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HIV LATENT RESERVOIR CURE STRATEGIES

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Research and development into pharmaceutical compounds targetted against HIV have resulted in significant improvement in health and changed the HIV diagnosis from a death sentence to a chronic, manageable infection. HIV patients that have high levels of adherence to their antiretroviral regimen achieve an undetectable plasma viral load. However, the virus is not totally eliminated from the body due to low-level replication primarily in tissue reservoirs (i.e. latent reservoir). If patients even attempt short treatment interruption, the HIV virus returns to detectable levels.

Research into the latent reservoir has focused on three main categories ^[1] (Fig 1). The majority of research into “HIV cure” has been to reactivate the latent reservoir, so called “shock” using cellular activation signals and transcriptional factors to activate the latent virus in the reservoir. The next step is to “kill” the reactivated HIV by strengthening the immune system. Other methodologies include permanently suppressing the latent reservoir. Finally, the use of genetic methods for CD4 T-cells to resist HIV infection has shown promise *in vitro*.

HIV attacks the CD4 T-cell lineage and produces chronic inflammation. Additionally, HIV patients have elevated expression of programmed cell death (PD-1) receptor ^[2] Blockage of these receptors has been successful as a treatment of solid tumors ^[3]. Blocking inhibitory cytokines (i.e. IL-10) ^[4] has resulted in increased T cell activity in a hepatitis C infection model ^[4,5]. Some of the first latency reversing agents (LRA) were histone deacetylase inhibitors (HDACs) and BET bromodomain inhibitors. These transcriptional factors induce chromatin and induce the release of positive transcription elongation factor b (P-TEF β) from the repressive complex ^[6] Compounds (HDACs) including SAHA, panobinostat, and romidepsin all reactive latent HIV in cells line models however, in primary human resting T-cells that were infected these compounds did not appear to work well. Protein kinase C agonists (PKC) such as prostratin and bryostatin can reactivate HIV in cell line models and primary T-cells ^[6] However, the narrow therapeutic ranges of these PKC agonists prevent their continued use. Thus, structural agonists of these compounds are being developed. Combination of several of these approaches may provide synergistic latency reversal at lower doses.

Removing HIV by cytotoxic T-cells (CTL) and natural killer (NK) cells or by broadly neutralizing antibodies has been associated with the “kill” strategy ^[7] However, due to HIV mutations, most patients are unable to totally eliminate the virus. Each broadly neutralizing antibody is able to inhibit only a narrow spectrum of isolates. Thus, multiple broadly neutralizing antibodies may be necessary to counter the HIV strains contained within each patient. Engineered chimeric antigen receptors (CARs) have been used to increase T-cell

receptor activation and has led to 90% remission rates in acute leukemia [8]. If the CARs can be engineered to recognize specific viral proteins and have minimal off-target effects, this would be a major advance.

Finally, gene therapy may be useful for HIV cure. The only successful HIV cure has been an individual who received transplanted cells containing the natural mutation of CCR5 [9]. Investigators are working to replicate this using a variety of modalities including zinc finger nuclease [10], and CRISPR/Cas9 [10] targeting of CCR5 to induce the natural delta 32 mutation. Early results of these gene therapies show promise but further research is necessary for all these modalities to bring to the forefront of a HIV cure.

Supplementary Material

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Figure 1 l.

Strategies to deplete the HIV latent reservoir. Shock and Kill strategies can be used separately or together to activate and remove latent reservoir.