CTAD Highlights October 26, 2018

Developing new AD therapeutics requires not only a full pipeline of diverse agents, but novel and efficient analytic tools and trial designs as well. Today at CTAD, investigators described tools ranging from low to high tech that are being applied to studies testing a diverse set of therapeutic agents.

Telephone-based assessments enable large, simple, cost-effective studies

At the low-tech end, for example, Mark Espeland and colleagues at the Wake Forest School of Medicine are examining the potential of cocoa-flavanol extract to improve cognition in older adults in the COSMOS-Mind study. To enroll and retain the 2,000 subjects needed for this trial required both a broad and cost-efficient recruitment strategy and an assessment protocol with minimal burden to participants. COSMOS-Mind is an ancillary study to the large COcoa Supplement and Multivitamin Outcomes Study (COSMOS), which invited nearly 3 million people to participate via mass mailings and the internet. Those interested in the COSMOS-Mind substudy were sent recruitment materials, contacted to confirm interest, screened via telephone, and if eligible, were then enrolled and randomized. Participants are assessed annually using a telephone-based cognitive composite outcome measure. Over the three-year study, the investigators will test whether the supplement slows the typical age-related decline in overall cognition. Although results will not be available for several years, Espeland said the study has already demonstrated the feasibility conducting a large, simple, cost-effective, and geographically diverse trial over the telephone; and has shown that older adults are willing to volunteer for telephone-based assessments.

Big data and predictive modeling enable recruitment and precision medicine

At the other end of the technology spectrum, Chaitanya Alamuri of IQVIA described a machine learning algorithm that helps identify prodromal AD patients in the general population. Alamuri noted that in the US alone, there are currently 150 clinical trials seeking about 70,000 participants, making recruitment an enormous challenge. Moreover, the landscape has become more complicated as the number of procedures involved in trials has increased by about 70% and the number of countries conducting trials has more than doubled. IQVIA's approach is to leverage huge healthcare datasets to build a predictive algorithm. To build the model, they used data from an initial cohort of more than 405 million subjects divided into a positive cohort (those with AD or who had been prescribed AD symptomatic drugs) and a control cohort (a matched sample of patients without an AD diagnosis or AD treatment). Using 24 months of medical history data from no more than 3 years prior to the AD diagnosis, they identified features such as diagnostic procedures, medical interventions, concomitant pathologies, and other characteristics that differentiated those with AD from those without AD across. They then compared the performance of different algorithms across different age groups and ranked risk factors for each age group based on the predictive value of that risk factor in that age group. Since the data indicate that most patients were evaluated in primary care settings, Alamuri and colleagues believe the algorithm will be usable in primary

care settings. He added that they are seeking collaborations to improve the algorithm, perhaps by adding genetic risk factors and biomarkers.

Predictive modeling can also enable precision medicine, according to data presented by Mohammad Afshar of Ariana Pharma in Paris, France. Afshar described the development of ANAVEX®2-73, an orally available selective sigma-1 receptor agonist. Using an unbiased, data-driven machine learning platform that integrated clinical and genomic data, they identified four key drivers of the response to the drug, including polymorphisms of two genes. This allowed them to extend their small open label study in a selected population, strengthening their hypothesis for this particular drug and supporting the notion that such a precision pharmacology approaches can be used to identify patients who will benefit from particular drugs across a wide range of neurodegenerative diseases.

Towards a complete solution for patients with AD

The combination of new and better drugs, improved methods for identifying individuals in the earliest stages of disease, and improved diagnostic and staging tools will lead to the development of what Rachelle Doody, global head of neurodegeneration at Roche called "a complete solution for patients with AD." This admittedly aspirational vision would start by providing self-assessment tools to individuals who are concerned about their cognitive health; following this with more accurate clinical tools to stage disease; and finally providing a menu of possible treatment options delivered using a precision medicine paradigm. "This vision extends to all patients, not just people at risk or with prodromal disease," said Doody. A total solution means having something available even for those in more advanced stages of disease.

Mary Sano, director of the Alzheimer's Disease Research Center at the Icahn School of Medicine, Mt. Sinai, New York said that self-detection of cognitive problems is indeed possible and has been demonstrated in multiple studies going back at to the late '90s. A more recent meta-analysis suggested that the presence of subjective memory concerns doubles the likelihood that a person has or will develop dementia, she said.

There is now the potential to do even better by utilizing digital technologies such as smartphones and wearables, said Sano. Although a recent study found that fewer than 50% of people over age 65 have smartphones and that their use is associated with higher levels of education and higher incomes, digital technologies nonetheless offer great opportunity to capture both subjective and objective measures of cognition. The challenge, she said, will be to match the technologies to the motivations and preferences of the population groups that need to be assessed.

With regard to diagnostic and staging tools, Christopher van Dyck of the Alzheimer's Disease Research Unit at Yale University said that recent studies from several groups suggest that assessment of amyloid beta in plasma "is probably ready for prime time in clinical trials, but not so much for clinical care." He noted that the Trial-Ready Cohort for Preclinical/Prodromal AD (TRC-PAD) project, funded by the National Institute on Aging will incorporate three different plasma biomarker assay platforms, which will enable multi-center comparative field testing of the assessment tools.

While plasma biomarkers offer huge advantages for screening and diagnosis in terms of reduced cost and much greater availability to large populations, van Dyck was also extremely optimistic about ultrasensitive immunoassays for amyloid beta oligomers in cerebrospinal fluid, which offer the ability to demonstrate target engagement in clinical trials with a small number of participants. The Yale PET center has also

recently developed a ligand for synaptic PET imaging, which could offer the first *in vivo* measure of synaptic density as an outcome measure in clinical trials of disease-modifying therapies, particularly those targeting synapses.

Ultimately, these advances in biomarkers and other diagnostic tools, as well as treatment insights from AD basic science studies should lead to more precise and effective treatment, said Dennis Selkoe of the Brigham and Women's Hospital and Harvard Medical School. "There is little doubt that this complex disease will be treated with combination therapies," he said.

Sselkoe suggested a new approach to treating AD, beginning with risk assessment in mid-life to generate an AD risk score. This score would incorporate family history, results from a cognitive screen and neuropsychological testing, genetic testing, plasma biomarkers, imaging studies, and CSF testing. Then a treatment approach would be designed based on the AD risk category into which a person falls.

"Like other chronic, multifactorial diseases, AD may often be treated with a combination of two or more disease modifying agents that target the same or different pathogenic factors," said Selkoe. He suggested that the best approach may be to start with one agent with proven benefits before adding a second agent. At least one of the agents should neutralize or clear diffusible amyloid beta oligomers he said, since they increasingly appear to be pathogenic. The second drug could be directed against tau or abeta through a different mechanism.