Tau Seed AD Detection Assay

In an article e-published on December 20 ahead of print in *Acta Neuropathologica*, Kraus et al. from the National Institute of Allergy and Infectious Diseases (NIAID) Rocky Mountain Laboratories (Hamilton, MT), the University of Kansas School of Medicine (Kansas City), the University of California San Diego (La Jolla), the University of Verona (Italy), and the Indiana University School of Medicine (Indianapolis) reported on development of a highly selective and ultrasensitive cell-free tau seed amplification assay optimized for Alzheimer disease (AD) with additional relevance in chronic traumatic encephalopathy (CTE). On the same day the article was published, NIAID issued a press release summarizing the findings.

The study was based on adaptation of the real-time quaking-induced conversion (RT-QuIC) test developed a decade ago to detect abnormal clusters of tau protein in prion diseases. The authors focused in this study on postmortem brain tissue samples from 16 individuals with AD and 2 individuals (boxers) with CTE, as well as numerous samples from patients with other brain diseases and controls. Their dual purpose was to explore the molecular basis for AD tau filament propagation and to improve detection of tau aggregates as potential biomarkers. Their AD RT-QuIC method detected seeding activity in all AD brains at dilutions as extreme as 10^7–10^{10}-fold and was 10^2–10^6-fold less responsive when seeded with brain tissue from most other types of tauopathy despite comparable loads of predominant 3- or 4-repeat (3R/4R) tau aggregates. The CTE brains had seed concentrations comparable to the weakest of the AD specimens. AD RT-QuIC was also able to detect amounts as small as 16 femtograms of pure synthetic tau fibrils. The authors concluded that "the distinctive seeding activity exhibited by AD and CTE tau filaments compared to other types of tauopathies in these seeded polymerization reactions provides a mechanistic basis for their consistent propagation as specific conformers in patients with 3R/4R tau diseases" and that the method offers "rapid ultrasensitive quantitation of 3R/4R tau seeding activity as a biomarker." They noted that the ability to selectively detect and quantitate AD and CTE tau aggregates by AD RT-QuIC may be useful in both research and diagnostics. In research, the technique could be used to explore which brain regions contain tau seeds at different stages of disease. Moreover, additional development of AD RT-QuIC for use with diagnostically relevant specimens, such as cerebrospinal fluid, "could provide a tau biomarker to help definitive diagnosis and selection of patient cohorts for clinical trials, in addition to longitudinal evaluation of AD tau levels in response to treatments." The assay also could be combined with a previously reported Aβ protein-misfolding cyclic-amplification assay to assess and monitor potential AD therapies.

Acta Neuropathologica

NIH Announces New BRAIN Initiative Awards

The National Institutes of Health (NIH) announced on November 2 its funding of more than 200 new awards, totaling more than $220 million, through the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, an ongoing transagency effort to "arm researchers with revolutionary tools to fundamentally understand the neural circuits that underlie the healthy and diseased brain." Supported by the U.S. Congress through both the regular appropriations process and the 21st Century Cures Act, the total 2018 support for the program was more than $400 million, 50% higher than support in 2017. "Brain diseases are some of the greatest mysteries in modern medicine. These projects will provide new tools and knowledge needed to discover answers for some of the most difficult neurological and neuropsychiatric disorders," said NIH Director Francis S. Collins, MD, PhD.

Many of the new awards focus on imaging or imaging-supported topics, including brain mapping, novel imaging technologies at the cellular and subcellular levels, and computational and in silico studies of brain function. Examples of the new round of awards include creation of a wireless optical tomography cap for scanning human brain activity, development of a noninvasive brain–computer interface system for improving the lives of paralysis patients, and the testing of noninvasive brain stimulation devices for treating schizophrenia, attention deficit disorders, and other brain disease. Through this expanded program, more than 100 research institutions received awards involving 500 investigators representing fields as diverse as engineering and psychology. Many of the awards will fund development of new tools and technologies to capture a dynamic view of brain circuits in action, including self-growing biologic electrodes for recording brain activity and creation of an indestructible hydrogel system to map neural circuits.

Launched in 2013, the BRAIN Initiative is a large-scale effort to accelerate neuroscience research by equipping researchers with tools and insights for treating a wide variety of brain disorders. The NIH BRAIN Initiative is managed by 10 NIH institutes with missions and current research portfolios that complement the goals of the BRAIN initiative. A list of funded awards is available at: https://www.braininitiative.nih.gov/funding/funded-awards.

National Institutes of Health

FDA and Evidence-Based Drug Development

On December 6, the U.S. Food and Drug Administration (FDA) announced through a statement from FDA Commissioner Scott Gottlieb, MD, a new strategic framework designed to advance use of "real-world evidence" (RWE) to support

development of drugs and biologics. In the FDA context, RWE refers to the use of advanced electronic technologies to collect data from across a broad spectrum of routine patient care and to analyze these data to inform regulatory health care decisions. The newly released *Framework for FDA's Real-World Evidence Program* (https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf) outlines a multifaceted effort to be launched in 2019. The program will involve demonstration projects, stakeholder engagement, internal processes to bring senior leadership input into the evaluation of RWE, promotion of shared learning and consistency in applying the framework, and guidance documents to assist developers interested in using real-world data (RWD) to develop RWE to support regulatory decisions. Data supporting the effort will come from multiple sources, such as electronic health records, medical claims, product and disease registries, laboratory test results, and advanced analytic technologies paired with consumer mobile devices. Gottlieb noted that not only will the data be used to support regulatory activities but "the collective evaluation of these data sources has the potential to inform clinical decision making by patients and providers, develop new hypotheses for further testing of new products to drive continued innovation, and inform us about the performance of medical products." The framework and related activities will involve pharmaceuticals and other medical products but will not pertain to medical devices.

Gottlieb added that RWD tools are intended to gradually shift some FDA studies and data collection to the point of care, making data collection and the development of actionable evidence more efficient. Some of these processes are already underway, he added, citing new oncology drug applications in rare tumor types. The utility of the RWD approach may have special impact on postmarket surveillance and monitoring. As the framework is developed, the FDA will issue additional guidance on ways to apply and interpret the agency's evidentiary standards in the context of rapidly developing informatics systems and advanced analytics.

U.S. Food and Drug Administration

IAEA and Japanese Universities Sign NM Agreement

On November 30 the International Atomic Energy Agency (IAEA) announced the signing of an agreement with a consortium of 11 Japanese universities and other institutions to strengthen human resource development in the global field of nuclear medicine. As one of the agency's Practical Arrangements, the agreement will boost training opportunities for medical professionals in IAEA Member States in the use of imaging techniques to diagnose and manage noncommunicable diseases, with a special emphasis on degenerative brain disorders such as Alzheimer disease and Parkinson disease.

The Practical Arrangement was signed in association with the November 28–30 IAEA Ministerial Conference on Nuclear Science and Technology: Addressing Current and Emerging Development Challenges, held in Vienna, Austria. The agreement will enable the IAEA to increase assistance to countries in clinical practice and research, along with opportunities for certified continuous professional development in the participating Japanese institutions. Another focus area is the development and implementation of nuclear medicine curricula and academic programs throughout Member States.

"This arrangement will support IAEA projects in human health," said IAEA Deputy Director General and Head of the IAEA Department of Technical Cooperation Dazhu Yang. "It will focus on fields where Japan can offer expertise in support of our Member States." "Japan is proactively promoting medical care projects," Kiyoto Tsuji, Parliamentary Vice-Minister for Foreign Affairs of Japan, said in a statement at the conference. "This collaboration will put nuclear science technology research and development into practical use and bring about a positive socioeconomic impact in a sustainable manner."

The consortium includes leading Japanese institutions in the field of nuclear medicine: the Osaka University Graduate School of Medicine, the Fujita Health University School of Medicine, the Hokkaido University Graduate School of Medicine, the International University of Health and Welfare (Otawara), the Kanazawa University Graduate School of Medicine, the Kyoto University Hospital, the National Cancer Center (Tokyo), the National Center of Neurology and Psychiatry (Tokyo), the Southern Tohoku Research Institute for Neuroscience, the Tohoku University, and the Tokyo Medical and Dental University.

International Atomic Energy Agency