Commentary

Patterns of Innovation in Alzheimer's Disease Drug Development: A Strategic Assessment Based on Technological Maturity

Jennifer M. Beierlein, PhD; Laura M. McNamee, PhD; Michael J. Walsh, PhD; and Fred D. Ledley, MD

Center for Integration of Science and Industry, Department of Natural and Applied Sciences and Department of Management, Bentley University, Waltham, Massachusetts

ABSTRACT

Purpose: This article examines the current status of translational science for Alzheimer's disease (AD) drug discovery by using an analytical model of technology maturation. Previous studies using this model have demonstrated that nascent scientific insights and inventions generate few successful leads or new products until achieving a requisite level of maturity. This article assessed whether recent failures and successes in AD research follow patterns of innovation observed in other sectors.

Methods: The bibliometric-based Technology Innovation Maturation Evaluation model was used to quantify the characteristic S-curve of growth for AD-related technologies, including acetylcholinesterase, *N*-methyl-D-aspartate (NMDA) receptors, B-amyloid, amyloid precursor protein, presenilin, amyloid precursor protein secretases, apolipoprotein E4, and *transactive response DNA binding protein 43* kDa (TDP-43). This model quantifies the accumulation of knowledge as a metric for technological maturity, and it identifies the point of initiation of an exponential growth stage and the point at which growth slows as the technology is established.

Findings: In contrast to the long-established acetylcholinesterase and NMDA receptor technologies, we found that amyloid-related technologies reached the established point only after 2000, and that the more recent technologies (eg, TDP-43) have not yet approached this point. The first approvals for new molecular entities targeting acetylcholinesterase and the NMDA receptor occurred an average of 22 years after the respective technologies were established, with only memantine (which was phenotypically discovered) entering clinical trials before this point. In contrast, the 6 lead compounds targeting the formation of amyloid plaques that failed in Phase III trials between 2009 and 2014 all entered clinical trials before the respective target technologies were established.

Implications: This analysis suggests that AD drug discovery has followed a predictable pattern of innovation in which technological maturity is an important determinant of success in development. Quantitative analysis indicates that the lag in emergence of new products, and the much-heralded clinical failures of recent years, should be viewed in the context of the ongoing maturation of AD-related technologies. Although these technologies were not sufficiently mature to generate successful products a decade ago, they may be now. Analytical models of translational science can inform basic and clinical research results as well as strategic development of new therapeutic products. (*Clin Ther*. 2015;37:1643–1651) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

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INTRODUCTION

Alzheimer's disease (AD) has proved to be a challenging target for drug discovery. It has been 12 years since the last approval of a new molecular entity (NME) aimed at treating the core symptom complex of AD. Moreover, there is a paucity of both validated drug targets and advanced-stage clinical candidates with the potential to modify the essential pathogenesis of the disease or its associated disabilities.

The challenge has been exacerbated in recent years by the Phase III failures of several lead compounds (most recently, bapineuzumab and solanezumab in 2012 and gammagard in 2013) designed to reduce β-amyloid plaque formation. These high-profile failures led many to conclude that β-amyloid may not be a viable target for AD.[1–7] The subsequent successes of a Phase I trial with aducanumab in prodromal (or mild) AD,[8] as well as optimism regarding the ongoing trial of crenezumab in a Columbian cohort of early-onset AD,[9] have rekindled interest in β-amyloid as a drug target.[10]

The meager product pipeline and limited number of validated targets for drug discovery seems incongruous with the dramatic advances in understanding AD that have come from positional cloning, genomics, transgenic disease models, positron emission tomography scanning, and sophisticated biomarkers. Perhaps the most important pathologic insight occurred when the protein comprising the amyloid plaques was identified as β-amyloid,[11] a cleaved form of the known genetic risk factor, amyloid precursor protein (APP).[12] It was hypothesized that the accumulation of β-amyloid plays a central role in the pathogenesis of the disease and its symptoms. Dubbed the "amyloid hypothesis," targeting β-amyloid with immunotherapies to reduce amyloid plaques has become a dominant strategy for treating AD.[13,14]

Other targets have also been identified. In addition, drug discovery efforts have focused on APP secretase enzymes, which are responsible for cleavage of APP to form β-amyloid.[15] Presenilin 1 and 2, components of λ-secretase, have also been identified as genetic risk factors for the disease[16] and are a significant focus of interest. The neurofibrillary tangles, which are a characteristic pathologic feature in diseased brains, have been identified as tau protein, a microtubule-binding protein that stabilizes the long microtubules involved in structural support of neurons.[17] AD research continues to identify putative pathways that impact the pathogenesis or core symptoms of the disease and propose novel targets for interventions.

Five NMEs have been approved for treating the core symptom complex of AD. These compounds, however, were not generated from recent molecular insights but originated from older research in other fields. Specifically, NMEs that target acetylcholinesterase (AChE)[18] or *N*-methyl-D-aspartate (NMDA) receptors[19] were discovered through research on these neurotransmitter pathways and were only later applied to AD therapy. Moreover, the most common genetic risk factor for both sporadic and familial forms of AD, the apolipoprotein E4 allele,[20] was first described as a risk factor for cardiovascular disease and is now considered an important biomarker in AD. In fact, 1 of the important strategies for current research is repurposing drugs from other indications.

The goal of the present article was to examine the status of innovation in AD by using an analytical model for the maturation of technology and the relationship between technological maturation and successful product development. We assessed whether the paucity of therapeutic products and recurrent failure of lead compounds arising from recent scientific advances are consistent with the time course of translational science observed in other therapeutic areas. Specifically, an analytical model of technology maturation was used to determine whether the recent failures of drugs designed to reduce β-amyloid should be interpreted as invalidating the amyloid hypothesis or whether amyloid-related technologies are not yet sufficiently mature to expect efficient generation of successful lead and therapeutic products.

PATTERNS OF INNOVATION IN BIOPHARMACEUTICAL DEVELOPMENT

Research on innovation in different technology sectors suggests that technologies mature through a characteristic, sigmoid growth cycle (S-curve) (**Figure 1**) and that the ability to generate successful products is predictably related to technology maturity.[21–26] The key feature of the technology S-curve is a stage of exponential growth sparked by a scientific insight or invention. This "initiation" event is followed by exponential advances that continue until limits are encountered and growth slows. At this point, the

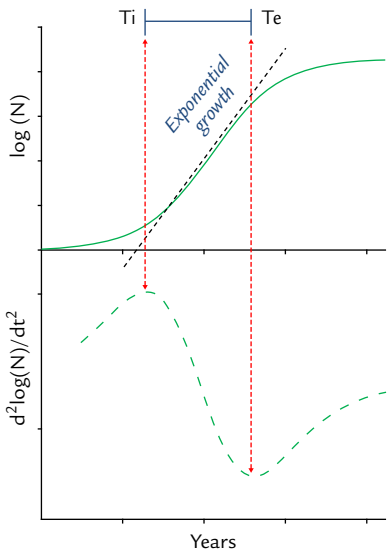

Figure 1. Quantitative model of the technology growth S-curve. The technology growth cycle is modeled as an exponentiated logistic function (solid green line) fit to cumulative publications (N) in a PubMed search. The technology initiation point (Ti) is the point of maximum acceleration (max d^2N/dt_2 [dashed green line]) or the beginning of an exponential growth stage. The technology established point (Te) is the point of maximum slowing (min d^2N/dt_2 [dashed green line]) or the end of exponential growth.

technology is considered "established." Although new insights and inventions offer the promise of new product opportunities, nascent technologies commonly fail to generate products that can meet the standards set by previous, established technologies.[21,22] Only as the nascent technologies mature to the point of being established are they able to generate state-of-the-art products that can satisfy prevailing performance standards.

Previous studies have applied these principles to biopharmaceutical development by using a bibliometric-based analytical model for technology maturation termed the Technology Innovation Maturation Evaluation model.[25,27–29] From these studies, we have shown that the accumulation of knowledge regarding specific biotechnologies, drug classes, or drug targets, as measured by the cumulative number of publications in PubMed, follows a S-curve growth pattern that can be modeled with an exponentiated logistic function (Figure 1). Using a nonlinear least squares fit of this function to the cumulative publication counts, we identify an initiation point (Ti) corresponding to the point of maximum acceleration of publication activity (max d^2N/dt^2), and an established point (Te) corresponding to the point of maximum slowing of publication activity (min d^2N/dt^2).[24] The analytical method is described in more detail in the Supplemental Appendix (see the online version at http://dx.doi.org/10.1016/j.clinthera.2015.07.003).

Validation studies revealed that the derived Ti corresponds to seminal events in the scientific literature that enabled exponential growth of the field[25,27] (Additional studies outside of the references have been reported by Walsh et al., personal communication). More importantly, our studies show that biopharmaceutical development follows the pattern observed in other technology sectors, with few successful projects being generated by nascent or growing stage technologies, and most new products arising from established-stage technologies.[25,28,29] Well-known examples of this phenomenon include monoclonal antibodies, gene therapies, and nucleotide therapies, in which there were hundreds of clinical failures during the >20 years before the first successful products were approved. Analytical studies show that these approvals occurred only after these technologies passed the established point.[25,27] Similarly, a study of 100 NMEs approved by the US Food and Drug Administration from 2010 to 2013 showed that the first approvals of targeted and biological NMEs occurred an average of 14 years after knowledge of the target passed the established point, with only 2 of 82 NMEs being approved before this point. It was also observed that the large majority (58 of 82) of approved NMEs only began clinical trials after the established point, and the clinical development time for these products was significantly shorter (8.5 vs 11.6 years; $P < 0.001$) than for those that entered trials before the technology was established. Thus, drug development becomes significantly more efficient once the associated technology passes the established point. Finally, our data suggest that the time between a scientific insight, or invention that gives rise to a new area of research, to approval of products based on this technology is 36 years,[29] an interval similar to that described by others looking at the elapsed time between seminal publications and drug approvals.[30]

MODELING TECHNOLOGIES FOR AD DISCOVERY

The Technology Innovation Maturation Evaluation model was used to examine the maturation of technologies associated with AD drug discovery. This analysis included novel targets emerging from AD research that have yet to generate therapies, as well as older technologies associated with approved therapies such as AChE and NMDA receptors (**Figure 2**). The PubMed search strategy and a glossary of search terms are provided in **Supplemental Table I** (see the online version at http://dx.doi.org/10.1016/j.clinthera.2015.07.003). For most of the technologies examined, the accumulation of publications exhibited a discernable exponential stage of growth and could be modeled with the best-fit, exponentiated logistic function.

Of the 5 NMEs currently approved for AD, 4 target AChE, and 1 targets the NMDA receptor (see **Supplemental Table II** in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.07.003). Both targets exhibit a characteristic, sigmoid growth curve (**Figure 2A**). For AChE, the initiation point was 1931, corresponding to early studies showing modulation of cholinergic functions with synthetic derivatives of natural alkaloids in 1930s[18]; exponential growth reached an established point in 1973. For NMDA receptors, the initiation point was 1971, corresponding to recognition of the role of glutamate in synaptic transmission in 1972[31] and identification of various excitatory receptors in 1968 and 1974.[32,33] Exponential growth of NMDA receptors reached an established point in 1993.

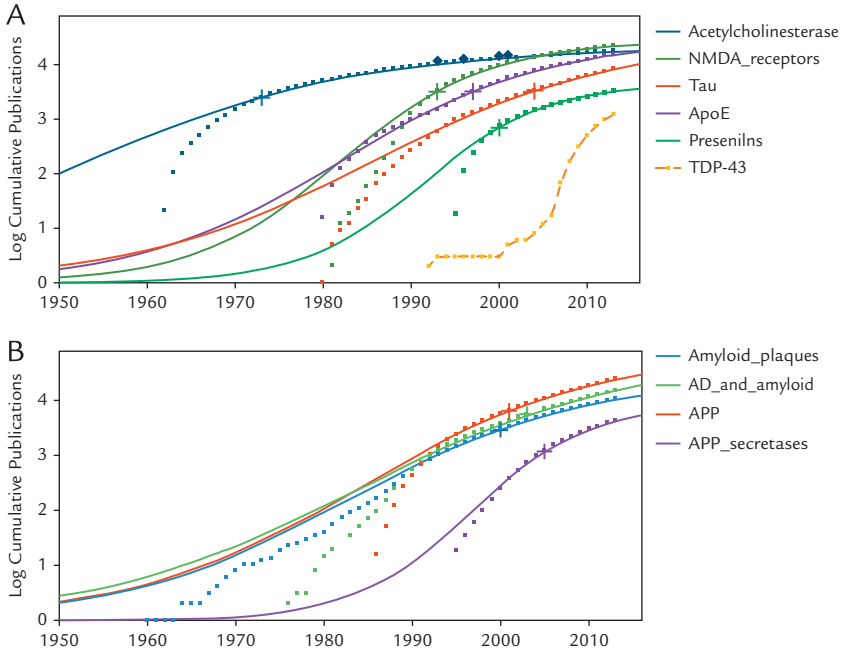

Figure 2. Technology Innovation Maturation Evaluation (TIME) models of various Alzheimer's disease (AD)-associated targets and technologies. The squares indicate the log of the cumulative publication data for each target or technology, whereas the corresponding colored line indicates the TIME projection model. Predicted year of the technology established point is indicated by the plus sign. The blue diamonds indicate year of new molecular entity approval for acetylcholinesterase inhibitors, and the green diamond indicates year of approval for *N*-methyl-D-aspartate (NMDA) receptor antagonists. Due to log-scale, disorder at the lower end of curve only represents a difference of ~10 publications between the model and actual publications. (A) Nonamyloid target curves; and (B) β-amyloid target curves. ApoE = apolipoprotein; TDP-43 = TAR DNA-binding protein of 43 kDa; APP = amyloid precursor protein.

None of these 5 products was approved before their respective technology passed the established point (Figure 3), with an average time from the established point to NME approval of 22 years. Only 1 of these products, memantine, entered clinical trials before the established point. It is notable that memantine was classified by Swinney and Anthony[34] as having been discovered by phenotypic screening for a non-AD target rather than as a targeted screen. This compound was, in fact, first synthesized in 1968, before discovery of the NMDA receptor. The early clinical entry date for this compound is consistent with the mode of discovery that was not predicated on knowledge of the target.

It is also notable that tacrine, the first of the AChE inhibitors to enter clinical trials and achieve approval, is no longer on the market. The 3 remaining AChE inhibitors entered clinical trials, on average, 17 years after the established point and were approved 26 years after this point. Although the number of approved NMEs for treating AD is too small for statistical analysis, these results suggest that the development of these products is consistent with quantitative patterns observed previously for drugs against other diseases.[35]

Identification of publications regarding β-amyloid in PubMed is complicated by the original use of the term "amyloid" to describe iodine-positive deposits. To identify publications specific to the AD-associated amyloid protein, we searched for "amyloid AND Alzheimer's disease," "amyloid plaques," or "amyloid precursor protein" (see Supplemental Table I in the online version at http://dx.doi.org/10.1016/j.clinthera.2015.07.003). All 3 analyses of β-amyloid terms identified an initiation point between 1964 and 1967 (Figure 2B), corresponding to the immunologic identification of an amyloid protein in 1967.[36] The technology growth curves for APP secretases identified an initiation point of 1988, corresponding to the cloning and sequencing of the APP gene in 1987.[12] Presenilin is a component of the APP secretase, γ-secretase, whose connection to AD was discovered through genetic linkage analysis in AD cohorts.[37] The technology growth curve for presenilin indicates an initiation point of 1983, corresponding to the first linkage maps of the human genome 1980 and 1985[38,39] and identification of AD cohorts. Looking broadly at β-amyloid, as well as targets known to be involved in generating amyloid plaques such as APP secretases and presenilins, our analysis suggests that each of these technology curves reached the established stage only in the early 2000s.

Three other analyses are also shown (Figure 2A). The technology growth curve for apolipoprotein E4 indicates an initiation point of 1967, which corresponds with the first separation of apolipoproteins from cholesterol[40,41] in 1968 and 1969.

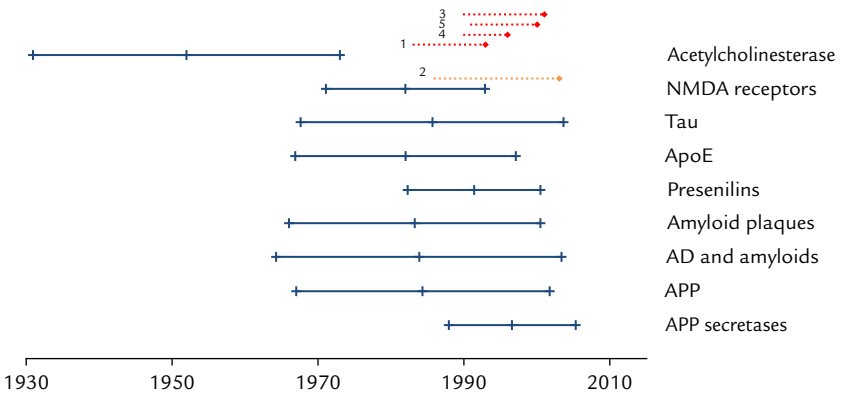

Figure 3. Time lines of Alzheimer's disease (AD) technologies. The Technology Innovation Maturation Evaluation modeled dates of technology initiation points, and technology established points are shown as a linear progression for AD targets. The dashed lines indicate time from clinical entry to approval by the US Food and Drug Administration for new molecular entities and are placed over their specified target. From earliest clinical trial entry, the new molecular entities are: (1) tacrine; (2) memantine; (3) rivastigmine; (4) donepezil; and (5) galantamine. NMDA = *N*-methyl-D-aspartate; ApoE = apolipoprotein; APP = amyloid precursor protein.

The technology growth curve for tau protein indicates an initiation point of 1968, which corresponds with the first isolation of proteins bound to microtubulins in 1967 and 1968.[42,43] Of particular interest is the technology growth curve for the transactive response DNA-binding protein of 43 kDa (TDP-43), a protein first identified for its association with amyotrophic lateral sclerosis and more recently associated with AD.[44–46] Growth of publications related to TDP-43 could not be modeled with the sigmoid function. Closer analysis suggests that this technology is still in the exponential, growing stage of the growth cycle and has not yet approached the established stage.

INTERPRETING CLINICAL FAILURES OF DRUG-TARGETING AMYLOID PLAQUES

Six products targeting the formation of amyloid plaques completed Phase III trials between 2009 and 2014 but failed to meet their clinical end points.[47] The high-profile clinical failures of lead compounds designed to clear amyloid plaques by passive immunization (eg, bapineuzumab),[48] as well as drugs designed to block improper cleavage of APP by inhibiting secretase (eg, semagacestat),[49] raised concerns about the amyloid hypothesis and the potential for treating AD by targeting amyloid plaque formation.

The table shows the Phase I start dates for 5 of these products, ranging from 1999 to 2006. The sixth, gammagard, entered clinical trials for AD in Phase III after being repurposed from its original indication for immunodeficiency disorder in 2005. All 6 of these NMEs entered clinical development before the point at which amyloid-related technologies would be considered established. In contrast, for all targeted and biological products approved from 2010 to 2013, the clinical entry point averaged 5 years after the established point,[29] and the 3 AChE inhibitors on the market entered clinical development 17 years after AChE technologies passed this point.

The recent success of aducanumab in a Phase Ib trial for prodromal (or mild) AD[8] and crenezumab in a Columbian cohort of early-onset AD[9] present a different picture. Aducanumab was first used in the clinic in 2011, while crenezumab was first used in 2008. These dates are listed in the table. Coupled with new reports supporting the importance of β-amyloid in AD[50,51] and endorsement of β-amyloid as a diagnostic tool in clinical trials by the US Food and Drug Administration,[52,53] the field appears to be moving toward more effectively operationalizing the amyloid hypothesis. We believe it is significant that these events are occurring at a time when analytical models of technology maturation suggest that these technologies have passed the established point.

Table. Selected β-amyloid therapies in clinical trials.

Drug Name	Mechanism of Action	Phase I Start
Tramiprosate	Aβ aggregation inhibitor	1999
Tarenflurbil	γ-secretase modulator	2002
Semagacestat	γ-secretase inhibitor	2004
Bapineuzumab	Humanized mAB direct at aa 1-5 of Aβ peptide	2004
Solanezumab	Humanized mAB direct at aa 16-24 of Aβ peptide	2006
Gammagard*	Immunoglobulin	2009
Crenezumab	Human recombinant anti-β amyloid mAB	2008
Aducanumab	Human recombinant anti-β amyloid mAB	2011

Aβ = β-amyloid; aa = amino acids; mAB = monoclonal antibody.
The first 6 products and their targets were identified from Karran and Hardy[47] as targeting the formation of amyloid plaques. These products completed Phase III trials between 2009 and 2014, failing to meet their clinical end points. The last 2 products are immunotherapies designed to reduce β-amyloid therapies and currently in clinical trials.
*Approved product for immunodeficiency, repurposed for Alzheimer's disease and entered clinical trials for Alzheimer's disease in Phase III.

CONCLUSIONS

The present analysis suggests that AD drug discovery has followed predictable patterns of innovation. All of the approved targeted and biological NMEs, and the recent clinical successes targeting amyloid plaques, have arisen from established technologies, whereas the often-heralded failures reflect less mature technologies.

It is often argued that the high failure rate of lead compounds in clinical trials reflects the innate complexity of biological systems. Certainly AD is complex. In this context, it is not surprising that the accumulation of knowledge, which our model uses

as a metric of technology maturation, reduces the apparent complexity and improves the efficiency of development.

Why does the established point, corresponding to a slowing of publication activity, predict the efficiency of clinical development? We have closely examined several examples, each of which involves distinct, tactical issues. For monoclonal antibodies, the path to maturity involved sequential growth from murine antibodies to chimeric, humanized, and finally human forms[25] that provided greater safety, bioavailability, and efficacy. For gene therapies, maturation involved emergence of a series of novel viral vectors as well as critical innovations designed to improve safety, gene expression, and production.[25,27] For protein kinase inhibitors, maturation involved growing recognition of the large number of protein kinases and a change in focus of drug discovery from specificity to class effects.[54] Although more research needs to be conducted to understand the dynamics underlying the predictable technology growth pattern, we suggest that the slowing may be an early indicator that uncertainties are reduced, and fewer new research questions emerge.

In the case of the amyloid-related targets, the failed clinical trials of recent years have contributed substantively to the maturation of these technologies. Data from the APP secretase inhibitor trials have increased knowledge regarding the selectivity of the target.[55] Immunotherapy trials have informed understanding of their potential adverse effects.[56] Previous studies have also informed the use of biomarkers, which are increasingly accepted by regulatory agencies.[57] Perhaps the most important growth has come from advances in the design of clinical trials. Clinical investigators now have a better understanding of which patient populations are most likely to respond to specific interventions,[58] better tools for characterizing clinical end points,[59] and new regulatory pathways for more efficient development.[60] Although key technologies in this field were not sufficiently mature to generate successful products a decade ago, they may be now. Analytical models of translational science can inform basic and clinical research results and strategic development of new therapeutic products.

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Each of the study authors materially participated in the research and preparation of this article and approved the final article.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

The funding source had no involvement in the conduct of the research or preparation of the article.

SUPPORTING MATERIAL

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.clinthera.2015.07.003.

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Address correspondence to: Fred D. Ledley, Center for Integration of Science and Industry, Jennison 110, Bentley University, 175 Forrest Street, Waltham, MA 02452. E-mail: fledley@bentley.edu

SUPPLEMENTAL APPENDIX. TECHNOLOGY INNOVATION MATURATION EVALUATION MODEL.

Derivation and validation of the analytical model have been described in detail by Walsh. Briefly, an exponentiated logistic function was used to model publication growth:

$$N = L^{\left(\frac{1}{1+e^{-r(t-t_0)}}\right)}$$

which also has the form

$$\log N = \frac{\log L}{1+e^{-r(t-t_0)}}$$

where N is the number of publications, L is the presumed upper limit of publications, r is the growth rate, t is time, and t_0 is midpoint of exponential growth.

This asymmetric sigmoidal function exhibits the common logistic sigmoid function over log scales. This gives it property of having a symmetric growth phase that is exponential on average. The *initiation* and *established* points, representing the beginning and end of exponential growth or $\log N''(t)_{\max,\min}$ (Figure 1) can be analytically determined by:

$$Established, nitiation = t_0 \pm \frac{\text{a cosh}(2)}{r}$$

The parameters were fit to time series publication data using a nonlinear least squares implementation of the Levenberg-Marquardt algorithm in Python, which can be found at http://lmfit.github.io/lmfit-py/.

Supplemental Table I. Alzheimer's disease (AD) targets, PubMed search terms, and technology initiation (Ti) and establishment (Te) points.*

Target/ Technology	PubMed Search Terms	Ti	Te
Acetylcholinesterase	"acetylcholinesterase"[MeSH terms]	1931	1973
NMDA receptors	"receptors, n-methyl-d-aspartate"[MeSH Terms]	1971	1993
AD and amyloid	("alzheimer disease"[MeSH Terms] OR "dementia"[MeSH Terms] OR "mild cognitive impairment"[MeSH Terms]) AND "amyloid"[MeSH Terms]	1964	2003
Amyloid plaques	plaque, amyloid[MeSH Terms] OR ("plaque"[All Fields] AND "amyloid"[All Fields]) OR "amyloid plaque"[All Fields] OR ("amyloid"[All Fields] AND "plaques"[All Fields]) OR "amyloid plaques"[All Fields]	1966	2000
APP	"amyloid beta-protein precursor"[MeSH Terms]	1967	2002
APP secretases	"amyloid precursor protein secretases"[MeSH Terms]	1988	2005
Tau	"tau proteins"[MeSH Terms]	1968	2004
ApoE	"apolipoproteins e"[MeSH Terms]	1967	1997
Presenilin	"presenilins"[MeSH Terms]	1982	2000
TDP-43	"protein TDP-43"[Supplementary Concept] OR "protein TDP-43"[All Fields] OR "tdp 43"[All Fields]	NA	NA

NMDA = N-methyl-d-aspartate; APP = amyloid precursor protein; ApoE = apolipoprotein E; NA = not applicable.
*PubMed searches were performed by using Medical Subject Heading (MeSH) terms, when possible. Searches for "amyloid"[MeSH] retrieved large numbers of publications unrelated to AD, reflecting historical use of the amyloid term to describe various iodine staining deposits other than AD-related protein. Searches for "amyloid plaques"[MeSH] resulted in 3.5 times fewer papers. The broader search terms used provided more comprehensive retrieval of relevant papers. TAR DNA-binding protein of 43 kDa (TDP-43) had no corresponding MeSH term.

Supplemental Table II. Alzheimer's disease drugs approved by the US Food and Drug Administration and analysis with Technology Innovation Maturation Evaluation model results.

NME	Target	Ti	Te	CE	AP	CE-Te	AP-Te	AP-CE	Te-Ti
Tacrine	AChE	1931	1973	1983[1,2]	1993	10	20	10	42
Donepezil	AChE	1931	1973	1990[3]	1996	17	23	6	42
Rivastigmine	AChE	1931	1973	1990[3]	2000	17	27	10	42
Galantamine	AChE	1931	1973	1991[4]	2001	18	28	10	42
Memantine	NMDA	1971	1993	1986[5]	2003	−7	10	17	22

NME = new molecular entity; Ti = technology initiation; Te = technology establishment; CE = Clinical Entry; AP = Approval; AChE = acetylcholinesterase; NMDA = *N*-methyl-d-aspartate.

AP dates from the US Food and Drug Administration were retrieved from the Drugs@FDA Web site. CE dates were identified by the earliest clinical publication in PubMed or in PharmaProjects, whichever was earlier. Ti and Te were generated by using the Technology Innovation Maturation Evaluation model.

[1]Brinkman, S.D. and S. Gershon, *Measurement of cholinergic drug effects on memory in Alzheimer's disease.* Neurobiology of Aging, 1983.4(2): p. 139-145.

[2]Ingram, N. and D. Newgreen, *The use of tacrine for tardive dyskinesia.* The American Journal of Psychiatry, 1983. 140(12): p. 1629-1631.

[3]PharmaProjects.

[4]Dal-Bianco, P., et al., Galanthamine treatment in Alzheimer's disease, in Age-associated Neurological Diseases. 1991, Springer. p. 59-63.

[5]Fleischhacker, W.W., A. Buchgeher, and H. Schubert, *Memantine in the treatment of senile dementia of the Alzheimer type.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 1986. 10(1): p. 87-93.