

## **Charting a path toward combination therapy for Alzheimer's disease**

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### **Introduction**

The latest round of disappointing clinical trials for Alzheimer's disease (AD) treatments has led researchers and clinicians to pursue novel intervention strategies with increased urgency. Looking to their colleagues in oncology and infectious diseases, where once uniformly lethal diseases are now often viewed as treatable or curable chronic conditions, investigators in industry, academia, and regulatory affairs have coalesced around the concept of combination therapy in AD. Recognizing that a unified, collaborative approach will be needed to support the development of optimized combinations, the Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) Coalition and the Critical Path Institute (C-Path), two organizations established to nurture such collaborations in the AD field, held a meeting in Washington, D.C., on November 29, 2012, to chart a path towards developing combination therapies. Participants at the meeting discussed the potential benefits as well as the challenges associated with combining pharmacotherapies for AD, from basic mechanisms through regulatory approval, and agreed that the time has come to move combination therapy to the forefront of AD drug development.

The realization that a single-target approach to a complex disease like AD has not yet yielded an effective therapy should come as no surprise, given mounting evidence that multiple molecular, biochemical, and cellular pathways converge to produce the disease [1]. Moreover, AD appears to be not just a single entity, but a spectrum of neurodegenerative disease processes that manifest as a trajectory across the lifespan, influenced and sometimes exacerbated by coincident conditions associated with aging such as diabetes and cardiovascular disease [2]. While this complexity offers multiple possible therapeutic targets, it also increases the scope of the effort required to find solutions.

### **Combination therapy: a proven solution**

Many diseases are often treated with multiple drugs simultaneously. Polychemotherapy has been used in the treatment of cancer since the 1960s, when a regimen of four chemotherapy drugs was shown to improve the remission rate of childhood leukemia dramatically, to the point that many patients were considered cured [3]. Over the subsequent decades, combination therapy became commonplace in all fields of oncology as well as in the treatment of AIDS, tuberculosis, autoimmune disorders, and other major diseases. One notable success in combining therapies came in trials that combined trastuzumab (Herceptin) with other chemotherapeutic drugs for the treatment of HER2-positive metastatic breast cancer [4]. This trial not only demonstrated the superior efficacy of the combined treatment, giving hope to thousands of women with breast cancer, but also demonstrated the importance of identifying the appropriate patients through the use of biomarkers (in this case, overexpression of HER2).

In 1993, Don Berry and colleagues designed a trial of three chemotherapeutic drugs using a 3X2 factorial design, which enabled the trial designers to evaluate the dose escalation benefits of two different drugs in a single trial [5]. Adaptive designs such as this one, where interim results are used to modify the subsequent course of the trial, have since been increasingly used not only in oncology but in other areas of clinical research as well [6]. They offer advantages in terms of fewer numbers of subjects needed per arm, and the ability to address a wider array of questions and provide more accurate conclusions. Moreover, because they involve frequent monitoring of drug effects and adaptation of the trial accordingly, treatments tend to be more responsive to the patients' needs. Such precision medicine approaches have yet to be applied in diseases of the nervous system.

A more ambitious adaptive factorial phase 2 design is being used in the I-SPY 2 TRIAL (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis) to evaluate the effect of multiple combinations of chemotherapy before surgery in patients with locally advanced breast cancer [7]. I-SPY 2 is sponsored by the Biomarkers Consortium, a partnership managed by the

Foundation for the National Institutes of Health (FNIH) and including numerous government, industry, and non-profit partners.

I-SPY 2 will compare standard therapy, which itself consists of drug combinations that vary according to the molecular characteristics of the patients' tumor, to standard therapy plus one of five or six new drugs. Interim analysis of tumor responsiveness to the drug regimen will enable an arm to be advanced to a small phase 3 trial or dropped if there is no sign of effectiveness. Other investigational drugs may also be added to the trial. Phase 3 trials based on the results of I-SPY can be as small as 300 patients with a projected success rate of 85%, a marked improvement from the 3,000 patients typically required for a phase 3 study that yields a success rate of only 30-40%. With a single control group for all arms of the trial, this design provides substantial cost savings, faster throughput, and rapid advancement to phase 3 studies based on Bayesian predictive probabilities. Adopting an I-SPY 2 model for AD trials would present numerous challenges, particularly in the absence of a biomarker that predicts clinical response.

### **An urgent need for new AD treatments**

In the AD field, the only approved drugs at this time are the cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) for mild to moderate AD; and the NMDA receptor antagonist, memantine, for moderate to severe AD [8]. Given that these drugs target different pathways, a recent trial was conducted combining memantine with the cholinesterase inhibitor donepezil in patients with moderate to severe AD [9]. The combined therapy showed no added benefit over either drug given alone. However, another trial in patients with amnesic mild cognitive impairment (aMCI), tested the combination of another cholinesterase inhibitor, galantamine, and memantine in patients with amnesic MCI [10]. Although this trial was stopped because of safety concerns, a subgroup analysis of data collected during the trial suggested that among those with presumed AD etiology, the combined drugs showed some benefit. A very recent more extensive analysis demonstrated that treatment of moderate to severe AD patients with

memantine/cholinesterase inhibitor produces consistent benefits that appear to increase over time and are beyond those of cholinesterase treatment alone [11].

Most of the drugs currently in advanced stages of development for AD target the amyloid pathway with the goal of disease modification; there are also a few investigational drugs that target tau and other cellular pathways that contribute to AD pathogenesis [12]. Even drugs that on their own are ineffective may, in combination with other drugs, provide synergistic or additive benefits, either by hitting multiple pathways or multiple targets within a common pathway. Thus, combined therapy for AD could conceivably employ two drugs that target different steps in the amyloid pathway, such as combining an anti-amyloid antibody to promote clearance of amyloid with a beta-secretase inhibitor to inhibit production of amyloid. Alternatively, two or more candidates that attack multiple pathogenic mediators is a viable approach, for example, targeting of amyloid and tau simultaneously. Recent preclinical data supports such an approach in that augmented reductions in amyloid lowering can be achieved by combining a BACE inhibitor with an anti-amyloid antibody [13]. Other potential approaches could combine, for example, a drug that targets amyloid with an anti-inflammatory drug.

### **Guidance from the regulators**

Combination therapies have traditionally been developed by adding a new drug to a standard regimen and then testing to see whether the combination is more effective than the standard treatment. However, it is increasingly realized that many biological systems include redundancies and compensatory mechanisms that render a therapy that targets a single moiety less than optimally effective. Given this, drug development in many therapeutic areas is increasingly turning to combination approaches in which two new drugs are simultaneously developed. Recognizing the need for regulatory guidance on the development of novel combinations of investigational drugs, the U.S. Food and Drug Administration (FDA) in 2010 issued a draft guidance on what the FDA defines as codevelopment, i.e., the development of two novel compounds intended to be used together, not as add-ons to existing drugs [14, 15].

Because codevelopment will generally result in less information on the safety and effectiveness of the individual drugs, the guidance stipulates that codevelopment is appropriate only for serious diseases and when there is a compelling rationale for combined therapy, as well as preclinical data supporting its use; or when there is a compelling reason for not developing the component compounds individually. The guidance goes on to provide a high-level roadmap for sponsors to follow in conducting Phase 1, 2, and 3 studies. In phase 1, toxicology and pharmacokinetics would need to be demonstrated in the usual ways for the drugs individually and in combination; generally step-wise dose escalation with one agent, followed by escalation of the second agent in combination with the first, is recommended.

Proof-of-concept (Phase 2) studies should demonstrate, to the extent possible, the contribution of each component, the effectiveness of the combination, and optimized dose or doses to be used in Phase 3. What is required and possible in this regard will vary depending on the specific drugs being tested. The guidance outlined several possible scenarios and possible proof-of-concept trial designs that might be appropriate. However, these scenarios may have limited direct relevance for the development of AD therapies, because the guidance was developed primarily with oncology and anti-infective therapies in mind, where the measurement of response can occur quickly, and the primary goals of combined therapies are often to overcome problems associated with toxicity and resistance. In addition, trial designs for combined therapies typically compare the drugs individually and in combination to the standard of care or in combination with the standard of care, and some independent dose- and regimen-ranging is generally recommended, as is some level of factorial testing. However, because a primary goal of combined disease modification therapy for AD is to modify disease progression, and there are currently no approved disease modifying drugs for AD, the appropriate study design for such a program is unclear. Specifically, disease modification trials need to have extended treatment periods due to the rate of progression of the disease and the insensitivity of the outcome measures, and independent dose- and regimen-ranging would seem to be infeasible in such a setting.

Thus, the design of combined therapy trials for disease-modifying AD drugs will likely require novel adaptive designs. The Agency has signaled its intent to be flexible in consideration of combined therapy trials, and encouraged further dialog with sponsors on novel trial designs. Despite the above challenges, the Agency is open to early and transparent dialogue with experts and sponsors as to what types of data and strategies are appropriate.

### **Required tools and infrastructure**

Because the rationale for combined therapy in AD is to target multiple pathways simultaneously, and because matching treatments with specific targets requires biomarkers [16], improving trial efficiency will almost certainly require the development of new biomarkers including those that reflect synaptic dysfunction [17]. Biomarkers that change in response to treatment and in a reasonable period of time are especially needed for drug development. Furthermore, target engagement biomarkers are key measures of pharmacodynamics activity which is key to identifying proper doses for combining therapies in light of the infeasibility of independently dose-and regimen-ranging two novel therapies in an Alzheimer's disease modification context based on clinical outcome measures.

The hypothetical biomarker trajectory paradigm proposed by Jack et al [18], is beginning to be populated with empirical data from clinical trials, including the the Alzheimer's Disease Neuroimaging Initiative [19-21] and the Dominantly Inherited Alzheimer Network (DIAN) studies [22]. However, to realize the promise of biomarkers, infrastructure is needed to map their trajectories across a heterogeneous population. One suggestion is to develop a long-term biomarker observational study of up to 30,000 individuals to define biomarker "fingerprints" across the trajectory of the disease. Such an initiative was recently launched by the Innovative Medicines Initiative (IMI) in Europe as the European Medical Information Framework (EMIF) project, Biomarker fingerprints could elucidate not only what treatments are likely to be effective, but also the correct time to initiate treatment. Cohorts defined by their biomarker profiles could also serve as potential candidates for future trials of treatments targeted to specific population subgroups.

For example, subjects with a profile that indicates they are cognitively normal but show the earliest signs of AD pathology might be considered for secondary prevention studies using a combination of drugs that block the production and facilitate clearance of A $\beta$ , such as monoclonal antibodies against A $\beta$ ,  $\gamma$ -secretase modulators, or BACE inhibitors. Meanwhile, subjects with biomarker profiles indicating the MCI stage of the disease might be enrolled in trials of symptomatic therapies along with drugs aimed at halting neurodegeneration, such as neuroprotectants, or drugs that target tau.

New trial designs are also urgently needed. The adaptive factorial design used in I-SPY 2 offers one possible approach, although this design requires a clear and relatively near-term primary endpoint, which has yet to be defined in AD. This design can also incorporate measurable auxiliary endpoints related to different drug mechanisms, and synergistic effects can also be modeled. Importantly, this design also can provide information on patient-specific responses to a single drug or combination of drugs. In combination with biomarker studies, this design could thus provide valuable information on how different population groups with different biomarker signatures respond to different treatments.

### **Going into COMBAT against AD**

COMBAT (Combination Therapy in Early AD) is a trial of combination therapy in early AD that is in the initial planning stages. The design of COMBAT has yet to be determined but could be modeled after the I-SPY2 design, with multiple combination therapies. Potential combinations to be tested include a BACE-1 inhibitor to decrease production of A $\beta$ , plus immunotherapy to boost clearance of fibrillar forms of A $\beta$ ; or multiple drugs that clear different forms of A $\beta$  simultaneously; or ideally an anti-A $\beta$  drug plus an anti-tau drug. Future arms might combine any of these drugs with a neuroprotective or anti-inflammatory agent. Dr. Reisa Sperling, who heads the team planning the trial in collaboration with Paul Aisen of the Alzheimer's Disease Cooperative Study (ADCS), noted that adaptive trial designs might be difficult to implement in early AD because of the lack of a short-

term marker that predicts clinical response, and potential differences in the optimal stage of AD for treatment with specific mechanisms. Other factors that may present challenges in trial design include different safety and monitoring requirements for different drugs and the difficulty of blinding placebo groups depending on the route of administration.

### **Fostering collaboration in the precompetitive space**

There is widespread agreement across all sectors of the need for more collaboration and “coopetition” as a means of expediting and de-risking drug development. “Coopetition,” or cooperative competition, is a business model in which competitor companies work together in precompetitive space to cooperatively solve problems that will benefit all. Potential areas of coopetition in the AD field include developing data standards, building de-identified data bases and data modeling infrastructure, standardizing protocols, developing reference materials, creating a registry of well characterized individuals for future clinical trials, and developing other drug development tools such as new biomarkers and clinical outcome measures. In AD, several precompetitive consortia have successfully made progress on the above areas and include CAMD (C-Path), Alzheimer’s Associations’ AARR, and GBSC and the Alzheimer’s Prevention Registry (Banner Institute).

Two successful examples of precompetitive collaboration specifically relevant to combination therapies in other diseases were discussed at the November meeting:

#### CPTR (Critical Path to TB Drug Regimens, Critical Path Institute).

Tuberculosis (TB) infects approximately one-third of the world’s population, with an estimated 8.7 million new cases and 1.4 million deaths from TB in 2011 [23]. Combination therapy administered over 6 to 9 months has long been the standard of care for treating TB, however compliance with the regimen is poor, resulting in an epidemic of multi-drug and extremely drug resistant strains of the bacterium. Before a new drug, bedaquiline, for TB was approved in December 2012, it had been more than 40 years since a new treatment was developed.



The enormous global burden of TB prompted C-Path to launch the Critical Path to TB Drug Regimens (CPTR) consortium in 2010. Funded by the Bill and Melinda Gates foundation, CPTR brings together scientists from industry, academia, and regulatory agencies, and other global organizations to speed the development of new and improved treatments for TB. Core to the mission of CPTR is combination therapy development and the application of modeling and simulation throughout all phases of drug development. In September 2012, C-Path and the Clinical Data Interchange Standards Consortium (CDISC) announced the development of TB data standards, which have been recognized by the FDA as a critical need in drug development.

NCATS – National Center for Advancing Translational Science. The National Center for Advancing Translational Science (NCATS) was established by the NIH in 2012 to expedite the translational of new scientific discoveries into drugs, devices, and diagnostics by breaking down barriers, developing new tools, and collaborating across institutes and regulatory agencies as well as with academic and industry partners.

Several programs initiated by NCATS are relevant to the development of combination therapies. The first is a drug rescue and repurposing program, which works with pharmaceutical companies to make both approved and abandoned compounds in their arsenals available for research in new indications. At the time of the meeting, NCATS had already assembled a collection of 58 compounds contributed by eight companies; and had identified and repurposed an old arthritis drug for treating chronic lymphocytic leukemia. Another NCATS program, funded by the Defense Advanced Research Projects Agency (DARPA) and NIH, is a microsystems initiative to develop a tissue chip that mimics human physiology for drug screening. To date, drug repurposing activities have been focused on single candidates.

Precompetitive consortia such as the Coalition Against Major Diseases (CAMD) [24], CPTR, and NCATS have been successful in part by developing tools that are available to multiple stakeholders across the research landscape and by convincing partners to share some data, such as placebo data from clinical trials.

Moving forward, sharing of treatment arm data, including biomarker data, would provide extremely valuable information that could be used to build and simulate novel clinical trial models. Achieving this level of sharing will require creative thinking about how to de-risk data sharing and incentivize companies to expand the precompetitive space.

### **Overcoming barriers: Next steps**

Meeting participants recognized the need for an unprecedented level of cooperation and collaboration among companies and with FDA towards developing drugs for AD disease modification. One of the major goals will be to address the numerous scientific, legal, regulatory, and business barriers that could derail progress. Foremost in the minds of many industry participants is the need to protect intellectual property (IP). Regulators stated that all data on each drug candidate would need to be made available to enable the optimal path for combination therapy approaches. Other major concerns arise with respect to the regulatory process; for example if a treatment utilizes two drugs from different companies, would two INDs be required and would data supporting the INDs be fully shared?

Many of these concerns have been addressed by existing collaborative agreements and can be used as models. For example, NCATS has developed template legal agreements for its drug repurposing program; DIAN developed a legal agreement to enable the use of drugs from competing companies; C-Path created a legal agreement that members signed in order to contribute placebo data into a unified clinical trial database from AD trials that is available to qualified researchers; and for I-SPY, the FNIH crafted a unified IP agreement, with the IND held by FNIH and a single control group used for all six arms of the trial. There are also existing regulatory mechanisms that enable sharing of proprietary data between two or more parties. Another concern of industry is that working with competitors may have negative legal or regulatory consequences; for example, violation of anti-trust laws, shared liability should something go wrong, or adverse

effects from the combined therapy hampering the regulatory approval of a drug in development as a single agent have been raised as potential issues.

Participants agreed to meet again in the Spring of 2013 for an intensive workshop to build consensus and begin crafting a strategic roadmap for developing combination therapies for Alzheimer's that addresses the legal, regulatory, scientific, and ethical concerns. Among the scientific challenges to be addressed are: (1) what is the underlying scientific rationale for combination therapies in AD, (2) How to assess the synergistic effects of combination therapies in a short timeframe in the early stages of AD, where clinical rate of change is slow and clinical outcome measures are relatively insensitive; and (2) How to better connect biomarkers with clinical outcomes in early and late clinical development. In addition, as with any treatment intended for people in presymptomatic phases of disease, there are ethical concerns to address about exposing high-risk but clinically normal individuals to the potential harms of a therapy.

Ideas and actions identified that could expedite the development of combination therapies include:

- Utilizing existing infrastructure in companies that enables multiple companies to jointly test combinations of drugs, or contribute drugs to repurposing initiatives.
- Building infrastructure to promote and support data sharing and provide wider access to data.
- Investing heavily in preclinical and translational tools for selecting optimal drug combinations.
- Developing, in the precompetitive space, modeling and simulation tools that take into consideration pharmacodynamics and pharmacokinetic parameters to enable dose selection and optimal trial design.
- Working in the precompetitive space to advance the regulatory process, in order to facilitate more expeditious review and approval of combination therapies.

- Developing a legal framework to support precompetitive and collaborative data mining of clinical trials databases.

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