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Drug Repurposing for the Treatment of NeuroAIDS: AI-Driven Discovery, Retrospective Analyses, and Experimental Validation

Drug repurposing can drastically shorten the timeline from discovery to clinical translation by leveraging established safety, pharmacokinetic, and blood–brain barrier (BBB) penetration profiles. Here, we describe an integrated AI-to-experiment framework that combines AI-driven literature mining, retrospective electronic health record (EHR) analysis, and experimental validation to identify therapeutic strategies for HIV-associated neurocognitive disorders (HAND), particularly in the context of substance use disorder.

We applied the AI-based literature mining platform AGATHA to systematically analyze biomedical literature and clinical trial data, prioritizing mechanistically grounded drug/gene associations relevant to neuroinflammation, neurodegeneration, and synaptic dysfunction. This approach identified multiple repurposing candidates spanning complementary biological pathways, including inhibitors of inflammatory signaling (Amlexanox, TBK1), epigenetic regulation (Tazemetostat, EZH2), ion channel mediated microglial activation (Senicapoc, KCNN4), metabolic and redox regulators (itaconate derivatives), and renin–angiotensin–aldosterone system inhibitors (RAASi).

Retrospective EHR analyses revealed a clinically meaningful distinction within RAAS inhibitors: BBB-penetrant ACE inhibitors and angiotensin receptor blockers were associated with a delayed onset of dementia in people with HIV compared with non–BBB-penetrant agents. This finding supports a central, rather than solely vascular, mechanism of action and suggests that drug selection within an existing therapeutic class may have immediate implications for clinical practice in PWH.

To validate hypotheses, we employed scalable phenotypic assays in primary neuronal and microglial cultures exposed to HIV-Tat and cocaine. Across multiple compound classes, treatment preserved neuronal viability and attenuated microglial activation. Individual agents engaged partially distinct signaling mechanisms but converged on restoration of microglial homeostasis and neuronal integrity, consistent with a combinatorial therapeutic rationale.

Together, these results establish an end-to-end framework integrating AI-driven hypothesis generation, clinical data analysis, and experimental validation. By identifying BBB-penetrant RAAS inhibitors and complementary repurposed agents that target convergent neuroinflammatory pathways, this approach enables rapid translation of actionable findings and supports rational development of combination therapies for HAND.

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