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H. 知的財産権の出願・登録状況

1　特許取得

1) パラミクソウイルスベクターを用いた経鼻噴霧型結核ワクチン（特願 2009－252218、PCT/JP2010/069435）

2) パラインフルエンザ 2 型ウイルスベクター(hPIV2)を用いたアトピー性皮膚炎治療薬（特願 2009－235915）

3) 遺伝子導入用ウイルスベクターの製造方法(特願 2011－025234)

4) 新規な組換え BCG ワクチン(特願 2011-199422)

2　実用新案登録

なし。

3　その他

なし。

groups	n	pre-SeV infection	DNA prime	SeV-Gag boost
I	6	naive	DNA	SeV-Gag **経鼻接種**
II	5	**pre-SeV 感染**	DNA	SeV-Gag **経鼻接種**
III	6	naive	DNA	SeV-Gag **筋注**
IV	6	**pre-SeV 感染**	DNA	SeV-Gag **筋注**

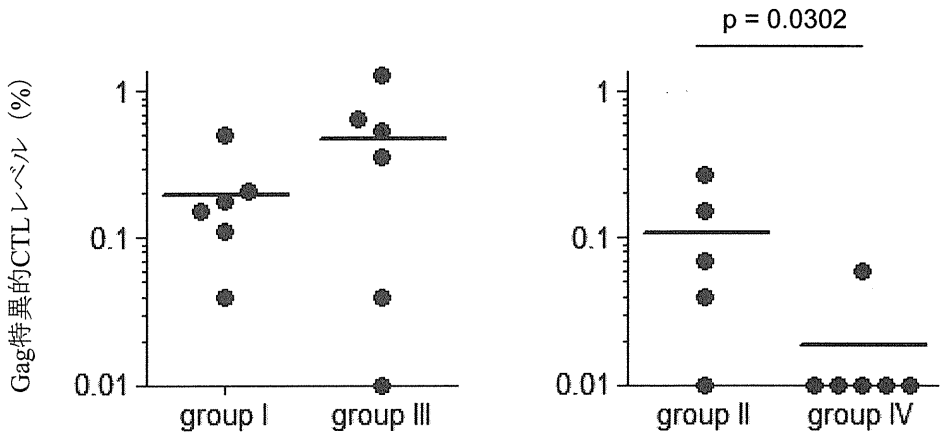

図１．抗SeV抗体存在下におけるSeV-Gag経鼻接種のGag特異的CTL誘導能。
カニクイサル23頭を表のとおり4群に分け実験を行った。第I・II群にはSeV-Gag経鼻接種、第III・IV群はSeV-Gag筋注を行った。第II群・第IV群には、ワクチン実験前にSeV経鼻感染を行っており、これらの個体では、SeV-Gag接種前には抗SeV中和抗体反応が検出された。SeV非感染個体では、SeV-Gag経鼻接種（第I群）・筋注（第III群）ともに効率よいGag特異的CTL誘導を示したが、SeV既感染個体では、SeV-Gag筋注（第IV群）によるGag特異的CTL誘導が阻害された。しかしSeV-Gag経鼻接種（第II群）は効率よいGag特異的CTL誘導を示した。

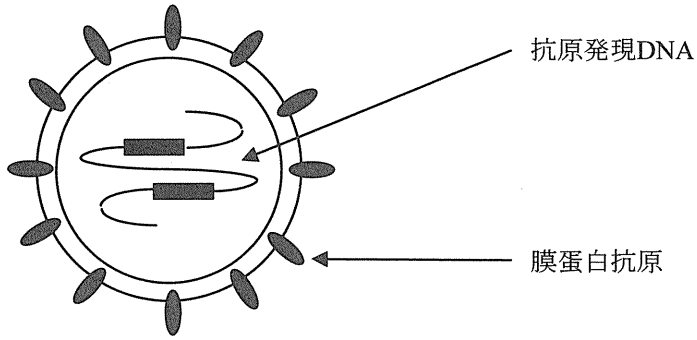

図２．HEV VLP-DNAワクチン粒子構造を示すシェーマ。

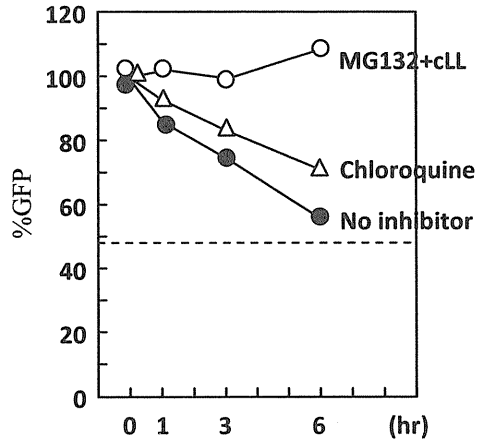

図３．細胞内Gag抗原の経時的分解。
HeLa細胞にGag-GFPを発現させ、蛋白合成阻害剤サイクロヘキシミドを添加するとともに、プロテアソーム阻害剤（MG132+cLL）あるいはリソソーム阻害剤（Chloroquine）を加えて培養し、経時的にGFP蛍光量をプレートリーダーで測定した。新規蛋白合成を止めると細胞内のGag-GFP蛍光量は経時的に減少し、その半減期は約8時間と概算された。クロロキン処理ではGag-GFP減少を止められなかったが、プロテアソーム阻害剤を処理すると減少が見られなくなったことから、分解の主な経路はプロテアソーム経路であると考えられた。

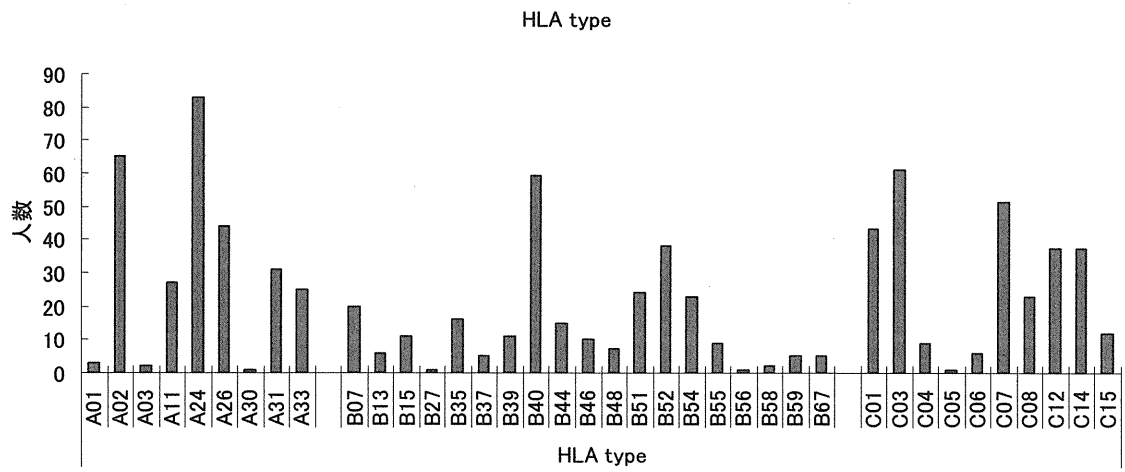

図４．日本人HIV感染症患者におけるHLAクラスI遺伝子型の分布。

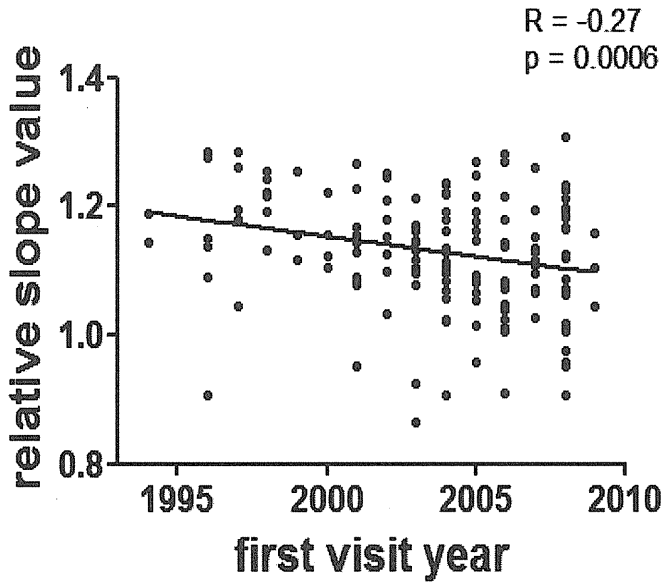

図５．感染者由来gag-pro組込みHIV-1の複製能と初診年との逆相関。
初診時HIV-1感染者由来のgag-proを組込んだHIV-1のin vitro複製能と初診年との間に有意な逆相関が認められた（clade B, n = 156）。

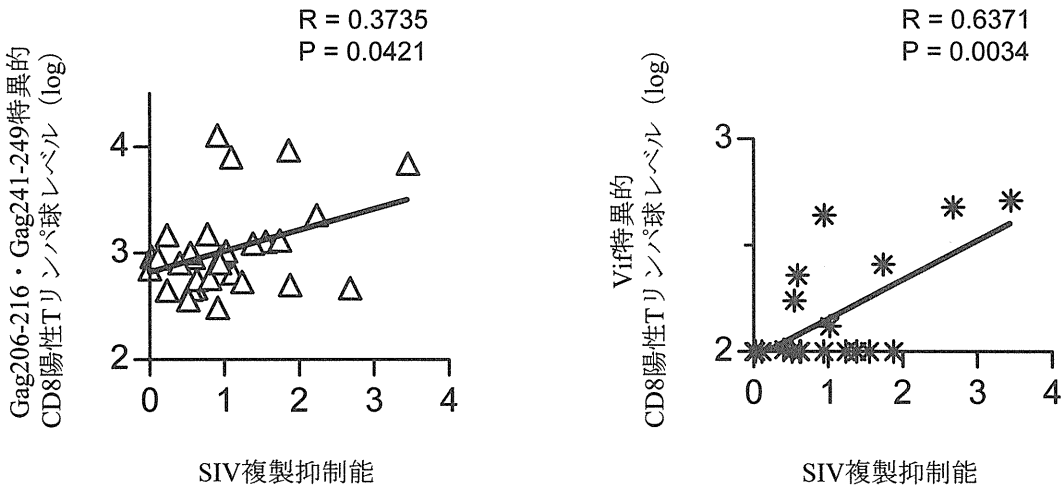

図６．抗原特異的CTLレベルとCD8陽性細胞のin vitroでのSIV複製抑制能との相関。
SIV複製制御サル群の感染初期と慢性期の各タイムポイントの末梢血リンパ球を用い、各種SIV抗原特異的CD8陽性Tリンパ球レベルおよびCD8陽性細胞のin vitroでのSIV複製抑制能を測定し、両者の相関の有無を調べた。特に、Gag206-216・Gag241-249特異的CD8陽性Tリンパ球レベルおよびVif特異的CD8陽性Tリンパ球レベルがSIV複製抑制能との有意な相関を示した。

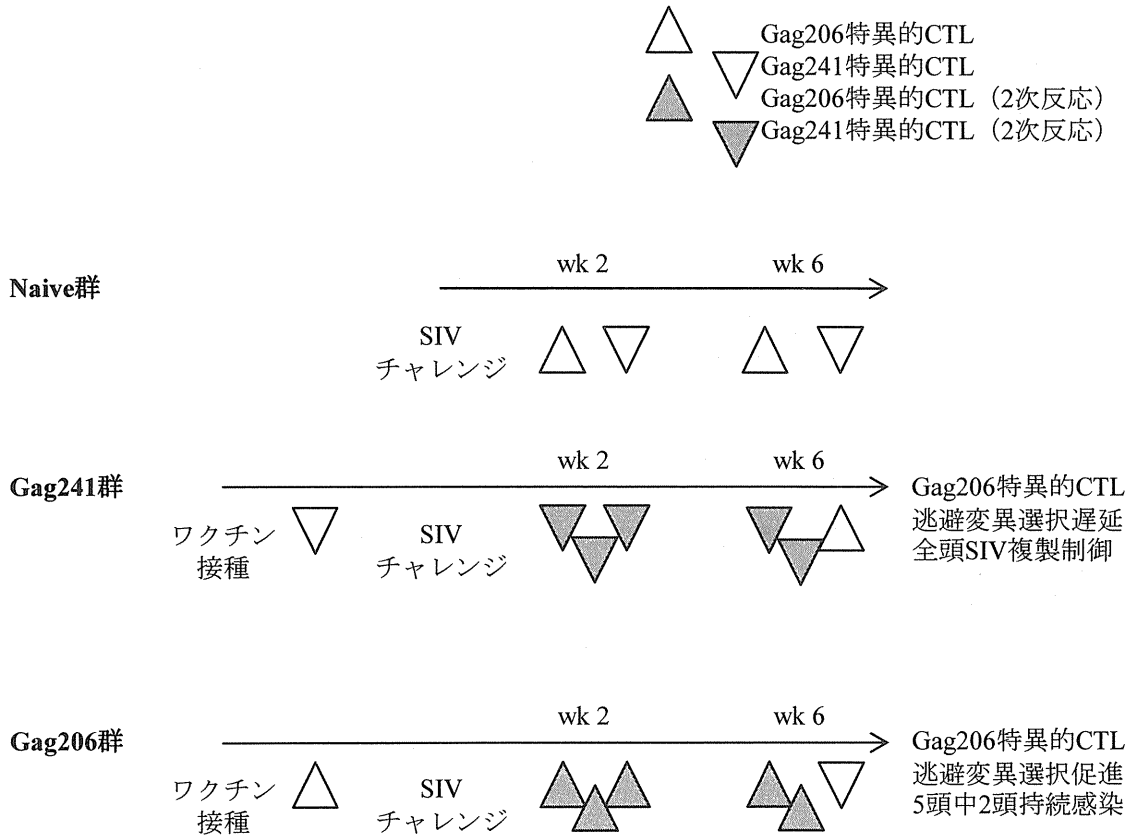

図７．エピトープ特異的CTLメモリー誘導効果を示すシェーマ。
SIV曝露後、Gag241群では、メモリー由来のGag241特異的CTL反応が優位となり、さらにナイーブ由来のGag206特異的CTL反応も加わってSIV複製制御にいたる。Gag206群では、メモリー由来のGag206特異的CTL反応が優位となるが、Gag206特異的CTL逃避変異選択が加速されることもあり、SIV複製制御にいたらない頻度が比較的高い。

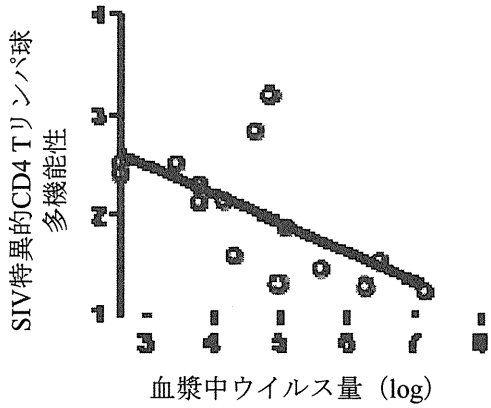

図８．SIV感染慢性期のウイルス量とSIV特異的CD4 Tリンパ球反応多機能性との逆相関。
SIV感染サルの慢性期（約8か月）の血漿中ウイルス量とSIV特異的CD4陽性Tリンパ球反応多機能性との間に有意な逆相関が認められた。

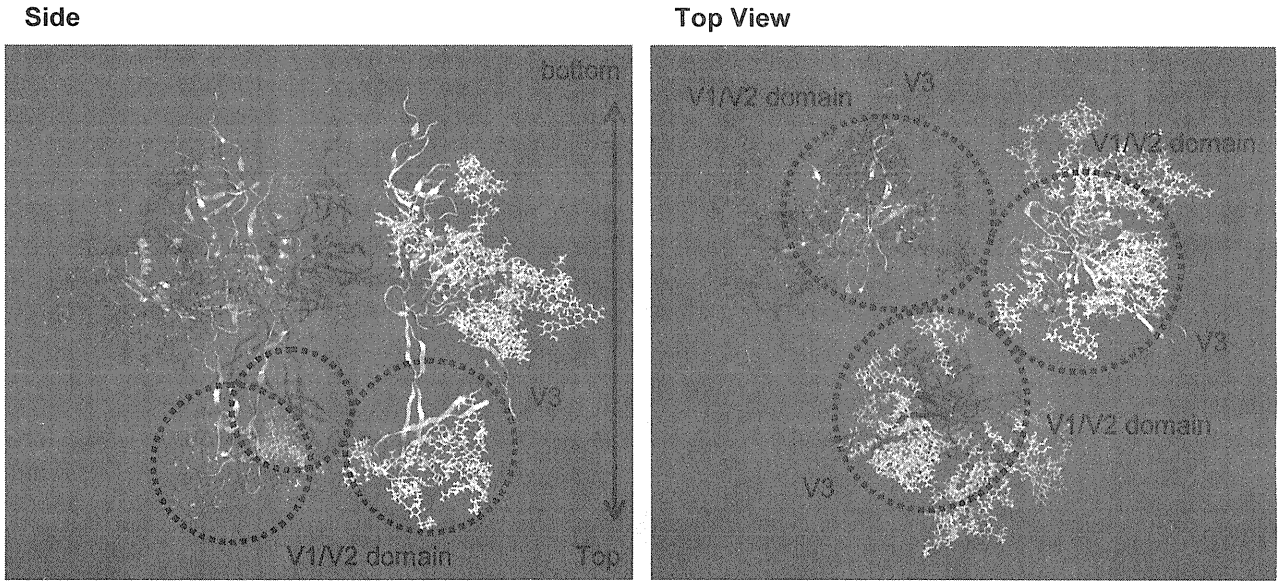

図９．V1/V2ループを含む糖鎖付HIV-1 gp120三量体分子モデル。
ホモロジーモデリング法および分子動力学計算により構築したHIV-1 gp120分子モデルを、クライオ電子顕微鏡法により得られた構造に重ね合わせることにより構築した。

Ⅱ．　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Ⅲ.　研究成果の刊行物・別刷

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Polyfunctional CD4$^+$ T-Cell Induction in Neutralizing Antibody-Triggered Control of Simian Immunodeficiency Virus Infection$^\nabla$

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Rapid depletion of memory CD4$^+$ T cells and delayed induction of neutralizing antibody (NAb) responses are characteristics of human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infections. Although it was speculated that postinfection NAb induction could have only a limited suppressive effect on primary HIV replication, a recent study has shown that a single passive NAb immunization of rhesus macaques 1 week after SIV challenge can result in reduction of viral loads at the set point, indicating a possible contribution of postinfection NAb responses to virus control. However, the mechanism accounting for this NAb-triggered SIV control has remained unclear. Here, we report rapid induction of virus-specific polyfunctional T-cell responses after the passive NAb immunization postinfection. Analysis of SIV Gag-specific responses of gamma interferon, tumor necrosis factor alpha, interleukin-2, macrophage inflammatory protein 1β, and CD107a revealed that the polyfunctionality of Gag-specific CD4$^+$ T cells, as defined by the multiplicity of these responses, was markedly elevated in the acute phase in NAb-immunized animals. In the chronic phase, despite the absence of detectable NAbs, virus control was maintained, accompanied by polyfunctional Gag-specific T-cell responses. These results implicate virus-specific polyfunctional CD4$^+$ T-cell responses in this NAb-triggered virus control, suggesting possible synergism between NAbs and T cells for control of HIV/SIV replication.

Virus-specific CD4$^+$ and CD8$^+$ T-cell responses are crucial for the control of pathogenic human immunodeficiency virus type 1 (HIV-1) and simian immunodeficiency virus (SIV) infections (5, 6, 20, 23, 30, 39, 40). However, CD4$^+$ T cells, especially CCR5$^+$ memory CD4$^+$ T cells, are themselves targets for these viruses, which may be an obstacle to potent virus-specific CD4$^+$ T-cell induction (10, 47, 52). Indeed, HIV-1/SIV infection causes rapid, massive depletion of memory CD4$^+$ T cells (26, 31), and host immune responses fail to contain viral replication and allow persistent chronic infection, although virus-specific CD8$^+$ T-cell responses exert suppressive pressure on viral replication (15).

Recently, the importance of T-cell quality in virus containment has been high-lighted, and T-cell polyfunctionality, which is defined by their multiplicity of antigen-specific cytokine production, has been analyzed as an indicator of T-cell quality (4, 8, 11, 41). However, there has been no evidence indicating an association of polyfunctional T-cell responses in the acute phase with HIV-1/SIV control. Even in the chronic phase, whether polyfunctional CD4$^+$ T-cell responses may be associated with virus control has been unclear, although an inverse correlation between polyfunctional CD8$^+$ T-cell responses and viral loads has been shown in HIV-1-infected individuals (4).

Another characteristic of HIV-1/SIV infections is the absence of potent neutralizing antibody (NAb) induction during the acute phase (7). This is mainly due to the unusually neutralization-resistant nature of the virus, such as masking of target epitopes in viral envelope proteins (24). Whether this lack of effective NAb response contributes to the failure to control the virus, and whether NAb induction in the acute phase can contribute to virus control, remains unclear. Previous studies documenting virus escape from NAb recognition suggested that NAbs can also exert selective pressure on viral replication to a certain extent (38, 45, 49), but it was speculated that postinfection NAb induction could have only a limited suppressive effect on primary HIV-1/SIV replication (34, 37).

By passive NAb immunization of rhesus macaques after SIV challenge, we recently provided evidence indicating that the presence of NAbs during the acute phase can result in SIV control (50). In that study, passive NAb immunization 1 week after SIVmac239 challenge resulted in transient detectable NAb responses followed by reduction in set point viral loads compared to unimmunized macaques. However, the mechanism of this virus control has remained unclear. In the present study, we found rapid appearance of polyfunctional Gag-specific CD4$^+$ T-cell responses after such passive NAb immunization postinfection. These animals maintained virus control

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