PRESENTATION TITLE: *Characterization of 3-Acylindoles as Potent AHR Agonists: Molecular Dynamics Simulation, Structure-Activity Relationship, and Therapeutic Application in Colitis*

ABSTRACT: The aryl hydrocarbon receptor (AHR) is a ligand activated transcription factor and controls the expression of interleukin-22 (IL-22), which plays a critical role in the maintenance and regeneration of barrier tissues of the gastrointestinal track, respiratory system, and skin. Computational and SAR studies of a series of novel 3-acylindoles revealed structural attributes important for AHR activation. Orally bioavailable AHR agonists were achieved via improvement of metabolic stability and permeability. We demonstrated in a murine model of inflammatory bowel disease that oral administration of the potent AHR agonists significantly reduced mortality and disease severity. Mechanistically, our studies confirm that these compounds potently increase IL-22 production by a direct effect on the gut innate and adaptive immune system and locally expand ILC3 and γδ T cell subpopulations. In the process, mucosal healing is accelerated, gut antimicrobial barrier function reestablished, and intestinal integrity restored.