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A New Regulatory Road-Map for Alzheimer's Disease Drug Development

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"bind me with chaffing ropes as I stand upright against the mast"

Homer. The Odyssey

Introduction

In *Nature Reviews Drug Discovery* we proposed that Alzheimer's disease (AD) drug developments become more soundly grounded with scientifically confirmed mechanistic theory and more strongly committed to the ongoing testing and refining of this neuroscience theory [1]. Earlier, in a series of articles since 2000, we emphasized the need for clinical researchers to become more concerned with the prevention of methodological errors that are interfering with the validity of clinical AD and neuropsychiatric research studies [2–10]. We found in these two study topics complementary evidence that a surfeit of errors and an absence of sufficiently rigorous neuroscience theory has led to failures of neuroscience drug developments and to less effective patient care [8]. We have recommend two changes to current AD drug development practices—stronger commitments both to advancing the mechanistic theory of how a drug works or fails when a clinical trial tests for efficacy and the removal of methodological error impediments that undermine clinical trial successes. To implement these changes we have recommended that researchers give priority specifically to the development of a molecular-mechanistic theory of AD that will be systematically tested and refined in clinical trials and the preemption of error sources identified recurrently as potential sources for AD clinical trial failures [1,7,8].

As we have argued earlier for neuropsychiatric drug developments in general, we are concerned that current lack of progress improving on earlier AD drugs derives, at least in part, from weaknesses in the underlying theories of the diseases [1,8]. We see in the next wave of AD drug developments opportunities for investigators to join medicine in its shift away from empiric diagnoses and treatment outcomes based on clinical observations of syndromes and to move towards molecular-mechanistic diagnoses of pathologies underlying diseases and associations of treatment induced clinical changes or lack of efficacy with these specific molecular pathological mechanisms [11,12]. For AD this molecular turn would entail systematic grounding of drug developments with mechanistic explanations at the level

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of DNA, RNA, transcribed proteins, post-transcriptional modifications, and organism and environmental functions and interactions. These changes would replace current trial and error approaches to the development of potential drug products [1].

Recently, Kozauer and Katz [13] endorsed proposed FDA regulatory guideline changes meant to support AD clinical trials [14]. They foresaw a combination of biomarkers and clinical assessments to be used in the earliest stages of clinical AD. Conditional FDA drug approvals would be based on a validated cognitive outcome measure and post-approval studies would verify clinical efficacy [13,14]. We question whether these changes can be supported by current knowledge of AD, by recent experiences with AD drug candidates, and by the need for methodologically sounder, better scientifically grounded, foundations for AD drug developments.

In this paper we propose that the priorities we have endorsed for AD drug developments—to respond to the realities of AD neuropathology, to become more focused on the development of clinical AD science, and to overcome avoidable errors that have been invalidating clinical trials—will not be supported by the emphasis on cognitive clinical symptoms in the FDA and Kozauer and Katz proposed guideline changes [13,14]. We foresee the need for regulatory revisions that will provide better balanced supports for advancing the AD scientific knowledge required to more effectively develop clinically useful drugs and for provisions to patients of drug candidates soundly predicted, based on documented effects on AD neuropathologies and safety, to slow or arrest the progression of persons at-risk to AD dementia.

Background

The focus of Current AD drug developments

$A\beta_{42}$ is the principal target of many presently planned AD clinical trials [1,15]. Kozauer, Katz [13], and the FDA [14], by requiring cognitive outcome evidence in the earliest stages of neuropathological risks for AD, propose highly consequential guidance for currently proposed anti-$A\beta_{42}$ and other clinical trials. They strongly tempt industry and their academic collaborators away from much needed foundational studies of molecular mechanisms of AD neuropathologies, drug interventions, and drug development methods. We regard this encouragement as counterproductive because it supports investigations to become prematurely too committed to clinical efficacy. We find this emphasis problematic in three ways. First, clinical trials do not take advantage of the opportunities they present to test the validity of underlying molecular-mechanistic assumptions about AD and the drugs being evaluated. AD science is not advanced. Second, they do not discourage current practices that have failed to address methodological flaws such as failures to engage drug targets. Third and perhaps most consequentially, there is too little chance that the clinical efficacy required in these new regulatory guidelines can be demonstrated in early stage AD clinical trials.

AD clinical trials focused on clinical efficacy have failed to advance our molecular-mechanistic theory AD and to improve the methodological groundings for future AD drug developments [8]. While efficacy must remain a core criterion for regulatory drug approvals, this need does not imply that clinical trials seeking efficacy can afford to neglect the testing

of mechanistic theoretical assumptions that underlie expectations of efficacy. Neither does it seem wise to focus regulatory guidance uncritically on clinical efficacy when evidence shows that methodological errors, such as failures to engage the brain target adequately to fairly test the drug for efficacy and failures to replicate, are undermining the validity of AD clinical trials [16–18]. Just as evidence based medicine requires valid and not just the best available evidence, so too regulatory agencies, organized to serve the public good, require sound clinical trials that avoid false positive and negative outcomes.

Finally, we have argued that, based on existing evidence, clinical efficacy cannot be predicted to occur in the early at-risk-of-AD-decades-later persons [1]. The FDA is responding to the needs of investigators who will study early pre- and Mild Cognitive Impairment (MCI) subjects [19], not to investigators who are about to study subjects not qualified for any AD or immediately pre-AD related clinical diagnosis. Current knowledge of AD indicates the need to intervene against AD neuropathologies decades before the onset of MCI [1]. We are concerned that the next generation of AD clinical trials, encouraged to depend on clinical efficacy as their outcome, will inevitably be insufficiently structured to develop and test mechanistic theories of AD essential if we are to better guide AD drug developments in the future towards success and to advance clinical neuroscience theory and practices [1]. We are also concerned that these trials will be unable to demonstrate the evidence of cognitive benefits required under the new guidance [1].

In the last 5 decades neuropsychiatric drugs and in the last 3 decades AD newly approved drugs have not improved clinical effectiveness over already approved drugs. In these decades a trial and error approach dominated the testing of drug candidates. Clinical investigators most frequently translated major advances in basic brain sciences directly into clinical trials without pursuing laboratory discoveries to understand how molecular mechanisms and targets are relevant for AD and for the efficacy of treatments. Without specific molecular mechanisms of pathologies and treatments to test and clearer specifications of the critical conditions needed for clinical trials to succeed, issues such as the adequacy of dosing, target engagement conditions, timing of an intervention in relation to the disease progression, and so forth can be expected to confound interpretations of future trial results [3,8,16]. For example, numerous instances of undocumented drug concentrations at brain targets have been cited as reasons why AD clinical trials failed and drug and underlying mechanistic hypotheses were abandoned [8,16,18]. This un-nuanced trial and error approach will not effectively identify, test, and refine the methodological and theoretical conditions we find essential to effective AD drug testing. Based on these considerations we propose the need for both developments of better methodological approaches to AD drug developments and for more robust molecular-mechanistic theory to ground AD and other neuropsychiatric drug developments [1,8].

AD neuropathology

Up to three decades may elapse between first detectable amyloid accumulations in some persons' brains at 45 years of age and younger and the onset of sporadic AD after age 65 [20]. In these decades we find no evidence of an AD neuropathologically induced cognitive deficit to be remedied as a demonstration of clinical efficacy. Emerging evidence supports

the view that self-sustaining neuropathologies responsible for clinical AD may be induced by $A\beta_{42}$ concentration increases over 2–3 decades [1,21]. For example, the phosphorylation of tau (p-tau), a possibly self-sustaining source for Chronic Traumatic Encephalopathy dementia not dependent on the presence of $A\beta_{42}$ [22], appears up to 15 years before clinical AD without documented accompanying clinical symptoms [20]. The importance of this neuropathological-clinical symptom gap for regulators is that clinical efficacy sufficient to support the importance of an anti-$A\beta_{42}$ intervention may very likely be out of reach within one clinical trial. $A\beta_{42}$ may induce p-tau or another source for clinical AD or $A\beta_{42}$ may accumulate irreversibly as amyloid with neuronal toxicity but without symptoms. Targets for antibodies to be tested in the anti-$A\beta_{42}$ currently planned clinical trials have not been fully characterized, for example it is not known if Aβ *56 will be affected by antibodies to be used in currently planned studies [23]. Any one of these sources may insure years-later onsets of clinical symptoms and AD. Because of the fundamental theoretical gaps in current knowledge of $A\beta_{42}$ relevance for the progression of AD neuropathologies, the currently planned clinical trials can neither test $A\beta_{42}$ variants for effects in AD or for their inductions of other neuropathologies. Currently planned clinical trials more likely will fail to support efficacy for any of the drug candidates being tested and be misinterpreted as having implications for the validity of the Amyloid Hypothesis [1]. The recently well-documented 15–25 year neuropathological-clinical efficacy gap of decades could by decades separate drug interventions able to be shown effective against critical AD neuropathologies from the appearances, in long-term follow-ups of these studies, of clinical benefits relevant to AD [1,19,24,25].

Clinical efficacy as an outcome for AD drug developments

Cognitive declines linked to $A\beta_{42}$ pathology have not yet been confirmed in earlier that immediately pre-AD persons. Under these current conditions cognitive changes in asymptomatic persons deemed to be at-risk for AD decades later cannot be assumed to derive from effects on AD neuropathologies. At present, outcome measures that rely upon clinical efficacy or symptomatic cognitive changes cannot reasonably be expected to meet the needs of clinical trials using either asymptomatic or symptomatic subjects. For asymptomatic subjects cognitive enhancing drug effects unrelated to AD neuropathologies can allow drugs without AD relevant efficacy to be further developed. When clinical efficacy does not appear drugs with potentially important demonstrated beneficial effects on otherwise irreversible neuropathologies will be at risk of mistaken abandonment [1,15,20]. For symptomatic subjects, those with MCI or AD, current knowledge provides little hope for success from drug interventions after over 200 failed attempts to develop AD drugs for this group [7]. AD drug developments face a Catch 22. Drugs cannot at present evidence that their activities against AD neuropathologies provide clinical efficacy. Drug regulatory approvals require clinical evidence of efficacy. Even more problematic is that pharmaceutical firms will be forced to abandon developments of AD drug candidates if, because of this inability to provide clinical efficacy, regulatory approvals cannot be granted for a drug.

Discussion

Given current evidence of the neuropathological-clinical efficacy gap in the emergence of AD, we expect that coordinated drug studies involving sequential clinical trials over many years will be needed for AD relevant clinical efficacy to be evidenced. We encourage regulators to consider the neuropathology-clinical efficacy gap implications. Clearly, we agree with others that valid tests of anti-$A\beta_{42}$ drugs will require preventive interventions in cognitively asymptomatic subjects at long-term risk of AD. Our primary reason for holding this view is the evidence for the slow cascade over decades of neuropathologies in which increased brain concentrations of $A\beta_{42}$, without directly affecting cognitive functions, may become, initiate, or track pathologies that go on to produce clinical dementia [1]. We foresee a need to deemphasize in clinical trial designs immediate cognitive outcomes from drugs in favor of increased emphases on advancing AD clinical mechanistic research and improving clinical methodologies so false negative and false positive clinical trial rates are reduced [7,8,25]. To accomplish these aims we propose that investigators and regulators 1) focus AD clinical research on understanding the inductions of reversible and irreversible neuropathologies and their roles in generating clinical dementia [1], and 2) through regulatory changes, create a vehicle for these studies, for example, conditional drug approvals based on other than immediately demonstrable cognitive changes.

This road-map re-routes anti-$A\beta_{42}$ and other AD drug developments off highways that have enchanted investigators with promises of immediate clinical efficacy but led only to failures **(see** Figure 1). Revised regulations would direct investigations onto currently untraveled routes that both avoid entrapments by currently prevalent errors and fully characterize the drug candidate's chemical target and the target's functional effects on AD neuropathologies [1]. Investigators would pilot test, first in laboratory and animal models and then in humans, the hypotheses, methods, conditions, designs, biomarkers, and other features critical to a clinical trial test of the mechanistic hypothesis associated with the drug's activities. Subsequent regulatory conditional approvals would be granted to further research into already predicted and confirmed neuropathologically-mediated preventive potentials of qualified drug candidates. This clinical trial research would test hypotheses of why the mechanism(s) affected by the drug cannot currently provoke clinical efficacy but can be predicted to provide prevention of AD disease progression.

To receive conditional regulatory approval, the proposed research would have to soundly predict that specific drug induced neuropathological disease modifications will be confirmed with later AD relevant clinical efficacy. Working under conditional approvals, investigators would pursue clinical efficacy over the anticipated long-term, using protocol-controlled prescription sales of drug. Conditional approvals would be based on drug effects on $A\beta_{42}$ targets, on other AD neuropathologies, on evidence explaining the current lack of clinical efficacy and on grounds for predicting preventive potentials against later cognitive symptoms and clinical AD.

Aims of conditional approvals would be 1) to advance scientific knowledge of AD as a molecular disease, 2) to seek clinical efficacy in follow-up, very long-term, longitudinal studies, 3) to provide possible neuropathological modification benefits to patients at risk,

and 4) to document long-term drug safety for patients. To enable these aims—to help if possible, certainly to do no harm—we recommend the FDA consider conditional approvals for any AD drug candidate meeting six requirements: 1) evidence for a specifically engaged drug target; 2) evidence for normalization of the target function by the drug; 3) evidence for a causal role of the target in the neuropathological progression into or of dementia; 4) evidence for arrest or reversal of the neuropathology associated with drug effects on the target; 5) evidence in tested theory supporting the uses of biomarkers as indicators and as potential surrogate endpoint candidates [1,6,27]; and 6) evidence for safety.

A drug candidate able to meet these conditions would typically be demonstrated in tissue and animal models to accomplish 1) required target normalization with drug engagement, 2) target associated neuropathological control, 3) blocking of AD relevant neuropathological inductions, 4) delayed pre-mortem neuropathologically associated behavioral functional differences supported by 5) post-mortem neuropathologically associated neuronal differences. These studies would be designed to develop specific mechanistic hypotheses to be tested in clinical trials [1]. Biomarkers would be validated by demonstrated brain changes in the model. These findings would then, with the exception of invasive tissue examinations and with recognitions of delayed onsets of cognitive or functional behavioral markers in humans, be confirmed in human subjects with safety. In each species the drug effects would be tested consistent with the intentions present in Koch's Postulates. In this context, drug development becomes a core resource used in support of scientific understanding of AD and of drug effects on neuropathology [8].

In the presence of convincing evidence that clinical efficacy cannot be elicited, that critical neuropathologies can be controlled safely, and that clinical efficacy can be soundly predicted to emerge for treated subjects, we propose that regulators allow sales for clinical research use under FDA required and approved investigational protocols. Independent investigators would design methods and monitor subjects to document safety and develop evidence for predicted emerging clinical efficacy. Requirements for studies to continue would be 1) safety over the long term of administration required to control the AD neuropathology, and 2) continued mechanistic evidence in support of why clinical efficacy is not immediately present but can be expected in the future from the drug reversal of the progression of this neuropathology.

For the advancement of neuroscience and best interests of patients a virtuous circle can be created. Regulatory modifications will allow the clinical research needed to inform robust molecular theories. Robust molecular theories, in turn, will strengthen the effectiveness of clinical research [1]. Access to a neuropathologically effective drug will potentially offer patients long-term benefits. Benefits or their absence for patients will be documented by evaluations of patients required for the conditional approvals. Close monitoring would be needed to insure that the balance of evidence continues to support the likelihood that the neuropathological intervention will provide ultimate clinical efficacy. Clinical evidence of disease modification, not symptomatic, efficacy would lead to full regulatory approvals.

Conclusions

We find a need for sounder understanding of the neuropathology of AD as essential to improve success demonstrating clinical efficacy for AD drug candidates. Our assessment of current resources leads us to conclude that this scientific understanding of AD will not be reached if investigators prematurely burden future anti-$A\beta_{42}$ drug studies with unrealistic concurrent demonstrations of clinical efficacy [13,14]. As we have concluded earlier, we reinforce that it is essential for the health of neuropsychiatric and especially AD drug developments that investigators radically change their attitudes to embrace in depth developments and uses of mechanistically explanatory neuroscience theory, preclinical confirmations of molecular-mechanisms of disease and drug functions, and medical error control as essential preparations for any human investigations with new drugs. If these prerequisites to human investigations are not incorporated into regulatory revisions as we have proposed, we could not support regulatory changes. Recent responses by a leading academic AD investigator to preclinical failures to replicate the data used to justify an AD clinical trial reflect the inattention to features we find essential to drug development, “The variability of outcomes in these preclinical studies might function as a case study in the challenges of translating preclinical observations to clinical research. The utility of bexarotene for human AD can be resolved only by studying human AD” [28]. Rather we propose the inability to replicate basic research, which leaves the clinical trial with no understanding of the mechanism of action or expectation of efficacy, provides a case study in how clinical investigators regard basic fundamental neuroscientific and translational research practices.

We view rigorous scientific grounding as a core feature of translational research, a feature essential to the successes of neuropsychiatric drug developments and underlying neuroscience (See Table 1). With the changes in attitudes, practices, and regulations we have proposed, we aim to open the road to identifying how anti-$A\beta_{42}$ and other AD drug candidates can be effective in prevention of AD. AD neuroscience, drugs, and development methods currently need clinical trials that offer more than clinical benefit-based confirmations of drug advantages over placebo. Clinical trials must, in addition to evaluating efficacies, advance our understanding of AD along mechanistic roadways that lead to clinically efficacious drugs and provide self-correcting improvements to methodologies so that errors, such as failures to engage the brain target, do not repeatedly corrupt clinical trials [1,7,8,16]. We encourage academic investigators, the FDA and other regulators, the NIH, and industry to use the current at hand opportunity to provide conditional research protocol controlled drug approvals or a similar vehicle and the leadership needed to insure improved scientific grounding for and sounder routes to successes in AD drug developments.

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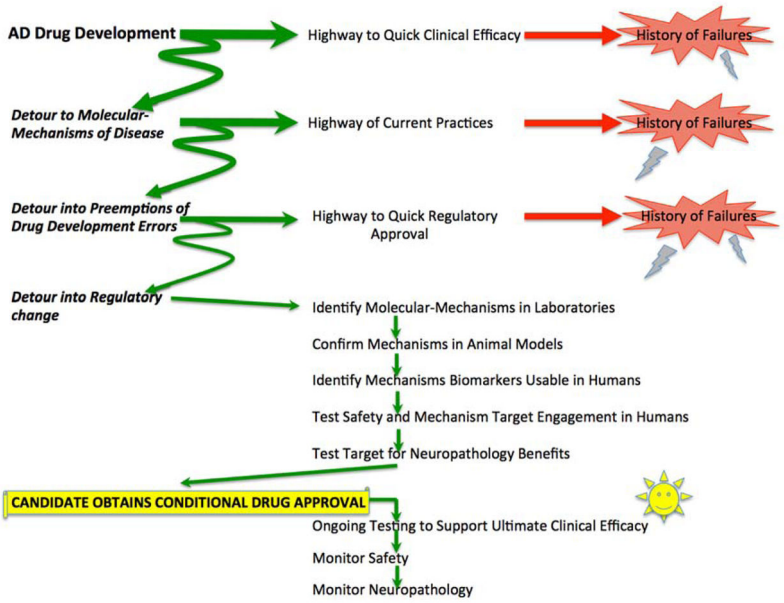

Figure 1.
A new regulatory road-map for Alzheimer's disease drug development

Table 1

Priorities for Translational AD Drug Development Research

• Molecular-mechanistic understanding of the evolution of AD and of drug interventions at molecular-mechanistic targets
• Methodological revisions sufficient to minimize risks of clinical trials failures due to errors.
• Regulatory revisions to support the advance of neuroscience as a precondition for studies of clinical efficacy.