JBS Special Issue: Innovative Screening Methodologies to Identify New Compounds for the Treatment of Central Nervous System Disorders

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There is a tremendous need for novel treatments of diseases of the central nervous system (CNS). It is widely appreciated that significant challenges are associated with first understanding the pathophysiology of chronic diseases and, second, designing new treatments. The slow progress of discovery and development can be devastating for patients, families, and caregivers as they await new treatment options. For chronic neurodegenerative disorders, drugs are not available that modify the course of these diseases. Symptomatic therapies are available for some but often are associated with significant side effects or are not highly effective for many patients. Despite the unmet medical need for new drugs, a number of companies have scaled back or eliminated work in nervous system diseases, citing high costs, lengthy development times, and low success rates.³

With the rising costs of drug discovery and development, initiation of new screening campaigns and medicinal chemistry programs require a solid rationale for each molecular and/or cellular target. However, for many CNS diseases, the molecular underpinnings are still poorly understood. Adding to these challenges is the paucity of valid animal models for new targets and mechanisms. Many discovery efforts in the CNS have lacked target engagement biomarkers. Although significant challenges remain, much advancement has been made. Improved understanding of the genetics of disease has directed focus on improved target validation.⁵ New examples of validated biomarkers are emerging to aid in patient selection and target engagement, thus facilitating clinical development.⁵ Furthermore, multiple novel assay systems are also contributing to target and compound discovery.⁶

This special issue of the Journal of Biomolecular Screening includes a mix of phenotypic- and target-based articles that describe new methods to identify compounds as starting points for CNS drug discovery efforts. Over the past several years, there has been a renewed interest in phenotypic approaches to screening. The article by Copmans et al.⁶ uses the photomotor response of zebrafish and a new behavioral data analysis paradigm to identify phenotypes associated with different classes of neuroactive molecules. Another example of the utility of a phenotypic screen is provided by Vela et al.,⁶ in which the ability of compounds to enhance production of leukemia inhibitory factor, a cytokine involved in neuroinflammation, is examined in a variety of cell lines. A targeted approach directed at inhibitors of macrophage migration inhibitory factor is described by Zapatero et al.⁷

Ion channels represent important targets for the development of new therapeutics to treat CNS disorders. A rise in the identification of mutations in ion channel genes responsible for diseases has further added to our understanding of their role in normal electrical signaling and importance as drug targets. Otvos et al.⁸ describe a screen of natural product extracts for activity at α7-nicotinic acetylcholine receptors using a novel method that combines assessment of channel activity in parallel with compound identification. An approach that combines high-throughput screening using fluorescent imaging followed by automated electrophysiology is used by Jambrina et al.⁹ to identify positive allosteric modulators of NMDA receptors. Whereas the previous two articles address methods to screen ligand-gated ion channels, the article by Finley et al.¹⁰ describes a screen of voltage-gated Nav1.7 channel antagonists using multiple methods of data analysis to identify Nav1.7-selective (vs Nav1.5) inhibitors.

As drug discovery efforts entail an iterative process of compound modification to achieve a drug with a desired target profile, assay systems also often undergo a series of improvements to enhance their capabilities and utility. The next three articles describe significant advances in existing assays systems. In the first example, Kimos et al.¹¹ describe utilization of homogeneous time-resolved fluorescence technology toward the enablement of a high-throughput enzyme

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assay for the identification of inhibitors of catechol-O-methyltransferase. Forster et al.\textsuperscript{12} present a study on the development of a differentiation protocol for SH-SY5Y neuroblastoma cells that yields a system with properties of enhanced sensitivity to energetic stress. Finally, Cotterill et al.\textsuperscript{13} describe the ontogeny of neural networks in primary cortical cells examined in multiwell microelectrode array plates.

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References
Erratum

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