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Evaluating nitric oxide and soluble guanylate cyclase signalling in vascular dementia

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The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cGMP signalling pathway plays a fundamental role in modulating diverse physiological processes including blood flow, inflammation, neuroprotection, fibrosis and metabolism. sGC is expressed throughout the CNS. sGC stimulators are small-molecule agonists of sGC that synergize with and enhance endogenous NO signalling. As such, sGC stimulators may provide therapeutic benefits in diseases either associated with loss of NO signalling or where stimulation of this pathway will restore homeostasis. Impaired endothelial cell function and reduced NO bioavailability have been observed across a variety of diseases affecting both micro- and macrovascular health, including vascular dementia where impaired blood flow, disrupted neurovascular coupling, inflammation and neuronal loss are thought to be core aspects of the disease. We are developing IW-1973 and IW-1701 as oral, once-daily sGC stimulators for both cardiovascular and non-cardiovascular indications. Phase 1 data in healthy human subjects demonstrate attractive pharmacokinetic properties and clear evidence of target engagement and expected hemodynamic effects, in a well-tolerated dose range. Phase 2 studies are currently ongoing. In addition, we are developing IW-6463, a novel, first-in-class CNS-penetrant, sGC stimulator with potential application to CNS disorders including vascular dementia and Alzheimer's Disease. Preclinical characterization of IW-6463 supports the broad therapeutic potential and multi-faceted pharmacology of this compound. We believe that sGC stimulation can afford therapeutic benefit for vascular dementia and other diseases, and that there are opportunities for multiple therapeutic products differing in their pharmacology, distribution and pharmacokinetics.

Biography

Christopher Winrow completed his Ph.D. at the University of Alberta and post-doctoral fellowship at the Salk Institute. He has authored 70 publications and has over 15 years of neuroscience drug discovery and development experience, delivering five compounds from HTS through successful clinical proof of concept. He led the Belsomra® discovery team from screening to regulatory approval in less than 10 years, resulting in this first-in-class CNS therapeutic garnering approvals by U.S. and international regulatory agencies. Dr. Winrow is Senior Principal Investigator at Ironwood Pharmaceuticals in Cambridge, MA where he is responsible for leading multidisciplinary teams through proof of concept for clinical-stage compounds. Christopher Winrow and the Ironwood team are employees and shareholders of Ironwood Pharmaceuticals and are developing sGC stimulators for therapeutic applications.

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