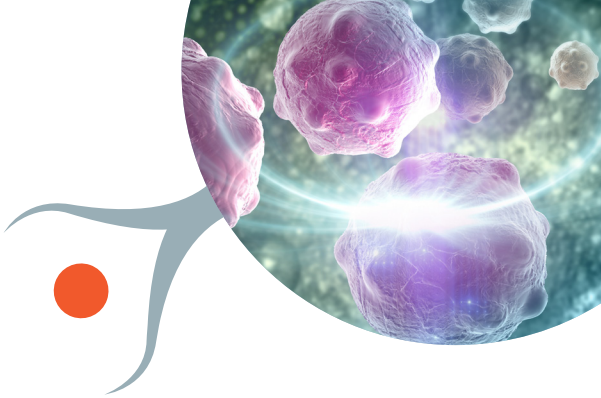
IMMUNOVATIVE Therapies Ltd.



ALLOSTIM™ MECHANISMS BENEFICIAL FOR HIV INFECTION

The following table summarizes the mechanisms of action of AlloStim™ and the benefit(s) the mechanism could have in HIV infection. References are provided for additional reading.

ALLOSTIM™ MECHANISM	HIV/AIDS PROBLEM	POSSIBLE BENEFIT	REFERENCES
Multiple intradermal injections induces a Th2 –> Th1 switch in cancer patients	A Th1 –> Th2 switch takes place in HIV infected people which causes suppression of cellular immunity. The switch is also correlated with AIDS	Correcting the Th1/Th2 imbalance can support cellular immune function and prevent opportunistic infection	1 | 2 | 3 | 5
Multiple intradermal injections increases the circulating titer of CD4+ Th1 memory cells specific for alloantigens	CD4+ cell s are targeted by the virus causing low CD4 counts and a lack of helper function HIV patients remaining CD4 cells are mostly of Th2 or Th0 types, resulting in decreased cellular immunity	Increasing the titer of CD4+ cells can restore helper function. HIV preferentially replicates in Th2 cells. Increasing the CD4+ Th1 memory cell titer might not "add fuel to fire" as these cells are resistant to HIV infection	4 | 5
IV infusion after priming increases serum IL-12 and sustains high levels for months	IL-12 is suppressed in HIV patients. IL-12 is an important cytokine produced by mature dendritic cells and macrophages. This cytokine promotes Th1 cellular immunity	Restoration of IL-12 production through maturation of dendritic cells should promote development of Th1 cellular immunity to against HIV, Dendritic cells/Macrophages that mature in the presence of IL-12 are resistant to HIV infection	6 | 7
IV infusion causes a sustained inflammatory 'cytokine storm' primarily including serum interferon-gamma	HIV infection results in loss of interferon-gamma production. This cytokine is produced primarily from Th1 helper cells. Interferon-gamma is important for suppression of viral replication	Restoration of the ability to produce interferon-gamma and maintain sustained plasma concentrations can serve to enhance cellular immunity to any viral infection and also suppress HIV replication	8 | 9
IV infusion down regulates CCR5 expression on T-cells and macrophages	CCR5 functions as the primary coreceptor for macrophage-tropic isolates of HIV-1. IL-12 has been shown to down-modulate the surface expression of CCR5	Transplant of donor immune cells which lacked CCR5 receptors resulted in long-term remission of HIV. Donors with this mutation are rare. This may be a natural way to reduce CCR5	10 | 11
The "Mirror Effect" permits the anti-tumor effects of allogeneic transplant without GVHD toxicity	The positive effects of the allogeneic transplant of CCR5 mutant immune cells into a HIV+ patient resulted in long term remission, but required pre-conditioning and GVHD	The 'Mirror Effect" may provide a powerful anti-viral effect of allogeneic transplant without GVHD or need for a CCR5 mutant donor	10 | 11
V infusion turns off Treg suppressor cells that inhibit cellular immunity against cancer and causes these cells to change into non-suppressor cells. Mechanism is, in part, through down regulation of CTLA4 and PD1 on T-cells	Treg suppressor cells are also active in HIV to suppress cellular immunity. PD-1 and CTCA4 are up-regulated on HIV-specific CD4 T cells and their expression correlates with viremia	Natural down regulation of CTL4 and PD1, as well as reversal of Treg function can create an immunological environment enabling HIV viral clearance	12 | 13 | 14 | 15
Increases CD40L expression	CD40L is expressed on viral particles and cause the activation of dendritic cells and macrophages, leading to increased CD4+ T cell activation, which promotes the replication of latent HIV in these lymphocytes	CD40L expression contributes to the immunological control of viral replication by inducing HIV-suppressive chemokines and supporting the production of anti-HIV antibodies and cytotoxic T cells	18
Activates Natural killer (NK) cells	NK cells are an important component of the innate immune response against viral infections. NK cell-mediated cytolytic activity is defective in HIV-infected individuals	NK cells can impose immune pressure on HIV	16 | 17

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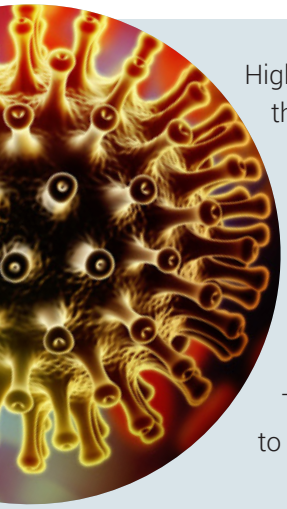

Highly active antiretroviral therapy (HAART) for the chronic suppression of HIV replication has been the major accomplishment in HIV/AIDS medicine. Many patients are now in their second decade of treatment, with levels of plasma HIV RNA below the limits of detection of clinical assays. However, HIV infection can persist in spite of efficacious antiretroviral therapies as evidenced by rapid rebound of viremia upon cessation of antiretroviral therapy.

This phenomenon is thought to be due to the early establishment of a stable reservoir of latently infected cells. Viral suppressive therapy is required to contain persistent infection in reservoirs, such as latently infected CD4+ lymphocytes and cells of the macrophage-monocyte lineage.

Thus, life-long antiviral therapy is needed to control HIV infection. Such therapy is expensive and prone to drug resistance, cumulative side effects and unknown effects of long-term treatment.