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**4:00pm**

*Discovery of LY3154885, a Second Generation Human Dopamine D1 Receptor Positive Allosteric Modulator with an Improved Drug-Drug Interaction Risk Profile*

Mevidalen (**1**) is a dopamine D1 receptor positive allosteric modulator (D1 PAM) currently in clinical development for the treatment of Lewy Body Dementia (LBD) patients. In pre-clinical assessments, **1** was found to be primarily cleared by CYP3A4-mediated metabolism, and therefore carried the risk of being a victim of drug-drug interactions (DDI) with CYP3A4 inhibitors and inducers. A back-up discovery effort was initiated to identify a new D1 PAM with an improved DDI risk profile by diversifying the clearance profile. Molecules that introduced additional CYP-isoform mediated metabolism were identified, however, these molecules suffered from significantly higher overall clearance rates and did not meet our criteria for advancement. Aware that a minor metabolic pathway for **1**was UGT-mediated glucuronidation of the primary alcohol, we profiled related analogs and found, surprisingly, that for the C5-chain shortened analog DPTQ (**2**), UGT-mediated metabolism was the dominant metabolic clearance pathway. Through additional structural modifications, we found that the relative contribution of CYP-mediated oxidation and UGT-mediated conjugation could be tuned to reduce the predicted CYP3A4-mediated victim DDI risk.  This work ultimately led to the identification of LY3154885 (**3**), a D1 PAM that possesses similar in vitro and in vivo pharmacologic properties as **1**, but that is metabolized mainly by UGT, resulting in lower predicted victim DDI risk.