IGNIS: Transcriptomic Analysis for Drug Repurposing Across the Gut-Brain Axis

Da Cunha, Gabriela (School: Colegio Visconde de Porto Seguro)

Neurodegenerative and intestinal diseases impact millions of people worldwide. Considering their gut-brain axis connection, IGNIS tested the hypothesis of a shared protein target for drug repurposing among ten of these illnesses. Using 17 gene expression profiling datasets (1,346 patients and 1,362 controls in total), more than 100 common differentially expressed genes were identified in subsets of up to seven diseases. Based on these genes, a shared target was selected through regulatory and protein-protein interaction (PPI) networks and functional enrichment. Alongside three reference inhibitors, 1,541 compounds approved by the FDA and/or EMA were subjected to docking, in which the top-ranked compounds advanced for a refined docking and a 50 ns molecular dynamics simulation. PPI networks revealed 28 central hub genes, five extensive clusters, and 14 key genes. There were 19 transcriptional factors and 17 miRNAs recognized as potential regulatory biomarkers for seven diseases, and functional enrichment highlighted inflammatory metabolic pathways. STAT3 was identified as a shared target of five diseases, and 24 samples outperformed STAT3 controls in average binding energy by up to 13%. In refined docking (exhaustiveness = 32), five samples matched or exceeded the performance of two controls in ligand efficiency, with an improvement of up to 9%. The 50 ns molecular dynamics simulations highlighted Nilotinib-STAT3 complex's stability, with a 31.43% lower peak than the control TTI-101 in RMSD. With reproducible procedures, this study provided evidence that Nilotinib, Avapritinib, Ubrogepant, Atogepant, and Zafirlukast are prioritized candidates for further drug repurposing validation aimed at new therapies in the gut-brain axis.

Awards Won: