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## Mechanisms of anti-retroviral drug-induced changes in amyloid precursor protein processing: Implications for HAND

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HIV-associated neuro-cognitive disorders (HAND) persist in 30-50% of HIV positive patients despite viral control by anti-retroviral therapy (ART). Several studies indicate a potential role for anti-retrovirals in the persistence of HAND and evolution from a sub-acute, sub-cortical dementia to a cortical, neurodegenerative disease. Based on their ability to induce ER stress in a wide variety of cell types, we hypothesized that HIV protease inhibitors (PI) induce ER stress in the CNS, resulting in chronic dysregulation of the unfolded protein response (UPR) which in turn alters amyloid precursor protein (APP) processing by inducing the  $\beta$ -site APP cleaving enzyme-1 (BACE1). Utilizing *in vitro* and *in vivo* models, we demonstrate that PIs induce neuronal ER stress leading to PERK-like ER kinase (PERK)-dependent phosphorylation of the eukaryotic translation initiation factor 2 $\alpha$  (eIF2 $\alpha$ ), and enhanced translation BACE1. Additionally, we demonstrate enhanced A $\beta$  production, by the PI, ritonavir, in primary rodent neuroglial cultures and Chinese Hamster Ovary (CHO) cells expressing human APP. Genetic excision of PERK in primary neurons abrogated the ability of PIs to induce the UPR, phosphorylation of eIF2 $\alpha$  and translational up-regulation of BACE1. Consistent with these findings, ARV administered to SIV-infected macaques resulted in elevated levels of BACE1 in the CNS coinciding with markers of neuronal damage. Altogether, these findings implicate PIs as potential mediators of neuro-degeneration in HAND.

### Biography

Kelly L Jordan-Sciotto completed her PhD at Thomas Jefferson University in 1996. She completed her Post-doctoral studies at University of Pittsburgh Medical Center with Dr. Robert Bowser and Clayton Wiley in the department of Pathology, Division of Neuropathology. She is the Chair of Pathology at University of Pennsylvania School of Dental Medicine. She has published more than 50 papers in reputed journals and is currently serving as Chair of the Neuro-Aids and End Organ Disease Study section at NIH.

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