Addressing Innovation in CNS Drug Discovery: Functional or Single Molecular Target Approaches to Novel Compounds that Attenuate Synaptic Dysfunction

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Background: Diverse CNS disorders display common pathophysiology themes. Ongoing efforts to develop disease-modifying therapeutics reflect the increasing appreciation of these core mechanisms. Major challenges include identification of disease progression time windows amenable to intervention, the linkage of disease related phenotypes to druggable molecular targets, and the need for clinical landmarks. Retrospective analyses of new molecular entity drug approvals reveal the differing impact of phenotypic vs single molecular target drug discovery approaches, dependent on the state of knowledge about druggable disease progression mechanisms. The less biased phenotypic approach allows probing for interventions in the absence of established mechanisms in areas of critical unmet medical need, whereas single molecular target approaches provide exceptional efficiencies in the context of established mechanisms. As part of a multi-site collaboratorium focused on innate immunity and synaptic dysfunction as a common pathophysiology progression theme, we explored the potential for novel small molecule drug candidate discovery using these two distinct approaches and a common molecular scaffold or fragment. Specifically, the functional approach focused on early stage overproduction of proinflammatory cytokines causally linked to synaptic dysfunction, and the single molecular target was brain p38αMAPK, an established regulator of innate immunity in glia and an intracellular neuronal kinase up-regulated in stress responses.

Methods: Our goal was to start with synthesis of a restricted set of novel small molecules compliant with chemoinformatic and pharmacoinformatic based considerations for brain penetrance and risk reduction and subjected to either:
1. an in vivo screening approach based on disease-relevant pharmacodynamic endpoints (functional approach; up-regulation of proinflammatory cytokine production), or
2. an activity screening based approach based on target structure-assisted design (p38αMAPK).

Results: An aminoarylpyridazine molecular fragment was the common core. Deliverables from each approach used a common secondary phase, pharmacology driven medicinal chemistry refinement. Novel small molecule deliverables from each approach showed efficacy in diverse preclinical animal models. Both showed in vivo attenuation of innate immunity related pathologies and behavioral deficits.

Conclusions: Our validated discovery platform has generated novel, CNS-penetrant, small molecule drug candidates are in early clinical trial stage or IND-enabling preclinical drug development.