

DIAN Forms Pharma Consortium, Submits Treatment Trial Grant

By Gabrielle Strobel

22 December 2011. In their quest to offer treatment trials to families with autosomal-dominant Alzheimer's disease, the scientists driving the Dominantly Inherited Alzheimer Network (DIAN) have cleared the next two (or rather, one and a half) hurdles. They have corralled signatures on the dotted line from 10 pharma and biotech companies for a collaboration agreement that is unprecedented in the field of AD clinical trials. They have also submitted a grant application to the National Institute on Aging to help fund the first two phases of treatment trials, together with private funds.

Until the agency reviews the proposal in early 2012, DIAN's attempted leap over the funding hurdle will remain suspended in mid-air. On the pharma collaboration front, however, the push to do something truly new—that is, test experimental therapies as secondary prevention in people destined to develop Alzheimer's dementia—has taken a definitive step forward. Before, the DIAN scientists and family representatives had convened various stakeholders to discuss the prospect of mounting such trials. At those meetings, pharma scientists had voiced intense interest, but also cited obstacles and remained non-committal. Since then, negotiations unfolded behind the scenes, and on 16 October 2011 in Washington, DC, a group of otherwise competing biopharmaceutical companies gathered after having formally agreed to help make DIAN trials a success. Each company has signed an agreement that it will jointly support the precompetitive aspects of DIAN clinical trials with time, expertise, and money.

“This is a milestone for DIAN,” said **Randall Bateman** of the Washington University School of Medicine, St. Louis, Missouri. “If you had asked me five years ago what the odds were that different pharma companies would sign the same agreement to get these prevention trials going, I would have said it would be hard to get one to do it. I would have said it is impossible to get 10 to do it. To me, that is a huge step.”

DIAN is a joint long-term project of families with autosomal-dominant AD and scientists in the U.S., Australia, and the U.K. It started in September 2008 with an NIA-funded observational biomarker study to characterize the natural history of AD starting in young adulthood. Yet from its conception, DIAN aimed to offer therapeutic trials to its participants. Since 2008, the momentum for secondary prevention trials in gene carriers, whose disease most closely represents the transgenic mouse models in which anti-amyloid drugs have been initially developed, has strengthened in the field at large in the U.S. and other countries as more researchers have come to view such trials as a unique opportunity to both prevent dementia and test the amyloid hypothesis.

While the pharma consortium was taking shape, DIAN has advanced on other fronts as well. On the national media front, it drew the eye of NBC's Robert Bazell, who interviewed DIAN steering committee member Denise Heinrichs for the network's *Nightly News with Brian Williams* last July (play [video clip](#); for more on Heinrichs, see [ARF related news story](#)). On the science front, DIAN continued to enroll new families and measure their biomarkers and cognition, bringing the network up to 230 participants

currently. Moreover, its scientists reached out to colleagues in Europe in an effort to make clinical trials available to additional families with autosomal-dominant AD there, whether they participate in DIAN itself or not. To that end, an online registry will enable clinicians and families worldwide to find out more about upcoming DIAN treatment trials starting in early 2012. And in preparation for a hoped-for start date of fall 2012, the scientists are designing a trial that would launch three drugs in parallel against a pooled placebo group prior to advancing the successful drugs into a larger trial. For details on the consortium, DIAN enrollment and data, families in other countries, and the trial design, read this update story on all things DIAN.

The DIAN pharma consortium at present comprises Biogen Idec, Elan, Genentech, Janssen Alzheimer Immunotherapy, Lilly, Mithridion, Novartis, Pfizer, Roche, Sanofi-Aventis, with other companies potentially joining later. These are the companies that may have an unapproved drug they hope to see trialed in DIAN and were able to reach a common denominator with the DIAN's academic home at Washington University, St. Louis, Missouri, on issues ranging from intellectual property to data sharing and funding. While the DIAN pharma consortium will assist with precompetitive issues, the DIAN Therapeutic Trials Unit (TTU) will develop and direct the planned trials.

How do the two groups relate? In essence, the consortium's charge is to add pharma expertise to designing and implementing DIAN drug trials. The TTU controls and coordinates the trials with help from the federally funded Alzheimer's Disease Cooperative Study (ADCS). Further, the TTU will manage a trial registry expanding into different countries and generally deal with patients and other groups such as regulators. The pharma consortium formed a biomarker working group that is analyzing DIAN data to help power trials adequately, as well as a separate group that works on identifying a cognitive outcome measure suitable to the presymptomatic and the earliest symptomatic phase of AD. Moreover, the pharma consortium funds needs, such as regular meetings with the TTU plus the expanded registry. It also funds a bank of fibroblast-derived stem cells currently being created from cheek swabs of DIAN participants for preclinical study of candidate drugs. Each consortium company may nominate a candidate treatment; however, the choice of what goes into DIAN trials is not theirs. DIAN's TTU is evaluating the nominations and submits a short list to DIAN's steering committee, who will make the final call.

What are the pharma companies getting in return? For one thing, a voice in shaping these trials, even if their drug is not chosen in the first round. A pharma company's drug is no longer precompetitive, and, indeed, discussion filled an entire day without anyone naming a single treatment. The consortium agreement stipulates as much. But even so, each company involved struggles with similar biomarker issues as it develops its respective treatments. By participating in DIAN, they get to see data on how AD biomarker trajectories change reaching back 30 years before symptoms set in. This dataset complements what they are learning from the Alzheimer's Disease Neuroimaging Initiative, which follows a different, i.e., non-genetic and older, population in otherwise directly comparable ways. Pharma company scientists can see natural history data on DIAN biological markers and cognition now, and they will see drug response data on the

same markers as trials get going. For example, any company developing, say, an anti-A β antibody or a secretase inhibitor, would like to learn if, and how strongly, any drug in this class can budge CSF and imaging markers in presymptomatic or early-stage patients.

In preparation for trials, DIAN itself has continued enrolling. DIAN is an observational biomarker study that started in September 2008. By December 2011, 230 people had joined, of whom 64 have completed year 3, and 27 people year 4 follow-up visits. The DIAN scientists use the age at which a person's parent became symptomatic to estimate when the adult child will develop AD. People aged from 15 years younger to 10 years older than their parent's age at onset are eligible to join a treatment trial. At present, about three-fourths of the participants are asymptomatic; of those, 85 percent are younger than their parent's age at onset. DIAN participants submit to what would for most people seem a grueling list of tests. But they are highly motivated. So far, 87 to 97 percent complete a long list of clinical, paper-and-pencil, and imaging assessments, and 76 percent consent to lumbar punctures.

What are those tests showing? At the October pharma consortium meeting in Washington, DC, Bateman summarized how mutation carriers compare to non-carriers. These are cross-sectional findings; longitudinal data are expected to come next spring. Clinically, mutation non-carriers are normal at all ages, whereas carriers subtly diverge from normal up to a decade before their parent's age at onset. Roughly midway through this decade, their clinical findings reach a CDR of 0.5, and by their parent's age at onset, carriers typically have a CDR of 2. Likewise, the MMSE starts trending down in carriers already a decade or so before. These emerging data look as though carriers might be getting sick somewhat younger than did their parents. In reality, the data may reflect the fact that carriers in DIAN are under such close observation that subtle deficits get picked up that in their parents were not recorded. The time point of five years earlier roughly corresponds to the stage at which incipient AD would be detected with a CDR of 0.5, said **David Holtzman** of WashU. These year estimates, and even the order of changes, are highly fluid at this point, as data are rolling in and being analyzed.

On the biomarker front, it appears at this early point in the study as if the CSF A β 42 concentration is higher in young adult mutation carriers than in non-carriers of the same age (see also companion API story). At older ages, CSF A β 42 declines in carriers. It transitions through the normal range starting at about -20 years, crossing lines with non-carriers (whose levels are similar at all ages) at about -15 years, and decreases further to levels typically measured in late-onset AD. "There is a strong trend to have elevated levels far earlier. Once we have a greater number of people and longitudinal change, we will know for sure," said **Anne Fagan** of WashU. Fagan's group measures all DIAN CSF samples to avoid the variation between groups that is seen worldwide and was recently confirmed in an ongoing quality control initiative ([Mattsson et al., 2011](#)). CSF tau was flat in non-carriers across ages but significantly higher in carriers by -10 years. As is also seen in people with sporadic AD, then, CSF tau in autosomal-dominant AD appears to rise some five years before a person becomes truly symptomatic, Holtzman said.

In plasma, A β is higher in carriers than in non-carriers; however, this measure appears to stay constant with age. To Fagan's mind, this suggests that CSF reflects A β in the brain, whereas plasma reflects primarily A β from the periphery.

Brain amyloid as measured by PIB PET imaging crops up in the earliest affected regions, the precuneus and caudate, even at -27 and -25 years, respectively, Bateman reported. The only mutation carriers who are completely PIB-negative are the youngest participants. FDG PET measurement of brain activity in the precuneus trends steeply down at -12 years; unlike CSF A β 42, FDG PET continues dropping as disease progresses. In toto, the biomarker findings available so far fit the story of autosomal-dominant AD being marked by A β overproduction, said **Paul Aisen** of the University of California, San Diego, a DIAN investigator and head of the ADCS.

Can More Families Join?

Autosomal-dominant AD is rare, and affected families tend to live scattered across many nations, not clustered conveniently near academic medical centers. Such families also speak of a sense of deep isolation. To help families connect, share experiences, learn about upcoming trials, and give their own input into trial planning, DIAN, together with the Alzheimer's Association, has set up an online forum for families with this form of AD. Called the ADAD Forum, it opened in February 2011 and so far has 51 members. It facilitates commentary, offline communication, and periodic conference calls and Webinars.

On 20 November 2011, family members from Australia, the U.S., and the U.K. joined DIAN scientists in such a Webinar. They listened to the latest trial updates, asked questions, for example, about genetic testing and trial participation (testing is optional, not required), and gave researchers their feedback on certain trial design features. To protect ADAD families' privacy, this forum is not listed publicly, but people who believe this form of AD runs in their family and are interested in joining can contact DIAN study coordinator **Wendy Sigurdson** at sigurdsonw@neuro.wustl.edu for more information.

From the get-go, it was clear that the small number of participants would place restraints on scientists' ability to power clinical trials. But as word about DIAN began to spread in other countries, scientists and families there became interested as well, opening the prospect of larger, more powerful trials. Last July at the 2011 Alzheimer's Association International Conference (AAIC) in Paris, France, some 25 physician-researchers from a dozen European countries and Canada met with Bateman, DIAN's principal investigator John Morris of Washington University, and other DIAN leaders for a dialogue on making DIAN trials more broadly available. As it turned out, 17 European research sites said at this gathering that they are working with 145 families including some 300 asymptomatic and 180 symptomatic individuals, many of whom may well be interested in participating in trials, Bateman told the pharma consortium at the October meeting in Washington. There may be even more families in Europe. In fact, at AAIC, researchers from several European groups independently presented data on autosomal-dominant families. For example, **David Wallon** from INSERM in Rouen, France, presented a poster with Dominique Campion and other geneticists from across France, which characterized 143

families with early-onset AD. Of those, 83 had a presenilin 1 mutation, 15 had an APP mutation, 12 had an APP duplication, and for 25 families the genetic reason for their disease is presently unknown. In these French families alone, 314 relatives are at risk for their parent's disease, and 31 have chosen to find out their genotype after genetic counseling, Wallon told Alzforum.

It is not clear yet whether any additional European sites besides London will become bona fide DIAN sites, start up their own studies, or simply decide to offer DIAN treatment trial participation to their families regardless of whether that family participates in a requisite observation study. To enable trial participation, DIAN intends to launch an expanded registry website hosted at WashU with links from the DIAN website, from Alzforum, the Alzheimer's Association, and national AD organizations in Europe. Through this registry, families with autosomal-dominant AD or their physicians can take first steps toward participating in a DIAN clinical trial. They can contact the DIAN research coordinator to obtain information; if needed, submit a saliva sample for confidential testing of whether an autosomal-dominant mutation indeed runs in the family; and then be matched to appropriate prevention and treatment trials within DIAN if they wish, Bateman said.

How to Test Drugs in This Unique Population?

Trial design took up much discussion at the pharma consortium meeting. In general, there was great interest in flexible designs that use run-in data from the observational period of DIAN to assess intra-individual change, as well as in trials with some adaptive elements roughly modeled after the [I-SPY 2](#) process of breast cancer trials (see [ARF related news story](#) on adaptive trials). There are still many open questions and restraints. For example, it's not decided yet up to what stage early symptomatic participants will be eligible. And even with the expanded registry, sample sizes will remain small enough so that most dose finding will have to have happened in company-run trials of each drug prior to the DIAN trials. That said, a draft design has taken shape, and the grant application DIAN scientists submitted to the NIA in October 2011 articulates it. The grant proposes a two-phase study backed by letters of support from the three companies whose drugs are named in the application, as well as support from the Alzheimer's Association, ADCS, Alzheimer's Disease Neuroimaging Initiative (ADNI), DIAN participants, and multiple external scientists. The first phase would determine whether the drug engages its intended target and whether it affects any downstream biomarkers of neurodegeneration. It would do that primarily by imaging whether amyloid deposition changes in response to the drug, and secondarily by comparing cognitive performance, biofluids, and other imaging markers before and after drug. The second phase would then look for a cognitive benefit of treatment, using primarily a to-be-determined composite panel of tests that are sensitive at that early stage, and secondarily, biochemical and imaging biomarkers of AD pathology and neurodegeneration, for example, MRI.

Importantly, the first phase would compare three different drugs to a shared placebo group. Each drug arm would enroll 80 people, assigning non-carriers to placebo to maintain genetic status blinding, and randomizing mutation carriers to drug versus placebo in a 3 to 1 ratio (a 75 percent chance of receiving drug). This design reconciles

the twin dilemmas whereby participants may not want to find out their mutation status in order to join a trial, yet scientists do not want to randomize too many carriers to placebo or non-carriers to drug, either. That is because carriers lose time on placebo and non-carriers expose themselves to needless procedures, adding risk to themselves and cost to the study while adding little information to the study. In the proposed design, three groups of 30+ carriers each would receive one of three chosen investigational drugs, while the others would be pooled into one shared placebo group.

This first phase would go on for two years, at which point drugs that met primary aims would be considered for longer-term cognitive endpoint studies. Those drugs would then be tested in the entire population for three more years. Such a larger, longer trial is necessary for this second phase because its cognitive endpoints are likely to be subtle and change slowly in asymptomatic or very mildly symptomatic family members. If none of the three drug hits its target or a downstream biomarker in the first four-arm phase, then it would also likely fail to provide a cognitive benefit later on. Three new drugs would then be chosen for a second stab at Phase 1. In their grant, the DIAN scientists named three of the 12 drugs nominated to date by the participating pharma companies for this plan, but could not say which ones they are at this time.

The price tag for this plan? Sixty million dollars over five years. The NIA, so the DIAN scientists hope, will pitch in \$3 million per year, and each sponsor of the three drugs would pay for one of the remaining thirds.

Reeling In Biomarker Data in Young Carriers, API Rocks Staging Boat

In the second half of 2011, scientists driving the Alzheimer's Prevention Initiative have been reporting at scientific conferences the first emerging biomarker findings from their human volunteers. These data provide tantalizing glimpses of what happens in the brains of young people carrying a deterministic Alzheimer's disease mutation when they are still in their twenties and thirties. While these imaging and fluid data at present represent but small snapshots of the disease 25 years before dementia, they nonetheless suggest that a quiet drama unfolds in the Alzheimer's-bound brain years before amyloid. "At present, it looks as if functional and structural changes may occur prior to fibrillar amyloid deposition," **Adam Fleisher** of the Banner Alzheimer's Institute said in a talk at the Clinical Trials in Alzheimer's Disease (CTAD) conference held 3-5 November 2011 in San Diego, California. If further data substantiate those initial findings, and if the findings generalize to late-onset Alzheimer's, they would then call for a refinement of the proposed biomarker staging diagrams that have captured the imagination of Alzheimer's disease researchers worldwide.

Fleisher belongs to a large collaborative team of scientists who have been developing the API as a program meant to pioneer secondary prevention trials in people who are at high risk of developing Alzheimer's disease. Led jointly by **Eric Reiman** and **Pierre Tariot** at the Banner Alzheimer's Institute in Phoenix, Arizona, and **Francisco Lopera** at the Universidad de Antioquia, Medellin, Colombia, the API has been doing the groundwork preparing for such trials in people who carry autosomal-dominant mutations that will give them the disease with near certainty. (The API also prepares for trials in aging people

who carry the ApoE4 risk allele.) “There are many people who are at very high risk of AD who are clamoring for therapeutic trials,” Tariot said.

The Initiative’s autosomal-dominant half is complementary to the Dominantly Inherited Alzheimer Network (DIAN, [ARF related story](#)), and its late-onset half is complementary to the A4 initiative. Together, the three programs share the goal of breaking ground on secondary prevention drug trials across the AD spectrum. That is, they range from rare, deterministic AD genetics on one end to risk genetics in the middle, and to the most common forms of late-onset AD on the other end. Success in any and all of these trials could energize earlier-stage trials throughout the field, the scientists believe. However, each program is also unique in some aspects. DIAN has fewer patients than the API, but subsumes all APP and presenilin mutations; A4 is potentially the largest study, but further behind in terms of funding and driven by biomarkers, not genetics. Along the way of gathering observational data and planning their respective programs, the leaders of all three meet frequently to work out where they can coordinate to enhance each other’s goals and ensure that their respective datasets can be analyzed together.

So what’s new with API since its last update on Alzforum (see [ARF API series](#))? In 2011, the researchers have enrolled some 1,300 relatives of the Colombian families afflicted with the E280A Paisa mutation in presenilin 1 into the observational biomarker and cognitive study phase meant to precede treatment trials. About a third are carriers. The scientists hope to bring the number of participants to 3,000 and the number of carriers close to a thousand by 2013.

That goal—as indeed all key goals of API, DIAN, and A4—hinges on new funding coming forward. In the case of API, its leaders are currently awaiting final review by the National Institute on Aging of a pending grant proposal for the first treatment trial with an identified (but undisclosed) experimental drug while simultaneously stitching together a funding coalition of company money and private philanthropy.

In the meantime, the scientists have expanded their original biomarker studies with the Colombian participants that started in 2010. In 2011, the scientists, led by Fleisher and **Yakeel Quiroz**, currently at Boston University, added new cohorts of cognitively older adults in age brackets from age 35 and up, all the way back to children aged eight to 17. The children are not undergoing spinal taps, but they are donating a blood sample and, importantly, lying still in the scanner for various modalities of magnetic resonance imaging.

Why children? The scientists want to chronicle the entire natural history of this form of AD from its beginning, meaning they will trace back at what age biomarker measurements begin to diverge between carriers and their non-carrying siblings. In the next-older age bracket—the 18- to 26-year-olds—mutation carriers already show distinct differences in brain function and even structure. Hence, Quiroz and colleagues reached back with the less invasive tests into even younger ages.

To date, MRI has been taken from some 200 volunteers age eight and up. This happens on a Siemens 1.5T scanner at the Hospital Pablo Tobón Uribe in Colombia. “MRI capability is very good there for API studies,” Tariot told the audience at CTAD. Plasma has been taken from some 130 volunteers age eight and up, CSF from some 90 people age 18 and older. Fluids are being drawn in Medellín following standard acquisition, preparation, storage, and shipping directions developed for DIAN. They are analyzed in the lab of **Anne Fagan** at Washington University, St. Louis, Missouri, to ensure that data are comparable with CSF measures in the DIAN and, indeed, the Alzheimer’s Disease Neuroimaging Study (ADNI). PET imaging with florbetapir started up in September, when the first of what will be 50 participants flew to Bogotá, and from there to Miami and then Phoenix for FDG metabolic and amyloid imaging with florbetapir (see [NYT coverage](#)). These people will travel to Phoenix in small groups to get PET studies going until a cyclotron that is currently under construction near Medellín can start providing labeled ligand for a local PET scanner that began operating in October 2011. “This travel is logistically challenging, and the team in Medellín is absolutely amazing in coordinating it,” Fleisher said.

All the above measures are also being taken in a much smaller group of relatives already affected with mild cognitive impairment or AD. The goal is to take sufficient biomarker measurements to pinpoint the earliest divergence between carrier and non-carrier for each of them, trace them forward into symptomatic AD, and integrate this information into a staged natural history of this form of Alzheimer’s. This information can then serve as a foundation for treatment trials, first in this population, but also, together with similar data from DIAN longitudinal biomarker studies of ApoE4 cohorts and ADNI and AIBL cohorts, for prevention trials in late-onset AD (LOAD). “Ultimately, we want to use treatment trials in early-onset AD as models for late-onset AD,” Fleisher said.

What are the results so far? The data for the children and adolescents are not available yet. But as shown at conferences, data for people in their twenties are trickling in, and they show functional and even subtle structural brain changes that appear to precede amyloid deposition. Specifically, carriers had abnormalities compared to their non-carrying siblings and cousins in their brain activation patterns when they performed an established fMRI task asking them to associate and subsequently remember face-name pairs ([Sperling et al., 2001](#)). Carriers performed the task as well as non-carriers, but in doing so, they activated their hippocampi more strongly and deactivated their precuneus brain area less strongly. This is essentially the same pattern of change as previously reported for the later preclinical stages of other forms of early-onset AD and, indeed, late-onset AD. Quiroz and colleagues presented these data at the Alzheimer’s Association International Conference (AAIC) in Paris in July 2011.

Also at this conference, Fleisher and colleagues presented a poster suggesting that this same group of twenty-somethings already have subtle morphological changes—meaning atrophy—in their brains. In a whole-brain comparison of gray matter volume between carriers and non-carriers, the 20 carriers had less gray matter in their temporoparietal and parahippocampal brain areas than 24 non-carriers who were otherwise matched in age, sex, education, and cognitive test scores. It’s well established that atrophy accelerates

three to five years before dementia onset (e.g., [Ridha et al., 2006](#)). In this earlier work, the new signature may not have come up because the group was smaller, the imaging was not generally done in people this young, and what was done used more global measures of how the boundaries of regions of interest shift. The new API research uses voxel-by-voxel comparisons independent of regions of interest in people twenty years younger than their expected age at onset.

MRI offers a growing number of increasingly sensitive measures for AD research, and the API team put one more to the test. In a cohort of 18 mutation carriers and 22 controls in their thirties to early forties, Quiroz and colleagues worked with **Brad Dickerson** at Massachusetts General Hospital, Boston, to look for the cortical thinning signature Dickerson had developed in four previous studies in mild LOAD, MCI conversion to AD, and cognitively normal people who have amyloid and are being followed longitudinally. Dickerson had pinpointed nine regions of interest per hemisphere and found that atrophy, as measured by a thinner cortex in those regions, predicted that a cognitively normal person would develop dementia some eight years prior ([Dickerson et al., 2011](#)).

This is the first study of cortical thinning in the API population. In this cohort, mutation carriers on average had a 4.75 percent thinner cortex in these regions, Quiroz reported at AAIC in Paris. Most shrunken, by 6 to 8 percent, were the angular gyrus, the superior parietal lobule, and the precuneus regions. All nine regions showed a trend in the same direction, though not all are statistically significant, Quiroz said. Consistent with previous studies in other populations, these results point to neurodegeneration well underway by this stage, which in this population corresponds to what is generally called pre-MCI. With the Paisa AD mutation, affected carriers generally meet MCI criteria by age 44, a bit older than this cohort. In neuropsychological testing, this cohort, whose average age was 38, performed similarly overall to the non-carriers, though trends toward subtle decrements in word recall, verbal fluency, and recall of drawings were apparent. The earliest known cognitive deficit clearly demonstrated in this form of AD—in carriers in their thirties just like the ones studied for cortical thinning—is the visual binding memory deficit reported by **Mario Parra** and colleagues (see [ARF related news story](#); [Acosta-Baena et al., 2011](#) and [Parra et al., 2010](#)).

How do all these findings on brain imaging relate to A β ? Amyloid PET results from API are unavailable as yet, but the first CSF and plasma data are beginning to roll in. At AAIC, Reiman presented the first cut, on 10 carriers and 10 non-carriers in the 18-26 age bracket. At this age, cognitive tests detect no difference, but brain function and structure measurements do. So far, Reiman reported, it looks as if carriers have elevated plasma A β 42 but not A β 40, suggesting that the presenilin 1 E280A mutation raises systemic absolute levels of this more aggregation-prone form of the peptide, as well as the A β 42/40 ratio. (To some audience members, this finding hinted that middle-age elevated plasma A β 42 might prove to be a risk factor in the general population as well.)

In CSF at this age, A β 42 but not A β 40 is elevated as well in carriers over non-carriers, Reiman reported at AAIC. This is consistent with the DIAN's prior finding of elevated A β 42 in carriers of a variety of early-onset AD mutations in their twenties (see [ARF](#)

[DIAN London story](#); see [ARF DIAN Honolulu story](#)). Scientists generally assume that this reflects overproduction of A β , implying elevated levels of the peptide in the brain at an age where there is no fibrillar amyloid deposition yet. Not everything fits neatly, though: The same study finds a paradoxical reduction of CSF tau in carriers at this young age, upwards of 20 years prior to dementia, Reiman noted at AAIC.

What does this mean? It's too early to make a strong statement, and it's not proven that this form of early-onset AD models LOAD, both Fleisher and Reiman cautioned in separate conversations. "Even so, at present it looks as if the functional and structural brain changes precede fibrillar amyloid deposition," Reiman said, noting that this would be consistent with published work on reduction on FDG PET or in mitochondrial glucose metabolism in young adult ApoE4 carriers. Some studies are beginning to hint that fibrillar amyloid deposition, as visible by PET, happens soon after CSF A β 42 has begun to drop. It is tempting, then, to speculate that the early functional and structural changes that Quiroz, Fleishman, and colleagues see might be happening in a situation of years of elevated A β levels but prior to when the brain deposits and, presumably, sequesters. This could imply that fibrillar amyloid deposition is an attempt by the brain to mitigate damage to synapses from an overabundance of prefibrillar forms of AD, Reiman said.

Both API and DIAN are pressing to add both cross-sectional and longitudinal data so they can address at what ages CSF A β 42 starts dropping and how all markers the studies are tracking fit together. "More data on larger numbers of volunteers will sort this out," Fleisher said. In the process, the currently proposed staging diagrams of preclinical (e.g., [Perrin et al., 2009](#); [Jack et al., 2010](#); [Weiner et al., 2010](#); [Frisoni et al., 2010](#)) may get updated as some curves change their shape and slope or even trade places.

The result will be a knowledge base on the natural history of AD as a foundation for better clinical trials. For now, the API scientists are planning a first clinical trial as outlined in its pending grant proposal to the NIA, provided they can secure an appropriate compound, funding, and regulatory and ethical approval. At CTAD, Tariot emphasized that this trial is designed without pre-formed assumptions on which biomarker patterns will prove to be good outcome markers. Instead, it is designed precisely to address this question. "We must be humble about what we know," Tariot said at CTAD, noting that regulators had advised API in previous planning meetings that their first trial should use a cognitive endpoint and include many biomarker readouts as secondary endpoints in order to learn as much as possible about them. Because the field does not know which biomarkers will prove to be outcome measures and how they will behave in response to a drug, the current trial is primarily frequentist with some adaptive elements. "We lack sufficient natural history data to build the computer models for a true Bayesian trial, and we have to be agnostic about the ability of biomarkers to predict treatment response. This is why we are not ready to use a Bayesian model yet," Tariot said.

The proposed API trial, then, would use a change in a composite cognition measure as the primary outcome, looking for a slower rate of decline on drug versus placebo. **Jessica Langbaum** at the Banner Institute and colleagues elsewhere are developing this measure (see [ARF related news story](#)). Because this change will emerge slowly, the trial needs to

be large and long. As proposed, the trial would enroll 300 participants. Two hundred carriers would be randomized 1:1 to treatment or placebo so no one would have to find out his or her mutation status; 100 non-carriers would be on placebo. The trial would feature an interim analysis after two years, guided by rules that assume biomarkers will change before cognition does. If the trial shows a positive biomarker pattern and/or clinical trends, then it will continue to five years, long enough to learn whether favorable cognitive changes are detectable.

Overall, the Alzheimer's research field went from thinking a few years ago that this is too out-of-the-box to multiple groups now doing the same thing. In particular, industry scientists previously pointed to the absence of a regulatory path (see [ARF eFAD essays](#)). That path is clearer now, and involvement and support on the part of regulators have been evident. "The feedback from the regulatory scientists to API and DIAN has been incredibly valuable," Tariot told the audience at CTAD (see [ARF related news story](#); [ARF news story](#)). With an emerging regulatory path, the patients, the protocols, the tools, and some biomarker data in hand, researchers know the fate of those initial trials at this point would seem to lie squarely in the hands of funders.

Anti-Amyloid Treatment in Asymptomatic AD Trial

Q&A With **Reisa Sperling**, Brigham and Women's Hospital, who leads the A4 trial with **Paul Aisen**, University of California, San Diego. Questions by Gabrielle Strobel.

Q: Many Alzforum readers have heard some reference about the Anti-Amyloid Treatment in Asymptomatic Trial, or A4 for short. What exactly is it?

A: A4 is a new secondary prevention trial effort aimed at treating older individuals at risk for developing Alzheimer's disease dementia on the basis of having biomarker evidence of amyloid. We will test the hypothesis that decreasing amyloid burden during the preclinical stages of AD will impact "downstream neurodegeneration" and hopefully delay cognitive decline.

Q: What's its status in December 2011?

A: We will propose the trial as part of the Alzheimer's Disease Cooperative Study's NIA grant renewal in March 2012. It will be reviewed over the summer, and we hope to start screening in early 2013. So right now we are in the planning stages for the proposal. For example, we have determined that it will be clear that, although the ADCS budget will provide a majority of support for the trial, we will need industry partners both for drug and for PET amyloid screening. We are in the midst of talks with a variety of industry partners to find out how we make this win-win for both sides so that we can keep it an academic trial but get the support we need. We are also seeking philanthropic support.

Q: Why push for this trial now, in a tight funding climate?

A: It is critical to start these studies as soon as possible, as the cost of waiting another five to 10 years is not tenable. The overall scientific rationale for secondary prevention is

strong. Plus, we have seen positive developments recently on what used to be a relative weakness, i.e., the absence of a suitable outcome measure. Specifically, there is more emerging data regarding evidence of subtle memory impairment ([Rentz et al., 2011](#)) and increased risk of cognitive decline in amyloid-positive older individuals ([Villemagne et al., 2011](#); [Morris et al., 2009](#)). Some additional longitudinal data are currently under review and will hopefully be out in the next few months. The converging data from multiple longitudinal studies will be helpful in allowing us to design a trial that will detect decline from “normal” to subtly “abnormal” within the three-year time frame of the A4 trial.

Q: What sorts of people will the A4 trial enroll?

A: Clinically normal older individuals (over 70 years old) who will be screened with PET amyloid imaging, and are found to be “amyloid-positive.” We will pick an anti-amyloid agent that has demonstrated activity against A β in humans. Potential therapeutic agents need to have at least one to two years of safety data, and that narrows down possible agents. Because we are looking to treat a population without a deterministic mutation, i.e., without a near-certain genetic risk, it is important to have adequate safety data to inform normal older subjects. We will treat subjects for three years with the anti-amyloid drug or placebo, and then ideally follow them even beyond treatment to see if we can impact the trajectory of cognitive decline.

Q: How will A4 be different from DIAN?

A: Of course, we are addressing a very different population: asymptomatic individuals who may be at the earliest stage of sporadic AD, as opposed to individuals with mutations associated with autosomal-dominant AD. We will take a somewhat different tack than DIAN, in that we will likely pick one drug and do a one-arm drug versus placebo. The reason is that our primary outcome will be cognition with biomarkers as exploratory. Our preliminary analyses suggest if we really start with cognitively normal people, we will need all the power we can get to detect a slowing in the rate of cognitive decline, as these individuals decline slowly and there is variability in the rate of decline. Nevertheless, it looks like we can detect a 25-35 percent drug effect on the rate of decline on a composite cognitive measure with 300-500 subjects per arm. Thus, we will likely choose a single drug. At this point, it is likely to be a monoclonal antibody, as several of these agents have shown evidence of biological activity against A β in humans.

In contrast, my understanding is that DIAN will test initially three drugs in smaller trials, and use an adaptive design based on biomarkers. DIAN may also have more power to detect clinical change, because DIAN will also include carriers who are already symptomatic. That is a terrific design for DIAN, as the autosomal-dominant population is very precious and a limited resource. The “good” news for A4 is that there is a nearly unlimited supply of Baby Boomers entering the age of risk for AD, and if one-third of these individuals are amyloid-positive, there will be many potential participants. We want to do a large enough proof-of-concept study to see a signal on a clinical measure, as that is what is really needed in the field!

Q: Why prior to MCI? What are the entry criteria?

A: I believe MCI may even be too late for an anti-amyloid treatment. We know that if we pick people who have a little bit of memory trouble—who are at the mean or below on a cognitive test, or demonstrated a hint of decline, or anything that says they are not quite normal—then we increase the likelihood they will decline over three years. That makes for an efficient trial design. But I am concerned that even this might be already suboptimal for intervening with an anti-amyloid therapy alone.

Q: What would you rather do?

A: My dream is a trial that can address this question. In other words, a trial that enrolls a large enough sample of amyloid-positive people and stratifies them on the basis of whether they have any evidence of downstream neurodegeneration or memory trouble as well. Then we could directly ask this question of whether the treatment response changes depending on where in the long pathophysiological process you intervene with an anti-amyloid. Does it matter at what point you intervene in the course of preclinical AD? This is a key question. Importantly, we will also get critical natural history data from the placebo arm.

Q: What do you suspect is the answer?

A: Some people argue that the right folks to enroll are amyloid positive but before their CSF tau is very high. But up to 50 percent of the amyloid-positive cognitively normal people already have high tau before any cognitive problems. My point is, by the time there are symptoms in amyloid-positive people, the vast majority have elevated tau. So that in my mind becomes the critical question: Can we still intervene with an anti-amyloid treatment when the downstream cascade has already begun? I'd like to have a trial big enough where we can ask that question.

Q: Are the participants going to be there?

A: I think so. Another thing I am working to figure out at this point in the planning is how to increase power with international collaboration. I believe we can find 600-1,000 participants in the U.S. using the excellent site infrastructure of the ADCS. To go beyond that, we would like to collaborate with the [Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing](#) (AIBL), who have several hundred individuals enrolled in their natural history amyloid studies, and potentially with Bruno Vellas in France, who has a large cohort. If so, then we can go beyond 1,000 and have enough power to stratify on a number of variables.

Q: How about frequentist versus adaptive designs?

A: We have been discussing adaptive designs in which we would do an interim analysis to look at amyloid-lowering on PET and degree of decline in the placebo group, and potentially extend the trial if the placebo group has not declined enough. However, right

now it is not clear that we have adequate information to make short-term decisions to adapt the design.

Q: Since we are speaking about dreams for a future trial, how about a second drug? For example, could A4 test a tau-based agent along with an anti-amyloid agent? I hear a lot of agreement that treatment combinations are the way of the future, but no one seems ready to test any.

A: If there is a tau agent with adequate safety data by 2013, we would love to do a 2x2 factorial design, but it is unlikely that there will be adequate safety data available in time, in particular, any safety data on combination therapy. Another possibility would be two anti-amyloid drugs, one that targets A β production and another that targets amyloid clearance. But I don't think we should wait to start the A4 trial, and it is unlikely we will have the ability to test combination therapy in a large, long trial within the next year or two. So I think we should take our best shot with one drug now and learn all that we can about the changes in biomarkers and cognition, so that the next trials can be more efficient, allowing us to test several agents.

Q: Thank you for this interview.