ISMS-PL02 **Allosteric Modulation of GPCRs: Leveraging Signal Bias**

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This talk will detail an industrial-academic collaboration between Janssen and the VCNDD that developed an orally bioavailable $mGlu_5$ PAM for the treatment of schizophrenia *via* a fundamentally new molecular mechanism. Leveraging subject matter and drug discovery expertise across the two teams, coupled with a deep basic science component, enabled the joint project team to recognize and understand signal bias as a potential approach to afford an acceptable therapeutic window. I will detail the structure-activity relationship of a novel series of (2(phenoxymethyl)-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-yl(aryl)methanones as potent, selective and orally bioavailable metabotropic glutamate receptor subtype 5 ($mGlu_5$) positive allosteric modulators (PAMs). On the basis of its robust *in vitro* potency and *in vivo* efficacy in multiple preclinical models of multiple domains of schizophrenia, coupled with a good DMPK profile and an acceptable therapeutic window, VU0409551/JNJ-46778212 was selected as a candidate for further development. Unlike other $mGlu_5$ PAMs, VU0409551/JNJ-46778212 was devoid of neurotoxicity. The question at hand is what distinguished VU0409551/JNJ-46778212 from other $mGlu_5$ PAMs. As expected, VU0409551/JNJ-46778212 potentiates DHPG-induced long term depression (LTD), induces calcium mobilization and ERK phosphorylation; however, VU0409551/JNJ-46778212 does not potentiate $mGlu_5$ modulation of NMDA receptor currents nor NMDA receptor–dependent long-term potentiation (LTP), suggesting a unique signal bias for this $mGlu_5$ PAM that may contribute to the observed, favorable therapeutic window. From a conceptual point of view, it is intriguing that selective $mGlu_5$ activation can provide antipsychotic and cognition-enhancing efficacy in the absence of potentiating NMDA receptor function.