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CTAD 2012 in Monte Carlo: Getting Preclinical Trials Ship Shape

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By Gabrielle Strobel and Madolyn Bowman Rogers

Turning the Ship Around Toward Early Trials

In a place where yachts sit jammed side by side in the harbor like so many gilded peas in a pod, a marine metaphor seems fitting. The conference showcased a field trying to steer therapy development out of the doldrums of the past decade and into swifter waters. Organized by **Bruno Vellas** of the University of Toulouse, **Jacques Touchon** of Montpellier University Hospital, with **Paul Aisen** of the University of California, San Diego, and **Mike Weiner** of the University of California, San Francisco, the conference drew a record 660 attendees from around the world to this city-state nestled against a hilly spit of land along the French Riviera. CTAD has become a magnet for scientists spanning the waterfront of AD therapy development, from preclinical to regulatory science.

Yachts moored in Port Hercule Harbor. *Image courtesy of Gabrielle Strobel*

Calling on researchers to make a difference in this disease, **Prince Albert II** of Monaco greeted attendees in the principality's Oceanographic Museum, perched grandly on a promontory overlooking the Mediterranean Sea.

Prince Albert II of Monaco addressed AD researchers on the eve of the 5th CTAD conference. *Image courtesy of Gabrielle Strobel*

In Monaco, the main buzz of conversation was about news from the ongoing analyses of intravenous bapineuzumab and solanezumab. These two anti-amyloid antibodies missed their primary endpoints in Phase 3, sinking the former, but an apparent cognitive benefit gave a second wind to the latter. Researchers continue to plumb the depths of the data generated by these trials for a better understanding of how biomarker changes align with safety and efficacy signals. “These datasets are very large, and have more to tell us yet,” Aisen said.

Beyond these trials, CTAD made clear that the field has tacked toward conducting trials at the prodromal, even presymptomatic, stages of disease, and is working to tighten the tools and designs necessary to do that. “We all agree by now that earlier intervention is a key strategy for success,” said **Chris van Dyck** of Yale University in New Haven, Connecticut.

The conference program kicked off with a keynote session on regulatory science. **Cristina Sampaio**, a neurologist who recently left the European Medicines Agency (EMA) to work for CHDI in Princeton, New Jersey, took stock of changes at the EMA over the past five years that have set the stage for new types of trials. She singled out the introduction of research diagnostic criteria that added specificity to the prevailing concept of mild cognitive impairment (Dubois et al., 2007). “For us, the MCI criteria of 1999 were too ill defined to represent a licensable entity. The International Working Group research criteria were closer to the disease and made it possible for us to move. We started to accept trials that use these criteria for inclusion in 2009,” Sampaio said. Those criteria combine a mild but measurable memory impairment with a biomarker change. The subsequently revised U.S. criteria (Albert et al., 2011) “are fine as well,” said **Karl Broich** of the German Federal Institute of Drugs and Medical Devices in Bonn, and the EMA.

Implementing these new criteria is no picnic, however. Van Dyck offered a reality check in his update on therapeutic trials that have since used them. Examples include Phase 2 trials of Bristol-Myers Squibb’s γ-secretase inhibitor avagacestat and of Pfizer-Janssen's AIP active immunization ACC-001, as well as a Phase 2/3 trial of Roche’s antibody gantenerumab. Details vary, but each trial essentially recruits for prodromal/predementia AD, aka MCI due to AD, by looking for

people who have both measurable memory loss and either an AD signature in CSF or brain amyloid as measured by PET. The problem? It's a hard slog for the trial sites to find those patients. In the avagacestat trial, 1,350 candidates had to be taken through informed consent and screened to obtain 550 who met criteria for amnestic MCI. Those underwent a lumbar puncture, and 48 percent met the cutoff for AD pathology. In toto, 81 percent failed screening, van Dyck told the audience. The clinical exclusion criteria, including the memory cutoff, thus contributed even more to screen failures than did the CSF threshold. Similarly, in the ACC-001 trial, many failed cognitive testing, and about half of those who made it through met the biomarker criterion.

Site investigators elsewhere in the U.S. and in Europe confirmed that recruitment for prodromal trials has been tough going. They urged that biomarker cutoffs and methods for determining PET positivity be set with great care, as the sites are seeing many near misses around those thresholds. "Think about the person right on the cutoff line who gets a call from me, the site PI. What do I say? 'The bad news is you are not eligible for this study, and the good news is you are not eligible for this study'," Van Dyck said, "This highlights that we are making dichotomous decisions about continuous variables that are fully distributed. We need to study this further."

Sometimes a patient who fails the biomarker component clearly seems to have very early AD, said **Steve Salloway** of Brown University in Providence, Rhode Island. Other site leaders noted that, once eager patients have undergone an invasive procedure, telling them they are ineligible becomes a more regretful conversation between patients and their physicians.

Those woes aside, enriching trials in this way is feasible. Two of the three trials mentioned here are fully enrolled. Their recruitment has shown high concordance between CSF and amyloid PET, meaning they are largely interchangeable, van Dyck said. Gantenerumab is enrolling. Phase 1 and 2 trials of additional drugs, such as Eisai's and Lilly's BACE inhibitors (see ARF Vancouver story), the new monoclonal antibody BIIB037 by Biogen, and an upcoming adaptive trial of the protofibril antibody BAN2401 by Eisai BioArctic are using either CSF or amyloid PET as part of their inclusion criteria as well.

"These studies are essential. We have to do this," van Dyck said. He added that consistent diagnostic guidelines across studies, and more cost-effective biomarkers, would make the process more efficient for the participating sites. Even as enrichment trials work out their growing pains, observational studies further substantiate the case for testing therapies in people who are on their way to develop AD dementia. Examples include AIBL and ADNI, as well as a Swedish cohort study that recently reported nine-year follow-up data (see Buchhave et al., 2012).

Besides Enrichment, What Else Is New?

The trial failures of the past decade offer ample learning opportunities. This topic bubbled up in sessions throughout the conference. For example, **Lon Schneider** noted that trials would be well advised to find ways to sample their participants on outcomes more frequently than is currently done. Data points on most outcome

measures have swung widely in recent trials; too few data points can elevate outliers and mask an overall trajectory. “As a result of infrequent testing, we miss drug effects,” Schneider said. He further recommended establishing run-in data before starting the treatment phase of a trial.

CTAD saw extensive discussion of cognitive outcome measures. Besides being brief, such tests should reflect the expected mechanism of action of the drug, Schneider said. He cautioned against using composites in which some tests have practice effects, as those may hide a drug response indicated by other tests in the mix. In fact, **Keith Wesnes**, of United BioSource Corporation, Goring-on-Thames, U.K., reported at CTAD that half of the cognitive tests used in ADNI showed practice effects. The list includes the Boston Naming and Trail Making tests, and others. ADNI-1 controls improved over six years’ time on those tests, even though prior research has established that cognitive function wanes with age; hence, the controls should have declined. In essence, Wesnes said that tests with practice effects show a longitudinal element, i.e., worse performance with age, when given once to people of different ages. When given repeatedly, as in ADNI, the practice effect can mask age-related decline.

The effect size of this "training" was in the range of that seen with acetylcholinesterase inhibitor drugs, hence, may swallow up small drug effects in clinical trials. The training effect calls the value of these tests in clinical trials into question, Wesnes claimed. “These tests are useful for cross-sectional use in longitudinal natural history studies; they are not suitable for drug studies in preclinical AD,” he said. Practice effects have been shown before (e.g., Wilson et al., 2002).

What about the most commonly used cognitive battery, the ADAS-cog? Schneider called it a "utility infielder," that is, a perfectly respectable, albeit overplayed, generalist. “It is used automatically whenever we test a drug. Whether Phase 2, Phase 3, no matter what the drug is,” Schneider said. Expectations have slid from a three-point ADAS-cog improvement in six months with the symptomatic drugs of the 1990s to “we’d be happy if we saw any improvement over 18 months,” Schneider said. “We should not continue to rely on it to advance drugs from Phase 2 to 3.”

On a separate note, Schneider advised against enriching Phase 3 trials for ApoE4 subsequent to analyzing Phase 2 trials by ApoE genotype. Rosiglitazone and bapineuzumab are two examples where analysis of Phase 2 data indicated a different drug response in ApoE4 carriers than non-carriers, but subsequent pharmacogenomic Phase 3 programs failed. Studies have shown that ApoE4 and CSF Aβ or brain amyloid are closely linked; glucose metabolism and connectivity change earlier in carriers than non-carriers as well. In ADNI, 89 percent of people with MCI due to AD who carried an ApoE4 allele had a positive CSF Aβ biomarker. Schneider’s argument against testing drugs separately in clinical trial samples enriched by ApoE4 status is that carriers essentially have more advanced disease than non-carriers, not necessarily a qualitatively different type of AD that would predict a different drug response.

To study enrichment by ApoE status, Schneider, with Richard Kennedy and Gary Cutter at the University of Alabama, Birmingham, simulated running trials in various samples ranging from all ApoE4 carriers to no ApoE4 carriers in a database of placebo data from 18 pooled ADCS trials. They found no differences in the trials' efficiencies. This leads to the contrarian conclusion that selecting prodromal AD patients for a trial based on CSF Aβ42 or ApoE4 status may identify more advanced cases of MCI, but not necessarily enhance statistical power. As trials are adding genetics or evidence of amyloid to their inclusion criteria, it might be preferable at this point to use these markers as an explanatory variable, not to stratify by ApoE status or to exclude people based on their CSF Aβ42, Schneider suggested. These findings are consistent with van Dyck's report that only 19 percent of potential MCI patients are severe enough, with both memory impairment and biomarker positivity, to be included in prodromal AD trials, Schneider wrote to Alzforum.

Many trials enroll a wide age range, typically from 55 to 90 years. This practice may be democratic but hazardous to the outcome, according to **Dominic Holland** of the University of California, San Diego. Holland studied how age affects disease progression in ADNI. He found that cognitive decline and atrophy tend to slow with advanced age in people who have MCI or AD, while, on the contrary, this decline speeds up with age in healthy controls. This implies that it is difficult to distinguish AD from normal aging in the oldest old, and that including very old people in a trial reduces statistical power. Younger cohorts with a tighter age range might better enable trials to measure drug effects, whereas studies in older people could help confirm safety and tolerability of a therapy, Holland said (Holland et al., 2012). Alas, a large proportion of dementia prevalence occurs in people older than 80 (Brayne and Davis, 2012).

New Data on Sola, Bapi, Spark Theragnostics Debate

The conference offered new data from ongoing analyses of the Phase 3 programs on solanezumab and bapineuzumab. Both programs missed their primary endpoints. The news added up to a curious situation where, at present, it looks as if the biomarkers that are showing predictable and strongly convergent trajectories across natural history studies are not, so far, behaving as expected in therapeutic trials. "We see a dissociation of biomarker and clinical outcome," said **Reisa Sperling** of Brigham and Women's Hospital in Boston. Solanezumab slowed cognitive decline without affecting CSF markers of neurodegeneration. Bapineuzumab did improve those downstream markers, but flopped clinically. On volumetric MRI, both antibodies delivered a head-scratcher that is clouding this marker's prospects as a potential surrogate and focusing renewed interest on more sensitive cognitive outcome measures. It is unclear at this point whether any of the known biomarkers are theragnostic, i.e., track or predict a drug effect. "We need better markers of synaptic response to fill this gap," Sperling added.

When considering the data's nuances—and there was a lot of nuance at CTAD—this disconnect begins to blur a bit, and the data may make more sense. Solanezumab mobilized soluble Aβ in plasma and appeared to nudge CSF concentrations. The finding recalled earlier studies with this antibody and led some attendees to wonder whether a peripheral sink effect might have been at play. Bapineuzumab, on the other hand, appears with more analysis to perhaps

have had a hint of functional benefit in the mild subgroup after all, but that came at the cost of more white matter changes than was initially thought. Whatever benefit there was appeared to be disease modifying, not symptomatic. At the same time, a growing number of researchers are downplaying this once-prominent issue as a distinction without a difference, joining an argument one presenter has been making for some time (Doody, 2008). Confused? You are not alone. At CTAD, the program featured five talks by Sperling, **Paul Aisen**, **Rachelle Doody**, **Nick Fox**, and **Steve Salloway**, as well as a panel discussion to grapple with the data. Small group conversations could be overheard outside the auditorium throughout the conference, and no doubt continued over dinners and nightcaps. Read on for summaries of the data presentations and discussions.

First, a word about how information on this story is coming out. CTAD continued a data trickle that will go on at least through next spring. After the companies disclosed topline news last summer that their programs had missed primary endpoints, the actual results have been presented in bits and pieces at conferences last September, October, and most recently at CTAD. Yet more is to come at the AAN meeting in San Diego in March 2013. Some researchers bemoaned this gradual dissemination. Others were further puzzled that Lilly released its solanezumab data to investors but not to scientists on 9 October on the day of a major neurology conference in Boston, where an independent academic analysis of Lilly's data was first presented (see ARF related conference story).

When asked about this, scientists at Janssen AIP, Lilly, and at various academic institutions pointed to the multiple forces that drive when data are released. All insisted that the drip-drip-drip was not strategic but a function of huge datasets being continually analyzed for successive questions. "As soon as we have new results, we present them at the next opportunity," said Salloway of Brown University, Providence, Rhode Island. Companies are required to release topline information as soon as they get it, hence, the summer press releases. The Securities and Exchange Commission requires disclosure to shareholders, hence, Lilly's posting of slides during the October investor call. Separate from that, Lilly and the Alzheimer's Disease Cooperative Study have negotiated a unique agreement whereby the Alzheimer's Disease Cooperative Study (ADCS) analyzes Lilly's raw data independently. Initiated by **Richard Mohs** and **Eric Siemers** at Lilly, this serves the field's collective desire to learn as much as possible from these enormous datasets and keep a version in the public domain. It also was a response to a demand by journal editors, said **Paul Aisen** of the University of California, San Diego, who leads the ADCS. The agreement stipulates that the ADCS presents its analysis at conferences and takes the lead on publication. This means, in effect, that the ADCS communicates Lilly's Phase 3 results through its lens with the scientific community, while Lilly uses its internal analysis for guidance from the Food and Drug Administration about what to do next.

Solanezumab: The New Data

Before presenting results, Aisen explained how the ADCS handled this industry dataset. Three ADCS statisticians—**Ron Thomas**, **Rema Raman**, and **Mike Donahue**—each conducted his or her own analyses of Lilly's raw solanezumab Phase 3 data. Each coded, input missing data, and programmed the models to reveal the implication of each statistical decision made along the way. Having

been collected by Lilly through contract research organizations, with different forms and procedures than the ADCS has developed over time for its own trials, the solanezumab data needed to be transferred, and in places restructured, to fit the ADCS system. The statisticians handled out-of-window visits, missing scores, and at times had to deviate from Lilly's statistical analysis plan (SAP). Why is this important? Because when the effect of a drug is small, as is true here, each decision the statistician has to make along the way can affect the p value of statistical significance, Aisen told Alzforum. At CTAD, Donahue gave a whole talk just on how ADCS statisticians treat missing clinical trial data. "We have analyzed Phase 3 data going back to tacrine," Aisen said, "We have our own approach to imputation and analysis. We opted to follow the spirit of Lilly's, yet apply some of the specific approaches we have gleaned from our experience."

Despite the statistical challenges, a coherent picture of a cognitive benefit emerged, Aisen said. The effect is very small but statistically robust in pooled analyses, holding up across variations of the data. The benefit amounts to a 30 to 35 percent slowing of cognitive decline in the mild subgroup. This number fits with the data Lilly released to investors on 8 October, which claimed a 34 percent slowing. The ADCS analysis showed 1.5 points less decline in ADAS-cog 11, and 1 point less in MMSE for solanezumab than placebo in patients with mild AD. The ADL functional score showed 1.5 points less decline in the mild group, though this result has less statistical confidence. Neither the neuropsychiatric inventory nor the CDR Sum of Boxes showed any difference.

On biomarkers, the main result came from plasma Aβ. Solanezumab caused a sharp and sustained increase that is consistent with the antibody's tight binding to monomeric Aβ. The CSF showed a more complex picture. The concentration of both Aβ40 and 42 rose in the mild to moderate AD group. The much smaller pool of free Aβ40 showed a decrease in treated patients, while free Aβ42 did not. The CSF numbers are based on smaller group sizes (13 to 66) than those for plasma (700s) or MRI (600s to 900s). To Aisen, the rise in plasma and CSF levels of total Aβ constitutes target engagement; many others agreed.

Florbetapir scans in the solanezumab PET imaging substudy showed no significant change between the groups. The mild subgroup had a trend toward less amyloid in the treated group, but it missed statistical significance. There was no effect at all on CSF tau or phospho-tau overall or in any of the subgroups. Whole brain volume was the same between groups. On hippocampal volume, too, the analysis showed no overall treatment effect. Of the subgroups the ADCS analyzed separately, one looking at people with confirmed amyloid positivity showed a trend. This is merely a hint in a subgroup of a subgroup. Still, its direction was toward more shrinkage in the treated group (for more on MRI atrophy, see below).

Solanezumab's clinical effect may be related to Aβ reduction at synapses as opposed to protection of cells, said **Rachelle Doody** of Baylor College of Medicine in Houston, Texas. Other scientists at CTAD agreed with this assessment. For example, **David Morgan** of the USF Health Byrd Alzheimer's Institute in Tampa, Florida, noted that the solanezumab data jibe with what is known from mice. APP mouse models of amyloid deposition have cognitive

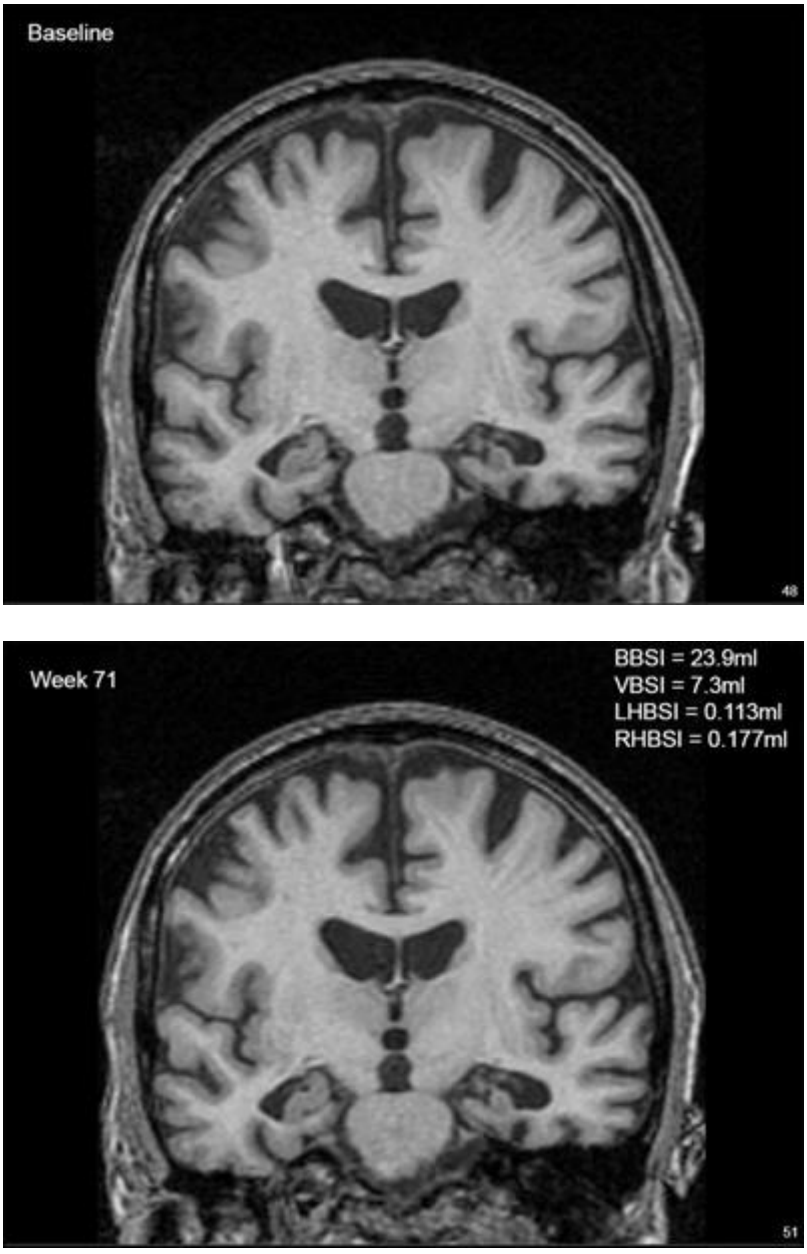
deficits independent of neurodegeneration, tau pathology, or atrophy (e.g., Kotilinek et al., 2002). The antibody used to engineer solanezumab, m266, was reported to restore memory in mice without a measurable effect on amyloid (Dodart et al., 2002). A large and rapid increase in plasma Aβ soon after m266 injection is known from mice (Demattos et al., 2002). **Lars Lannfelt** of Uppsala University, Sweden, said that solanezumab prolongs the half-life of Aβ in plasma and delays its degradation in the liver and kidneys. This might explain the sustained elevation in plasma, though how much of this plasma Aβ might come from brain as opposed to from peripheral cells was not shown.

In toto, the Phase 3 solanezumab data support a small cognitive benefit and may call for a confirmatory study in mild AD, Aisen said. Researchers hope that studies in prodromal or preclinical AD (see ARF related news story on DIAN) will yield a larger effect. At CTAD, speculation was rampant about whether these data alone might sway regulators to approve the therapy.

Bapineuzumab: The New Data

Steve Salloway presented a prespecified subgroup analysis of the bapineuzumab patients with mild AD. It differed from a previous analysis in that it used a cutoff of 20, not 21, on the MMSE, because 20 is what the solanezumab analysis used. "We thought it would be informative to see how the data compare," Salloway told Alzforum. On most measures, this analysis, like the first one, found no difference between antibody and placebo for either the ApoE-carrying or non-carrying patients. On one, however, it sighted a bit of a signal, that is, a statistically significant treatment effect on the DAD functional measure. Non-carriers showed a benefit of about four points on both doses, while the pooled analysis of carriers and non-carriers showed a similar benefit only for the higher dose. "We are not making very much of this effect," Salloway said, and Janssen scientists reiterated that clinical development of intravenous bapineuzumab has ended. Also new in Salloway's presentation was the analysis of the secondary clinical endpoint consisting of the CDR-SB, the NTB and the MMSE: no differences in the total study population in either study; subgroup analysis is ongoing.

Most of the new bapineuzumab data at CTAD came on biomarkers. **Nick Fox** of University College London toggled between MRI scans taken of the same subject at baseline and weeks 19, 45, and 71 to show how the brain's ventricles subtly expanded, and the cortex and left hippocampus ever so slightly contracted.



Can you see it? Slight ventricular expansion in bapi-treated subject.
Image courtesy of Nick Fox/Janssen AIP, from CTAD website

Pooled analysis of both Phase 3 studies confirmed a mildly increased rate of brain volume loss in the bapineuzumab group at the higher dose, and in the mild subgroup at both doses. The difference came to about 2 milliliters per year for whole-brain volume, Fox said. In the left hippocampus, the difference was significant in non-carriers at the higher dose only. The ventricular effect was most pronounced, showing up as significant in the carriers, non-carriers, and pooled analyses.

Taken together, then, biomarker data on intravenous bapineuzumab suggest that the treatment nudged amyloid deposition but not soluble Aβ, clearly decreased CSF tau and phospho-tau (this was presented at a previous conference), and led

the brain to shrink a bit faster. This means the antibody engaged its target, but it hardly helped at all clinically, Fox said.

If one includes the faint hint on solanezumab, this bapineuzumab MRI finding would be the third demonstration that anti-amyloid immunotherapy can subtly shrink the brain. (The first came in 2004 with AN1792, a discontinued Aβ42 vaccine; see ARF related news story). Why? The first instinct—that the shrinkage equals more neuronal death—is probably wrong because CSF tau went down with bapineuzumab. Is it amyloid removal? Maybe not alone, because the extent of amyloid removal was small. Does immunotherapy reduce the inflammation and debris associated with amyloid deposition? Does it change CSF absorption, or cause other fluid shifts in the brain? These notions warrant active study, Fox said. "We have to understand this."

A propos fluid shifts, bapineuzumab has gained some notoriety for causing white matter changes, perhaps indicating leakage of fluid, proteins, or cells from vessel walls after amyloid drainage. Called amyloid-related imaging abnormality (ARIA), this finding has since been reported for other anti-amyloid therapies such as Bristol-Myers Squibb's γ-secretase inhibitor BMS-708163/avagacestat and Roche's antibody gantenerumab as well. The FDA requires close monitoring of this poorly understood finding, and the massive amounts of MRI data subsequently generated from this surveillance were the subject of a CTAD talk by Sperling.

There are two kinds of ARIA: E for vasogenic edema, indicating fluid seeping out of blood vessel walls or collecting in sulci, and H for hemosiderin deposit, indicating a microhemorrhage. At CTAD, Sperling presented preliminary results of a large study that determined the incidence of ARIA-E by giving a final read to every one of the 15,000 MRI scans taken during the bapineuzumab Phase 3 program. Two radiologists independently viewed the scans. Every time they found an ARIA-E, they pulled up that person's prior scan to see if the abnormality had been there before. In this way, they called some 30 percent more cases than had been noted during the conducting of the trial.

The incidence of ARIA-E rises with ApoE status and with dose. About 1 percent of patients on placebo had ARIA-E, but so did one in five ApoE4 carriers on 0.5 mg/kg bapineuzumab. Among ApoE homozygote patients, it was one in three. Among ApoE4 non-carriers, the ARIA-E incidence at that dose was 5.6 percent, but the highest (and discontinued) dose of 2.0 mg/kg brought it to 19.9 percent. Most ARIA-E developed after the first three infusions.

Why were some ARIA-E incidences overlooked? Awareness of this side effect is new; indeed, it emerged during bapineuzumab's development. Local radiologists missed some edemas on the first read. In many cases, the first ARIA-E was small, Salloway told Alzforum, and grew by the time of the subsequent scan. Midway through the study, a central read was instituted, but there, too, not all radiologists picked up every finding right away. Some site PIs did not acknowledge all findings, Sperling told the audience.

Sperling told Alzforum that the people with ARIA-E tend to be prone to ARIA-H as well, but this analysis is still underway.

How bad is ARIA? It is too early to say, Sperling said. A majority were asymptomatic, but about one in six were linked to symptoms such as headache, confusion, and cognitive changes. When patients were taken off the drug, the abnormality resolved over a period of months. A preliminary analysis of the Phase 3 final-read data shows that, clinically, ARIA-E appeared to make no difference on the course of a person's Alzheimer's disease. People with ARIA-E did not decline any faster or slower on the ADAS-cog or DAD than those without, though the scientists need to dig deeper into the data to check if differential dropout might have biased this finding. Some scientists believe that ARIA-E is a sign of amyloid clearance. Others noted that it will be important to watch what becomes of these patients in the longer term. In ApoE4 carriers but not non-carriers, the treatment group had more seizures than the placebo group.

Finally, on imaging, Sperling emphasized that 36 percent of ApoE4 non-carriers who joined the bapineuzumab amyloid PET substudy fell below the preset threshold for amyloid positivity. At CTAD, Sperling told the audience that a look at amyloid PET data of the solanezumab Phase 3 trials, which Lilly had shared with her, showed the same thing for the ApoE-negative participants in those trials. Both large Phase 3 programs appear to have enrolled a third of patients who arguably may not have Alzheimer's disease but something else. Florbetapir is clinically approved to rule out Alzheimer's. "This is a large number, and it is a problem," Sperling said.

In discussion, researchers expressed a consensus that bapineuzumab failed over dose. It could not be safely given at high enough doses to make a difference. Others noted that the picture was still incomplete. For example, critical data on drug exposure antibody levels in plasma and CSF are still missing for both programs, as is a full analysis of the amyloid-positive versus negative participants. Several researchers cautioned that when a drug effect is as small as solanezumab's, type 1 error, aka false positive, is always a concern, even when the statistics look internally consistent.

"These are valuable data, but I can't overstate how disappointing that was to our patients and families," said Fox. Other site leaders agreed, but noted that their patients felt they did contribute to science and want to participate again.

Some slide sets on Bapineuzumab, plus a one-hour audio recording on solanezumab, have been uploaded to the CTAD website. The recording features an attempt by Sperling to synthesize the data available thus far on both antibodies, as well as a subsequent panel discussion. Play it to get a sense of where the field stands at this point.

Regulatory Science Gains Prominence in AD Research

At the conference, six talks covered "regulatory science." Call it "soft" if you will, but this interface between science and the regulatory process is becoming an integral part of Alzheimer's therapy development as more researchers wade into the uncharted waters of evaluating drugs in the disease stages before dementia.

Regulatory science drives governmental health, legislative, and judicial decisions. As this discipline is becoming more active, transparent, and collaborative among agencies and outside groups in the Alzheimer's field, it is gaining visibility, and researchers increasingly consider it important to understand. Here is a digest of what the health authorities and their partners on both sides of the Atlantic had to say.

Cristina Sampaio spent 13 years at the European Medicines Agency before moving earlier this year to CHDI in Princeton, New Jersey. She told the audience that in the past five years, work at the EMA was marked by a shift away from the standard model of drug evaluation in Alzheimer's. In particular, the revision in both Europe and the U.S. of consensus diagnostic criteria set the stage for the EMA to facilitate its incorporation into clinical trials. Since then, the agency has issued three opinions on qualifying biomarkers for enrichment of clinical trial populations. In February 2011, the EMA gave a first nod to CSF biomarkers with its draft opinion that a pathological signature based on low Aβ42 and high tau was acceptable for identifying prodromal-stage patients who are at risk to develop Alzheimer's dementia for inclusion in trials. In October 2011, the EMA issued a draft opinion on using hippocampal volume to enrich trials (see ARF related news story). In January 2012, the final positive opinion on volumetric MRI followed. In February 2012, the EMA issued a qualification opinion for amyloid PET as a biomarker to enrich predementia trials.

Each of these opinions followed a systematic review of data, rounds of intense discussion, and a public comment period, said **Remy Cahn**, a regulatory scientist at Bristol-Myers Squibb in Rueil, France.

On 12 October 2012, the EMA recommended that florbetapir be licensed for clinical use; a final decision by the European Commission is pending. Qualification for enrichment and licensing for clinical use are different processes, Cahn said. For example, qualification is independent of the particular product used, whereas licensing is specific to the product.

The EMA and the FDA do this work in an ongoing dialogue with non-governmental organizations such as the ACT-AD umbrella coalition of advocacy groups involving in issues of aging, and CAMD, the Alzheimer's/Parkinson's consortium of the Critical Path Institute based in Phoenix, Arizona (see ARF related news story).

This pace is not fast enough for some. "For industry to continue to make investments, there needs to be greater predictability and regulatory certainty on how products will be judged. Without that we will lose the support needed to see through the next generation of therapies," said **Dan Perry**, who chairs ACT-AD.

Monte Carlo's Casino, located 800 feet from the CTAD site. NGOs such as ACT-AD are working with regulators in hopes of making drug development less of a gamble for patients and companies. *Image courtesy of Gabrielle Strobel*

No new AD therapeutics have been approved in nearly a decade. Sampaio said that besides metrifonate, the EMA had not actually turned down a single new AD drug application in that time. The reason for the drought is that, after memantine's approval in 2005, companies submitted no more applications. With the prevailing investigational compounds and trial designs at the time, no Phase 3 program achieved enough success to even come before the regulators and ask for marketing authorization. Most of the EMA's licensing work concerned labeling extensions, safety issues such as mortality of antipsychotics in AD, formulations, and generics.

"The real action in my time at the EMA was in the scientific advice working party," said Sampaio. Besides dealing with the investigational drugs that ultimately failed these past 10 years, the working party laid the groundwork for a wave of different trials that is now starting to take hold. "Both the EMA and the FDA are committed to using good science," Sampaio said. "The principles we developed are likely to facilitate the next generation of successful medicinal products."

Besides the diagnostic criteria, the second key factor driving change at the EMA was that the working party took up the issue of prevention trials in AD. "Presymptomatic carriers were never discussed at EMA until we set up a workshop in 2010. This was important. Rusty Katz and colleagues from FDA were there by video. Both sides endorsed the goal of presymptomatic trials, and the discussion has been going in a very positive mode since then," Sampaio said (see ARF related series). Preclinical trials have become an engine of change in the field, as the DIAN, API, and ADCS A4 trials are gearing up.

For his part, **Rusty Katz** of the U.S. Food and Drug Administration addressed CTAD once again by video. Katz said that the agency may apply different rules to

different populations. That is because presymptomatic patients with inherited Mendelian mutations will all become symptomatic, whereas that is not known to be true for ApoE4 carriers or A4 participants. At the moment, the FDA is not ready to accept that an effect in ADAD can be extrapolated to sporadic AD, though Katz said this may change with more data.

What does this distinction mean in practice? For one, the safety bar will be lower for autosomal-dominant AD than for LOAD. The FDA does not take the view that a drug to treat asymptomatic patients must be completely safe. The agency is prepared to accept risk from a drug that works. “We stand ready to look at drugs that have toxicity if they have a significant effect in delaying cognitive decline in AD,” Katz said. This effect can be symptomatic or disease modifying. Going a step further, Katz said that even though the FDA encourages enrichment to enroll mostly patients who truly have AD and will become symptomatic, the FDA does not require an absolutely benign safety profile even for those trials that contain some proportion of patients who may not get AD during the course of the trial.

For another, the FDA’s distinction between autosomal-dominant AD and more common forms of the disease means that the former is a valid indication by itself. The FDA would consider granting an indication for a drug developed entirely in this small population, Katz said. For other risk factors such as ApoE, this is not the case.

The challenge for scientists lies in being able to tell if the drug is useful in patients who have no symptoms. “That is the paramount question,” Katz said. The answer hinges on the outcome measures. On that, Katz reiterated that the FDA has always insisted on evidence that the drug effect is meaningful to the patient. “It does not matter to the patient if (s)he remembers one more word on a list,” Katz said. He acknowledged that showing global functional change is very difficult in patients who have no symptoms. “The whole concept of clinically meaningful change has to be reconsidered for preclinical trials,” Katz said.

Scientists are increasingly finding that preclinical patients do have subtle cognitive changes on sensitive tests. Together with a surrogate marker, improvement on such tests could be sufficient. "We are not entirely there yet, but have told sponsors that if they show a result on a cognitive marker and a surrogate marker, we will at least consider a claim,” Katz said. The CTAD conference is not the first occasion Katz made this statement, but it is worth repeating because it constitutes a significant departure from the FDA’s previous position insisting on co-primary cognitive/global outcomes. On 5 November 2012, the FDA and the Coalition Against Major Diseases (see below) jointly hosted a workshop at the FDA campus outside Washington, DC, where Katz and others at the FDA, as well as the EMA, academia, industry, and other groups discussed what might constitute suitable cognitive outcomes in predementia trials.

In addition, the FDA wants AD trialists to begin using adaptive designs, and some are starting. Katz cautioned trial designers to be wary of type 1 error, i.e., a false-positive finding. Specifically, Katz recommended using early biomarkers adaptively to determine the future conduct of the study, for example, which of

many initial doses to take forward, but to steer clear of adapting the outcome partway into the trial.

Karl Broich of the Federal Institute for Drugs and Medical Devices in Bonn, Germany, co-leads EMA's scientific working party on AD. The working party reports to the Committee for Medicinal Products for Human Use (CHMP). "FDA's and EMA's positions are not far away from each other. Both agencies have moved," Broich said. Both agencies need evidence that a surrogate marker predicts a subsequent clinical outcome. That said, in light of both the urgency of the Alzheimer's problem and how difficult it is to validate a surrogate endpoint to published standards (Bucher et al., 1999), the EMA may not actually insist on full validation in the end, Broich said. As a case in point, Broich noted that the CHMP had cut the scientific community some slack in its recommendation, issued on 18 October 2012, to authorize florbetapir/Amyvid for clinical use. "We usually require more of a diagnostic," Broich said.

Broich called on trialists in the audience to avail themselves of CHMP's scientific advice working party from the get-go, and in this way avoid surprises late in the process.

Historically, the path to persuade regulatory agencies to accept a biomarker was costly and cumbersome, as each company needed to advance, on its own, the marker it wanted to use. Sometimes an agency would require co-development of a drug and a biomarker in parallel, a high bar in many instances. Each agency dealt with each company's proposed markers case by case, and each marker was accepted over time. This started to change when the EMA began to lead the way in qualifying a biomarker for the entire field, said **Diane Stephenson** of the Coalition Against Major Diseases. CAMD engages a broad base of scientists from governments, industry, patient groups, and academia to build shared drug development tools. Besides helping push biomarkers out of the exploratory stage, CAMD has engaged nine pharmaceutical companies to pool data from 22 treatment trials, map these disparate data to a common CDISK data standard, and make it into an open database of aggregated clinical data. From that, CAMD built an in-silico, quantitative tool to model disease progression and drug response in a therapeutic trial setting, which is currently under FDA review. Stephenson hopes to further expand the precompetitive space for all trialists in the field by way of sharing more clinical trial data.

Stephenson urged that the EMA and FDA work toward issuing qualification opinions together. This would streamline the rules by which companies conduct their increasingly international trials. "This is a lofty goal, but given the fact that we do communicate across agencies, it is possible," Stephenson said.

Scientists who traveled to Monaco to learn about new Alzheimer's drugs and trials discovered that, solanezumab and bapineuzumab aside, the program of the conference was mostly stocked with methodological topics. This may not be surprising, as it reflects a field moving to implement a better paradigm for drug testing. And wedged in between talks on cognitive composites, standardization, and power calculations, the program did feature some news on the next wave of potential treatments. For example, one upcoming trial is venturing into the brave

new world of Bayesian statistics (see below). Another will enrich by ApoE genotype.

The Grimaldi Forum Convention Center, Monte Carlo.
Image courtesy of Gabrielle Strobel

The news and blogosphere last week were abuzz with post-election chatter about how Bayesian probability allowed a statistics geek to call last week's U.S. presidential contest—in all 50 states and down to the number of electoral votes—long before November 6 (e.g., Phys.org; Times Live). In the afterglow of this sudden popularity, Bayesian analysis is on the rise in the field of Alzheimer's research as well. That's because—stumped by standard designs again and again—AD researchers this past year started experimenting with Bayesian adaptive trials. The API, DIAN, and ADCS A4 trials are dipping their toes into the waters by incorporating adaptive elements. At CTAD, **Andy Satlin** of Eisai Inc. in Woodcliff Lake, New Jersey, described how his team is set to test a new antibody with a headfirst plunge into the depths of Bayesian probability—which statisticians have described as more than a little intimidating.

For a layperson's description of how adaptive trials work, see this ARF related news story. Put facetiously, it's a bit like the trialists' version of governing by poll. Adaptive trials don't execute a fixed design, i.e., stick to every detail no matter how the trial is going. Instead, they take the trial's temperature periodically and adjust certain things. Underpinning such designs are Bayesian statistics. Combining that with information on the disease's natural history and progression, scientists build a model that forecasts a variety of potential drug responses and assigns probability distributions to each envisioned scenario. As the trial unfolds and initial data come in, the model adjusts parameters such as randomization, for example.

Adaptive trials came onto the scene as Eisai scientists were planning the Phase 2 evaluation of BAN2401. This is an antibody against Aβ protofibrils that Eisai licensed from BioArctic Neuroscience, the Swedish biotech company co-founded by the discoverer of the Arctic APP mutation, **Lars Lannfelt** of Uppsala University (see ARF related news story). To advance this new type of therapy, Eisai scientists need to answer questions such as which of many possible doses to choose, how often to dose, and what effect size they could reasonably expect—in

other words, how many patients they would need. “Answering these with a fixed Phase 2 design could result in a lengthy, expensive failure in Phase 3,” Satlin told the audience. Adaptive designs, in theory, can cut down the time to decide whether the drug is likely effective and settle on doses for Phase 3.

Working with **Don Berry**, of the University of Texas MD Anderson Cancer Center in Houston and a leader in adaptive trial design, the Eisai scientists spent months building a statistical model for how this could work. They will start the trial with a "burn in," meaning the first 200 enrollees get randomized in a fixed distribution either to placebo or to one of five doses of antibody. Then the "polling" begins; that is, every time 50 additional patients are enrolled, the researchers will conduct an interim analysis. If the trial continues to full enrollment of 800 patients, then the scientists will conduct quarterly analyses.

These interim analyses are there to do three things, all while the scientists at Eisai remain blinded to the interim results. While the trial enrolls, they will guide the reallocation of disproportionately more subsequent enrollees to those doses that seem to generate the best response, and relatively fewer to the inactive or toxic doses. Once as few as 200 patients are randomized, interim analysis can indicate that the drug is not working and trialists can then end the trial. Once 350 people are randomized, the sponsor can declare success and stop the trial. This trial model allows scientists to find out whether the drug likely works and which doses to take into Phase 3 with an estimated 200 fewer patients and up to a year earlier than if the trial followed a fixed design, Satlin said, “The goal is to find the most effective dose with fewer subjects by adapting the randomization.”

Regulators have encouraged the field to use adaptive designs since 2004. That is when the Food and Drug Administration’s Janet Woodcock and others issued the Critical Path Initiative in an effort to bridge the translational gap between rapid scientific advances and stagnating drug approval. The cancer field heeded the call before Alzheimer’s, but this is now changing.

Besides using a new design, the BAN2401 Phase 2 program will use a different outcome measure. At CTAD, **Veronika Logovinsky** of Eisai described a new composite scale. It is stitched together from individual tests of established scales that have been the mainstay of AD drug trials but are increasingly seen as inadequate for upcoming trials in earlier stages of AD. Working with others at Eisai and with **Suzanne Hendrix**, an independent biostatistician in Salt Lake City, Utah, Logovinsky pressure-tested how each component of the ADAS-cog, the MMSE, and the CDR performed in previous MCI trials done by Eisai, by the Alzheimer’s Disease Cooperative Study, and in ADNI. They picked the tests that were least heterogeneous and most sensitive to disease progression and to drug effects at the predementia stage. The new composite uses four items from the ADAS-cog, two from the MMSE, and all six from the CDR, Logovinsky said. Eisai hopes that regulators will accept this combination of some cognitive and some clinical/functional tests as a single outcome measure.

Beyond this study, similar initiatives are afoot across academia and industry. Up and down the field, neuropsychologists and biostatisticians, partly inspired by Hendrix’s work, are probing placebo samples from prior drug trials and natural

history datasets for test combinations that detect the most change at the MCI stage with the least noise (e.g., ARF related news story).

ApoE Carriers Sought for Trial of NSAID Derivative

The conference featured a new Phase 2 program that uses genetics to enrich an MCI population for an early-stage therapeutic trial. The drug at hand is called CHF5074. This erstwhile γ-secretase modulator has been recently recast as a microglial modulator that may hold promise for people who carry the ApoE4 allele. CHF5074 is about to enter the first of two long-term pharmacogenetic biomarker studies.

At CTAD, **Bruno Imbimbo** of Chiesi Pharmaceuticals in Rockville, Maryland, reminded the audience of the finding that long-term use of NSAIDs confers a degree of protection against Alzheimer's, particularly in ApoE4 carriers (e.g., Szekely et al., 2008; Breitner et al., 2011). NSAIDs drew intense interest in AD research for some years after a widely noted finding by Sascha Weggen and colleagues that certain NSAIDs lower Aβ42 production independent of their action on the Cox enzymes (Weggen et al., 2001). Much of the subsequent research was driven by the goal of lowering Aβ by tweaking the γ-secretase complex with new NSAID derivatives.

This is how CHF5074 began in 2007, and PubMed papers on it up to January 2012 call it a γ-secretase modulator. Early studies measured its ability to affect Aβ- and other amyloid-related outcomes (e.g., Imbimbo et al., 2009). As the researchers tried to pin down exactly what the compound does, subsequent papers proposed other mechanisms of action, such as restoring neurogenesis (Imbimbo et al., 2010), reorganizing the astrocytic cytoskeleton (Lichtenstein et al., 2010), or reducing tau (Lanzillotta et al., 2011) and rescuing synaptic plasticity (Balducci et al., 2011).

At CTAD, Imbimbo built an argument for treating neuroinflammation in the years leading up to Alzheimer's disease. He said that certain NSAIDs lead microglia to adopt either the M1 phenotype associated with cytokine and nitric oxide synthase production, or the M2 phenotype associated with amyloid phagocytosis. "It is very important in which way microglia get activated," Imbimbo told the audience. In mixed glial cultures, CHF5074 blunts the M1 and stimulates the M2 response, Imbimbo said, and the cells' subsequent phagocytic appetite decreases plaques and reverses cognitive deficits in several different lines of transgenic AD mice.

Chiesi Pharmaceuticals, an Italian drug company based in Parma, ran Phase 1 studies in healthy volunteers, as well as one Phase 2 study in people with MCI that currently continues in open-label extension (see ClinicalTrials.gov). That work has shown that the compound enters the brain and lowers CSF concentrations of sCD40L and TNF-α, biomarkers of neuroinflammation, in a dose-dependent fashion, Imbimbo told the CTAD audience. The MCI trial showed signals of benefit on executive function as measured by the Trail Making B Test, and in verbal memory as measured by word recall after 52 weeks of treatment. This was particularly true in ApoE4 carriers, Imbimbo said. The main side effect was mild diarrhea (Imbimbo et al., 2012).

With this, Chiesi decided to go ahead with a Phase 2 program called Genetically Enriched Population At Risk of Developing Alzheimer's Disease (GEPARD-AD). Twenty-five U.S. sites led by **Joel Ross** of the Memory Enhancement Center in Eatontown, New Jersey, will participate. The protocol received input from **Rachelle Doody** of Baylor College of Medicine in Houston, Texas; **Pierre Tariot** of the Banner Alzheimer's Institute in Phoenix, Arizona; **Lon Schneider** of the University of Southern California; and **Paul Thompson** of UCLA School of Medicine in Los Angeles.

One trial will enroll 87 MCI patients each for placebo, 200 mg, or 400 mg of drug per day; a potential second trial currently in planning is designed to enroll 141 cognitively normal people per group into the same regimen. Treatment will last for two years. As the name suggests, the trials enrich their predementia population not by measuring CSF or amyloid PET, but by seeking people who carry at least one ApoE4 allele. The second trial, of asymptomatic ApoE4 carriers, would attempt to enrich by requiring that a parent had Alzheimer's. The program enrolls fairly young participants, aged 45 to 65, because both the influence of ApoE and the inflammatory component of AD on progression change with age, Imbimbo said. Outcome measures to be used in this trial include MRI volumetry, synaptic function by way of FDG-PET, CSF markers of AD, as well as CSF sCD40L and TNF-a, verbal and visuospatial memory, and the CDR-SB. The first trial is set to start enrolling in December 2012.

EEG Gains Luster as More Trials Incorporate Biomarkers

The conference showcased the field's pressing need for biomarkers as outcome measures. Several talks focused on electroencephalography (EEG), a somewhat overlooked technique. EEG directly measures the brain's electrical activity, and therefore synaptic health. Some researchers believe this approach could provide a more immediate and physiological measure of drug response than do fluid biomarkers and brain amyloid imaging. One talk reported that EEG distinguished between control and treatment groups in a six-month trial of the medical food Souvenaid. Another presentation noted that a form of EEG shows promise for the early diagnosis of AD in a multicenter setting. Better-known AD biomarkers made an appearance, also, with a large French prevention trial reporting significant imaging findings among older adults receiving lifestyle interventions.

EEG shares some similarities with functional MRI. Like that technique, it comes in two flavors: resting state and task related. In the task-related variety, researchers give a visual or auditory stimulus to participants and then record the brain's response, known as an event-related potential (ERP) (see ARF related news story and ARF news story). Whereas ERPs measure cognitive function, resting-state EEG, like fMRI, can be used to map the brain's connectivity and organization, said **Ilse van Straaten** at VU University, Amsterdam, the Netherlands.

Van Straaten presented data from the 24-week Souvenir II trial, which compared Souvenaid to placebo in 259 participants with mild AD at 27 centers in Europe. At last year's CTAD conference, researchers reported that the intervention improved scores on several memory tests (see ARF related news story; Scheltens et al., 2012). The milkshake-like drink is being developed by Nutricia, a unit of

the food company Danone. Souvenaid contains nutrients that promote the growth of neurites and dendritic spines, leading the authors to hypothesize that it improves synaptic function. To test whether this might be true, they turned to EEG, van Straaten said.

To map connectivity, the authors first compared data from 21 electrodes placed across the scalp to record from different brain regions. Van Straaten and colleagues quantified the amount of similarity in the signals using a measure called the phase lag index. Functionally coupled brain regions tend to synchronize their activity, so similar signals reveal connections between regions, van Straaten said. The researchers then used the coupling data and modern network theory to determine the organization of the brain. In a healthy brain, each electrode makes many local connections and only a few long-distance connections, because this is the most efficient model, van Straaten said. In AD brains, by contrast, functional coupling declines and the networks become disorganized.

In the Souvenaid trial, participants taking the supplement maintained stable connectivity and organization, while the control group declined on both of these measures, van Straaten reported. "That was really surprising for us, because we did not know that in 24 weeks, AD patients would show deterioration," she said. The results suggest that EEG has potential as a clinical trial outcome measure and should be investigated further, she added.

Van Straaten noted that few researchers perform this type of complicated analysis on resting-state EEG data. "I think few people know about the possibilities EEG has in this respect," she said. The method is not new, however. For example, Andrew Leuchter at the University of California, Los Angeles, has used EEG to analyze brain connectivity in depression and Alzheimer's disease (see Leuchter et al., 2012; Cook and Leuchter, 1996; Leuchter et al., 1992). The methodology has become more accessible in the last couple of years because EEG data moved to a digital format, making sophisticated computer analyses possible, van Straaten said. EEG has the advantage of being cheaper and more readily available than fMRI, but it suffers from a much lower spatial resolution.

Many researchers believe EEG also holds potential for early diagnosis of cognitive problems. Since synaptic function falters early in AD, before amyloid plaques form, quantitative EEG and ERPs may detect the first stages of disease, said **Karim Bennys** at Montpellier University Hospital, France, in his talk at CTAD.

Greg Jicha at the University of Kentucky, Lexington, told Alzforum that ERPs show promise as a screening tool for widespread clinical use. The problem is that EEG measurements typically require a skilled technician, limiting their use to specialized settings. To make ERPs feasible in clinical practice, the method will need to be easy to use, reproducible, and largely automated, Jicha said. Jicha participates in an ongoing U.S. trial at six clinical sites to evaluate the effectiveness of a handheld ERP system made by biotech company Neuronetrix, Louisville, Kentucky. At CTAD, company president **K.C. Fadem** reported that among the first 100 participants, those with probable mild to moderate AD had distinct ERP waveforms from age-matched controls, with the difference reflecting

poorer memory and cognitive performance in AD patients. Measurements varied little from site to site, Fadem claimed, suggesting the method is reproducible.

ERPs could also make good trial outcome measures, Jicha said. "Pharmaceutical companies want cheaper, less invasive biomarkers, and have shown a lot of interest in this," he told Alzforum. He noted a caveat, however: ERPs will not necessarily distinguish between symptomatic and disease-modifying effects. "A drug that makes nerve cells fire better might be potent in restoring normal ERP function and yet might not touch the disease state," Jicha pointed out. "We are always going to have a need for molecular biomarkers." These would include amyloid imaging and fluid measurements of tau and Aβ, he said.

Lon Schneider at the University of Southern California, Los Angeles, suggested that a positive ERP signal might not always translate to better cognitive performance. For example, α power is associated with attention and memory, but a drug that improves α power will not necessarily pump up these faculties. Nonetheless, he thinks EEG measurements have value in clinical trials. "EEG/ERP provides methods for assessing that a drug is directly or indirectly affecting brain function, and within a narrow time interval of millisecond resolution," he told Alzforum. "In my view, it is important for Phase 1 and 2 development to be able to demonstrate neurotropic and psychotropic effects of brain-active compounds." He also noted that EEG would provide a more sensitive marker for drug effects than fluid or brain imaging biomarkers.

Meanwhile, at CTAD, preliminary results from the Multidomain Alzheimer Preventive Trial (MAPT) in France focused on such imaging markers. This ongoing three-year prospective study, funded in part by the French Alzheimer Plan, investigates whether lifestyle interventions can slow cognitive decline or lower the risk of AD (see ARF related news story). More than 1,600 cognitively healthy adults over 70 years of age receive one of four interventions: placebo; omega-3 supplements; a multi-domain intervention consisting of nutrition advice, exercise, cognitive training, and social activities; or both omega-3 plus the multi-domain intervention. The study will conclude in March 2014, with the main outcome measure being performance on the Free and Cued Selective Reminding Test. This study resembles other European initiatives such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (aka FINGER). At CTAD, several talks presented baseline and preliminary data from three MAPT imaging studies performed on subsets of participants.

In the smallest study, 68 participants received FDG-PET scans, which measure brain glucose metabolism. Half of these people got the multi-domain intervention and half did not; both groups contained a mixture of people on omega-3 supplements and placebo. Those who received the multi-domain intervention showed improved brain metabolism over baseline at six months, and remained stable at 12 months, while the control group declined at both time points, project leader **Bruno Vellas** of the University of Toulouse, France, told ARF. This hints that the intervention might slow degeneration, and supports FDG-PET as a useful outcome measure, he said.

In a second study, more than 400 participants had a baseline structural MRI scan, which will be followed by a final MRI at the end of the study. In the baseline data, people who were judged frail, meaning they walked slowly or could not perform some activities of daily living, had lower hippocampal volumes than their peers who were not frail. Small hippocampal volume is associated with AD, suggesting that frailty might provide a cheap surrogate for dementia risk, Vellas said. A third study examined baseline amyloid PET scans in about 200 people. Nearly 37 percent of participants had a positive brain amyloid signal, with this group also having lower cognitive scores on the Mini-Mental State Exam, Clinical Dementia Rating, and the Free and Cued Selective Reminding Test than those who were negative for brain amyloid. This amyloid-positive percentage is similar to what is reported in the literature, but a bit lower than that seen in the Alzheimer's Disease Neuroimaging Initiative, Vellas said. As **Mike Weiner** of the University of California, San Francisco, noted playfully, this goes to show that drinking red wine and eating duck and foie gras is good for your brain.

AD Treatment Might Not Lower Healthcare Costs

Stakeholders in the Alzheimer's disease field often cite the tremendous burden the disease puts on the healthcare system—estimated at $600 billion annually worldwide (see World Alzheimer Report 2010 and ARF related news story)—as a compelling reason to treat the disorder. The argument assumes that an effective, disease-modifying treatment for AD would lower healthcare costs. This may not be the case, according to an analysis presented at the 5th Clinical Trials in Alzheimer's Disease conference, held 29-31 October in Monaco. Researchers led by Anders Wimo and Bengt Winblad at the Karolinska Institutet, Stockholm, Sweden, modeled a hypothetical disease-modifying treatment and found that the expense of the drug could more than offset the money saved in nursing home care, leading to a higher price tag overall. The scientists stress, however, that the gains in quality of life for AD patients would be big enough to make such a treatment cost effective for society. The research appeared in the October 2 Current Alzheimer Research.

To create the model, first author Anders Sköldunger and colleagues used Swedish data for factors such as the incidence and prevalence of AD and mild cognitive impairment, conversion rates from MCI to AD, and the costs of caring for people with these conditions. They faced a challenge in modeling the disease-modifying drug, however, since no such drug has yet hit the market and therefore no actual data on cost or efficacy exist. The researchers assumed that a hypothetical disease-modifying treatment might lengthen life by about a year. (AD shortens lifespan by two to four years on average, Wimo noted.) They set the cost of the drug at $7,400 per year—about five times the cost of brand-name cholinesterase inhibitors in Sweden. Then they used a 20-year Markov mathematical model to look at the effects of long-term treatment.

Under this scenario, treated AD patients would incur about $35,000 more in lifetime medical costs than untreated patients. The price tag for untreated patients included the cost of nursing home care, home health services, and informal care. Wimo pointed out that most people in the early stages of the disease receive care at home, only incurring expensive nursing home fees in the end stages of the disease. Treated patients were assumed to need less nursing home care, but the

cost of the drug itself and patients' longer life expectancy more than wiped out these savings. The researchers varied cost and efficacy parameters to see how this would affect the final result. For a drug that did not lengthen life, costs came out about equal for treatment or no treatment, Wimo reported.

"Before we did this model, my colleagues and I thought there would be enormous cost savings. It was a bit surprising when we tested all the assumptions and there were no savings," Wimo told Alzforum.

Should this discourage society from developing disease-modifying drugs? Not at all, Wimo said. Health economists use a measure called "quality adjusted life years" (QALYs) to take quality of life into account when comparing treatments. To arrive at this number, economists multiply life expectancy by the quality of the remaining life-years. On the quality scale, perfect health rates a value of 1, while death equals 0. This quality measure takes into account factors such as mobility, mood, pain, and ability to care for oneself. Some health outcomes are considered worse than death and are given a negative value—for example, a treatment that prolongs life but leaves the patient confined to bed in extreme pain would score below 0. Health economists then divide the QALYs gained from a treatment by its cost to get a rough idea of its value. A drug that costs less per QALY delivers better value compared to one with a high cost per QALY, the thinking goes.

By this measure, the hypothetical disease-modifying treatment scored well. Wimo and colleagues noted that Swedish society is willing to pay about $90,000 per QALY, based on actual decisions made by Swedish health reimbursement authorities. This number may be even higher in the U.S., as some chronic treatments such as kidney dialysis cost as much as $200,000 per QALY (see commentary by economist Alex Tabarrok on the blog Marginal Revolution). The hypothetical Alzheimer's drug came in at about $43,000 per QALY, less than half the assumed Swedish limit. "For me it's a signal to go on [developing treatments]," Wimo said.

Howard Fillit, founding director and chief science officer of the Alzheimer's Drug Discovery Foundation, New York City, noted that models like this one are important, but remain very hypothetical at this point. The cost of the drug is a critical variable, he noted. "We have no idea what any potential disease-modifying drug might cost," Fillit said, pointing out that some biological agents could be much more expensive than this model assumes.

The difficulty of determining quality of life in AD also complicates the analysis of drug benefit. Most likely, a drug that prolonged the mild stages of the disease would have much more value to people than one that prolonged the later stages, Fillit said. A final challenge for any model is to factor in the comorbidities that typically afflict older people. These also drive healthcare costs and can lead to death from causes other than AD. All of this points to the need for real-world data. "Ultimately, the true economic value of a disease-modifying agent will have to be shown in some sort of cost-effectiveness trial, such as a Phase 4 study comparing the agent to standard of care," Fillit said.

Reference:

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