Research Workgroup Purple Ribbon Task Force Draft

Introduction.

The major demographic risk factor for the development of Alzheimer’s disease (AD) is age. After 65, the chances of having AD nearly double every 5 years. By the age of 85, one’s chances of having dementia due to AD are 40% or more. The prevalence of AD is also expected to nearly double every 20 years in the future, largely due to predicted increases in the average life span length. While it is estimated that 35 million people worldwide have AD today, over 125 million individuals are predicted to have AD in 2050. The personal, economic and societal impact of the ongoing AD epidemic will be immense.

The State of Florida should be a leader, not a bystander, in the fight to cure AD by 2025. Florida is the epicenter of the AD epidemic in the US. Florida has over 500,000 AD patients and a large elderly population at risk for AD or living with an undiagnosed condition. The current and future economic impact of AD on the State of Florida is massive and growing. With nearly 10% of the AD cases in the US, the total cost of care for AD patients in Florida is estimated at $20 billion annually. AD costs the State an estimated $1 billion in Medicaid funds annually. As outlined in the National Alzheimer’s Prevention Act, there is a growing national commitment to address the AD epidemic. As a country we cannot afford inaction. Given the burden of AD in Florida and early efforts in the 1980’s with the Alzheimer’s Disease Initiative, the State of Florida should continue its leadership commitment to implementing and funding Alzheimer’s disease public policy initiatives by implementing support for AD clinical research.

Effective therapy for Alzheimer’s disease (AD) is a major unmet medical need. For the typical AD patient, current symptomatic therapies (acetylcholinesterase inhibitors and memantine), demonstrate limited symptomatic benefit that is not sustained. Moreover, there is virtually no evidence that either of these types of treatments alter disease progression. AD is one of the 10 most prevalent diseases in the US that cause death. Yet Despite tremendous advances in understanding certain aspects of AD pathogenesis, there are no therapies that significantly impact the course of the disease. Many other prevalent diseases, such as heart disease and cancer, also still cause tremendous morbidity and mortality but scientific and medical advances have led to novel therapies and preventative behavior that can alter these disease courses, reduce mortality, or at least significantly relieve symptoms for some period of time. AD is the exception. It is the only leading disease without a therapeutic treatment that will significantly halt the course of the disease.

Scientific advances over the last 25 years have provided sound rationale for the development of potentially disease-modifying AD therapies. These therapies primarily target the suspected trigger or triggers of the disease (proteins called Aβ and tau). Thus, therapeutic advances coupled with advances in premorbid detection of underlying AD pathology in non-demented
individuals, suggest that concerted translational research efforts focusing on prevention or early intervention could dramatically reduce the incidence and prevalence of AD. Indeed, it is now well recognized that AD actually begins 15-20 years before it is clinically diagnosed, providing a window for intervention prior to a patient becoming symptomatic. Moreover, as researchers illuminate the downstream pathways that contribute to the degenerative process there is also hope that we can better intervene and slow or even reverse the progression in those with clinically diagnosed AD.

**Infrastructure to support AD research**

Many Florida institutions and hospitals have independently invested in both infrastructure and intellectual capital to support AD and related dementia research. The state currently supports funds the 15 out of 15 statutorily designated ADI memory disorder clinics (MDCs) and previously invested in the Byrd Alzheimer’s Institute that is now part of the USF. Though the MDCs were originally designated and funded to function as recruitment centers for clinical research studies. However, over the last two decades their role has largely evolved into a service and referral mission. It is our general belief that the existing MDCs provide access to diverse patient populations that could be leveraged further to enhance statewide patient oriented research efforts. Overall, there are dozens of laboratories and hospitals focusing on AD research in the state of Florida, with focused efforts at Mayo Clinic Florida, USF, UF, Mount Sinai and UM. In fact, virtually all of the academic institutions and teaching hospitals in Florida have some investigators with active AD research programs. Currently yearly direct funding from the National Institute of Health to investigators studying varying aspects of AD and related dementias is >$25M. Other non-state funding sources likely bring in an additional $10M+ to support research efforts.

Notably, in the AD and broader neurodegenerative field there are preeminent scientists in the AD and broader neurodegenerative field are based in Florida. They have a history of research breakthroughs as well as commercialization of their discoveries. Numerous Florida scientists have won national and international prizes in recognition of their contributions to AD research advances. Examples of their contribution to the scientific advances in AD are:

- Florida scientists have played major roles in defining the genetic underpinnings of AD and related dementias
- Florida scientists have established key therapeutic targets for prevention or treatment of AD
- Florida scientists developed best-in-class models that are used by virtually all companies engaged in development of AD therapeutics

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3The Wien Center for Alzheimer’s Disease and Memory Disorders at Mount Sinai.

http://www.mcisymposium.org/webinar
Florida Scientists and physicians developed novel diagnostic tests for AD.

- Florida Scientists also identified therapies that advanced to late-stage human clinical trials.
- Florida scientists and physicians have participated in clinical studies that drive FDA approval for treatments.

Florida Scientists also play prominent roles in national organizations that support Alzheimer’s research including the Alzheimer's Association, American Federation for Aging Research and the American Health Assistance Foundation.

AD research programs support high paying “STEM” jobs, but also provide training and international visibility for Florida. Indeed, each year a large number of foreign students, postdoctoral fellows and other trainees are hosted in various laboratories within academic medical centers throughout Florida.

Additionally, while there is always a need for more trained neurologists and geriatric psychiatrists nationwide, Florida has some of the most clinically advanced AD physicians participating in clinical research. Florida physicians and hospitals with dedicated AD programs bridge the gap between the laboratory and the patient.

The Need for More AD Research Support

There are many private foundations, other significant public sector funds, both in the United States and other countries, and private sector funds devoted to supporting AD research, as well as the efforts of pharmaceutical companies in drug discovery. However, it is generally acknowledged that, with few exceptions, the NIH is the largest single source of research support. Thus, NIH funding is often a reasonable benchmark, and one of the few transparent ones that can be used to compare relative investments in research for various diseases. Current NIH funding for AD is at a level of approximately $450 million, with perhaps another $100 million to $200 million in NIH funding that might have some relevance to the study of AD (cognitive decline in aging, related neurodegenerative conditions). With a current prevalence of approximately 5.4 million individuals affected with AD in the United States, this equates to a maximum of $130 of NIH funding per person affected with the disease. This contrasts with National Institute of Health funding for HIV/AIDS in the United States, which is currently approximately $3 billion. With approximately 1 million HIV-positive subjects in the United States, this equates to $3,000 of NIH funding per person with HIV/AIDS. So, on a per affected individual basis, NIH funding for HIV/AIDS is 23 times greater than NIH AD funding. Notably, concurrent with the rise in research funding for HIV/AIDS, new medications and preventive efforts were instituted, which have stemmed the HIV epidemic and for those with access to medications turned a deadly disease into essentially a chronic disease.

Of course, there are many different ways to evaluate proportional or relative funding. Another one that is quite germane is economic impact. For AD in the United States this is estimated at...
~$200 billion per year (and worldwide at $600 billion per year). **Again focusing only on the United States, the yearly funding for research by the NIH represents 0.4% of the yearly costs of the disease in the United States. In other words, for every $2 the AD costs the United States, we spend less than 1 cent on research.**

The current measures of disease burden for AD show that it is underfunded. Recent efforts to raise awareness of the societal and economic impact of AD have resulted in limited increases in research funding. As to why these advocacy efforts have not more successful might speculatively be attributable to several factors. AD is a disease of the elderly, and until recently was not universally accepted as a disease entity, but to some considered to be an inevitable consequence of aging. This lack of clarity regarding AD as a process distinct from normal aging, the sense of inevitability, as well as the diminished social stature of the elderly, may all have undercut efforts to increase AD research funding. Another aspect is that AD patients, due to the cognitive impairment, tend not to be adequate good spokespersons or advocates for more funding. The very nature of AD limits the ability of an affected person to articulate their experience, particularly as the illness progresses. Furthermore, there are no AD survivors, with compelling narratives of struggle and success. Finally, spouses and caregivers of AD patients are typically consumed with care giving that they simply do not have the time to devote to raising awareness of the disease and the need for more funding.

A final factor in defining public sector funding levels, and certainly the paramount one for private sector funding, is whether there is a potential to not only gain an enhanced understanding of the disease but also to translate that into effective therapies. Typically, though not always, one needs a mechanistic understanding of the disease in order to treat it. Although there is much work left to do, major transformative advances in defining the mechanistic underpinnings of AD have led to novel therapeutic target identification. So with the recognition that, in general, developing new therapies for central nervous system disease poses unique challenges and that many current AD therapies may be being tested in the wrong patient populations, there is abundant evidence that AD is likely to be a preventable disease and that new therapies may also be able to slow or reverse the course of patients who already suffer from AD.

Given this last assertion that we are potentially on the verge of making breakthroughs with respect to new AD therapies, one might question whether additional incremental funding is needed. Funding over the past two decades has been sufficient to support substantial scientific advances. However, these scientific advances must be translated and the translational efforts are extremely expensive. In the current environment of decreasing NIH and general public sector funding, there is a great concern that these necessary and expensive translational efforts will further erode funding for more basic discovery research. And, though we do know a lot more about AD than we did 25 years ago, there are a number of fundamental questions we do not know the answers to that have direct therapeutic relevance. Moreover, there are also concerns that optimal design for translational work (clinical therapeutic trials, longitudinal biomarker studies) may be compromised due to budgetary constraints. Current levels of funding may reduce the number of therapeutic trials that can be conducted or the number of individuals within a given trial, thereby limiting our ability to identify optimal therapeutic
agents. Also, long-term trials studying intervention to either prevent AD pathology from developing or from progressing to cause early symptoms will require a sustainable long-term increase in funding.

In proportion to the billions of dollars spent on AD care, Florida’s the amount that the State funds for spending on AD research is minuscule. Likewise the amount of funding for AD research is small compared to other State funded research areas such as cancer. Compared to the billions of dollars spent on AD care, a relatively small investment in research with an assured short-term return on investment can enable physician and scientists in Florida to accelerate the long-term goal of finding a cure for AD. In the interim these funds can help to reduce costs of AD care, help us to better manage our burgeoning population affected by this devastating disorder, and build both the academic and private sector research enterprises to take on this devastating epidemic. For example, developing therapies or critical care pathways that delay institutionalization of an AD patient by 1 day could save the state $3M/yr. Likewise, early diagnosis through memory screenings, clinical evaluation at MDCs and caregiver education series can delay institutionalization. Providing matching support for investigators at academic institutions and hospitals that are part of the existing Alzheimer’s disease research network allows the leveraging of greatly increase their likelihood of obtaining other federal and other sustained funding sources leading to a superb return on investment for the state.

How can the state support AD research?

Support research Consortia to enable successful competition for National Institute of Health (NIH)’s funded Alzheimer’s Disease Research Centers (ADRCs) designation and program grant.

ADRCs serve a role much like a national cancer center designations. They create infrastructure that supports clinical care for patients with AD, but also serve as hubs of translational science that are necessary to advance the science in order to reach a shared goal of preventing or treating AD. ADRCs are essential to increasing enrollment from industry sponsored clinical trials, and also for ensuring that advances in the science and care of AD are efficiently and rapidly disseminated to the wider community based medical practices.

In order to successfully compete for ADRCs, we need investment in missing infrastructure. Funds could be used to create the infrastructure in terms of both human capital, launching of prerequisite collaborative studies, and database support needed to successfully compete for these grants.

Why ADRC?

Currently, Notably, in contrast to Florida which has no active ADRCs and 500,000 AD patients, California has 6 active ADRCs and ~600,000 patients with AD— and 6 active ADRCs.
Supporting efforts to compete successfully for NIH ADRC designations in Florida would provide an excellent return on State investment, similar to the leveraging that already takes place with biomedical research funding.

- ADRCs would be funded by the National Institute on Aging at up to $1.5 million annually for 5 years.
- Once funded, most centers are renewed a second time providing at least another 5 years of funding, potentially doubling the return on investment.
- Because of its large aging demographic, Florida has a major opportunity to enroll patients in studies that advance promising Alzheimer’s drugs. Enhanced clinical trial capacity in AD research resulting from ADRC collaborations would result in ~100 additional clinical trial subjects enrolled annually in the state of Florida. This would conservatively generate an additional projected $2 million annually as the ADRCs become more established.
- The vast majority of these funds would be from the pharmaceutical industry.
- The head of AD research at a major pharmaceutical company views Florida with its huge number of elderly as a major opportunity for enrolling the large number of elderly subjects needed to advance promising Alzheimer’s drugs.
- As center grants, ADRCs are mandated to support other research and clinical trial activity. After 5 years one can expect an additional ~$1 million of extramural support (commercial, public sector, private philanthropy/foundations).
- These centers also serve as hubs for both established STEM employees as well as training centers for those interested in STEM jobs.
- These centers will result in medical tourism, as they represent a sign of clinical and scientific excellence to the outside world.
- These centers provide a basis for many private-public partnerships in the battle to cure AD.

Provide competitive funding for AD research.

Institute a program to support bridge funding for AD investigators who have a scored NIH grant. This bridge funding will enable these investigators to generate new data needed to resubmit and be awarded those grants. One year of bridge funding would be leveraged into 4-5 years of extramural funding, again providing a superb short-term ROI.

Institute a fellowship program supported by the state to support the training of physicians and scientists in AD research.
**Improve Upon the Existing Network**

*Provide Incentives to Attract Private Sector Investment in AD research and Clinical Trials*

Increasing capital funding for Memory Disorder Clinics that have already developed large clinical research programs could build upon existing state resources. New funds could be used to link the original MDCs into a mobile PET/MRI Neuropsych unit? [This will not work!! Need to support for a few dedicated units in major metropolitan areas]

*a statewide Clinical Trials Network in the ADI-MDCs? Yes!!* fund greater community outreach to support both translational and public health research, and ensure that Florida’s existing MDCs fulfill the mission to recruit patients for Alzheimer’s research.

Support existing Conferences to promote AD research and care, elevating them.

By building upon existing resources such as established conferences, the existing network can work together to bring more world known researchers to Florida, with the eventual goal of permanent relocation.

Train more experts in Florida, to establish it as the clinical care leader for AD.

Increased support in funding and physician manpower for Other? Training sessions for MDC staff-staff that translates the latest findings into an efficient and methodical system for enhanced diagnostic accuracy for early diagnosis that also improves the patient’s throughput with quality of care [Develop a training team] and experience.

Fund efforts to lead the nation in instituting critical care pathways for patients with dementia to reduce increased costs of care due to increased hospital stays, unnecessary er visits, etc...

Support a yearly Conference to promote AD research and care. Yes!!