

## PE36 LB

### Novel activators of latent HIV-1 from natural products

*I. Tietjen*<sup>1,2</sup>, K. Andrae-Marobela<sup>3</sup>, X.T. Kuang<sup>4</sup>, B.M. Abegaz<sup>5</sup>, D. Fedida<sup>2</sup>, Z.L. Brumme<sup>1,6</sup>, M.A. Brockman<sup>1,4,6</sup>

<sup>1</sup>Simon Fraser University, Faculty of Health Sciences, Burnaby, Canada, <sup>2</sup>University of British Columbia, Anesthesiology, Pharmacology, and Therapeutics, Vancouver, Canada, <sup>3</sup>University of Botswana, Department of Biological Sciences, Gaborone, Botswana, <sup>4</sup>Simon Fraser University, Department of Molecular Biology and Biochemistry, Burnaby, Canada, <sup>5</sup>African Academy of Sciences, Nairobi, Kenya, <sup>6</sup>University of British Columbia, British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada

**Background:** While “shock-and-kill” strategies have the potential to eliminate latent HIV, they have yet to succeed in clinic, in part because existing latency activators display toxicity and do not uniformly activate latent viral reservoirs. Thus, new chemical leads with reduced toxicity, improved efficacy, and/or ability to synergize with existing agents are needed. Natural products are a promising but undervalued resource for identifying new anti-latency agents that may act via distinct mechanisms.

**Methods:** We examined 9 extracts from plants used by traditional healers in Sub-Saharan Africa to treat HIV symptoms and 85 pure compounds obtained from the pan-African Natural Product Library (p-ANAPL), which also derive from traditional medicinal plants. Extracts and compounds were screened using the J-Lat 9.2 GFP-reporter T cell line that contains an integrated NL4.3- $\Delta$ env/ $\Delta$ nef proviral genome. TNF $\alpha$  was used as a control. Natural products that induced GFP expression in >5% cells while retaining >30% cell viability at 5  $\mu$ g/mL were assessed for 50% activation and cytotoxic concentrations (EC50 and CC50), intracellular p24Gag expression, and synergism with histone deacetylase inhibitors (HDACi) panobinostat and romidepsin.

**Results:** Medicinal plant extract “Mokungulu” at 5  $\mu$ g/mL induced GFP expression in >5% cells and p24Gag production, but displayed ~3-fold less cytotoxicity than panobinostat or romidepsin. Pure compound “p61” at 5  $\mu$ g/mL also activated GFP expression. Interestingly, both products exhibited synergy with panobinostat and romidepsin, inducing GFP expression in up to 50% of cells when combined with suboptimal doses of HDACi and up to a 38-fold increase in mean GFP intensity vs. untreated cells (i.e., both similar to 50 ng/mL TNF $\alpha$ ). We also identified 6 pure compounds that activated nearly 100% of cells but with lower intensity (i.e. 2 to 7-fold increased mean GFP intensity vs. untreated cells) with no evidence of toxicity.

**Conclusions:** We have identified potential new HIV latency activators of natural origin guided by indigenous medicinal knowledge. These agents display low toxicity and synergy with HDAC inhibitors currently under evaluation, indicating that they may be promising lead compounds for additional study.