26G-ISMS04 **SAR Exploration of Selective Kinase Inhibitors based on the "Head-to-Tail" Approach: Discovery of PI4KIIIα Inhibitors Bearing Diverse Scaffolds**

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In typical kinase inhibitor programs, a hinge binder showing best potency with preferential specificity is initially selected, followed by fine-tuning of the accompanying substituents on its core module. A shortcoming of this approach is that the exclusive focus on a single chemotype can endanger all the analogues in the series if a critical drawback is revealed. Thus, an early effort to prepare such a potential risk by having a multiple series of compounds is rationalized, although there have been very few examples to follow such a policy. PI4KIIIα is one of four mammalian phosphatidylinositol-4 kinases and has recently drawn significant attention as an emerging target for hepatitis C virus (HCV) treatment. Inhibition of this host factor seems to provide a higher barrier to vial resistance as well as activity against all existing HCV genotypes. In this presentation, a novel "Head-to-Tail" approach to discover a diverse set of PI4KIIIα inhibitors is reported. We believe this method will generate distinct core scaffolds, a rational strategy to circumvent potential risks in general kinase programs.