developed and optimized an NR pulldown and untargeted metabolomics pipeline that can identify novel NR ligands from various complex mixtures, including tissues, fecal samples, microbiotic cultures, environmental waste and compound libraries. In a first proof of concept screen using brain extracts, a novel omega-3 fatty acid ligand was identified using PPARα as bait. 7(S)-HDHA was selectively isolated despite the presence of other more abundant previously published PPARα ligands. Mass spectrometric detection of 7(S)-HDHA in mouse and rat brain, time-resolved FRET analyses, and thermal shift assay results collectively show that 7(S)-HDHA is the strongest activator and highest affinity natural PPARα ligand identified to date. We also show that 7(S)-HDHA activation of PPARα in cortical neurons effectively stimulates neuronal growth and arborization, key measurements of synaptic capacity in neurons. Since many NRs are expressed in or near the gut, and the interplay between NRs and gut-derived metabolites is largely unaddressed, we have since focused the majority of our efforts on intestinal and microbiome extracts. Dozens of new ligands for xenobiotic-sensing receptors have been identified, including fatty acid, phytoestrogen, peptide, and secondary bile acid, with identities soon to be made available in a public database. A subset will be pursued in-house or with collaborators to identify bacterial sources and receptor-based outcomes. Examples of new PPARα, CAR, PXR, and/or RORα ligand-NR interactions and outcomes will be presented. These discoveries will facilitate new directions for drug development, nutritional supplements and probiotic therapies for the prevention and treatment of a wide spectrum of diseases.

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Untargeted Nuclear Receptor-Wide Screening reveals Novel Ligands From the Brain and Gut.

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The 48-member family of human nuclear receptors (NRs) plays major roles in metabolic homeostasis, immunity, and inflammatory responses, largely under the control of small lipophilic molecule interactions. A critical barrier precluding major breakthroughs in the discovery of new metabolic ligands is a lack of new methods that allow comprehensive mining of the natural metabolome, most of which remains uncharacterized in terms of identity and function. To address this challenge, our group has