

# Substance P and neurokinin-1 receptor modulation of HIV

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## Abstract

There is a high incidence of life event stress, depression, and associated symptoms in individuals with HIV infection/AIDS. Psychological and psychiatric symptomatology in individuals with HIV and AIDS may be related to the progression of AIDS disease. The association between depression, anxiety, and stress with HIV disease progression suggests that neurobiologic and neurophysiologic factors have an important role in modulating HIV. The immune effects caused by changes in behavioral state or brain activity are affected, at least in part, through the neuroendocrine-immune pathways. Life stress and depression may be associated with altered blood levels of CNS-released neuropeptides, including substance P (SP). SP is a powerful immunomodulator which is a critical link between the nervous and immune system. We have investigated the role of the neuropeptide SP and its preferred receptor, neurokinin-1, in HIV infection and AIDS. There are compelling data from our laboratories, as well as the findings in the literature, which demonstrate that SP may play an important role in the pathophysiology of neuropsychiatric disorders, including stress and depression in HIV-infected individuals and in the immunopathogenesis of HIV disease. Modulation of SP activity and SP receptor may offer a novel approach to the treatment of psychiatric disorders and to the design of new anti-HIV therapy.

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## 1. Introduction

Life stress and/or depression are emerging as significant cofactors that contribute to the disease pathogenesis in various stages of HIV infection and/or its progression to AIDS (Evans et al., 2002a,b). Kopnisky, Stoff, and Rausch have recently reported on a workshop sponsored by NIMH on the effects of psychological variables on the progression of HIV-1 disease. This report summarized important aspects of immune-neural communication in chemokines in the brain and noted the importance of other mediators, including substance P (SP; Kopnisky et al., 2004). The association between depression, anxiety, and stress in HIV disease

progression suggests that neurobiologic and neurophysiologic factors play a role in modulating HIV infection and responses to antiretroviral therapy (Cole and Kemeny, 1997; Cole et al., 2001). The immune effects caused by changes in behavioral state or brain activity are mediated, at least in part, through neuroendocrine-immune pathways (Petitto et al., 2000; Gunnick et al., 2002; Evans et al., 2002b). Life stress and/or depression are associated with altered immune cell function and HIV disease (Evans et al., 1995; Leserman et al., 1997). Several parameters of cellular immunity are altered in patients with depression (Evans et al., 1992; Herbert and Cohen, 1993; Irwin, 2002). In HIV-seropositive individuals, there is an association between depression and both early and late HIV disease progression (Leserman et al., 1999; Mayne et al., 1996). There is a significant association between depression and HIV morbidity and mortality in HIV-seropositive women (Ickovics et al., 2001). Approximately 20% of HIV-seropositive women without current substance abuse have major depression (Morrison et al., 2002). This is a

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prevalence rate approximately twice that reported for HIV-seropositive men (Ickovics et al., 2001). Ickovics et al. (2001) reported that the mortality rate of HIV-seropositive women was doubled in the presence of chronic depressive symptoms compared to women with intermittent or no depressive symptoms. Life stress and depression are associated with altered blood levels of CNS-released neuropeptides, including SP (Fehder et al., 1997). SP acts as a potent modulator of neuroimmunoregulation. SP has a role in the pathophysiology of several neuropsychiatric disorders (Malek-Ahmadi, 1992). Modulation of SP activity may offer a novel approach to the treatment of depression, anxiety, and stress (De Felipe et al., 1998; Kramer et al., 1998). In a placebo-controlled trial in patients with moderate and severe depression, the SP antagonist MK-869 had robust antidepressant effects (Kramer et al., 1998; Kramer et al., 2004), supporting the concept that SP and its preferred receptor (neurokinin-1 receptor, NK-1R) are involved in the pathophysiology of depression and, possibly, anxiety disorders (Stout et al., 2001). Mapping studies indicate that the SP-preferring receptor is highly expressed in brain regions that are critical for the regulation of affective behavior and neurochemical responses to stress (Harrison and Geppetti, 2001). Stress reactions lead to altered-release of neuropeptides, such as SP, that have the ability to modulate immune cell functions, and thus may contribute to the progression of HIV disease (Evans et al., 2002a; Hassan and Douglas, 1990; Ho et al., 2002a,b; Lai et al., 2001).

## 2. Substance P

SP was initially isolated from a crude alcoholic extract of equine intestine and brain. Von Euler and Gaddum (1932) found that the compound had a potent stimulant action in rabbit jejunum and produced hypotension. SP was unique and was referred to as substance P on the tracings. It is an undecapeptide with the amino acid sequence Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH<sub>2</sub> (Severini et al., 2002; Baby et al., 1999). Subsequently, SP was termed a “tachykinin” because it produced a rapid contractive response in smooth muscle. Chang and Leeman (Chang and Leeman, 1970; Chang et al., 1971) isolated a sialagogic peptide from bovine hypothalamic tissue that they characterized as SP. In 1971, Chang and Leeman reported the amino acid sequence of purified SP. SP, an 11-amino-acid neuropeptide (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH<sub>2</sub>), is the most extensively studied and most potent member of tachykinin family, which has three members (SP, neurokinin A and B, Diagram). The structure of SP is similar to the structure of other tachykinins. Tachykinins share the C-terminal sequence Phe-X-Gly-Leu-Met-NH<sub>2</sub> (Harrison and Geppetti, 2001; Takahashi et al., 1992). The tachykinins in mammals are the products of two genes, preprotachykinin-A (PPT-A) and preprotachykinin-B (PPT-

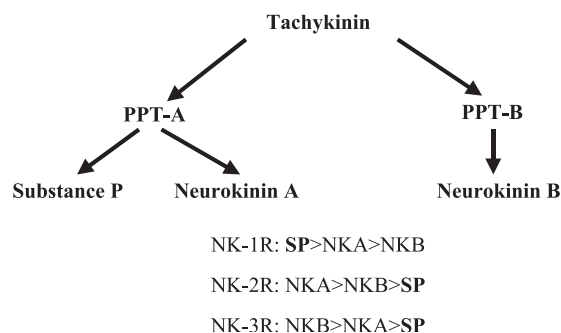


Fig. 1. Tachykinin family. From Ho et al. (2002a); CNS Spectrums 7, 867–874.

B; Fig. 1). The PPT-A gene comprises seven exons and is transcribed into three different mRNAs as a result of alternative splicing (Takahashi et al., 1992). SP is translated from the PPT-A gene, which contains seven exons that undergo differential splicing to yield alpha, beta, and gamma PPT-A mRNA. The alpha form codes for the SP precursor, whereas the beta and gamma forms code for both the SP and substance K (neurokinin A) precursors (Takahashi et al., 1992). SP precursor sequences are encoded by all three PPT-A mRNAs. Thus, multiple tachykinin peptides with related biological activities can be derived from the SP gene. The mammalian tachykinins (SP, neurokinin A, and neurokinin B) are widely distributed throughout the central and peripheral nervous systems, where they serve as neurotransmitters or neuro-modulators (Longmore et al., 1997; Payan et al., 1986).

SP is the most abundant neurokinin in mammalian CNS. SP is synthesized by neurons and is transported to synaptic vesicles. SP is released by calcium-dependent mechanisms and has a depolarizing action (Malek-Ahmadi, 1992). SP is released from sensory nerves in skin in response to injury, axon reflex, and antidromic stimulation (Lembeck and Gamse, 1982). SP also plays a role in inflammation (Payan, 1989). SP concentrations are elevated at local sites of inflammation (Payan et al., 1986). SP contributes to the inflammatory response mediated by respiratory syncytial virus infection, which is inhibited by treatment with anti-SP antibody (Tripp et al., 2003). SP can cause vasodilation and plasma exudation leading to swelling and edema (Nieber et al., 1992). SP and other neuropeptides modulate immediate hypersensitivity reactions by stimulating mast cells to release histamine (Matsuda et al., 1989). Intradermal injection of SP also causes erythema and edema via both histamine dependent and histamine independent pathway (Cappugi et al., 1992).

## 3. SP receptors

All three human neurokinin receptors (NK-R) have been cloned (Gerard et al., 1990; Takeda et al., 1991; Takahashi et al., 1992). The expression of these receptors in cell lines

has facilitated the ability to rapidly screen agents for receptor selectivity (Swain, 1998). The human NK-1R has been cloned, and its gene localized to chromosome 2 (Gerard et al., 1990; Hopkins et al., 1991; Takeda et al., 1991). The NK-2R gene is localized to chromosome (Gerard et al., 1990; Kris et al., 1991). NK-3R (Buell et al., 1992; Huang et al., 1992; Takahashi et al., 1992) has more extended C and N termini in comparison to NK-1R and NK-2R. NK-1R and NK-2R are receptors of the seven transmembrane G-protein-coupled type.

The nervous system modulates immunologic and inflammatory responses, most likely through neuropeptide receptors on leukocytes and the effects of these peptides on lymphocyte function (Dunn, 1988; Payan, 1989; McGillis et al., 1990). There are at least three neurokinin receptors (NK-1R, NK-2R, and NK-3R) in the tachykinin family (Fig. 1). These receptors are all promiscuous, binding to SP as well as other tachykinins (Fig. 1). Neurokinin A and neurokinin B preferably bind NK-2R and NK-3R, respectively. The biologic responses to SP are mainly mediated by NK-1R, a G-protein-coupled receptor bearing seven transmembrane domains (Payan, 1989; McGillis et al., 1990). The SP receptor (NK-1R) is made of 407 amino acid residues (Takahashi et al., 1992) and has a molecular weight of 58,000. Gene-targeted disruption of NK-1R protected the lung from immune complex injury indicating that immunoreactive SP amplifies the inflammatory reaction (Bozic et al., 1996).

#### 4. SP and NK-1R in immune cells

SP is produced mainly in the primary sensory neurons and the intrinsic enteric neurons. We and others have demonstrated that immune cells, including human and murine dendritic cells (Lambrecht et al., 1999; Marriott and Bost, 2001), human fetal brain microglia (Lai et al., 2000), human peripheral blood-isolated mononuclear phagocytes (Ho et al., 1997), and lymphocytes (Lai et al., 1998a,b; De Giorgio et al., 1998) also express SP mRNA and protein. Because microglia reside in an environment with direct and frequent communication with other CNS cells that are the major sources of SP, it is likely that the microglia and CNS neurons may interact in a bidirectional manner. These human immune cells have autocrine regulatory effects (Lai et al., 2002) and may affect other cell types in a paracrine-like manner. The biological responses to SP mediated by the NK-1R have been identified on immune cells (Table 1). NK-1R is present on T lymphocytes (Payan et al., 1984; Stanisz et al., 1987), including CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes (Payan et al., 1984; Stanisz et al., 1987), B lymphocytes (Stanisz et al., 1987), monocytes/macrophages (Ho et al., 1997; Lucey et al., 1994), neutrophils (Wozniak et al., 1989), and mast cells (Shanahan et al., 1985). We recently demonstrated that human immune cells (microglia, mono-

Table 1  
SP receptor expression on immune cells

Cell type	References
Stem cells	Li et al. (2002); Rameshwar and Gascon (1995)
T lymphocytes	Lai et al. (1998a); Payan et al. (1984); Stanisz et al. (1987)
B lymphocytes	Bost and Pascual (1992); Stanisz et al. (1987)
Macrophages	Bost et al. (1992); Ho et al. (1997); Lucey et al. (1994)
Dendritic cells	Lambrecht et al. (1999); Marriott and Bost (2001)
Microglia	Lai et al. (2000)
Neutrophils	Wozniak et al. (1989)
Mast cells	Shanahan et al. (1985)
Natural killer	Feistritzer et al. (2003)

Table modified from Ho et al. (2002a); CNS Spectrums 7, 867–874.

cytes/macrophages, and lymphocytes), as well as stem cells, express NK-1R (Ho et al., 1997; Lai et al., 1998a,b, 1999, 2000; Li et al., 2000). NK-1R is present on both murine and human dendritic cells (Marriott and Bost, 2001). NK-1R found in many immune cells is similar or identical to the NK-1R found in neurons (McGillis et al., 1990; Bost and Pascual, 1992). There is also evidence that other receptor types and mechanisms are involved in SP-mediated biological activity. Human monocytes express a nonneurokinin SP receptor that is functionally coupled to MAP kinase (Jeurissen et al., 1994; Kavelaars et al., 1994a). SP induces modulation of voltage-gated potassium channels on T lymphocytes (Schumann and Gardner, 1989). SP also induces G-protein activation through a receptor-independent pathway in T lymphocytes (Kavelaars et al., 1994b). Thus, there is a biological link between the SP and the immune system.

#### 5. SP receptor antagonists

The SP-preferring receptor (NK-1R) is a potential pharmaceutical target, following the concept that SP antagonists may be useful for pain relief. NK-1R antagonists have been developed that have activity directed against each of the three mammalian tachykinins: SP, neurokinin A, and neurokinin B (Baby et al., 1999; Giardina et al., 2003; Rupniak, 2002; Swain, 1998). Chemically, NK-1R antagonists fall into peptide and nonpeptide classes (Swain, 1998; Giardina et al., 2003). The NK-R antagonists are classified as diamines, amino ethers, perhydroisoindoles, 4-amino-2-benzylpiperidine amides, quinoline, and 1,7-naphthyridine amides and tryptophan analogues (Swain, 1998). The first nonpeptide NK-1R antagonists discovered by Pfizer in 1991 (Snider et al., 1991) have been extensively investigated. Several investigators have linked NK-1R antagonists to antidepressant pharmacotherapy (Baby et al., 1999). SP-induced chemotaxis of human monocytes and T cells is abolished by an NK-1R antagonist, indicating a functional activity between the antagonist and NK-1R on these immune

cells (Hood et al., 2000). Two SP antagonists, spantide and CP-96,345, a potent nonpeptide antagonist of NK-1R, blocked the SP effect on TNF- $\alpha$  production in peripheral blood monocytes and macrophages, providing indirect evidence for the NK-1R-mediated nature of the response (Lai et al., 2001; Lee et al., 1994). Experiments in NK-1R knockout mice indicate that a block in the neurogenic tachykinin protects the animal against the adverse effects of pulmonary inflammation (Bozic et al., 1996). A novel nonpeptide NK-1R antagonist, RP-67,580, ameliorated the meningoencephalitic inflammatory response to *Trypanosoma brucei* (Kennedy et al., 1997) and LY-303,878 reduced the severity of inflammatory bowel disease induced by *Cryptosporidium parvum* (Sonea et al., 2002).

## 6. SP and immune cell function

There is a functional interaction between the immune and nervous systems (Black, 1995; Dunn, 1988; McGillis et al., 1990), and SP is an important immunomodulator of this interaction. SP elicits a wide variety of responses from human monocytes/macrophages. SP increases phagocytic response in macrophages and other phagocytes (Hartung and Toyka, 1983; Hartung, 1988). The treatment of monocytes and macrophages with SP leads to several functional events (Hartung and Toyka, 1983; Hartung et al., 1986), which include stimulation of arachidonic acid metabolism, generation of thromboxane A<sub>2</sub> and thromboxane B<sub>2</sub>, prostaglandin E<sub>2</sub> release, leukotriene release, increased superoxide production (Serra et al., 1994), and down-regulation of membrane-associated 5' nucleotidase. SP specifically activates nuclear factor-kappa B (NF- $\kappa$ B), a key transcriptional factor involved in the control of cytokine expression (Lieb et al., 1997; Marriott et al., 2000). SP stimulates immune cells to produce the inflammatory cytokines, including IL-1, IL-6, and TNF- $\alpha$  (Table 2), which are important constituents of immune cell activation that act as physiological inductive signals in the regulation of immune responses. TNF- $\alpha$  is a major mediator of inflammation, which up-regulates HIV expression in T cells and monocytes in vitro (Folks et al., 1987, 1988; Clouse et al., 1989). We demonstrated that SP, in a synergistic fashion with LPS, enhances IL-10 secretion in monocytes and macrophages (Ho et al., 1996a). SP also induced IL-12 production by murine macrophages, suggesting that SP plays a role in the induction of cell-mediated immunity (Kincy-Cain and Bost, 1997).

SP causes a shift in protein kinase C location in brain microvessels, suggesting SP may induce a response in the blood–brain barrier (Catalan et al., 1989). SP binds to the chemotactic receptor, leading to chemotaxis in monocyte/macrophages, as well as polymorphonuclear cells, and neutrophils (Helme et al., 1987; Sacerdote and Panerai, 1993). SP influences inflammatory response by stimulat-

Table 2  
Effect of SP on cytokine production by immune cells

Cytokine	Effect	Target cells	References
IL-1	↑	Monocytes	Bozic et al. (1996); Clay and Morris (1997); Davies et al. (1994); Sylvestre and Ravetch (1994)
IL-2	↑	T lymphocytes	Angel et al. (1995); Lotti et al. (1995)
IL-3	↑	Bone marrow	Payan et al. (1986)
IL-6	↑	Macrophages	Bozic et al. (1996); Clay and Morris (1997); Davies et al. (1994); Sylvestre and Ravetch (1994)
IL-7	↑	Stroma of bone marrow	Manske et al. (1995)
IL-8	↑	Macrophages, lymphocytes	Park et al. (2004); Serra et al. (1994)
IL-10	↑	Peripheral blood mononuclear cells	Kim et al. (2003)
IL-12	↑	Macrophages	Kincy-Cain and Bost (1997)
IFN- $\gamma$	↑	Monocytes	Bozic et al. (1996); Clay and Morris (1997); Davies et al. (1994); Sylvestre and Ravetch (1994)
TNF- $\alpha$	↑	Monocytes	Bozic et al. (1996); Clay and Morris (1997); Davies et al. (1994); Sylvestre and Ravetch (1994)
GM-CSF	↑	Bone marrow	Rameshwar and Gascon (1995)

Table modified from Ho et al. (2002a); CNS Spectrums 7, 867–874.

ing mononuclear and polymorphonuclear leukocyte chemotaxis by regulating the release of inflammatory mediators, such as IL-8, from macrophages and lymphocytes (Serra et al., 1994). SP has an important role in signaling immune cell trafficking and activation at sites of inflammation or infection. SP stimulates mitogen-induced proliferation of lymphocyte (Stanisz et al., 1986), and this stimulation can be blocked by the NK-1R antagonist. In vivo, SP also increases lymphocyte traffic from lymph nodes to the periphery (Moore et al., 1989) and may have a role in controlling traffic through the high endothelial venules (Moore, 1984). SP acts preferentially on CD4+ (helper) T lymphocytes (Rameshwar and Gascon, 1995). Immunoglobulin production in B lymphocytes can be increased by SP (Eglezos et al., 1988). When SP is depleted from nerves within the lymph nodes by capsaicin, immunoglobulin synthesis by B cells is decreased (Bost and Pascual, 1992). SP enhanced IgA and IgM, but not IgG production in the spleen, mesenteric lymph nodes, and peyers patches (Stanisz et al., 1987). Furthermore, SP acts as a B cell differentiation factor, requiring an additional trigger mechanism (Pascual et al., 1992).



## 7. SP and HIV

The finding that SP is secreted by human immune cells and participates in immunoregulation of immune cells may be of importance for the pathogenesis of immune-mediated diseases, including neuroimmunologic diseases and AIDS. In AIDS patients, abnormal circulating neuropeptide levels may be related to neuropsychiatric disorders. Neuropeptides, including SP, may play a central role in stressed HIV-infected patients by affecting immune cell functions (Fig. 2), which may further trigger disease progression and immunologic deficiency. Because SP enhances inflammatory cytokine production by immune cells, such as macrophages and these cytokines modulate HIV infection of human immune cells that also are the targets for HIV infection, it is postulated that SP promotes HIV infection of these immune cells. Homologies between SP and the fusion domain of measles, and fusion domains of HIV-1 gp41, suggest that the SP receptor on immune cells may facilitate the postbinding, fusion step of measles, and HIV-1 infection (Dorig et al., 1993; Harrowe et al., 1992; Bost et al., 1992).

We demonstrated that SP enhances HIV expression in macrophages isolated from some healthy individuals (Ho et al., 1996b), and that SP activates HIV replication in latently infected immune cells (Li et al., 2001). The NK-1R antagonist (CP-96,345) inhibits HIV replication in human mononuclear phagocytes (Lai et al., 2001), at least in part, through down-regulation of CCR5, a principal coreceptor for HIV entry into macrophages and inhibition of endogenous SP production (Lai et al., 2001). SP released from HIV-infected immune cells, in return, may enhance HIV infection by directly facilitating virus replication and/or by indirectly affecting HIV proliferation through

induction of inflammatory cytokines, such as IL-1, IL-6, and TNF- $\alpha$ . These cytokines are HIV-enhancing factors (Folks et al., 1987, 1988). In addition, SP may modulate expression of these cytokines through activation of NF- $\kappa$ B (Lieb et al., 1997; Marriott et al., 2000). In support of the immunopathogenic relevance of these in vitro findings, several ex vivo and in vivo studies also have demonstrated that SP is involved in the immunopathogenesis of HIV disease. HIV-seropositive patients had a greater incidence of abnormal patterns of immunoreactivity of SP in enteric nerves and enteroendocrine cells than HIV-seronegative subjects (Sharkey et al., 1992). SP had an inhibitory effect on lymphocyte proliferation, suggesting the existence of an alteration in the in vivo immunomodulatory properties of SP in AIDS patients (Covas et al., 1994). SP plays a critical role in HIV gp120-induced increase in permeability of rat brain endothelium cultures, and this effect of SP on gp120-induced increase in albumin permeability is abrogated by the SP antagonists (Annunziata et al., 1998). SP immunoreactivity is present in HIV gp120 transgenic mouse brain vessels, suggesting that SP is involved in HIV gp120-induced changes in the vascular component of blood–brain barrier (Toneatto et al., 1999). HIV-infected children had higher plasma levels of SP in comparison to HIV-seronegative children born to HIV-positive mothers or healthy control children (Azzari et al., 1992).

There is a bidirectional relationship between SP and HIV infection of human immune cells. We demonstrated that HIV infection and activation induced SP expression in human immune cells (Ho et al., 2002a,b). We have observed increased levels of plasma SP in HIV-infected men in comparison to uninfected control subjects (Douglas et al., 2001). We have extended this observation to a cohort of HIV-infected women (Douglas, Evans et al., 2004, unpublished observation). Although the pathophysiologic consequences of increased circulating levels of SP remain to be determined, it is possible that SP released from HIV-infected immune cells may contribute to the compromised immune function observed in patients infected with HIV, because SP has the ability to enhance HIV by directly facilitating HIV replication within macrophages and CD4<sup>+</sup> T cells and/or by indirectly affecting HIV replication through induction of inflammatory cytokines, such as IL-1, IL-6, and TNF- $\alpha$ .

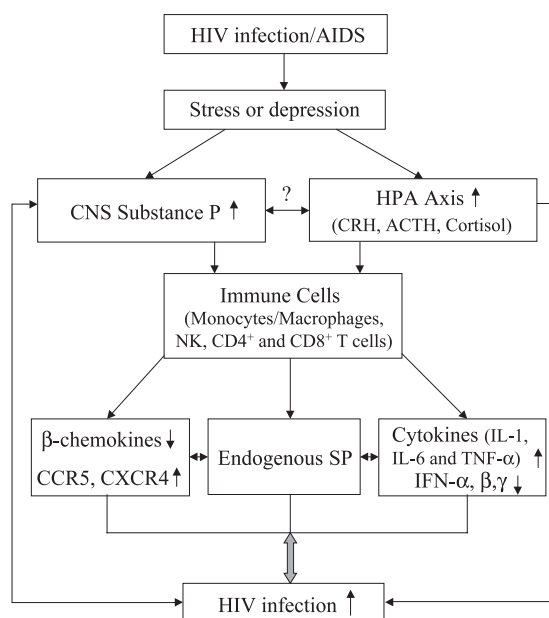


Fig. 2. Hypothetical pathways by which SP affects CNS and immune systems, potentiating HIV infection.

## 8. Conclusion

The implications of SP in neuroimmunoregulation are likely to have in vivo relevance to the immunopathogenesis of the psychological, psychiatric, and neurological complications of HIV disease. Our data on the effects of the SP antagonist on HIV infection and the functions of human immune cells, including attenuation of TNF- $\alpha$  production, inhibition of endogenous SP production, and down-regulation of the expression of CCR5 receptor, a primary coreceptor for HIV entry into macrophages, may

offer approaches to the design of new anti-HIV therapeutics. Future investigations are necessary to determine molecular and cellular mechanisms responsible for SP-mediated immunoregulation.

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