Neurobiologically Informed Schizophrenia Therapeutics: Multi-Modal Characterization and in vitro Modulation of HERV-K–Associated Neuroinflammation

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Schizophrenia is a chronic neurodevelopmental disorder affecting approximately 24 million people worldwide. Despite its severity, its biological mechanisms remain poorly understood, and current treatments fail to address the disorder's root cause, leaving one-third of patients treatment-resistant. To address this gap, this project investigates the neuroinflammatory profile of schizophrenia, identifying HERVK–associated endogenous retroviral pathways as a key contributor, and evaluates targeted therapeutic strategies to modulate this mechanism. Diffusion-weighted magnetic resonance imaging analysis of 147 control-matched participants identified 14 white matter tracts with significant fibre density and cross-section abnormalities, with 12 driven primarily by fibre density reductions. 9 tracts overlapped with regions identified in prior functional connectivity analyses, suggesting convergent structural-functional disruption. Hypothesis-driven RNA sequencing analysis revealed a dysregulation of antiviral immune response genes, which correlated with an activation of evolutionarily young endogenous retroviral elements, implicating HERVK as an upstream driver of neuroinflammation. In vitro, 2 targeted therapeutic strategies were assessed: an analog to a small molecule aimed at restoring the convergent structural-functional dysregulation and a novel antisense oligonucleotide (ASO) targeting HERVK gag. The analog showed dose-dependent, sublethal effects on neuronal morphology, and the ASO achieved a 69% reduction in expression. These results demonstrate that HERV-K–associated pathways contribute to neuroinflammatory processes in schizophrenia and that targeted interventions can effectively modulate this pathway, supporting the development of precise schizophrenia therapeutics.

Awards Won:

The Knowledge Society: 2nd Place