships. A principal partner to the UCLA-Easton Alzheimer's Center is the Alzheimer's Association California Southland Chapter. This is the largest chapter of the Alzheimer's Association in the United States from both a population and geographic point of view. The Alzheimer's Association has been an important supporter of AD research at UCLA. Collaborative projects include annual conferences, participation of faculty in the medical and scientific advisory committee, participation of UCLA-Easton Alzheimer's Center faculty in guidelines development and dissemination projects, and collaboration on an annual award to a junior faculty member (Turken Family Award).

The John Douglas French Alzheimer's Foundation is also a long time collaborator and supporter of the UCLA-Easton Alzheimer's Center. Funding projects and supporting academic chairs for junior faculty, the Foundation, led by Michael Minchen, has provided funding to faculty at a particularly vulnerable time in their career.

The Leeza Gibbons Memory Foundation has placed its signature activity, Leeza's Place, in many cities nationally and internationally to meet the needs of families of individuals with memory impairment. These family-friendly facilities provide a variety of patient and family services and counseling to individuals that can in turn be educated about research and clinical trial activities at the UCLA-Easton Alzheimer's Center.

The Alzheimer's Foundation organizes dementia screening and provides services to caregivers. Its activities are supported by the UCLA-Easton Alzheimer's Center.

COLLABORATION WITH PHARMACEUTICAL AND BIOTECHNOLOGY COMPANIES

The UCLA-Easton Alzheimer's Center collaborates actively with pharmaceutical and biotechnology companies. New drugs for AD will be developed by biotechnology or pharmaceutical companies and will need to be commercialized by major pharmaceutical companies if they are to reach large segments of the world's population [75,76]. The NIH has articulated a policy of private/public partnerships to enhance the commercial application of academic discoveries and advancements [77]. The ADNI project is an example of combined public and private financing of a research program critically important to understanding AD and to advancing pharmacotherapeutic development. Exchanges of compounds, assays and information enhance the enthusiasm of both academic investigators and industry scientists for their work. Both the Deane F. Johnson Center for Neurotherapeutics at UCLA and the Jim Easton Consortium for Alzheimer's Drug Discovery and Biomarker Development have articulated within their mission collaboration with pharmaceutical and biotechnology companies. The UCLA-Easton Alzheimer's Center faculty provide training to pharmaceutical personnel and meet regularly with pharmaceutical scientists to advise on scientific issues related to AD drug development.

UCLA NEUROSCIENCE AND UCLA-EASTON ALZHEIMER'S CENTER

The UCLA-Easton Alzheimer's Center thrives in part because it is imbedded in the rich neuroscience environment of UCLA. The UCLA Department of Neurology receives the largest amount of NIH funding of any department of Neurology in the world. LONI is among the most advanced imaging venues in the nation and is the archiving and informatics

site for images obtained for ADNI [74]. Atlases of AD brains have been constructed by LONI faculty scientists for studies of AD, MCI, or normal aging. Other resources at UCLA with which the UCLA-Easton Alzheimer's Center interacts include the Morris Udall Center of Excellence for Parkinson's Disease Research, The Claude Pepper Older Americans' Center, the Semel Institute for Neuroscience and Human Behavior, the Brain Research Institute, and the Ahmanson Brain Mapping Center. The Department of Veterans Affairs of the Greater Los Angeles Area houses the laboratories of Drs. Cole, Frautschy, and Teter and provides services for maintenance of transgenic animal colonies.

SUMMARY AND NEXT STEPS

The Mary S. Easton Center for Alzheimer's Disease Research at UCLA is an integrated multi-component collaboration of excellent faculty and staff serving the Center's theme of *the therapeutic imperative* and striving to advance understanding and treatments for AD and related disorders. Center investigators are developing new knowledge regarding the basic mechanisms of AD, tg models of AD, clinical manifestations of AD and non-AD dementias, features of prodromal dementia states, and neuroimaging and biomarker manifestations of AD. An active clinical trials program tests a variety of therapeutic agents. Education and recruitment increases awareness of AD and encourages patients to participate in AD-related research and clinical trials of AD therapeutics. Community partners collaborate to advance AD research objectives. Investigators of the UCLA-Easton Alzheimer's Center have national and international collaborations to promote the growth of research that will lead to optimal treatment. The UCLA-Easton Alzheimer's Center encourages the intellectual growth of junior faculty, supports identification of promising trialists who might be advanced to lead trials testing therapeutic agents, encourages the development of novel technologies, and promotes creativity and new conceptual approaches that may mature to influence the national research agenda

AD is poised to overcome the resources our society can devote to the care of its elderly citizens. The costs of AD could soar to 1 trillion dollars annually by 2050 [78] if successful interventions are not developed. The investment in AD research must increase commensurate with the magnitude of the threat it poses to the US and the world. Research into the many pathways by which AD produces its effects in the brain and how best to address these in human therapeutics must be expanded and enhanced. The UCLA-Easton Alzheimer's Center plans to expand its resources, increase its collaborations, and enhance its productivity to meet the scientific and social challenges posed by AD.

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Fig. 1.
Continuum of research.

Fig. 2. Organization and Cores of the Mary S. Easton Center for Alzheimer's Disease Research at UCLA.

Fig. 3. Mapping strategies of MRI used by Dr. Liana Apostolova to identify change in brain structure in MCI and AD (figure courtesy of Liana Apostolova, UCLA).

Fig. 4. Interactions of the Neuroimaging and Biomarkers Core with other cores of the UCLA-Easton Alzheimer's Center. The diverse modalities and study are also shown.

Fig. 5.
Amyloid immunostain demonstrates amyloid deposition in the vessel walls in a patient with AD (figure courtesy of H Vinters, UCLA).