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Recombinant protein guided activation of HIV; a means for target specific purging of proviral reservoirs in the brain

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The eradication of HIV is a collective goal that is hampered by viral persistence through the formation of provirus, burdening patients with life-long anti-retroviral therapy (ART). To functionally target HIV in the context of ART and within the confines of the latent reservoir, a method to activate latent provirus is needed. Currently, latency reactivating drugs are being tested, but suffer from variable efficacy in different latent models as well as non-specific activation of a broad range of host genes, which may cause unwanted toxic side-effects. A therapeutic compound that can specifically target and sustainably activate latent provirus would prove transformative. Over the last decade much progress has been made towards the development of Zinc Finger Protein (ZFP) technology, which allows for recombinant proteins to be developed that can target specific genomic loci. We describe here the development and testing of an HIV specific ZFP protein fused to a VPR activation domain (ZFP-362-VPR), which potently activates HIV transcription in reporter and latency models. Furthermore, recombinant ZFP-362-VPR contains a cell and blood brain barrier penetrating Tat peptide domain, allowing for direct addition to cells to transcriptionally activate HIV in a targeted manner. The observed transcriptional activating effects were maintained in a range of HIV latency models and appeared to be relatively specific compared to a similar defective CRISPR-VPR system. The advent of recombinant protein therapeutics may prove useful in targeting and purging reservoirs of HIV infected cells that could be used in conjunction with CAR T-cell and/or CRISPR based approaches.