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In vivo Neuropathology: Detecting the Neurotoxicity of Candidate Drugs during Early Drug Discovery

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Twenty-five percent of small molecules in drug development for CNS indications fail in clinical trials due to complications with neurotoxicity [1]. Unfortunately, this is not discovered earlier. Indeed, it is very infrequent that a drug is flagged for neurotoxic side effects in early drug discovery (1). The consequences are two-fold: 1) loss of time and money in bringing new drugs to market and, 2) the unwitting exposure of patents in clinical trials to the neurotoxic side effects of what otherwise could be a drug candidate that is effectively treating the problem. Known ahead of time, this could have helped guide the chemistry in the early stages of development to modify the molecule to eliminate the neurotoxicity [2].

The Health and Environmental Sciences Institute (HESI) committee on Biomarkers of Neurotoxicity proposed a framework for identifying new drug candidates in preclinical studies at risk for CNS toxicity [3]. The committee recommended that early detection should include a combination of fluidic biomarkers and imaging. The neurotoxin trimethyl tin (TMT) was proposed as a gold standard to be used in the lab to further this research. To this end, a recent study by Kulkarni and colleagues [4] used diffusion weighted imaging (DWI) to follow changes in brain gray matter microarchitecture in rats exposed to TMT. Measures of apparent diffusion coefficient (ADC) were used as a surrogate marker of brain cytotoxic edema caused by TMT-induced neuroinflammation. Because magnetic resonance imaging (MRI) is noninvasive, disease progression was followed at 3- and 7-days post TMT in the same rats. The use of a 3D MRI rat atlas allowed for the quantification of ADC values in 173 different brain areas. Multiple brain areas were identified as sites of putative neuroinflammation and cytotoxic edema at 3 days that grew in number by 7 days. Putative sites of neurotoxicity were subsequently confirmed by traditional postmortem histology.

These results based on technology combining DWI, a 3D MRI rat atlas, and computational analysis were not unexpected. Kulkarni et.al. [5] published an earlier work using this method coined "*In Vivo* Neuropathology" (IVN) to identify common brain areas that were at risk for neuroinflammation following head injury to the front or back of the brain. Using changes in ADC values the study identified specific brain nuclei in the amygdala and thalamus that were at risk, independent of where on the brain the impact occurred. Again, the predictions made by non-invasive DWI were confirmed with postmortem histology.

One of the more compelling aspects of IVN using ADC values as a measure of neuroinflammation is the minimum use of animals. The Kulkarni TMT study used a sample size of only four rats. The variance in the raw data between subjects and within brain areas was minimal allowing a power analysis to recommend sample sizes of three-four rats. This aspect of IVN, while significantly reducing the cost and time in assessing the neurotoxicity of drug candidates, also meets and probably exceeds the expectations of the laws and regulations around the humane care and use of laboratory animals.

While the Kulkarni TMT study was stopped at 7 days after drug exposure it could have continued for one month or longer in compliance with standard drug toxicity studies. With IVN the rat can be scanned and assessed for site-specific changes in neuroinflammation at any time. This ability to follow disease progression in the same rat over time, identifying specific brain areas at risk for neurotoxicity, is a huge advantage over traditional CNS toxicology methods. IVN does not obviate the need for postmortem histology but makes it more effect and less time consuming because it provides a road map of where to look for putative neurotoxic changes.

IVN maybe the needed imaging technique to pair with fluidic biomarkers suggested by the HESI in early CNS toxicology studies. IVN offers an alternative to the traditional tests for assessing CNS neurotoxicity, can minimize the cost, expedite

the process, and identify subtle changes in site-specific brain areas. Future studies on IVN will require generating a data base from drugs known to have neurotoxic side effects. Such a data base would be used for validating the technology and developing algorithms using artificial intelligence to identify early drug candidates at risk for CNS toxicity.

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