Building a Roadmap for Shared Combination Drug Trials

13 June 2013. As potential Alzheimer's disease drugs continue to post disappointing Phase 2 and 3 results, many in the field are considering upping the artillery by testing experimental drugs in combination. On 28-30 May 2013, about 65 representatives from academia, industry, regulatory agencies, and advocacy groups met in Washington, D.C., to define the challenges in making such trials a reality, brainstorm solutions, and lay out a path forward. The meeting was jointly hosted by **Dan Perry** and **Cynthia Bens** of the D.C.-based ACT-AD coalition, which serves as an umbrella for Alzheimer's activist groups; **Maria Carrillo** at the Chicago-based Alzheimer's Association; and **Diane Stephenson** at the Critical Path Institute in Tucson, Arizona. C-Path is an applied research organization that facilitates precompetitive drug development. The conference followed from a foundational meeting in November 2012 (see ARF related news story). On 10-11 June 2013, a partly overlapping group of 57 scientists met in New York City under the auspices of the New York Academy of Sciences to advance the discussion further. That meeting focused in particular on running Phase 2 trials on a continuous, adaptive platform that could test both combinations and single drugs against a shared control group.

The scientists agreed to emulate a combination trial model pioneered by the cancer field and use existing infrastructure for an initial trial of two amyloid-lowering agents. As a next step, a taskforce will identify available drugs and resources and lay the groundwork for future efforts. Much of the conversation revolved around how to mitigate risk for pharmaceutical companies and encourage them to participate. The U.S. Food and Drug Administration, which dispatched 10 representatives to the D.C. meeting, demonstrated strong support for combination trials, along with a willingness to be flexible on requirements. "When you become aware of how much is wrong in the AD brain, it makes sense to treat multiple pathways," said the FDA's **Rusty Katz**.

Some companies have already started testing combinations internally. At the AD/PD 2013 Conference in Florence, Italy, scientists at F. Hoffmann-La Roche Ltd., Basel, Switzerland, reported that an anti-amyloid antibody and a BACE inhibitor together suppressed amyloid in an AD mouse model better than did either alone (see ARF related news story). Roche sent no representatives to the D.C. meeting. Other companies are talking privately to regulators as well as to AD consortia and research centers about testing combinations. However, few companies have enough drugs in the pipeline to do this in-house, meaning that eventually industry will have to collaborate in a shared platform.

Challenges and Barriers

At the D.C. conference, participants agreed that drug combinations are the wave of the future, but differed on when the field will be ready to ride that wave. Some industry representatives questioned whether the science is in place. They pointed to the absence of robust outcome measures for short-term trials, as well as the need to combine therapies rationally based on an understanding of disease mechanisms. "We all believe combination therapy will be the way forward, but we have to be scientifically driven," said **Rachel Schindler** at Pfizer. Pharma is reluctant to incur additional costly failures, and innovative approaches carry more risk, noted **Bob Brashear** at Janssen. "Companies are hesitant to commit money right now," said **John Alam** at Sanofi. At the same time, researchers agreed that the record of the past decade—every company running negative, single-drug trials on their own—calls for change.

To help break the logjam, conference participants looked to the I-SPY 2 adaptive Phase 2 trial platform developed originally for breast cancer. It is sponsored by the Foundation for the National Institutes of Health. In this model, different companies provide investigational drugs after internal Phase 1 testing. The foundation assumes the cost of the Phase 2 trial and monitors patient safety on a monthly basis, said co-developer **Don Berry**, an adaptive trials expert at the MD Anderson Cancer Center in Houston, Texas. The trial uses a factorial design with separate arms for each drug and combination. If a drug performs well, it returns to the company, which can then run proprietary confirmatory Phase 3 trials. This design not only saves industry the cost of Phase 2 testing, but it also eliminates lengthy trial startup, guarantees sufficient enrollment, and avoids duplication of effort among companies. For unsuccessful drugs, the goal is to have "fast, frugal failures," according to **David Dilts**, co-founder of the healthcare consulting firm Dilts Partners in Plano, Texas.

The I-SPY 2 platform is a standing trial. In other words, it is an "engine" that promptly replaces each drug leaving Phase 2 with a new one rather than winding down operations at the end of one trial and gearing up again with IRB approval, site training, recruitment, etc., for the next trial, said **Laura Esserman** of the University of California, San Francisco. Esserman is a cancer surgeon who leads I-SPY 2. In the cardiology field, the ability to quickly test numerous drugs in clinical trials was crucial for drug development, said **Tony Ware**, who runs product development at Eli Lilly and Company.

While meeting participants expressed enthusiasm for this "plug and play" model, they were unsure about how to apply it to AD. The biggest uncertainty is how to tell if a given combination works in a short-term trial. In cancer, there are more biomarkers that are either FDA approved for clinical use or at least qualified for a given context of use in research than is the case in AD. "We have a critical need for validated biomarkers," Ware said. Existing AD biomarkers have proven useful for selecting the right patients for trials, but not at predicting clinical outcomes (see ARF related news story). Here, the FDA offered to help. Over the next few months, the agency's statistician **Kun Jin** will analyze clinical trial data submitted to it by various sponsors of past trials to look for biomarkers that track with clinical outcome. This prospect intrigued industry executives.

Without good outcome markers, the first combination trial might have to be long enough to show significant clinical change, i.e., three or even up to five years. Initial trials should embed a large suite of biomarkers to discover which ones reliably correlate with subsequent clinical benefit, said **Reisa Sperling** at Brigham and Women's Hospital, Boston, Massachusetts. For an I-SPY 2 engine chugging through successive Phase 2 trials in AD, researchers need to find biomarkers that change robustly in six months. Katz noted that in the absence of surrogate biomarkers, drugs can be approved based on a biomarker change that is "reasonably likely" to predict a clinical benefit, in combination with cognitive improvement (see ARF related news story). Several research groups are developing more sensitive cognitive measures to track changes in preclinical or prodromal AD populations (see ARF Webinar). Others are trying to validate computerized online cognitive assessments that can be taken frequently and do not require study participants to visit the clinic every time.

Questions of intellectual property and data sharing seemed worrisome to some attendees. Industry representatives said these problems can be solved, because companies enter into partnerships all the time and have developed models for sharing data. In I-SPY 2, as well as in the DIAN Pharma Consortium, which tests drugs by Lilly and Roche in one trial, the sponsor companies retain the rights to their drugs. However, researchers wondered how a combination drug would be handled. If the two products come from different companies, who owns the combination? There are no set rules, the FDA answered; specifics would be negotiated on a case-by-case basis.

Turning Ideas Into Action

Despite the challenges, researchers at both meetings decided to dive in, starting small with a single trial and building up the platform. "If we don't do this now, we will not be ready when later drugs come along," Sperling pointed out. Borrowing a line from the movie *Field of Dreams*, Berry advised, "If you build it, they will come." This strategy has worked for DIAN, where interest snowballed once the legal details were settled and the first companies had signed on.

Participants recommended that combination trials be run with existing infrastructure, including the Alzheimer's Disease Cooperative Study (ADCS) and the NIA's system of Alzheimer's Disease Research Centers. The platform will be a public-private partnership. Companies that contribute money stand to receive a return on their investment due to the cost savings and shared risk, said **Chas Bountra** of the University of Oxford, U.K. As an example, Bountra cited the success of the Structural Genomics Consortium, a nonprofit organization based at the Universities of Oxford and Toronto that has eight pharma partners engaged in its goal of deciphering the three-dimensional structure of proteins.

To control cost, the AD Phase 2 platform, like I-SPY 2, will use an adaptive trial design. It will run simulations on in-silico models of Alzheimer's disease to determine how many participants will be needed and to predict the odds of success (see ARF related news story; ARF news story). This may help avoid costly failures. Previous Phase 3 trials were designed based on traditional power calculations of how many participants would be needed to show an effect. However, simulations that incorporate sensitivity analyses, which take uncertainty into account, show that the probability of success in many of these trials was "abysmal," Berry claimed.

The taskforce will have to identify resources—above all, a list of drug candidates. Pharma companies may have AD drugs on the shelf that have good safety data but were sidelined for lack of efficacy, said Bountra. Companies might be willing to donate these for Phase 2 combination testing, with the promise of getting them back for Phase 3 if they showed a signal. Other scientists recommended checking whether any of the 58 compounds available at the National Center for Advancing Translational Science (NCATS) drug repurposing program might be active in AD. Yet others insisted that only a company's best asset be considered, quipping that one does not fight a war with one's B team. This issue sparked debate in both D.C. and New York, with some participants advocating for topline drugs only. "We want the best therapies," Sperling said.

The D.C. group agreed that the first combination trial should test two amyloid-lowering agents, such as an antibody and a BACE inhibitor or two antibodies that hit different forms of Aβ, in a preclinical or prodromal population. At this point, only these types of therapy are sufficiently advanced, having already demonstrated safety and some effect on biomarkers in clinical trials. Drugs must be shown to hit their target before being tried in combination, advised **Bill Klunk** at the University of Pittsburgh, Pennsylvania. "You can't add zero and zero and expect to get anything other than zero," Klunk said. A combination of two amyloid-lowering drugs would provide a test case for the amyloid hypothesis, Sperling noted. This is exemplified in the cardiology field, where doctors often prescribe several anti-hypertensives together to boost efficacy while keeping side effects low.

The Holy Grail: Targeting Multiple Disease Mechanisms

In the longer term, researchers want to expand the platform and test combination therapies that hit different disease pathways. As new drugs complete Phase 1 testing, they will become eligible. Possible future targets include tau, lipid metabolism and ApoE, neuroinflammation, neuroprotection, calcium channels, endocytosis, other aggregating proteins such as α-synuclein and TDP-43, insulin-sensitizing drugs, and α7 nicotinic acetylcholine receptors, to name a few. For many of these, researchers will have to

develop novel biomarkers in parallel. Some targets may be more appropriate at later stages of disease, and determining the appropriate population for a given drug could be done adaptively, Berry suggested.

Particularly at the beginning of both meetings, some participants emphasized the need to gain a better understanding of disease mechanisms. However, by the end, consensus was strong that the effort to set up a shared adaptive platform and run combination trials has to press ahead. As Bountra put it, "If we wait until we understand AD, we won't have anything for 20 years." Combination trials for other conditions such as asthma were done pragmatically, with targets validated by clinical success, Bountra noted.

An I-SPY 2-like adaptive platform allows researchers to embrace what is otherwise seen as a problem—that is, the heterogeneity of late-onset Alzheimer's disease, Berry insisted. Adaptive trials use data coming in as the trial unfolds to gradually match drug combinations to individual responders, i.e., people with different forms of LOAD. In I-SPY 2, a successful cancer drug "graduates" with a grade in each of 10 biomarker signatures, Berry said. This gives the company an idea of what type of patient population will benefit from a particular agent. This could be helpful in the AD field, where many patients suffer from mixed dementias or have different vascular or metabolic comorbidities and might therefore respond to unique blends of medicines.

For success in treating AD in the long term, the medical community will at some point need to involve insurers in the development process, participants suggested. This includes giants such as the Centers for Medicare & Medicaid Services (CMS), which set federal coverage guidelines, as well as private payers. Industry needs to know what kind of data payers want to see on combination drugs in order to cover those therapies. Insurance reimbursement is currently a contentious issue in the field of amyloid imaging (see ARF related news story). Increasingly, companies investing in AD trials consider insurance coverage an even greater hurdle than FDA approval. Primary care physicians should also be engaged, scientists said, because these doctors are the ones who can diagnose and refer preclinical patients for trials.

Both in Washington and in New York, participants expressed a strong commitment to see the process through. "In every other disease where we've had success, we put drugs together," Sperling said. In conclusion, Katz said in D.C., "This is one of the most important meetings I've been to. Combination therapy is the next step in AD therapy." Katz himself, to the field's collective dismay, is soon to retire. But even from retirement, he teased, "I'll be watching."—Madolyn Bowman Rogers, with reporting by Gabrielle Strobel.

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