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Building a Roadmap for Developing Combination Therapies for Alzheimer's Disease

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Introduction

Combination drug therapy has proven to be an effective strategy for treating many of the world's most intractable diseases, from tuberculosis in the 1950s, to childhood leukemia in the 1960s, to HIV/AIDS in the 1990s. Thus, it is not surprising that in the face of so many disappointing clinical trials for Alzheimer's disease (AD) drugs, interest in combination therapy for AD has captured the interest of many investigators in academia, industry, and regulatory agencies, as well as foundations and advocacy organizations.

This interest has spawned a series of meetings among stakeholders across the field to lay the foundation and develop a roadmap for conducting a combination trial in AD. The first of these meetings was held in Rockville, Maryland in November, 2012 at the ACT-AD annual FDA/Alzheimer's Disease Allies Meeting [1]. Co-sponsored by ACT-AD and the Critical Path Institute (C-Path), the meeting brought together scientists from diverse sectors and fields to lay the groundwork for future efforts to develop trials of combined therapies. At this meeting, a number of issues were identified that need to be sorted out in order to move forward with developing combination therapy, and participants agreed to meet again in May, 2013 to settle open questions and articulate a coordinated path forward to implement combination trials in AD.

In the period between these two meetings, two new guidances relevant to this effort were issued by the FDA. The first of these in December, 2012, outlined the Agency's thinking with regard to enrichment strategies for clinical trials [2]. The second draft guidance, issued in February 2013 addresses the Agency's thinking regarding drug development for prodromal AD [3] These documents, in combination with a previously issued guidance on developing combination therapies [4], provide a framework for a regulatory path forward for combination therapy. Moreover, the participation of officials from FDA and EMA in these meetings demonstrates regulators' interest in working with researchers and drug developers to ensure that trials of combination therapies are designed to be as effective and efficient as possible.

The May meeting, co-hosted by ACT-AD, C-Path, and the Alzheimer's Association, was designed to delve more deeply into 1) the scientific rationale for pursuing multiple targets, and the questions that remain to be answered regarding conceptual models of disease; 2) how to build an efficient mechanism to advance different targets and molecules through the drug development pipeline, which will de-risk the process for individual companies and incentivize them to join a collaborative effort to develop combination therapies; and 3) how to structure a partnership for combination development that will foster collaboration and provide benefits for all participants. The meeting concluded with an agreement to establish a leadership group and steering committee, as well as think tanks and workgroups to ensure efficient development of a combination trials program aligned with other efforts across the field to find effective ways of treating AD and related dementias.

The scientific rationale for pursuing multiple targets

Research over the past 30 years has broadened our view of the multi-factorial nature and heterogeneity of AD, yet we still lack a full understanding of the complex pathogenic mechanisms that interact across the spectrum of the disease. Much of the research in recent years has focused on validating the hypothetical model of disease progression proposed by Jack and colleagues, as defined by biomarkers developed around the amyloid beta (Aβ) pathway [5–7]. This model posits that Aβ aggregation and deposition in the brain triggers a cascade of events that result in neuronal dysfunction and degeneration, eventually leading to clinical symptoms including cognitive impairment. The availability of model systems has supported the development of Aβ as a tractable target, and thus led to many drugs aimed at either clearing Aβ plaques or preventing their production. Yet Aβ is only one of the proteins associated with disease in the AD brain. The protein tau forms neurofibrillary tangles that are associated with neurodegeneration in the brains of people with AD and other types of dementia. About 50% of AD patients also have Lewy bodies composed of the α-synuclein protein, and 50% also have inclusions of the TDP-43 protein. Moreover, there have recently been revelations about the role of cell-to-cell, prion-like spread of disease proteins in the brain [8], which suggest an additional approach to targeting these proteins. Meanwhile, many other targets have emerged and continue to emerge from genome wide association studies (GWAS) [9] and integrated systems approaches [10], although there is still much to do to translate these studies into a meaningful understanding of how pathways such as neuroinflammation, innate immunity, lipid metabolism, microglial dysfunction, etc.

contribute individually and in concert with each other to the progression of disease pathology over the trajectory of the disease.

Animal models have been created that express many of these disease pathologies, yet there is no single model that expresses all of them or that accurately reflects the neuropathology seen in humans with AD. This lack of an integrative model limits our ability to explain how the different pathways interact or how intervening in multiple pathways simultaneously might prove more effective than hitting only a single target. However, if treatment effects can be demonstrated in independent models, for example one drug showing efficacy in a model of nerve degeneration and another showing efficacy in a model of inflammation, it might still be reasonable to put these drugs together and test in people with AD, assuming toxicology studies suggest the two drugs are safe when delivered together. Validating these models in human patients, however, will require novel biomarkers and the definition of biomarker profiles that reflect treatment effects.

Moreover, these pathologies need to be modeled across the different stages of AD. Since late stage disease is frequently complicated by a variety of comorbid conditions as well as age-related physiological changes, both the potential and the complexity of combined therapy may be greatly enhanced but difficult to study in animal models. Natural history studies that incorporate intensive biomarker studies are thus needed across the trajectory of the disease.

Designing trials for combination therapies to treat AD

Donald Berry of the MD Anderson Cancer Center, presented the I-SPY 2 TRIAL (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis) design as one that could potentially be used to test combination therapies for AD. I-SPY 2 uses an adaptive study design that enables simultaneous testing of multiple treatment regimens in patients with breast cancer [11]. Individual treatment arms may be dropped or graduated to small phase 3 studies based on interim results, enabling investigators to learn and adapt the trial as it progresses. In addition, incorporation of a single control arm in the study design substantially reduces costs and the number of subjects required. Adaptive designs are especially useful for heterogeneous diseases in which there are many unanswered questions, according to Berry. Modeling and simulation of interim data enable investigators to build an understanding of the various trajectories in meaningful subgroups. Simulations are also used to determine the number of subjects needed per arm to obtain sufficient power.

Breast cancer, like AD, is a hugely heterogeneous disease. Adaptive trials like I-SPY 2 are ideal for such diseases because they enable investigators to use Bayesian methods of adaptive randomization to assign drugs to different subsets of patients based on clinical, phenotypic, genetic, or biomarker profiles. Interim results using biomarkers that correlate with a pathological complete response allow decisions to be made relatively rapidly about whether to continue or discontinue for a particular subgroup. This results in lower exposure of patients to treatments that have little chance of success.

Trials can also be adapted to different stages of disease, which could be extremely useful in AD since it is not clear which therapeutic mechanisms will be helpful at which stages of the disease.

However, one of the major challenges identified in pursuing an adaptive trial for AD is the lack of markers of treatment efficacy that can be assessed in a relatively short time frame, particularly in the early stages of the disease. While there are empirical data that track the change in various biomarkers over the course of the disease, there are no data showing that if you are able to move a biomarker through treatment, there will also be clinical improvement. Adaptive trials that incorporate many biomarkers will themselves provide information/validation for those biomarkers; and modeling throughout the study will allow adaptation according to the information provided by the biomarkers. However, the lack of markers that can show disease progression in a short time frame means that trials aimed at early stages of disease would most likely have to be longer than those conducted for breast cancer.

Combinations of drugs can be included in the I-SPY 2 model either as fixed combinations or using a factorial design, where separate arms test the drugs individually as well as in combination. Dr. Russell Katz, who recently retired as director of the Division of Neurology Products at the FDA's Center for Drug Evaluation and Research (CDER), advocated considering combinations even in the earliest stages of pre-clinical drug development, including multiple drugs that attack a single pathway as well as those that attack multiple pathways. He added that while synergism would be an advantage, even additive effects are potentially sufficient for approval according to the FDA guidance on codevelopment.

Adaptive trials are only one possible strategy that could be used to test combination therapies. Other new approaches that allow the field to try new things are also needed. For example, FDA expressed a willingness to consider seamless phase 2/3 trials. Whatever design is selected, there will be a need for better clinical measures, particularly early in disease, and it will be important to embed biomarker development into the trials in order to develop better predictive models of long-term response. There will also be a need for toxicity studies of drugs in combination. Figuring out how to do this with which animal models is one place where it might be possible to build collaborations.

Viable targets for immediate exploitation in combination

The target space can be divided into those that are already existing and those that would need more exploratory research to understand if they are viable. Aβ –focused targets are clearly the most advanced, and multiple mechanisms have been shown to lower Aβ. Thus, one of the most viable approaches given what is currently available would be to pair a BACE inhibitor with an antibody. Preclinical data for such an approach was recently reported [12].

While there was no clear consensus on a short term path to advance other targets, there was agreement that regardless of the mechanism that is pursued, demonstration of robust target engagement is critical. The classes of targets discussed at the workshop that currently seem most viable include, in addition to Aβ and tau, targets related to lipid metabolism such as

APOEɛ4, TDP-43, α-synuclein, and targets related to inflammation. Other targets that were mentioned included those that could be ready to interrogate in a relatively short period of time due to the availability of chemical compounds. These include growth factors, receptor modulators insulin, mitochondrial agents, calcium-channel modulators, and neuroprotective agents.

The targets and compounds discussed at the workshop were not identified in advance so the list of targets highlighted only represent those deemed most viable based on the knowledge and the expertise of the participants assembled. To move forward in this space, participants at the workshop recommended that an expert group be convened to explore more intensively where drugs that address various targets, including those targets not covered at the workshop, are in the development pathway, and what would need to be done to advance these drugs. Available drugs could already be tested as combinations in animal models to begin gathering safety data.

Enabling combinations through modeling and simulations

Modeling and simulation can be used across the stages of drug development to better understand both fundamental aspects of target development as well as clinical and biomarker endpoints in clinical trials. For the former, a large knowledge gap exists with regard to understanding the pathophysiology of the disease; and other gaps exist with regard to linking pathophysiologic changes with biomarkers and then with clinical outcomes. An AD drug-disease-clinical trial model was developed by CAMD and submitted to FDA and EMA for approval as a drug development tool. Since the May meeting, both agencies approved the tool, which represents the first ever modeling and simulation tool to achieve regulatory approval.

The CAMD tool was built on a placebo database that incorporates control arm clinical data from mild to moderate already AD trials contributed by member companies, as well as natural history patient-level data from ADNI and summary data from other studies reported in the literature. Biomarker data were not incorporated into this modeling tool but could dramatically improve the capabilities of the tool. Modeling that incorporated biomarker data could enable identification of a subgroup close to MCI that is showing faster disease progression on a certain biomarker or other endpoint, although there are gaps in relating changes in biomarkers to clinical meaningfulness, so it will be important to link biomarkers to clinical endpoints.

There have been some 20 phase 3 trials that have failed to reach their primary endpoints. Questions have been raised as to whether or not some of those studies should have advanced from phase 2 to phase 3. Data from those trials could be used to simulate various trial designs that could help determine the reasons that the trials that were actually conducted trials failed, i.e., were they pursuing a wrong hypothesis or was there a defect in the trial design. Models and simulations allow investigators to quantify uncertainty by including everything you know about the subjects, the drugs, the trial design, etc.

One suggestion was to mine existing longitudinal data from ADNI as well as clinical trial data from phase 2 and 3 programs and build trials *in silico* to simulate all kinds of

possibilities and come up with a more manageable set of biomarkers that are predictive. Concurrently, data are needed from clinicians, patients, and caregivers about what they consider to be clinically relevant outcomes. Modeling with all of these data in combination may help to identify a subgroup that is showing disease progression on a clinically meaningful endpoint.

Structuring a partnership for combination development

There was widespread agreement that the time has come to create a roadmap towards building a platform for moving this effort forward. However, there was less agreement on whether this would require the formation of a new consortia or partnership, or could be built on existing partnerships. Successful models of pre-competitive partnerships were discussed at the November meeting, including CAMD, the Critical Path to TB Drug Regimens (CPTR), and the National Center for Advancing Translational Science (NCATS). Other partnerships that provide lessons relevant to this discussion include the Dominantly Inherited Alzheimer's Network (DIAN), the Alzheimer's Prevention Initiative (API), and the Anti-Amyloid treatment for Asymptomatic AD (A4) trial. The Foundation of the NIH (fNIH), which oversees DIAN for example, has developed a legal framework for companies that contribute compounds to protect their intellectual property while enabling data sharing.

A different model, presented at the May meeting by Chaz Bountra, is the Structural Genomics Consortium, a public private partnership established to discover new medicines through open access research. The eight companies that contribute expertise, infrastructure, and resources to SGC agree to share reagents with no claims of intellectual property and immediately publish both successes and failures. The result is more rapid dissemination of knowledge and the discovery of many novel targets. Companies are free to develop proprietary assets from this work, which has resulted in at least one spin-off company.

Building in incentives and sharing risks

Incentives are needed that will convince companies to participate in pre-competitive collaborative efforts. For example, a consortium might be built to test combinations of drugs that were submitted by consortium members in a series of animal models, looking for both toxicity and efficacy signals. The incentive for companies would be the possibility of seeing enhanced signals that could suggest alliances. Other incentives that a consortium could provide include:

- Access to animal models.

- A cohort of well-characterized, ready-to-enroll subjects in whom biomarker and genetic status is known.

- Access to cutting edge tools for assessments.

- Modeling, simulation, and statistical expertise.

- Cost savings and faster completion of early stage drug development efforts.

- Open communication with regulatory authorities.

- The fact that cooperation is viewed positively by NIH and the philanthropic community, possibly enhancing the ability to raise necessary funds for early stage efforts.

Consortia and funding

A working group will be created to consider how to build a program that would bring value to companies and encourage collaboration. This group will work out the logistics, organizational structure, and financial structure needed to develop combination therapies for AD. Questions remained as to whether a new consortium should be created or if existing organizations have the bandwidth and the motivation to pursue combination therapy. One potential model would be to expand the capability of the Alzheimer's Disease Cooperative Study (ADCS) to bring companies together and use ADCS to conduct phase 1 trials. One of the advantages of an academic NIH-funded backbone such as ADCS, DIAN, or ADNI is that they have already been successful in acquiring data from multiple companies. Another model that was suggested was to build a consortium where companies would donate assets that are not being developed within the company and the consortium would conduct the Phase 2 studies with public funding (similar to the NCATS model). If these phase 2 studies are successful, the companies themselves would then fund Phase 3 studies.

Financial support for building a collaborative network will be essential. Perhaps a specific initiative could be created and funded by the NIH or other funding agency to do toxicology around compounds nominated by different companies. Other innovative funding approaches will also be needed, including venture philanthropy approaches such as those brought together by FasterCures in the form of the Research Acceleration and Innovation Network (TRAIN) [13].

Data sharing

A critical aspect of any trial that incorporates assets from multiple sources is that data are shared in order to build knowledge, avoid duplication of efforts, and learn from mistakes. The I-SPY 2 model of data sharing is that the I-SPY 2 team controls the data until the time that a drug graduates or is dropped. Graduation of a compound indicates that it has a high predictive probability of being successful in phase 3. At that point, the company that owns that sponsored that experimental arm is provided information about the predictions. Six months later they get the data, and six months after that the data become available to other participants in the trial. This model gives the company contributing the compound a six-month lead time to move forward with proprietary efforts, but ensures that the information gathered in the trials is available to the field.

Next steps

Meeting participants left with agreement to establish a leadership group and steering committee, as well as think tanks and workgroups with technical experts as needed to:

- Develop consensus on the mechanistic rationale for combination therapy, including gathering empirical evidence to show why attacking a single target is unlikely to be effective in treating AD.

- Develop an inventory of targets and develop consensus on prioritizing targets or classes of targets.

- Inventory compounds and develop a process for promoting compounds for further development.

- Build an inventory of databases and data repositories and tackle issues that prevent companies from sharing data.

- Inventory modeling and simulation tools that currently exist and begin planning how to use these tools to develop combination trials in early AD patients, including identifying data that are needed for optimal modeling.

- Develop a clinical trial infrastructure for combination trials, either by building on existing infrastructure (e.g., ADCS, ADNI, DIAN Pharma Consortium) or creating a new partnership.

- Explore innovative funding mechanisms to begin planning a combination trial.

Over the longer term, participants in the workshop agreed that on the need to focus attention of all stakeholders on the importance of information sharing in order to expedite progress by avoiding duplication and redundancy, and the need to reexamine conceptual models of disease. The Alzheimer's Association's Research Roundtable and CAMD were mentioned as existing partnerships that have provided forums for exploring these issues.

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