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Editorial

Prevent Alzheimer's disease by 2020: A national strategic goal

1. Introduction

This editorial is a call to arms, advocating a national strategic goal to prevent Alzheimer's disease (AD) by 2020. The vision articulated in this issue of *Alzheimer's & Dementia* is based on the overall tenor of the deliberations of three think-tank meetings: the Leon Thal Symposium on the Prevention of Dementia 2007 (LTS'07), the Webinar on Prevention of Dementia October 2008, and the Leon Thal Symposium on the Prevention of Dementia 2008 (LTS'08). The culmination of these three think-tank meetings is an array of specific recommendations for action, ''A roadmap for the prevention of dementia II: Leon Thal Symposium 2008'' [1]. The reports published in this issue represent the collective thoughts of over 70 worldwide leaders in dementia research. These meetings were convened by the Lou Ruvo Brain Institute to bring about radical changes in current paradigms of therapy development for the prevention of dementia, and to honor the memory of Dr. Leon Thal, a scientist and physician. He was an influential leader in the field of AD research before his untimely death in 2007. The LTS'08 was organized in collaboration with the Alzheimer Study Group (ASG), and the webinar was a joint coventure with Alzforum and the ASG.

The national strategic goal to *prevent* AD within a decade is no more difficult, ambitious, or premature than the 1960s Apollo space program. The vision of preventing AD by 2020 is an attainable scientific objective. However, success will require:

- Unwavering national commitment;
- Consensus on clearly defined scientific and technical objectives;
- Creation of an efficient organizational and management system, i.e., a single, centralized administration and coordination center;
- A systems approach to the execution of the mission, including a system for the free and rapid exchange and integration of scientific information and technical knowhow; and
- Sustained investment of resources and funds to support the mission: one billion dollars in additional funds per year for 10 years.

The urgency of a national goal to mitigate and forestall the *problem of dementia* is mandated by the looming financial catastrophe facing the United States national healthcare system. The Congressional Budget Office (CBO) estimates that total national spending on healthcare has more than doubled as a share of the gross domestic product (GDP) over the past 30 years. The CBO further expects that this share will double again to 30% of the GDP by 2035, 40% of the GDP by 2060, and almost 50% by 2082 [2]. Federal spending on Medicare and Medicaid, which accounts for 4% of the GDP today, is projected to rise to 9% by 2035 and 19% by 2082 under current law.

The problem of AD is a generic example of a broad range of chronic disorders that require long-term, labor-intensive, and expensive care. As a prototypical chronic disorder, AD is destined to become a significant cost component of the pending healthcare crisis facing the aging cohort of 78 million baby-boomers. An exponentially increasing segment of this cohort, perhaps as high as 4 out of 5, is already at risk for some form of dementia or neurological disorder.

The idea for a national initiative to *prevent Alzheimer's disease* was first conceived in 1987 by the proposition that *delaying the onset of the AD symptoms by 5 years will reduce the prevalence of AD by half*. This concept was published as a 1992 editorial entitled ''The Five-Five, Ten-Ten Plan for Alzheimer's Disease'' [3]. Today, after nearly 20 years of impressive progress in research, the ''problem'' of AD still lacks a tangible clinical solution, i.e., there are no long-lasting treatments that are meaningful to the person with the disease or to their families. Despite advances in understanding the biology of the disease, the major scientific challenge of the field remains untouched because of the lack of effective interventions that would: 1) delay the onset of symptoms by slowing the progression of neurodegeneration, and 2) eventually preventing the disease. Therefore, the goals of *reducing the number of people at risk for dementia by 50% within the next 5 years, and aiming for prevention within a decade* should be the highest priority of the *National Strategic Plan for Alzheimer's Disease* being formulated by the ASG.

Current paradigms of interventions that primarily focus on evaluating and treating people with AD after its symptoms appear in the late stages of the disease will not be adequate

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to stem the rising tide of people with dementia. The inadequacy of current treatment regimens is attributable to the fact that neurodegenerative processes leading to dementia start many years before symptoms appear. Thus, available interventions are too little and too late. Interventions are more likely to succeed when applied at earlier stages of the disease, before symptoms appear. However, the task of discovering means of ''early detection'' and ''early prophylactic interventions'' must overcome a number of scientific, conceptual, theoretical, administrative, financial, and regulatory hurdles.

The array of challenges for the mission to prevent AD within a decade are no less daunting than those faced by similar national endeavors such as the Apollo space program, the Manhattan Project, or the Human Genome Project. Ultimately, the execution of this national enterprise will require decisive actions by both public and private entities, as well as bold public policies that foster radical changes in: 1) the governance and organization of research, 2) mechanisms or programs of research funding, 3) deployment of resources and infrastructure, and 4) paradigms for developing interventions/treatments.

2. Governance of the mission

One of the most critical challenges for the national mission to prevent AD is the need for centralized control and coordination of all AD-related activities. Although the prospects of delaying the onset of symptoms or preventing disability may now be technically feasible, the more difficult challenge is to translate the basic knowledge on neural repair/regeneration into practical applications. The barriers to the discovery of a ''cure'' include not only inadequate funding, the high cost of clinical studies, and a lack of adequate resources and appropriate modeling systems, but also *the inadequate management of discovery programs*. The current administrative and decision-making structure for supporting research simply cannot meet the needs of the rapidly evolving scientific world. There is a need for a flexible system that supports rapid decision-making and can handle unexpected opportunities and breakthroughs.

Over the last three decades, numerous programs on AD were established and administered through different agencies within the government (primarily, the National Institute on Aging/National Institutes of Health [NIA/NIH]) to address various aspects of the AD problem. These programs include:

- Alzheimer's Disease Research Centers (ADRCs), established in 1984 to provide resources and infrastructure for longitudinal clinical studies and to support translational research;
- Alzheimer's Disease Satellite Clinics, developed to encourage the recruitment of minority subjects and provide a mechanism to provide services for underserved populations;
- Consortium to Establish a Registry for Alzheimer's Disease, designed to develop and standardize assessment tools for the diagnosis of AD;
- Leadership and Excellence in Alzheimer's Disease, established to cultivate the research careers of promising investigators under the tutelage and mentorship of senior experienced leaders in the field;
- Alzheimer's Disease Clinical Studies (ADCS), a national consortium for clinical trials;
- Alzheimer's Disease Drug Discovery Program;
- National Research Bank for Genetic Studies of Alzheimer's Disease;
- National Alzheimer's Coordinating Center (NACC), a clinical database;
- Office of Alzheimer's Disease Research, created by the Director of the NIH (James Wyngaarden) in 1985 to serve as the home of the NIH Alzheimer's Disease Research Coordinating Committee; and
- Alzheimer's Disease Neuroimaging Initiative (ADNI), established to foster industry, government, and academic collaboration in a longitudinal study.

Since the launch of these programs over the past two decades, the needs of the field have changed substantially. Therefore, a complete review and overhaul of these programs may be timely. For example, the efficiency and effectiveness of these programs could be substantially improved by integrating several of them into a single, well-coordinated, larger program. The ADRC's large number of current ''centers'' (P30s and P50s) can be trimmed and converted into Comprehensive Alzheimer's Centers (P60s). A small number (5–10) of such regional centers could not only support research, demonstration projects on care/treatment, clinical trials, and education, but also allow for the integration of several multisite collaborative studies such as ADCS, ADNI, and Patient Registry or Clinical Data Bank programs into a single administrative structure. The integration and administration of these programs through Regional Comprehensive Centers would be more efficient and cost-effective, and each regional center could serve as the coordinating hub of several smaller centers within a region.

In recent years, a number of programs related to various aspects of AD have emerged in agencies other than the NIH, as well as in industry and nongovernmental organizations (NGOs). One of the important needs of the field is to reduce the fragmentation of these efforts and increase communications and coordination among all key players. An important challenge for the field is to leverage and build upon ongoing programs, initiatives, and existing resources within government, industry, academia, and other NGOs. This aim can be achieved by a new administrative structure for the coordination of planning and resources among all stakeholders.

The Office of Alzheimer's Disease Research (OADR) as the central locus for control and coordination at the NIH was created in 1985 by the Director of the NIH, James Wyngaarden. The OADR served as the home of the NIH's Alzheimer's Disease Research Coordinating Committee from 1985 to 1995. The equivalent of an OADR should be revived to serve the functions of control and coordination of all AD-related programs and activities across all agencies and NGOs.

The creation of a quasi-government entity (a new OADR) could serve the function of coordination by establishing and managing an Interagency Committee for Coordination of AD Programs. The overall goal is to leverage the combined capabilities and expertise of all ongoing efforts.

3. Scientific challenges

There is a need for new conceptual models of dementia that will provide better explanations of the clinical underpinnings of the disease and identify new therapeutic targets. Current conceptual models of the pathogenic mechanisms or pathways fail to provide a complete account of the relationship between the clinical and biological phenotypes of the disease. In addition, the mission to prevent AD requires the development of a battery of well-validated early markers of the disease, which will be used not only to identify asymptomatic people at risk for AD, but also to monitor the progression of the disease and the effectiveness of treatments in changing the course of the disease. The only way the current pipeline of potential treatments can be enriched is by expanding drug-discovery programs to identify and validate new therapeutic targets that focus on protection against synapse loss, prevention of dendritic pruning, and repair/regeneration of dying neurons. These efforts will require building the appropriate infrastructure for long-term longitudinal studies.

4. Infrastructure and resources

One of the major barriers to progress is the lack of appropriate research infrastructure. Although many programs launched by the NIA during the last three decades (e.g., ADRCs, ADCS, ADNI, and NACC) created essential infrastructures and resources for many collaborative studies, these programs need to be restructured and expanded to meet the changing needs of the field. One of the most urgent needs is for a large cohort of well-characterized, asymptomatic volunteers at risk for the disease who would be willing to participate in trials to validate biomarkers and test preventive treatments. A second critical need involves the establishment of a multinational collaborative network of investigators to discover and validate methods and/or devices for the early detection of people at risk for dementia. Third, we need to identify samples and homogenous subgroups within the population who would be available for clinical trials to test new interventions and other therapeutic modalities for prevention. Such a national research resource, a Registry of Asymptomatic People at Risk, could serve multiple needs, e.g., clinical trials on prevention, epidemiological studies to discover/validate risk factors, the discovery and validation of biomarkers, and other longitudinal studies.

5. Financial

One of the important barriers to the development of therapies for prevention is the long duration and high cost of prevention trials. There is a need to develop new models for financing the high cost of prevention as well as new approaches aimed at reducing the duration and cost of trials.

One of the key recommendations articulated in ''A Roadmap for the Prevention of Dementia'' (2008) is the need for more time-efficient and cost-efficient models for conducting randomized clinical trials for new therapeutics that are aimed at slowing progression in the early, prodromal stages of the disease. The reports cite several inherent challenges to the present system, including the inability of standard recruitment paradigms to support ever-increasing sample-size requirements, inadequate federal funding to support the existing biomedical research infrastructure, the fragmentation of clinical care for research volunteers, high indirect costs, and increasing burdens on investigators because of federal and institutional rules, policies, and procedures.

6. Conclusions

As implicitly conveyed by the LTS'07 and LTS'08 [1] recommendations for an action plan, the current widely applied paradigm of phased drug development and clinical trials may be particularly ineffective when the goal is to evaluate and develop preventative therapeutic products, especially when the goal is to develop compounds to treat asymptomatic people at risk or early-diagnosed but unaffected populations.

Meinert [4] articulated best the conceptual differences in approaching the challenges of validating the efficacy of interventions for ''*treatment*'' in contrast to ''*prevention*.'' Meinert [4] observed that the problems and difficulties of a randomized trial for ''treatment'' or ''prevention'' are the same. The only differences between the two classes of trial relate to the purpose of the trial, the choice of study treatments, the choice of outcome measures, the approach to recruiting subjects and establishing inclusion/exclusion criteria (such as age), and issues related to monitoring. Meinert [4] also noted fundamental differences between the ''approach'' and the ''philosophy'' of a treatment trial in contrast to prevention: ''An important factor that sets a prevention trial apart from treatment trial is the risk-benefit calculus of the two trials. Treatment trials are undertaken to 'cure' or ameliorate disease, whereas prevention trials are undertaken in the hope of preventing or delaying onset of disease. The risks of harm in treatment trials are contemporaneous with prospects for benefit, making the calculus reasonably straightforward. But that time relationship does not exist in long-term drug prevention trials where the risks from treatment start accruing on initiation of treatment, but where the prospect of benefit is down the road and comes, if at all, in the form of disease avoided. This separation of risk versus benefit makes for difficult decisions as to how long to continue a trial in the absence of a difference in the test-assigned versus the control-assigned group'' [4].

The mission to prevent AD by 2020 requires not only radical changes in the current paradigms of organizing research and development therapies for prevention, but also an unwavering national commitment to allocate appropriate levels of

funding in the next decade. The success of this venture will require a sustained investment of $1 billion per year in new funds over current expenditures for the next 10 years. An investment of $10 billion dollars to solve the most urgent looming public-health problem is not too high a cost. The high-priority initiatives/programs that will require special attention and additional support include:

1) Discovery and validation of new therapeutic targets, focusing on neural repair/restoration and disease-modifying agents;
2) Development and validation of technologies (including biomarkers and imaging) for early detection of neurodegeneration in asymptomatic people at risk for dementia;
3) A National Registry/Omnibus Database to serve as a national resource for epidemiologic and clinical studies, including prevention trials;
4) Ten Comprehensive Alzheimer Research Centers;
5) Alzheimer's Disease Clinical Studies-Virtual Pharmaceutical Research Consortium; and
6) Alzheimer's Disease Neuroimaging Initiative.

As the ''baby-boom'' generation ages and brain diseases become more prevalent, the need to confront the pending healthcare crisis posed by this demographic change will become more urgent than ever. As resources become more difficult to allocate, we must reconsider our national priorities. As part of that exercise, it is critical to expand research expenditures on AD significantly, with special focus on prevention. Ultimately, investment in prevention research is the only cost-effective means to avoid the pending public-health catastrophe this country faces. The new battlefront for the mission to prevent AD by 2020 is much broader than the heated scientific disputes on various theories or scientific approaches. *The ultimate enemy is the problem that patients experience and families have to face every day, the loss of memory that is a common feature in a number of brain diseases*. The goal of the proposed National Strategic Plan is to create a new paradigm for planning and supporting the organization of worldwide cooperative research networks to develop new technologies for the early detection and treatment of various forms of memory impairments. To accomplish this goal, the federal budget must be increased for research aimed at: 1) developing national resources to discover new interventions for memory disorders, and 2) creating a streamlined decision-making process for the selection and support of new ideas.

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References

[1] Khachaturian Z, Snyder PJ, Doody R, Aisen P, Comer M, Dwyer J, et al. A roadmap for the prevention of dementia II. Leon Thal Symposium 2008. Alzheimers Dement 2008;5:85–92.
[2] Congressional Budget Office, Congress of the United States. The long-term outlook for health care spending. CBO publication no. 8758. Washington, DC: US Government Printing Office; 2007. Retrieved from: http://www.cbo.gov/ftpdocs/87xx/doc8758/11-13-LT-Health.pdf.
[3] Khachaturian Z. Five-five ten-ten plan for Alzheimer's disease. Neurobiol Aging 1992;13:197–8.
[4] Meinert C. Long-term drug prevention trials. Clin Trials 2008; 5:168–76.