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Commentary

Development of Fluidic Biomarkers to Detect Neurotoxicity

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DESCRIPTION

The goal of this study is to see if there are any more sensitive and specific biomarkers that can aid in the diagnosis and assessment of neurotoxicity. If these biomarkers were applicable in animal models and could be converted from nonclinical to clinical data, they would be even more useful. Furthermore, fluid-based biomarkers in serum, plasma, urine, and Cerebrospinal Fluid (CSF) are considerably easier to sample than tissue-based biomarkers.

The committee on biomarkers of Neurotoxicology (NeuTox) has met on a number of occasions to define the scope and propose an experimental model to address the challenge. Several experimental models have been considered, but the committee chose Trimethyl Tin (TMT) in rats for a variety of reasons; Rat is a selective hamster species in preliminary testing and the rat-induced injury by TMT is well described in the hippocampus. Prodrug 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) was also considered; MPTP is a prodrug to the neurotoxin MPP^+, which causes permanent symptoms of parkinson's disease in mice by destroying dopaminergic neurons in the substantia nigra in the brain. However, MPTP is ineffective in mice and is not relevant to drug discovery and development models. The core of the project is to link the expression of fluid biomarkers of interest to imaging and functional parameters but particularly to the traditional histopathology endpoints.

Mice were given a single dose of TMT and evaluated at 2, 6, 10, and 14 days. The nerves of the brain, liver, thymus, adrenal, kidney, spinal cord, and hip, as well as the back tissue of the thigh, were sampled along with biological fluids (CSF, plasma, serum, and urine). Micronutrients such as microRNAs, F2-isoprostens, transcellulose protein, Glial Fibrillation Acidic Protein (GFAP), ubiquitin C-terminal hydrolase L1, myelin basic protein, microtubule-associative protein-2. In addition, several neuroimaging methods have been used, including Magnetic Resonance Imaging (MRI), magnetic resonance spectroscopy, and positron emission tomography.

Based on the study showed good relationships between GFAP, specific miRNAs, certain metabolites such as biogenic amines and phospholipids, and T2 relaxation in the hippocampus as measured by MRI. Fluid accumulation in humans and animal specimens. Overall, the results so far show that we have found ways to detect neurotoxic damage in fluids (CSF, plasma and serum) in this TMT-induced neurological damage model. Additional analyzes, including bioinformatics, are underway to analyze other potential biomarkers arising from other studies related to brain damage. Learning from these studies of brain damage and disease patterns provides opportunities for nonclinical toxicologists to improve the tools available to them, as well as better ways to anticipate potential neurotoxicity as well as effectively monitor patients during clinical development.

Clinical applications of CNS biomarkers-Traumatic Brain Injury (TBI)

GFAP has been proposed as a marker of TBI and in recent exciting developments, the FDA has approved GFAP as a test for TBI that can be used to monitor biochemical changes in patients and to evaluate response to treatment. Previously, UCH-L1 was also cited as a potential marker for measuring serum diagnostically for mild TBI. It is recommended that these markers be used as an acute diagnosis (within 12 hours) when a CT scan is needed to detect concussion. It will be interesting to see if the UCH-L1 TMT model is expressed along with the biomarkers already found (miRNAs, biogenic amines and phospholipids).

Although the above-mentioned fluid biomarkers have been found and validated in the toxicant model, they have the potential to be useful in the clinical development of new therapies for neurodegenerative and other neurological disorders such as parkinson's and Multiple Sclerosis (MS). Currently, it is very difficult to identify a signal for efficacy for such conditions in early clinical trials; The duration of the experimental new drug therapies will be limited to one month by the toxicology cover, as long-term (≥ 3 months) toxicology studies will not be conducted until later in the drug development program required to support chronic exposure. In addition, patients may have advanced and complex disease conditions due to failure of other treatments. Any biomarker that can provide potential evidence

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for therapeutic benefit would be very helpful in this case. But is it true to guess the cross-over from the TMT toxicant model and the biomarkers identified in such disease conditions. To answer this, we can look at the commonly used animal models and their translations.

Animal specimens of parkinson's

Parkinson's disease is a progressive disorder of the nervous system that affects movement. It develops gradually, sometimes beginning with a barely noticeable tremor in one hand. Although tremor is a well-known sign of parkinson's disease, the disorder usually causes stiffness or slowing of movement. Similar to many models of neurodegenerative disease, samples of parkinson's are toxicant administration.

In drug research and development, detecting neurotoxicity enhances a variety of outcomes, including diagnosis efficacy and accuracy, as well as our ability to intervene with therapeutic therapy. Neurotoxicity can be detected early, which allows for early management, which improves outcomes. The use of neurotoxicity biomarkers enables ongoing monitoring of illness states and treatment efficacy, resulting in better disease management. However, high-level brain function endpoints like suicidal ideation and depression will continue to be difficult to measure in the future. As a result, much of the current research focuses on using imaging and fluid biomarkers to detect structural change. Toxic sample tests revealed a panel of indicators capable of learning from damage and disease specimens like TBI and MS. In clinical trials of new treatments for alzheimer's, parkinson's, and other neurodegenerative diseases, these toxicity indicators may enable an early detection of efficacy. Overall, such processes should be part of a logical, step-by-step screening process that uses *in silico*, *in vitro*, and *in vivo* methodologies to identify, decrease, and manage risk.