Panobinostat and Romidepsin enhance Tax transcription but only moderately Tax protein in Tax-expressing, HTLV-1-infected cultured, and patients' T-cells

Authors:
Schnell A P[1], Kohrt S[1], Aristodemou A[2], Taylor G P[3], Bangham C R M[2], Thoma-Kress A K[1]

[1] Institute of Clinical and Molecular Virology, Friedrich-Alexander-Universität Erlangen-Nürnberg, [2] Section of Immunology of Infection, Department of Infectious Disease, Imperial College London, [3] Section of Virology, Department of Infectious Disease, Imperial College London

Background:
The viral transactivator Tax plays a key role in HTLV-1 latency and de novo infection. Previous approaches focused on the Histone Deacetylase Inhibitor (HDACi) Valproate, as latency-reversing agent (LRA), to boost Tax expression and expose infected cells to the host immune response. Despite a transient decrease in the proviral load of HAM/TSP patients, Valproate treatment failed to achieve a permanent reduction. We hypothesized that other compounds, including more selective HDACi and activators of the positive transcription elongation factor b, might prove superior to Valproate in manipulating Tax expression.

Methods:
Thus, a panel of LRAs was selected and tested for toxicity and potency in enhancing Tax expression. The impact of the compounds was evaluated in different model systems, including transiently transfected T-cells, HTLV-1 chronically infected T-cell lines, and PBMCs from HTLV-1 infected patients *ex vivo*.

Results:
We identified the pan-HDACi Panobinostat and class I HDACi Romidepsin as particularly potent agents at raising Tax expression. qRT-PCR analysis revealed that these inhibitors considerably boost *Tax* and *Tax-target* gene transcription. However, despite this significant increase in *Tax* transcription and histone acetylation, protein levels of Tax were only mildly to moderately enhanced.

Conclusion:
In conclusion, these data demonstrate the ability of Panobinostat and Romidepsin to successfully manipulate Tax expression and provide a foundation for further research into eliminating latently infected cells. Collectively, these findings also contribute to a better understanding of conditions limiting transcription and translation of viral gene products.

Disclosure of Interest Statement:
None