Novel therapeutics for HIV-1: Small molecule modulators of RNA processing

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Current therapeutics is highly successful in blocking disease progression following HIV-1 infection but the development of resistance due to the high mutation rate of this virus remains a constant threat. To explore alternative approaches of controlling HIV-1 replication that would complement existing drugs, we are examining the impact of altering various processes regulating host RNA splicing for their ability to modulate HIV-1 gene expression. Previously, our group demonstrated that cardiotonic steroids (digoxin) are potent inhibitors of HIV-1 replication due to alterations in viral RNA processing associated with the selective modification of the host RNA processing factors SRSF3 and Tra2ß. In more recent work, we demonstrate that the anti-HIV-1 effect of digoxin is the result of MEK/ERK signaling pathway activation. In support of the importance of this pathway in regulating HIV-1 RNA processing, parallel studies identified other activators of this pathway (anisomycin and a benzoxadiazol-4-amine derivative designated 191) as potent inhibitors of HIV-1 gene expression. Like digoxin, 191 induced a marked alteration of HIV-1 RNA processing (reduced accumulation of unspliced and singly spliced viral RNAs) as well as loss of Tat and Rev Expression and changes in SRSF3 and Tra2ß phosphorylation. At doses of 191 sufficient to suppress HIV-1 replication, we observe only minor changes in host RNA alternative splicing (<30 events showing >20% alteration in exon inclusion of 9800 events detected) consistent with HIV-1 having a great sensitivity to modulation of the host RNA splicing apparatus. Subsequent tests have confirmed 191's ability to suppress HIV-1 replication in the context of PBMCs. Furthermore, 191 are able to inhibit replication of different HIV-1 clades as well as variants resistant to existing RT, PR, or IN inhibitors. In parallel with the above studies, we have also examined the effect of modulating the activity of other host cell signaling cascades (AKT, PI3K, GSK-3) for their effects on HIV-1 gene expression. Of these pathways, only inhibition of GSK-3 with CHIR98014 was found to result in loss of viral protein expression that correlated with reduced HIV-1 RNA accumulation. CHIR98014 is a potent inhibitor of HIV-1 gene expression in all cell lines tested and is currently being evaluated for its anti-viral potency in the context of PBMCs. Current tests have not detected changes in host SR protein phosphorylation/abundance that correlate with CIHR98014's anti-HIV effect. However, shRNA depletion of either GSK-3α or ß resulted in a loss of HIV-1 Gag expression confirming the important role of this signaling pathway in regulating HIV-1 gene expression. Together, these findings demonstrate the feasibility of modulating host RNA processing to generate a state within the cell unable to support HIV-1 replication.

Speaker Biography

A Cochrane completed his PhD in 1988 from Queen's University and Post-doctoral studies from Roche Institute of Molecular Biology. He is a Professor at the University of Toronto. He has published more than 70 papers and serving on the Editorial Board of Retrovirology. Over the last several years, his research has been focused on the regulation of viral RNA processing, with particular focus on the identification of small molecule modulators of RNA splicing and their utility in the suppression of HIV-1 and adenovirus replication.

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