

# Back to the future: the ‘old-fashioned’ way to new medications for neurodegeneration

Peter T Lansbury, Jr.

**Despite the increasing prevalence of Alzheimer’s disease, Parkinson’s disease and less common neurodegenerative diseases—and despite the large amount of primary research that has been carried out into the causes and pathogenic features of these conditions—progress toward effective treatments has been remarkably slow. Why is this, and what can be done to accelerate it? There are a number of obstacles to effective drug discovery for neurodegeneration, but by considering these problems it is possible to identify lessons for the future.**

As each day goes by, our susceptibility to Alzheimer’s disease (AD) and Parkinson’s disease (PD) increases<sup>1</sup>. To make matters worse, no medications have been approved, nor are there any clearly in sight, that address the progressive neurodegeneration that underlies these diseases (existing symptomatic treatments are only transiently effective). But this is not just a personal problem; in the industrialized world, the population over 65 years of age will approximately double by 2050. This translates to well over 20 million patients with AD in the United States and Europe. Although the pharmaceutical industry aggressively markets the currently approved drugs for AD—such as donepezil hydrochloride (Aricept)—these cognition enhancers offer only marginal and transient symptomatic benefit to a subset of AD patients. Millennium and Genentech, innovative leaders of the new generation of pharmaceutical companies, have dropped their neurology research altogether. Finally, the research efforts in those companies that remain committed to developing treatments for neurodegenerative disease are smaller than one would predict on the basis of growing patient populations. The truth is that progress toward innovative small-molecule therapies for neurodegenerative diseases has been very modest. The goal of this review is to point out some of the scientific, regulatory and cultural obstacles that are responsible for this situation, and to suggest new approaches to drug discovery that could allow these to be overcome. The literature concerning therapeutic targets in AD and PD will not be reviewed here (that has been done by others<sup>1–6</sup>), nor will therapeutic strategies other than small-molecule drugs, some of which seem to be quite

promising (for example, the AD vaccine<sup>7</sup>), be discussed. Finally, it should be emphasized that the many other debilitating and life-threatening neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Huntington’s disease and frontotemporal dementia, though individually less prevalent than AD and PD, combine to affect millions of individuals.

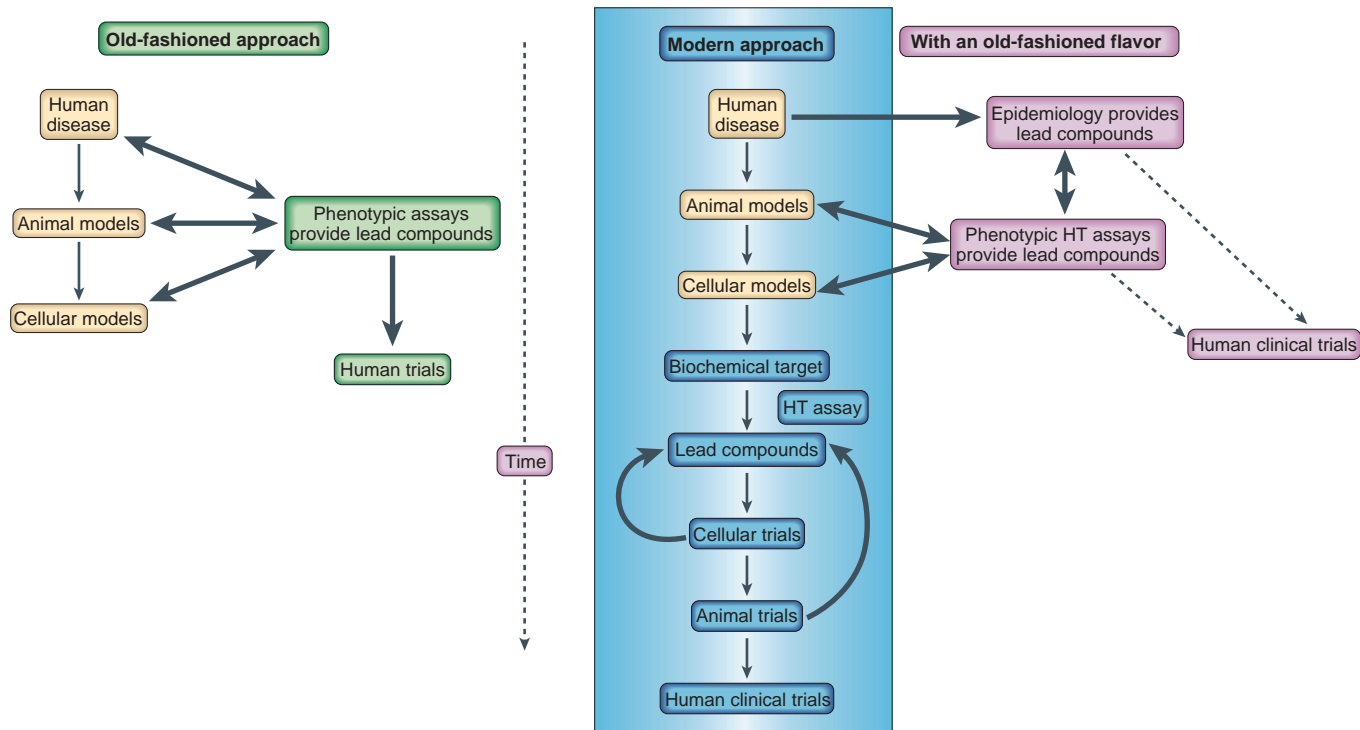
## Is a detailed understanding crucial?

If one asked a group of academic or pharmaceutical scientists why there are no effective drugs for AD, they would probably respond that the underlying etiology of AD is not understood at the level that is required for drug discovery. Although continued investigation of the pathogenic pathways and potential therapeutic targets is important, the lack of this information does not justify the lack of progress toward a drug. Aspirin was developed long before its target was known, as were penicillin, cisplatin and many other lifesaving drugs. So why does this argument persist? Academic scientists recognize that their work must be seen as essential for the development of new therapies and argue that ‘hypothesis-driven’ basic science is the backbone of all progress. The implication is that these advances will inevitably be translated into therapies, but this is not the case. One reason for this is that the incentive structure in academia rewards the delineation of creative, controversial and intellectually stimulating hypotheses concerning disease etiology, rather than the translation of these ideas into therapies. As a result, the last decade of AD research has witnessed a parade of high-profile publications offering alternatives to the well-supported ‘amyloid hypothesis’ of AD. Most of these alternative theories have never inspired research outside of the originating laboratory. In fact, many of these ‘alternatives’ have turned out to support the amyloid hypothesis; the case study presented later is an excellent example. Although this contentious academic culture stimulates and motivates academic research, however, it might have had the opposite effect on drug development.

For its part, the pharmaceutical industry seems to believe that the existence of controversy reflects a lack of knowledge about pathogenesis, rather than being the product of the academic culture. I believe that the current state of our scientific understanding is more than adequate to justify major initiatives against AD and PD, but that a series of unscientific obstacles make the risk of such programs too great to mount a credible effort. AD might be an exception, however, because the patient pool or market is so large that a higher level of risk is acceptable. To change this situation, three contributors to this risk have to be addressed. First, we need new methods for studying these diseases *in vivo* (obstacles 1–3 presented later) that will shorten

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**Figure 1** Evolution of the pathway from studies of a human disease to trials of a candidate therapeutic agent. Before molecular biology, drugs were discovered by testing new compounds in cells, in animals and sometimes in people. The success of this ‘old-fashioned’ approach (green) was limited by the throughput of the phenotypic screen and the need to optimize each compound’s physiological properties. Present-day drug investigators usually focus on identifying a target molecule (blue), typically an enzyme or receptor protein, that may be responsible for a cellular phenotype; the proposed link often cannot be validated. They use the target to screen large compound libraries, typically containing proprietary molecules with unknown physiological properties. Hits from these libraries are optimized, then returned to a more complex model of disease to validate the relevance of the target and to reduce side effects. Two problems with this approach are (i) the difficulty of assigning a complex phenotype to a single protein target, and (ii) ignorance, through optimization of initial hits in an oversimplified model, of alternative targets that produce unwanted effects in humans. My proposal adds a hint of the old-fashioned approach (red), emphasizing high-throughput (HT) phenotypic screening. Screening in cellular and animal models addresses issues such as toxicity and side effects and allows the observation of effects generated by drug binding to several targets (Fig. 2). Screening of libraries comprising compounds known to be safe in humans or compounds that are safe in animals and have not yet been tested in human trials avoids the time-consuming optimization process (back arrows). In addition, the identification of hits with known pharmacological properties can inform the search for molecular targets.

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clinical trials, increase the odds of observing efficacy and allow the patient pool to be expanded. Second, the regulatory system that governs drug discovery and development must be reformed so as to encourage innovative research (obstacle 4). Finally, new approaches to drug discovery, which harness modern technologies to update old-fashioned approaches, must be encouraged (obstacle 5). In the following paragraphs, I discuss these issues in more depth, before making several suggestions that might hasten the development of medicines for these terrible diseases.

**Obstacle 1. The nature of the disorders.** Most neurodegenerative disorders are heterogeneous, genetically complex and difficult to diagnose. This is especially true for AD and PD, in that >90% of cases are not linked to a single mutation (Huntington’s disease is the most prevalent purely genetic neurodegenerative disease). It is estimated from postmortem pathological studies that >15% of cases of AD and PD are misdiagnosed in the clinic. A large portion of cases that are diagnosed as probable AD turn out to be diffuse Lewy body disease, a neurodegenerative disease of the cortex that is characterized by PD-like Lewy bodies comprising  $\alpha$ -synuclein, the aggregating protein of PD<sup>8</sup>. For the pharmaceutical industry, the heterogeneity of the clinical population causes problems, because a large number of patients are unlikely to respond to the strategy of choice. This is compounded

by the slow progression of these diseases, which requires that trials be extended for long periods to observe substantial benefits.

In the future, more homogeneous subtypes of these diseases could be defined by a ‘genetic fingerprint’: a combination of genetic polymorphisms, haplotypes, mRNA expression patterns or all of these. Susceptibility variables that are related to genetic polymorphisms are already well known. For example, a polymorphism in the apolipoprotein E gene is an established susceptibility variable for AD. Individuals carrying one *APOE4* allele (10–20% of caucasian populations) are three times more likely than others to develop AD<sup>9</sup>. In the case of PD, several polymorphisms in the  $\alpha$ -synuclein promoter region and one polymorphism in the *UCH-L1* coding region influence susceptibility<sup>10–13</sup>. The combined risk is greater than the sum, indicating that these two genes are linked to the same pathogenic mechanism<sup>14</sup>. It has not been determined whether affected individuals bearing the risk factors respond to medication differently than do affected individuals who do not bear the risk factors (do these two groups suffer from different types of disease?). It is clear, however, that there should be a great effort to determine whether this is the case, because the ‘homogenization’ of clinical trial populations will facilitate clinical trials, and this could, in turn, boost drug discovery efforts. There might have been some resistance in the pharmaceutical industry to subdividing clinical populations, because the approval achieved through such a

trial would be limited by the same criteria that were used to subdivide. Companies such as Millennium and GlaxoSmithKline, however, have recognized that the flood of genetic information is unstoppable and have embraced the idea of personal medicine.

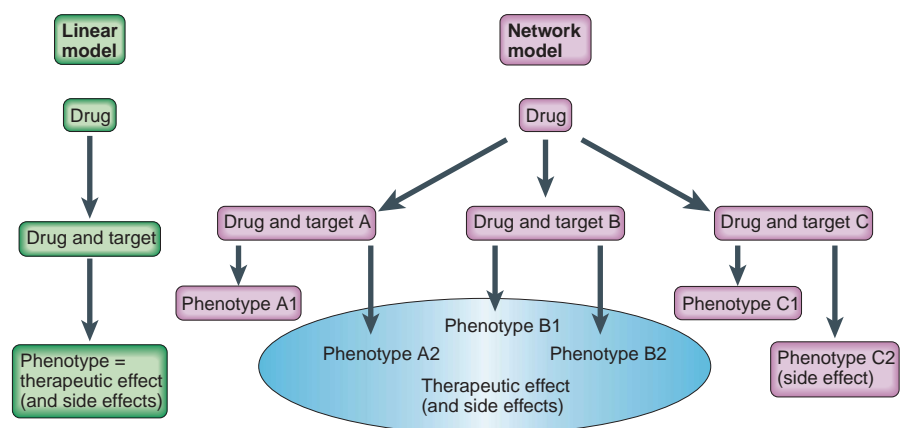
**Obstacle 2. Lack of biomarkers for progression.** The neurodegenerative diseases are characterized by a complex and slow-progressing clinical picture. So, assessing the efficacy of a candidate drug by clinical measures alone is difficult, expensive and time-consuming (see later)<sup>15,16</sup>. The process could be accelerated (and made more attractive to pharmaceutical companies) by the existence of accepted biomarkers for disease. A biomarker that reliably and quantitatively correlates with clinical measures and can be used to predict clinical outcomes is designated a surrogate marker and is accepted by the FDA as a measure of clinical efficacy. So, rather than measuring the prevalence of heart attacks in placebo and treated groups after prolonged drug use, the efficacy of drug candidates in these patients is measured by their shorter-term effect on serum cholesterol levels. Although an FDA-approved surrogate marker is most desirable, even a generally accepted biomarker would stimulate pharmaceutical drug discovery efforts. This has been the case for multiple sclerosis (MS), which, despite affecting many fewer individuals than PD, is the subject of an intense marketing battle between Biogen Idec and Serono/Pfizer. In the case of the relapsing-remitting form of MS (a precursor to the progressive, chronic form), MRI technology has allowed brain lesions to be correlated to the probability of relapses, a clinical endpoint recognized by the FDA.

**Obstacle 3. Identifying preclinical AD and PD.** All of the neurodegenerative diseases involve a long preclinical phase during which neuronal loss is not detected by the affected patient. In the case of PD, the loss of as much as 70% of the nigral dopaminergic neurons can be undetectable in the clinic. Those individuals with 60% loss are probably headed for clinical PD, however, and they would also presumably be most responsive to and benefit most from a neuroprotective therapy. Moreover, importantly for the pharmaceutical industry, these preclinical PD patients would allow the market for a PD drug to be significantly expanded (the story of cholesterol and heart disease shows the economic and public health benefits of treating preclinical patients). Expanding the market by changing the definition of disease to include preclinical patients will compensate for market contraction caused by the drive for personal medicine. Despite the availability of the tools that could allow identification of subclinical PD (such as genetic polymorphisms and gene expression profiles to identify high-risk populations, followed by single-photon emission computed tomography (SPECT) imaging to determine nigral volume), however, the lack of an effective neuroprotective therapy means that there has been no concerted effort to do so. This is, of course, a Catch-22 situation, and it must be overcome.

**Obstacle 4. The regulatory system.** The current regulatory system does not promote the discovery of new therapies. Although this

section focuses on regulatory issues that are specific to US law, the principles enumerated here can be generalized to western Europe, Japan, South Korea, Australia, Canada and so on.

First, the Bayh–Dole Act has encouraged some American nonprofit institutions to put the marketing of publicly funded discoveries ahead of scientific progress. Although this change has resulted in the proliferation of university technology transfer groups and startup biotechnology companies, the steady reduction in the rate of approval of new drugs over the past 10 years argues that it has impeded progress. Of course, the protection of new chemical entities is crucial to ensure that they will be developed and marketed as prescription drugs. Unfortunately, however, there has been an alarming trend among academic institutions toward patenting general knowledge that allows the discovery of such entities. One example is the attempt, by the University of Rochester, to patent the identification of cyclooxygenase 2 (COX2) as a therapeutic target (this patent was invalidated in court because no specific inhibitory compound was described). I would argue that it is the mission of academic research, especially that which is supported by public funds, to freely disseminate such enabling information. The marketing of ‘enabling’ intellectual property has inhibited progress toward a therapy for AD. For example, the transgenic mouse model of AD generated in 1996 by researchers at the University of Minnesota and the Mayo Clinic<sup>17</sup> was marketed to the pharmaceutical industry and to the research community with strings attached: ‘reach-through’ clauses that guaranteed Mayo and Minnesota a percentage of the royalties generated by any invention whose discovery depended on these mice. This type of agreement is anathema to the pharmaceutical industry and clearly impeded AD research. Several pharmaceutical companies went to great lengths to purchase and sequester these mice, so that in the event of a legal challenge, they could prove that the mice were not used to develop their AD drug. There is no doubt that AD research would have progressed more rapidly if the Mayo–Minnesota mouse had been sold to a



**Figure 2** The clinical effect of many drugs could result from a combination of molecular events. Two extreme possibilities are presented here. In the linear model—the basis of current drug discovery approaches—a drug binds a single target to produce an isolated event that results in the desired therapeutic effect and undesired side effects. In the network model, two sources of potential complexity are recognized. First, a drug might bind to multiple targets (A, B and C). Second, each drug–target complex could produce more than one phenotype (for example, the presenilins seem to be involved in more than one signaling pathway). The therapeutic effect could be a combination of molecular events (blue circle). Side effects might result from drug binding to the predicted target or to a target that does not contribute to the therapeutic effect. This networked model is more consistent with what is known about protein–protein interactions. The model shown is difficult to address by the target-driven approach (Fig. 1), because the therapeutic effect could not be produced via a single target.

company that could have made it widely available at a reasonable cost with no strings attached. Funding agencies should take a more aggressive stance to prevent this type of situation from occurring. In the United States, the Bayh–Dole Act should be modified to forbid the use of publicly funded research in a way that is counter to the interests of the public.

Second, the patent law no longer protects innovators but rather encourages imitators. Developing and marketing a ‘copycat’ drug is much less risky than attempting to discover a breakthrough medication for an untreated disease such as PD or AD. But how can a copycat drug be patented in the first place, seeing that a patentable invention must be nonobvious to a person ‘schooled in the state of the art’? Unfortunately, this requirement is currently interpreted as though that person’s ‘schooling’ ended in 1960. Specifically, the obviousness of a discovery still depends solely on the chemical structure of the drug (composition of matter) but ignores information about its target. In 1950, it was not obvious that two very different chemical structures (for example, pramipexole and L-DOPA) could both relieve the symptoms of PD. Therefore, both of these chemical entities were rightly patentable. Now, though, drug discovery is largely target-driven, and it is no surprise that two D2 receptor agonists, albeit with very different structures, have the same *in vivo* effect. Yet the patent law still allows both compounds to be patented. This archaic interpretation of the criterion of obviousness is the origin of the copycat school of drug development. It is profitable and not all that risky to generate new, patentable versions of existing drugs. So we have esomeprazole replacing omeprazole and desloratadine replacing loratadine. Although they are designated ‘new chemical entities’, these copycat drugs do not significantly benefit the public—albeit some have more favorable side-effect profiles—and, more importantly, their development diverts resources from risky research in AD and PD. Until the patent law is changed to reflect its original intent, the magnitude of drug discovery efforts for neurodegenerative diseases will not appreciably increase.

Finally, the time and expense of demonstrating clinical efficacy also results in drug loss. Before 1962, the goal of the US Food and Drug Administration (FDA) was to protect the public from unsafe drugs, with no concern about efficacy. The addition of efficacy trials in 1962 has resulted in an expanded mission, but in addition to protecting us from ineffective drugs, the FDA discourages breakthrough research of the type required to resolve AD and PD. This problem has been recognized and corrected in the case of HIV-AIDS and cancer, where the patient’s right to obtain potentially lifesaving drugs clearly justifies a relaxation of the efficacy requirements. This type of thinking should also be applied to AD and to PD<sup>18</sup>. Many individuals with PD would be willing to take risks to find a medication that could slow or halt the inexorable progression of their disease. Indeed, that lack of effective drugs has led many of them to undergo brain surgery to temporarily alleviate their symptoms. How can we claim that eliminating a relatively slow death from a debilitating and dehumanizing neurodegenerative disease is not a societal priority?

**Obstacle 5. A target-driven, reductionist approach.** Drug discovery began as an entirely human phenotype-based endeavor; this approach produced aspirin, caffeine and the pharmacopoeia of Chinese herbal medicine. As our understanding of disease pathogenesis advanced, we moved to disease models of decreasing complexity but also decreasing relevance to the human condition: mouse models, cellular models and, most recently, protein models (Fig. 1). The complete clinical and pathological pictures of neurodegenerative diseases are difficult to model in a mouse or rat, but transgenic and knockout

technology has allowed considerable progress to be made<sup>19</sup>. Mouse models that highlight a crucial aspect of the pathology of AD ( $\alpha\beta$ -amyloid deposition) or PD (Lewy body formation) have been produced by overexpressing the relevant aggregating proteins. Cellular models of these diseases have been harder to come by, partly because of the inability of neurons to divide in culture; yet some advances have been reported<sup>20,21</sup>. In the past, animal and cellular models have been responsible for many breakthroughs in drug discovery, including penicillin and cisplatin. As a result of the scientific community’s evolving definition of what constitutes an adequate level of ‘understanding’ of a pathogenic process, however, most current drug discovery efforts focus on single-protein targets, whose relevance is deduced from studies in more complex systems (and validated later on). We regard these systems as somehow more intellectually sophisticated, despite evidence that the leap from a cellular phenotype to a molecular target is an uncertain one (as is the leap back to the cellular system; Fig. 1); target-oriented drugs often fail to produce the desired effect in cell culture. Medicinal chemists are particularly insistent on target-based screens, because they can approach optimization of a single drug–protein interaction, whereas optimization of multiple interactions is thought to be too complex. I believe that the widespread attitude that target-driven drug discovery is the only or even the optimal pathway to new drugs has created an obstacle to practical progress against neurodegenerative diseases. The existing forms of neurodegeneration are late-onset phenomena that are unlikely to have been affected by evolutionary optimization. In this sense, the target processes differ in a fundamental sense from the target processes of infectious disease, which have been evolutionarily optimized; the bacteria or virus has evolved to infect the host. As a result, it is unlikely that a single target or pathogenic pathway for AD or PD can be identified; reductionism might not be possible. It is therefore necessary to return to ‘old-fashioned’, phenotype-driven approaches, which can inform target selection but also produce advances themselves (Fig. 1). Before making specific recommendations as to how this approach could be facilitated, I discuss one recent example in AD drug discovery that illustrates the potential of the old-fashioned approach to get around the problems of ‘modern’ drug discovery.

#### A case study

The amyloid hypothesis of AD was first put forward by Alzheimer himself, who proposed that cortical amyloid plaques might cause the clinical entity that now bears his name. More than 80 years later, Glenner identified the protein amyloid  $\beta$  ( $A\beta$ ) as the primary component of amyloid plaques in AD. The subsequent discoveries that  $A\beta$  is cleaved from a precursor protein, amyloid precursor protein (APP), and that mutations in APP, flanking the  $A\beta$  sequence, cause early-onset familial AD, pointed to the APP-to- $A\beta$  conversion as a possible therapeutic target<sup>5</sup>. By 1993, a cell culture system had been reported that modeled this conversion<sup>22,23</sup>. Despite the existence of this screenable system and compelling evidence that this process was a viable target, few major screening efforts were begun until around 7 years later, when the proteases responsible for  $A\beta$  generation ( $\beta$ -secretase<sup>24</sup> and  $\gamma$ -secretase<sup>25</sup>) were identified. Compounds derived from state-of-the-art biochemical screens of these two targets are just starting to enter clinical trials, 10–12 years after the key advance. Why has it taken so long? The 7-year lag between the generation of relevant cellular models of the crucial phenotype,  $A\beta$  generation, and the identification of molecular targets, the secretases, can be traced to the insistence in the industry on following the ‘modern’ target-oriented approach, which is a product of the unsupportable notion that a

complete mechanistic understanding is a requirement for therapeutic development. As demonstrated by the case study here, the insistence on one approach prevents new and therapeutically relevant target pathways from being discovered, lengthens the time required for drug development and increases the probability that early lead compounds will have significant side effects.

The example here illustrates how a nontraditional pathway led to inhibitors of A $\beta$  production and even uncovered new therapeutic targets that could not have emerged from a target-driven approach. The discovery, in the early 1990s, that individuals with chronic arthritis had a decreased risk of AD led to the recognition that certain nonsteroidal anti-inflammatory drugs (NSAIDs) might protect against AD<sup>26</sup>. This finding initially received attention because it was consistent with the theory that inflammation was crucial to AD pathogenesis (ironically, this connection was later proved to be irrelevant; see later). More than 10 years after the initial report of this effect, it was demonstrated that certain NSAIDs reduce A $\beta$ 42 (but not A $\beta$ 40) production by cultured cells<sup>27</sup>. This effect does not depend on binding by these drugs to their anti-inflammatory target, COX2, or to any other known NSAID target<sup>28</sup>, but depends, at least in part, on the membrane-attached G-protein Rho and on Rock, a kinase whose activity is modulated by NSAIDs<sup>29</sup>. The interaction between Rho–Rock and  $\gamma$ -secretase activity had not been detected by the state-of-the-art methods for identifying protein–protein interactions<sup>30</sup>. Furthermore, the connection between AD and this pathway and the NSAIDs could not have been discovered by target-driven approaches using screens for inhibitors of  $\beta$ -secretase or  $\gamma$ -secretase. Finally, this approach, which starts with a clinically tested drug, takes on the issue of side effects early in the process. In contrast, the secretase-targeted approach might produce side effects due, for example, to blocking the processing of an alternate substrate; incidentally, the NSAIDs do not substantially affect the processing of Notch<sup>27</sup>.

#### How can we accelerate drug discovery?

As the example just given makes clear, our thinking with respect to drug discovery and development has become too linear, connecting drug candidate to target to pathway to phenotype or disease (Fig. 2). Examples that apparently conform to this simple model, such as imatinib (Gleevec), are glorified as confirmation that the modern approach is the one true path. But many drugs are known to bind to more than one target, and I suspect that this is the rule rather than the exception. So a network of drug–protein interactions, analogous to the protein interaction network that has launched the field of systems biology, is a better model than a pathway (Fig. 2). In addition to many drug–protein interactions, the few protein–disease or protein–phenotype interactions that are currently recognized probably represent the tip of the iceberg, and many more remain to be discovered. Our ignorance of these two levels of cross-talk is demonstrated by the frequent finding that drugs developed for one indication are effective against a different condition. These discoveries often demonstrate unrecognized target–disease interactions, but the case above and that of adamantylamine demonstrate that multiple drug–target interactions exist. Adamantylamine was originally used as an antiviral agent but was later noticed, by an alert neurologist, to decrease the symptoms of PD. The latter effect is probably governed by its interaction with the vesicular dopamine transporter, a target that is not likely to be involved in its antiviral activity. Despite the insistence of the pharmaceutical industry on target-driven drug discovery, several successful drugs have been recently developed with no knowledge of their targets (metformin for type II diabetes, levetiracetam for refractory epilepsy and ezetimibe for high cholesterol).

#### Lesson 1. Phenotypic screens complement target-oriented screens.

Because of the complexity of the *in vivo* situation and the probability that unappreciated interactions could produce undesirable *in vivo* effects, it is important to develop screens that closely resemble the *in vivo* situation. Human trials of drugs for which there is no mechanistic basis are not ethical, although epidemiological evidence can substitute for mechanistic understanding. Unfortunately, epidemiological studies of the effects of drug use on disease susceptibility are limited by statistical considerations to situations in which the disease or the drug, or both, are relatively prevalent (phase 3 studies are typically too small). For example, it has been determined that caffeine and nicotine protect against PD, but it will not be possible to determine the effects of anti-epilepsy drugs, for example, unless the effect is enormous. It is therefore important to develop more practical analogs of human clinical trials and human epidemiological studies. Mice and rats are impractical in this regard, but some initial studies suggest that *Drosophila melanogaster*, zebrafish and possibly *Caenorhabditis elegans*<sup>31</sup> might be excellent model organisms. Transgenic *Drosophila* models of PD<sup>32</sup> and AD<sup>33</sup> have disease-like protein deposits and behavioral phenotypes; the choice of transgene in both cases is based on a hypothesis of pathogenesis that is as yet unproven, emphasizing the need to use several models. Several examples of hypothesis-driven drug testing in *Drosophila* models of neurodegeneration demonstrate the potential usefulness of *Drosophila* for more extensive screens. First, overexpression of the heat shock protein HSP70 in a *Drosophila* model of PD inhibits neurodegeneration, as does treatment with geldanamycin, which upregulates HSP70 expression<sup>34</sup>. Second, a *Drosophila* model of Huntington's disease responded to treatment with a histone acetyl transferase inhibitor<sup>35</sup>. Finally, treatment of nontransgenic *Drosophila* with a  $\gamma$ -secretase inhibitor induces the notched-wing phenotype, indicating that Notch is a substrate of  $\gamma$ -secretase *in vivo*, a potential roadblock to the application of such compounds<sup>36</sup>. It would be of value to note whether this compound affected the emergence of A $\beta$ 42 deposits or the behavioral phenotype in the *Drosophila* model of AD<sup>33</sup>. Although *Drosophila* are useful for testing hypotheses concerning pathogenic mechanisms, as are mice, the unique promise of *Drosophila* models of AD and PD lies in the ability to use them to screen large numbers of potential drugs (see later), chosen without a particular bias concerning the pathogenic mechanism (*C. elegans* might also be useful for such screening). These studies will undoubtedly uncover new target–phenotype links and new therapeutic approaches.

**Lesson 2. Clarifying unrecognized targets.** In addition to creating novel and structurally diverse chemical libraries, an emphasis should be placed on clarifying the unrecognized targets of known drugs, drug candidates and combinations thereof. Extrapolation of the linear model for drug discovery leads to the conclusion that more compounds are required to target the existing proteome. Many laboratories are dedicating effort toward generating libraries containing millions of novel compounds for screening. Whether these compounds have the requisite properties to allow their development into drugs (in terms of adsorption, distribution, metabolism, excretion and toxicity) is not clear. On the other hand, many existing compounds have been demonstrated to have druglike properties, and some have been shown to be safe in human trials. These compounds include the FDA-approved drugs, of which there are over 3,000. It is probable that many of these drugs have targets in addition to those that explain the 'approved' effect; some of these alternate targets might be responsible for their side effects. Many groups are engaged in systematic screening of libraries of FDA-approved drugs against

phenotypic assays that are relevant to neurodegenerative disease. One such library has been distributed by the National Institute of Neurological Disorders and Stroke, in conjunction with several private foundations, for this purpose. Preliminary results suggest that this method will uncover new pathogenic pathways that can be approached by a target-oriented strategy. In addition, compounds discovered in such a screen can be immediately tested in animal models of disease and, possibly, in human trials. A variation of this theme is being practiced by the biotechnology company CombinatoRx<sup>37</sup>, which is screening binary mixtures of approved drugs to uncover synergistic effects. The idea that neurodegenerative diseases, like many cancers, will be most effectively treated by combination therapy is an attractive one. A publicly available library of binary combinations of approved drugs would be extremely valuable.

Two other classes of compounds could be very useful for drug discovery for neurodegeneration. The first comprises compounds that have passed phase 1 trials for safety but have failed to demonstrate efficacy against the targeted indication in phase 2 or 3 trials. The second larger class comprises those compounds that have cleared all pre-clinical hurdles and could be classified as investigational new drugs (INDs). A *Drosophila* screen of both of these groups might uncover compounds with unappreciated efficacy. The pharmaceutical industry has traditionally tightly guarded these proprietary compounds, because they have already invested considerably in their development. Given the undeniable value of these compounds and the clear therapeutic need for a breakthrough, however, there must be a way to make these compounds available for screening purposes. One could imagine a mechanism whereby any intellectual property resulting from such a collaboration would be split between the original owner of the composition of matter patent (an invention without a use should not be patentable) and the discoverer of the usefulness of the invention for neurodegenerative disease (the use itself, without a compound, is not patentable). Both parties would benefit considerably from such a system, not to mention millions of patients.

**Lesson 3. Reform the drug approval process.** Before 1962, the only requirement for drug approval was to show that a drug was safe in humans. Since that time, demonstration of drug efficacy in phase 2 and phase 3 clinical trials has been required. A relaxation of the current emphasis on 'proof' of efficacy, stopping short of eliminating all efficacy trials, would stimulate drug discovery efforts. It is important to remember that the great majority of drugs approved before 1962 were concluded to be effective after careful retrospective analysis of clinical data. In fact, many drugs that were retroactively denied approval in the aftermath of the 1962 change might actually have been effective<sup>18</sup>. Two US programs, the Orphan Drug Act and the Fast Track Program, have successfully decreased the costs and the time involved in getting approval for new drugs that address unmet medical needs. The Orphan Drug Act provides incentives to develop drugs for otherwise unattractive markets, defined as fewer than 200,000 US patients. In light of the other difficulties associated with developing drugs for neurodegenerative diseases (see earlier), I propose that the definition of an orphan disease be expanded to include diseases such as PD, which despite affecting well over 200,000 US patients, is an unattractive market opportunity.

**Lesson 4. Invest in nonprofit drug discovery programs.** The rise of the pharmaceutical industry as a research-intensive industry is relatively new (and, some would argue, coming to an end), and many medical breakthroughs were made in nonprofit research environments. Many academic institutions are now exploring the possibility of returning to

this role, especially for areas such as neurodegeneration that are negatively affected by the current system of drug development. Both the Scripps Research Institute and Harvard Medical School (the Laboratory for Drug Discovery in Neurodegeneration)<sup>38,39</sup> have started drug discovery groups, and many more such groups are being planned. The crucial steps for the success of these ventures will be, first, to generate the required startup capital, and, more importantly, to obtain the funds required to sustain each program. The latter will require the investment of government agencies and private disease-focused foundations. The National Institutes of Health has endorsed translational research via the 'Roadmap' initiative, which specifically funds the development of a public molecular library. This program seems to be focused on the generation of novel research tools, but it will clearly have implications in drug discovery.

### Could these changes make a difference?

To evaluate the potential impact of the changes just proposed, it is instructive to return to the case study presented earlier. A cell-based model of the APP-to-A $\beta$  conversion existed in 1992 and could have been modified for screening the relatively small libraries just discussed. If the academic culture had been more encouraging of translational research and nonprofit screening facilities had been available, it is probable that the connection between NSAIDs and A $\beta$ 42 generation would have been discovered independently of the epidemiological studies, and probably in 1993 or 1994 instead of 2001. In addition, the simultaneous screening of approved drugs, drug combinations and IND candidates would probably have led to new insights that remain undiscovered. Whether we would have produced an approved AD drug by now is unknown, but it is clear that the process would have been considerably accelerated. It is important, especially to the millions of patients who, after all, indirectly fund our research, that our future efforts as efficient as possible.

### COMPETING INTERESTS STATEMENT

The author declares that he has no competing financial interests.

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