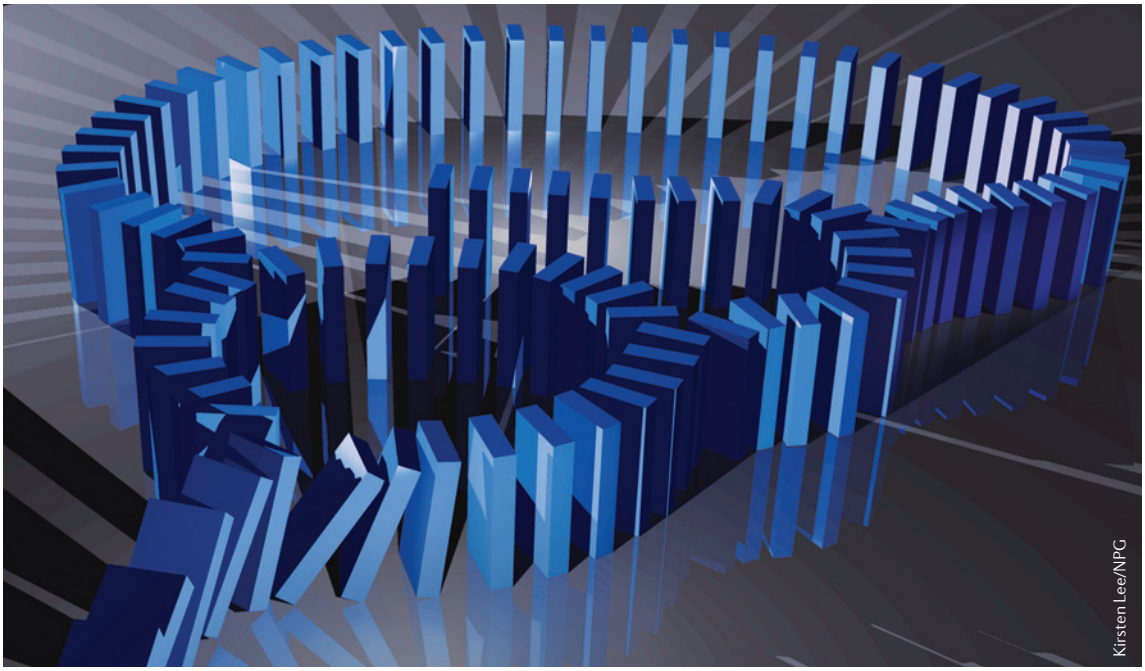

Sting of Alzheimer's failures offset by upcoming prevention trials

Three prevention trials in asymptomatic Alzheimer's disease patients will attempt to validate the amyloid hypothesis, evaluate biomarkers and set the stage for drug approvals.

Asher Mullard

Two recent Phase III failures of bapineuzumab in patients with mild-to-moderate Alzheimer's disease (AD) were disappointing, but hardly unexpected. Yet while the full implications for Pfizer, Johnson & Johnson (J&J) and Elan and their amyloid-β (Aβ)-targeting monoclonal antibody (mAb) will only become clear after detailed biomarker data are presented at the European Federation of Neurological Societies meeting in September, the next chapter of AD drug development is nearly underway: three complementary prevention trials will start within months to test whether anti-amyloid treatments are effective in asymptomatic AD candidate patients.

The first trial to launch could be run by the Alzheimer's Prevention Initiative (API), who are going to study the effects of Genentech's Aβ-specific mAb crenezumab in asymptomatic patients with a presenilin1 (*PSEN1*) E280A mutation that predisposes carriers to early onset disease. The Dominantly Inherited Alzheimer Network (DIAN), meanwhile, is planning to test three different, as yet undisclosed, therapies in a broader cohort of genetically defined early onset AD patients. And the A4 trial (short for anti-amyloid treatment in asymptomatic AD) will study a single unnamed drug in elderly patients who are at high-risk of developing disease, as assessed by amyloid imaging.

The API has already secured funding for its trial and is due to start enrolling patients in the first quarter of 2013. DIAN and A4 are still waiting on final funding decisions, but also aim to start their trials soon (see TABLE 1 for a summary of the trials' designs).

"It's the right step forward," says Todd Golde, Director of the Center for Translational Research in Neurodegenerative Disease in Florida, USA, who is not involved in any of the trials. If all goes to plan, the trials may not only help test drugs, but also validate the amyloid hypothesis, legitimize AD biomarkers and speed the future clinical development of drugs for broader patient populations.

Table 1 | **Summary of upcoming prevention trials in Alzheimer's disease**

Trial	Main patient population	Number of subjects*	Drugs (all versus placebo)	Primary aim and trial duration
API	Asymptomatic *PSEN1* E280A carriers, within 15 years of expected age of onset	216	Crenezumab	Cognition at 5 years
DIAN	Asymptomatic ADAD mutation carriers, 15 years before and up to 10 years after expected age of onset	160	Three undisclosed drugs	Target engagement at 2 years; a subsequent trial will assess cognition 3 years on
A4	Asymptomatic elderly patients with PET-amyloid positivity	1,000	An undisclosed drug	Cognition at 3 years

*Only including mutation carriers and positron emission tomography (PET)-amyloid positive-patients; all trials will also enrol negative biomarker patients for ethical reasons. A4, anti-amyloid treatment in asymptomatic Alzheimer's disease; ADAD, autosomal-dominant Alzheimer's disease; API, Alzheimer's Prevention Initiative; DIAN, Dominantly Inherited Alzheimer Network; PSEN1, presenilin 1.

"But this is tough stuff from a clinical trials point of view; there are still a lot of issues," Golde adds. The key challenges include having to select drugs, biomarkers and clinical cognitive end points on the basis of incomplete data sets.

The scientific basis for these trials, nevertheless, is clear, despite the growing list of Phase III AD failures. If the amyloid hypothesis is true, then AD pathogenesis begins long before cognitive decline sets in. By the time symptoms appear (and clinical trial enrolment begins) Aβ plaques and fibrils have done their damage and neurons are already dead and dying.

Advocates of prevention trials argue, moreover, that we need to test the AD drugs in the patient populations for which they were designed. The industry-wide focus on anti-amyloid drug development has been based largely on the discovery that mutant variants of amyloid precursor protein (APP), PSEN1 and PSEN2 (the latter two of which are components of the γ-secretase complex that cleaves APP to release Aβ; FIG. 1) can lead to aberrant amyloid processing and early onset disease. The transgenic mice that are used during preclinical drug development not only derive their AD-like symptoms from such mutations, but are also thought to be better models of asymptomatic patients than of symptomatic ones. The subjects in the API and DIAN trials in particular, therefore, are an ideal population for the range of disease-modifying candidates that have come out of industry laboratories (see TABLE 2 for selected pipeline of potential candidates, and FIG. 1 for a summary of where these act on the amyloid cascade).

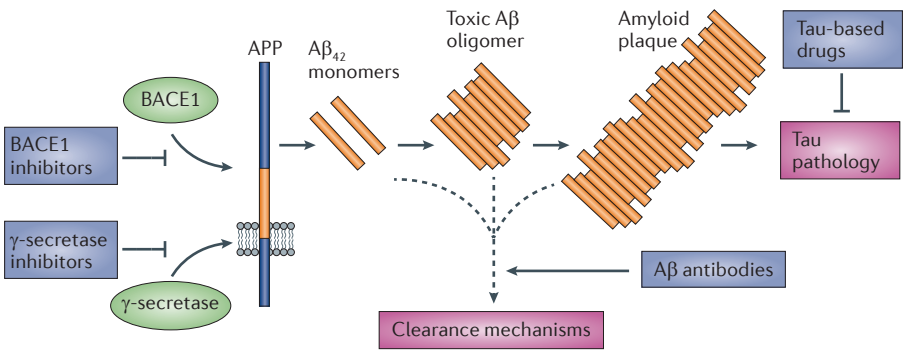

Figure 1 | **The amyloid cascade and therapeutic points of intervention.** The amyloid precursor protein (APP) is cleaved sequentially by β-secretase (also known as BACE1) and γ-secretase, releasing various amyloid-β (Aβ) peptides. The aggregation-prone $A\beta_{42}$ isoform can exist as monomers, oligomers and as amyloid plaques, which trigger downstream effects including tau hyperphosphorylation. BACE1 and γ-secretase inhibitors prevent the production of Aβ, whereas monoclonal antibodies (mAbs) — which can target different isoforms of Aβ — promote clearance. Vaccines could drive an immune system response that would clear Aβ, and tau-based therapies may moderate downstream effects of toxic build-up. Figure modified, with permission, from Citron, M. Alzheimer's disease: strategies for disease modification. *Nature Rev. Drug Discov.* **9**, 387–398 © (2010) Macmillan Publishers Ltd. All rights reserved.

API

The plans for the API's first trial were announced in May this year, when the group disclosed that it had received US$100 million in funding from academic funders and industry partners.

The 5-year trial will enrol asymptomatic subjects from a Colombian kindred with the inheritable *PSEN1* E280A mutation — which typically predisposes carriers to develop mild cognitive impairment by age 44 and AD dementia by age 49 — who are within 15 years of their parent's age of onset. One hundred carriers will be randomized to receive treatment and 100 carriers will be randomized to receive placebo (all three prevention trials will also enrol standard-risk volunteers to receive placebo so that subjects are not forced to learn their carrier status by participating). A further 16 carriers of different early onset AD mutations will also be enrolled in the United States and randomized to receive either treatment or placebo, in part to help bridge findings to a broader autosomal-dominant AD (ADAD) population.

API's drug of choice is Genentech's crenezumab. When the group first announced its choice, says Golde, his response was "What? We know the least amount about crenuzumab out of all the antibodies." As more data have been presented on the drug, he says he has come around to the view that it is a "reasonable choice".

Eric Reiman, executive director of Banner Alzheimer's Institute, Arizona, USA, and co-lead of the trial, concedes that the group took a risk in selecting a Phase II mAb backed by a small biomarker and safety dossier, but points to several factors behind their decision. Preclinical data suggest that it has good affinity against $A\beta_{42}$ monomers, oligomers and fibrils, enabling the group to hedge its bets in regards to uncertainty about which of these species are most pathogenically relevant in AD. It also seems to have a good ability to penetrate the blood–brain barrier, and, as yet, has not induced vasogenic oedema in trials (both bapineuzumab and the other amyloid-specific mAb in Phase III trials, Eli Lilly's solanezumab, were associated with the cerebral swelling, although there is some speculation that this manageable side-effect may be a necessary evil associated with amyloid clearance).

Beyond the drug, however, Reiman points out that the trial is largely about validating AD biomarkers and establishing an approval pathway that can accelerate future trials. "We have been arguing for years that the roadblock to finding effective treatments may be the time it takes to evaluate drugs

using conventional methods," he explains. Companies are caught in a vicious catch-22 scenario in which they cannot speedily develop AD drugs because of a lack of robust biomarkers, and they cannot validate biomarkers because of a lack of effective drugs. The homogeneous clinical course of the Colombian patient population, he hopes, will simplify these challenges.

The primary end point of the API trial is the change in cognitive function. Accepted cognitive end points such as ADAS-cog were designed to measure disease severity in symptomatic patients, and so the group has worked to develop a more sensitive tool that could detect the earliest changes in asymptomatic patients. The API has adopted an untested composite end point that combines the results of five cognitive tests. (DIAN and A4 are likely to use similar, though not identical, composite cognitive end points in their trials.)

Golde agrees that accepted cognitive end points are not up to the task for prevention trials, but cautions that the new composite end point carries its own complications. "They are really testing a hypothesis about a drug and a hypothesis about whether the battery of behavioural cognitive tests can show something," he explains. "They have two concurrent hypothesis that are being tested, and that always creates problems."

DIAN and A4

DIAN is also studying AD in a genetically defined early onset population, but is taking a staged approach in a broader cohort of patients.

In the first stage, 160 asymptomatic patients with any ADAD mutations in PSEN1, PSEN2 or APP — within a range of 15 years before to 10 years after their expected age of onset — will be randomized to receive one of three treatments or placebo. The first stage of the trial will run for 2 years, with a primary goal of determining whether the selected drugs engage their targets and modulate downstream factors. For example, positron emission tomography (PET)-amyloid imaging could show whether Aβ-specific mAbs are binding and clearing Aβ, and levels of phosphorylated tau in cerebrospinal fluid could help establish downstream activity.

The second phase of the trial will then test promising candidates for a further 3 years against a cognitive efficacy end point.

DIAN has not yet disclosed which candidates it will study, but should do so soon. "The goal is to test drugs of different classes and mechanisms," says DIAN investigator Randall Bateman, of the Washington University School of Medicine in St Louis, Missouri, USA. While antibodies against different forms of Aβ are one clear possibility, inhibitors of β-site APP-cleaving enzyme 1 (BACE1; FIG. 1) — three of which are due to enter Phase II trials soon — are also high up on the list. γ-secretase modulators, amyloid stabilizers and non-amyloid-based therapeutics are also in contention. γ-secretase inhibitors might face a particularly high hurdle for inclusion though, because poor efficacy and poor safety results have already setback the class and because data suggest that these drugs can be more active against wild-type versus mutant γ-secretase.

The trial "will be an iterative process," adds Bateman. Although DIAN will initially only test three drugs, he explains, it could study other candidates as they mature, potentially by adding them to the trial using a rolling enrolment mechanism.

Both Reiman and Bateman note that regulators have given them encouraging signs that the API and DIAN trials could be sufficient to register drugs for approval, at least for narrower ADAD populations. The extent to which success in the ADAD populations could predict success in sporadic AD (SAD) populations, however, remains unclear. "They are not the same diseases, and I don't think any of us would claim they are," says Bateman. "But the evidence between SAD and ADAD appears to be converging."

Accumulating evidence suggests that the commonality between patients with ADAD or SAD begins early, perhaps 15–20 years ahead of symptoms. In one recent study of the natural history of patients with ADAD, biomarkers moved both directionally and quantitatively in step with expectations for SAD patients, says Bateman (*N. Engl. J. Med.* 12 Jul 2012; doi:10.1056/NEJMoa1202753). And although the various ADAD mutations lead to different patterns of amyloid build-up

Table 2 | **Select list of potentially disease-modifying drugs for Alzheimer's disease**

Name	Lead company	Current phase
Amyloid-targeting mAbs		
Bapineuzumab	Johnson & Johnson	III
Solanezumab	Eli Lilly	III
Gammagard*	Baxter	III
Gantenerumab	Roche	II
Crenezumab	Roche/Genentech	II
BACE1 inhibitors		
ACI-91	AC Immune	II
LY2886721	Eli Lilly	I/II
MK-8931	Merck & Co.	I
E2609	Eisai	I
RG7129	Roche	I
γ-secretase inhibitors		
NIC5-15	Humanetics	IIb
Avagacestat	Bristol–Myers Squibb	II
CHF5074	Chiesi Farmaceutici	II
Tau-based therapies		
TRx-0237	TauRx Therapeutics	II
BMS-241027	Bristol–Myers Squibb	I
Anti-amyloid vaccines		
ACC-001	Johnson & Johnson	II
CAD106	Novartis	II
AFFITOPE AD02	GlaxoSmithKline	II
ACI-24	AC Immune	I/II
V950	Merck & Co.	I

*Whereas most amyloid-targeting monoclonal antibodies (mAbs) bind specifically to amyloid-β, gammagard consists of pooled immunoglobulin G antibodies with broad specificity. BACE1, β-site amyloid precursor protein-cleaving enzyme 1.

throughout the brain, the API has presented data showing that the pattern of accumulation in *PSEN1* E280A carriers and in SAD patients is similar.

Further differences between patients with ADAD and SAD may also be bridged in part by the A4 trial, which will run in elderly asymptomatic patients who have amyloid build up, as assessed by PET-amyloid imaging positivity.

"This is a thornier trial," says A4 trial co-lead Reisa Sperling of the Harvard Medical School, USA, in part because there is less certainty about which subjects will decline and when. As a result, the A4 trial is larger, enrolling 500 subjects to receive the drug and 500 to receive placebo. The trial will include some patients who are carriers of the mutant apolipoprotein 4 (*APOE4*) — who have an increased risk of developing SAD — and will run for 3 years. It will primarily assess cognitive outcome. "I like biomarkers, but to me it doesn't matter whether we change amyloid or lower tau, it matters whether we make people's memory better, and I'm concerned that we don't know enough about what changes in a biomarkers mean for clinical outcomes," she says.

A4 has not yet selected which drug to use, but Sperling says they are likely to choose a mAb with a large dossier of clinical biomarker data backing up its amyloid-lowering activity. The biomarker data for bapineuzumab will therefore be important for assessing whether it is still in the running.

"If someone has an extra $100 million to give us, I'd love to do a 2×2 factorial design where we would test an anti-secretase inhibitor and a clearance agent on their own and in a combined group. Or to test an anti-tau agent in a 2×2 design," she adds.

The next wave

Although academic groups are driving all three prevention trials, industry is clearly keen to participate. Several firms are showing willingness to contribute resources — including drugs — to the trial investigators. In part, says Reiman, this may be because the trials have a precompetitive aspect to their design. Husseini Manji, global therapeutic head of neuroscience at J&J, agrees. "Whichever drugs get picked for these is almost incidental: the trials are more about learning how early you have to intervene, what biomarkers might change and at what time, and how end points change," he says.

Industry, adds Manji, is keen on keeping its options open. "Everyone believes that the earlier you get in the better, but we hope that if you get in later you will still see some benefit". Although Pfizer and J&J have discontinued the Phase III development of intravenous bapineuzumab in patients with mild-to-moderate AD, they are still considering the option of developing the mAb for prodromal patients, who have only the earliest signs of cognitive decline.

Plans are also in the works for future prevention trials. Manji and colleagues have proposed a trial in subjects with Down's syndrome, who have an increased risk of developing AD because they carry an additional copy of the *APP* gene (see the article on page 655). The API, meanwhile, hopes to launch a prevention trial in asymptomatic carriers of *APOE4* in 2014, and Sperling has her eye on an 'A6' trial that would test a treatment in asymptomatic amyloid-negative patients (possibly enrolling *APOE4* carriers or subjects with a family history of disease).

Golde argues, however, that a broader, bolder strategy rethink is needed. Academic groups and industry alike have focused on conservative product development rather than high-risk discovery work, he says, and as a result there has been minimal progress in advancing our understanding of the disease and identifying novel targets. And although these prevention trials are a step in the right direction, they still fall into the product development silo. "I'm concerned that if we can't develop these Aβ therapies, we don't have much waiting in the wings."