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EDITORIAL

Right sizing funding for Alzheimer's disease

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Finding novel, effective, Alzheimer's disease (AD) therapeutics has emerged as one of the major unmet medical needs in most developed nations [1,2]. AD is quite unique among highly prevalent diseases within these nations in that, despite tremendous advances in understanding certain aspects of AD pathogenesis, there are no proven disease-modifying therapies and only minimally effective symptomatic therapies. Though many other prevalent diseases still cause tremendous morbidity and mortality, for many of them scientific and medical advances have led to novel therapies that alter disease course, reduce mortality, or at least significantly relieve symptoms for some period of time. Typically, these therapies are not panaceas, or true cures, but nevertheless significant therapeutic inroads have been made.

Perhaps the most striking example of recent success in curbing a major emerging epidemic is HIV/AIDS. Within two decades of the identification of HIV as the cause of AIDS, rapid development of multiple anti-viral therapies turned a rapidly progressive and fatal disease into a more chronic disease, at least in industrialized nations [3,4]. Of course, there are no widely deployable cures yet for HIV/AIDs, and it is still a potentially lethal disease. Moreover, anti-viral pharmacotherapy needed to control disease progression has numerous and significant side effects. Nevertheless, given the continued progress, there is reasonable hope that either prophylaxis with vaccines or further advances in anti-viral therapies will further reduce or eliminate HIV-related morbidity and mortality. Notably, the historical timelines for discovery of the presumed causative agents of HIV and AD are similar, with HIV definitively identified in 1981 and the suspected protein triggers of AD identified in the mid-1980s, with strong links to causality established for amyloid beta (Aβ) and tau aggregates established in the 1990s.

Given this interesting parallel in timelines for HIV/AIDs and AD, it is worthwhile to explore the question: "Why have we not made more inroads with respect to disease-modifying therapeutics for AD?" This question needs to be asked in the context of the question: "What factors were enabling in the development of novel anti-HIV therapies?" Although there are certainly many germane medical and scientific issues, one critical aspect may simply be that the funding for HIV/AIDs research, at least in the United States, appears to have been sufficient, and therefore in retrospect "right sized", to enable not only basic understanding of the disease-causing entity and the disease it causes but also to translate that enhanced understanding into novel and effective therapeutics.

If one assumes that funding for HIV/AIDS was right sized to enable translation of basic discoveries to successful therapies, then given the lack of effective AD therapies, one possible implication is that funding for AD has been insufficient. A quick comparison of funding levels for HIV/AIDs relative to AD in the United States suggests this may be at least one factor that has hindered the translation of AD discovery to effective therapies. Based on publicly available data, National Institute of Health funding for HIV/AIDS in the United States is currently approximately $3 billion [5]. With approximately 1 million HIV-positive subjects in the United States, this equates to $3,000 of NIH funding per person with HIV/AIDs. In contrast, current NIH funding for AD is at a level of approximately $450 million [5], with perhaps another approximately $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 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. So, on a per affected individual basis, NIH funding for HIV/AIDs is 23 times the level of that for AD.

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 more than $170 billion per year (and worldwide at $600 billion per year) [6]. 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 disease costs the United States, we spend less than 1 cent on research.

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There are no doubt many sources of bias in any cursory attempt to determine the amount of research dollars relative to disease prevalence or impact. First, only looking at funding from the NIH provides a simplistic view of the funds spent to support AD research, or for that matter, any research directed towards any given disease. There are many private foundations, other significant public sector funds, both in the United States and other countries, and private sector funds devoted to AD research, as well as the efforts of pharmaceutical companies in drug discovery. There are many challenges to collating this funding, however, and 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 a given disease. Second, there will be bias in these figures whether one focuses on incidence, prevalence, morbidity, mortality, or economic impact. All of these factors contribute in overlapping ways to what might be considered as the societal impact of the disease, and depending on one's own perspective, one might weigh these various factors differently. Indeed, most advocacy groups for any given disease will tend to provide data that are most supportive of advancing their cause.

Funding levels for research on any disease have legacies that have evolved over time and can potentially be attributable to a plethora of complex factors. Likely major influences on public sector funding for various disease entities are: a combination of the aforementioned objective and subjective measures of disease burden; societal pressures from either individual or group-based advocacies for research into a given disease; and perception or promise of ability to impact a given disease process. Many other factors that are less tangible, such as pure academic interest or perceived threat to future welfare, also contribute. Until recently, private sector funding has largely been driven by potential return on investment, with funding focused on therapeutic discovery and development programs for major diseases with defined and potentially druggable targets.

Clearly, as described above, current measures of disease burden for AD suggest that it is underfunded. Moreover, at least in recent years, numerous advocacy groups have increased efforts to raise awareness of the societal and economic impact of AD, but to date this has failed to translate into significantly increased research funding. As to why these advocacy efforts have not resulted in enhanced funding is difficult to pinpoint, but might speculatively be attributable to several factors. First, 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 nosology, the sense of inevitability, as well as the diminished social stature of the elderly, at least in the United States, may all have undercut efforts to increase AD research funding. Another aspect of advocacy is that AD patients, due to the consequences of the disease process, tend not to be good spokespersons. The nature of AD limits the ability of an affected person to articulate their experience, particularly as the illness progresses. Unlike HIV or cancer, there are no AD survivors, with compelling narratives of struggle and success. Consider, in contrast, Michael J Fox and his advocacy on behalf of Parkinson's disease [7]. Mr Fox can speak eloquently about the impact of his disease in public. Not only does he speak eloquently but he concurrently displays the debilitating motor symptoms characteristic of Parkinson's disease while he is advocating for more research funding. Notably, spouses and caregivers of AD patients are often so 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. Indeed, personal stories of caregivers can be incredibly effective but most often when they tangibly illustrate the effects of the disease on the patient (see, for example, Judith Fox talking about her ongoing efforts on behalf of her husband who has AD [8]), but rarely receive the same level of publicity as seen in many other diseases. Noteworthy exceptions in the United States regarding attempts to raise public awareness have been the recent ongoing reporting by the New York Times on AD, AD research and its personal and societal impact, Maria Shriver's Annual Report, the Alzheimer Breakthrough ride and ongoing efforts by the Alzheimer's Association.

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, as highlighted in a recent review, many current AD therapies may be being tested in the wrong patient populations (for example, anti-Aβ therapies in patients with symptomatic AD), there is abundant evidence that AD is likely to be a preventable if not treatable disease [9].

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. Indeed, historical 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 relatively unchanged or slightly decreasing NIH and general public sector funding, there is a great concern among AD investigators 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 [10]. 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.

To conclude, there are no easy answers to the question regarding right sizing funding for AD. Based on arguments presented here, we would simply say that public sector investment in AD research is far too small and that targets such as proposed in the Alzheimer's Breakthrough Act of $2 billion per year of NIH funding would likely be transformative. Similar increases in public sector AD research funding in other industrialized nations would obviously have great impact as well. Though for most endeavors there is a point where benefits of increased investment yield increasingly poorer returns, we would argue that we are far from this scenario in AD. Current funding levels are restricting promising research and driving investigators to pursue other lines of research. As bolus increases can sometimes be misdirected, we would suggest a stepwise increase in NIH funding for AD research of 15 to 20% per year until the $2 billion target is reached or it is clear that the hoped-for breakthroughs are imminent and achievable given some future funding level. We must all advocate for additional funding to support our collective fight against AD, and in the meantime continue to use our resources as wisely as possible to ensure that we advance our understanding of this devastating disease and translate that understanding into effective therapies.

Abbreviations

Aβ, amyloid beta; AD, Alzheimer's disease.

Competing interests

DG and TG are Editors-in-Chief of Alzheimer's Research & Therapy and receive an annual honorarium. The authors declare no other competing interests.

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