リア機能障害による神経前駆細胞分化抑制. 第 21 回日本エイズ学会、広島、2007.

20) 芳田剛、 河野祐治、 安藤良徳、佐藤佳、 駒野淳、三浦義治、 田中勇悦、小柳義夫.受容体分子の表面発現を輸送小胞レベルで調節する機構；ＨＩＶのコレセプター分子の細胞質膜発現を調節する、第 30 回日本分子生物学会年会・第 80 回日本生化学会大会 合同大会、横浜、2007.

21) 佐藤佳、 山元誠司、小柳義夫. HIV-1 の粒子産生過程における Ral GTPase の機能解析. 第 30 回日本分子生物学会年会・第 80 回日本生化学会大会 合同大会、横浜、2007.

H. 知的所有権の出願・登録状況

1．特許取得

該当なし

2．実用新案登録

該当なし

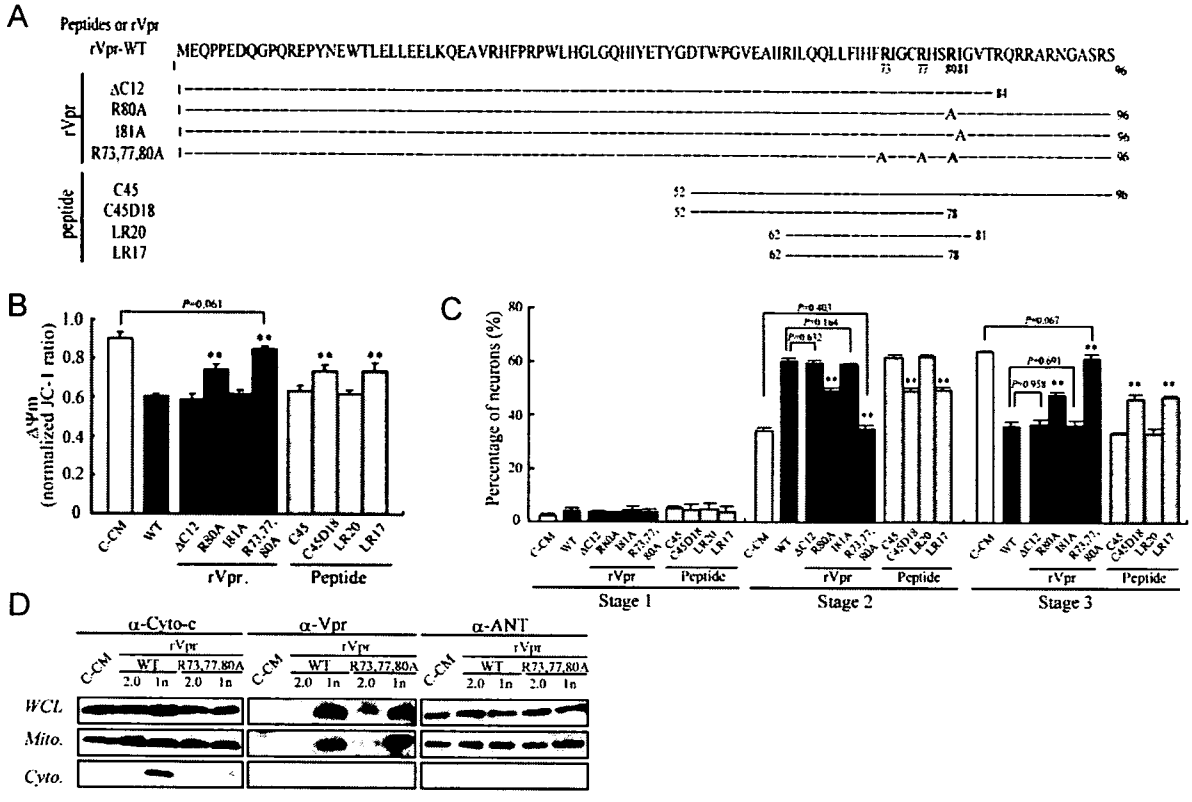
表 1. Vpr-induced apoptosis in neuronal cells

Condition	Concentration of Vpr (pM)	Percentage of active form of Caspase-3^{+} neuronal cells
C-CM	0	5.83±0.97
Vpr-0.2	0.2	6.23±2.04 #
Vpr-2.0	2	7.12±3.08 #
Vpr-10	10	8.60±1.80 #
Vpr-100	100	14.69±2.71 **
Vpr-1n	1000	17.33±0.42 **

There was no significantly difference compared to C-CM

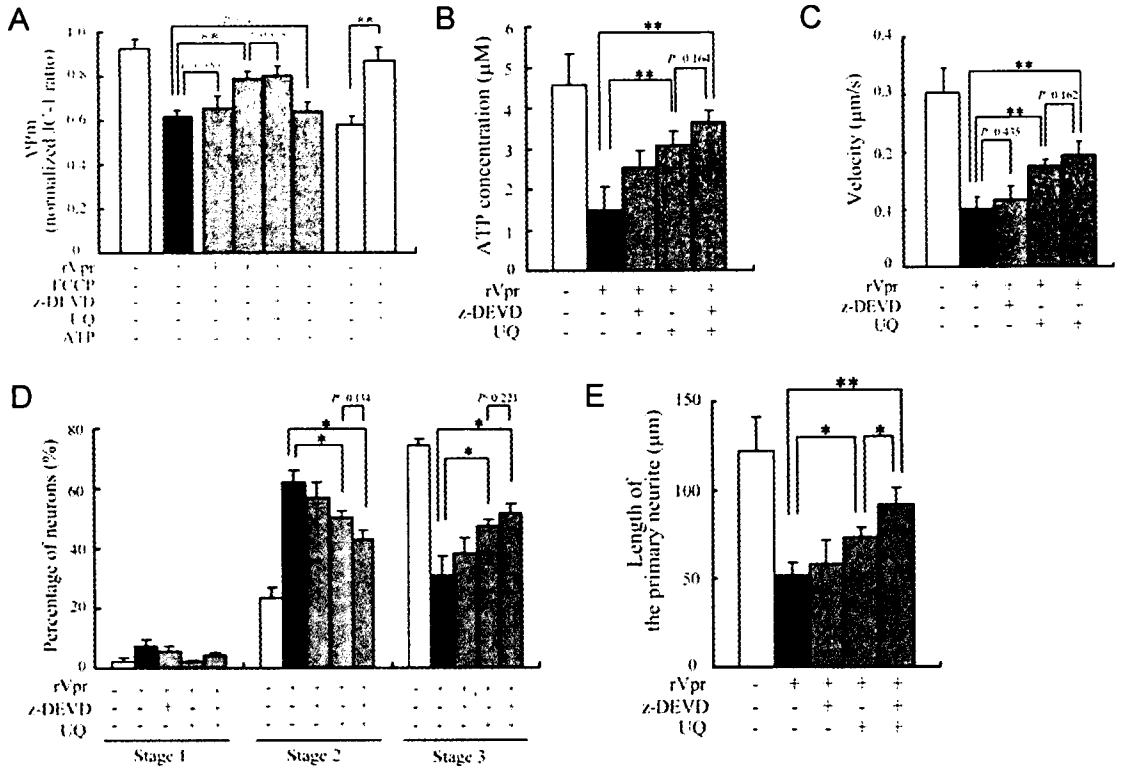
** $P<0.01$ compared with C-CM

図1, Inhibition of neuronal development caused by Vpr-induced mitochondrial membrane depolarization



(A) 組換え Vpr 変異体蛋白質とペプチドのアミノ酸配列を示した。野生型 Vpr 蛋白質(rVpr-WT)のアミノ酸配列は最上段に、組換え Vpr 変異体蛋白質(rVpr-ΔC12, rVpr-R80A, rVpr-I81A, rVpr-R73,77, 80A)の変異部位と Vpr 変異体ペプチド(C45, C45D18, LR20, LR17)のアミノ酸を下段に示した。(B) Control condition medium (C-CM)あるいは、それぞれ 2.0 pM の rVpr-WT, rVpr 変異体, Vpr ペプチドを添加した神経未分化細胞を JC-1 で染色し、ΔΨm を定量した。**, $P<0.01$ (rVpr-WT と比較して)。(C) rVpr-WT, rVpr 変異体あるいは Vpr ペプチドをそれぞれ 2.0 pM 添加後の神経細胞の分化誘導過程を Stage 1 から Stage 3 まで分類した。**, $P<0.01$ (rVpr-WT と比較して)。(D) rVpr-WT あるいは rVpr-R73, 77, 80A をそれぞれ 2.0 pM と 1.0 nM ずつ添加し、分化誘導した細胞のミトコンドリア分画(Mito.)、細胞質分画(Cyto.)ならびに whole cell lysate (WCL)を抗 cytochrome-c(α-Cyto-c)、抗 Vpr(α-Vpr)、抗 ANT(α-ANT)抗体を用いて western blotting を行った。

図2, Restoration of mitochondrial dysfunction by treatment with ubiquinone-10 (UQ)



(A) 神経未分化細胞に condition medium (C-CM), 2.0 pM rVpr, 100 μM FCCP を添加し、分化誘導後、ΔΨm を定量した。また、それぞれに z-DEVD-fmk (z-DEVD), ubiquinone-10 (UQ)あるいは ATP を同時に添加し、同様にΔΨm を定量した。**, $P<0.01$。(B) 2.0 pM の rVpr 存在下での細胞内 ATP 濃度を測定した。**, $P<0.01$。(C) rVpr 存在下での神経前駆細胞の神経突起内のミトコンドリアの輸送速度を定量した。**, $P<0.01$。(D) rVpr 存在下における z-DEVD-fmk ならびに UQ 添加時の神経細胞の分化過程をそれぞれ形態学的に Stage 1 から Stage 3 まで分類した。*, $P<0.05$。(E) rVpr 存在下における-DEVD-fmk ならびに UQ 添加時の神経細胞の神経突起の長さを測定した。**, $P<0.01$、*, $P<0.05$。すべての実験系において使用した試薬類の濃度は、rVpr は 2.0 pM、z-DEVD-fmk は 100μM、UQ は 100μM、ATP は 10μM で使用した。

III. 研究成果に関する刊行一覧表

研究成果に関する刊行一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kubo M, Nishitsuji H, Kurihara K, Hayashi T, Masuda T, Kannagi M	Suppression of human immunodeficiency virus type 1 replication by arginine deiminase of Mycoplasma arginini.	J Gen Virol	87	1589-1593	2006
Nishitsuji H, Kohara M, Kannagi M, Masuda T	Effective suppression of human immunodeficiency virus type 1 through a combination of short- or long-hairpin RNAs targeting essential sequences for retroviral integration.	J Virol	80	7658-7666	2006
Kanzawa N, Nishigaki K, Hayashi T, Ishii Y, Furukawa S, Niiro A, Yasui F, Kohara M, Morita K, Matsushima K, Le MQ, Masuda T, Kannagi M	Augmentation of chemokine production by severe acute respiratory syndrome coronavirus 3a/X1 and 7a/X4 proteins through NF-kappaB activation.	FEBS Lett	580	6807-6812	2006
Deforche K, Camacho R, Grossman Z, Silander T, Soares MA, Moreau Y, Shafer RW, Van Laethem K, Carvalho AP, Wynhoven B, Cane P, Snoeck J, Clarke J, Sirivichayakul S, Ariyoshi K, Holguin A, Rudich H, Rodrigues R, Bouzas MB, Cahn P, Brigido LF, Soriano V, Sugiura W, Phanuphak P, Morris L, Weber J, Pillay D, Tanuri A, Harrigan PR, Shapiro JM, Katzenstein DA, Kantor R, Vandamme AM	Bayesian network analysis of resistance pathways against HIV-1 protease inhibitors.	Infect Genet Evol	3	382-390	2006
Hara M, Kikuchi T, Sata T, Nakajima N, Ami Y, Sato Y, Tanaka K, Narita T, Ono F, Akari H, Terao K, Mukai R	Detection of SRV/D shedding in body fluids of cynomolgus macaques and comparison of partial gp70 sequences in SRV/D-T isolates.	Virus Genes	35	281-288	2007

Tsunetsugu-Yokota Y, Ishige M, Murakami M	Oral attenuated Salmonella enterica serovar Typhimurium vaccine expressing codon-optimized HIV type 1 Gag enhanced intestinal immunity in mice.	AIDS Res Hum Retroviruses	23	278-286	2007
Nitahara-Kasahara Y, Kamata M, Yamamoto T, Zhang X, Miyamoto Y, Muneta K, Iijima S, Yoneda Y, Tsunetsugu-Yokota Y, Aida Y	Novel nuclear import of Vpr promoted by importin alpha is crucial for human immunodeficiency virus type 1 replication in macrophages.	J Virol	81	5284-5293	2007
Takayanagi R, Ohashi T, Yamashita E, Kurosaki Y, Tanaka K, Hakata Y, Komoda Y,Ikeda S, Tsunetsugu-Yokota Y, Tanaka Y, Shida H	Enhanced replication of human T-cell leukemia virus type 1 in T cells from transgenic rats expressing human CRM1 that is regulated in a natural manner.	J Virol	81	5908-5918	2007
Monde K, Maeda Y, Tanaka Y, Harada S, Yusa K	Gp120 V3-dependent impairment of R5 HIV-1 infectivity due to virion-incorporated CCR5.	J Biol Chem	282	36923-36932	2007
Kubo Y, Yokoyama M, Yoshii H, Mitani C, Tominaga C, Tanaka Y, Sato H, Yamamoto N	Inhibitory role of CXCR4 glycan in CD4-independent X4-tropic human immunodeficiency virus type 1 infection and its abrogation in CD4-dependent infection.	J Gen Virol	88	3139-3144	2007
Kondo K, Okuma K, Tanaka R, Zhang LF, Kodama A, Takahashi Y, Yamamoto N, Ansari AA, Tanaka Y	Requirements for the functional expression of OX40 ligand on human activated CD4+ and CD8+ T cells.	Hum Immunol	68	563-571	2007
Biasin M, Piacentini L, Lo Caputo S, Kanari Y, Magri G, Trabattoni D, Naddeo V, Lopalco L, Clivio A, Cesana E, Fasano F, Bergamaschi C, Mazzotta F, Miyazawa M, Clerici M	Apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G: a possible role in the resistance to HIV of HIV-exposed seronegative individuals.	J Infect Dis	195	960-964	2007

Tanaka-Takahashi Y, Yasunami M, Naruse T, Hinohara K, Matano T, Mori K, Miyazawa M, Honda M, Yasutomi Y, Nagai Y, Kimura A	Reference strand-mediated conformation analysis-based typing of multiple alleles in the rhesus macaque MHC class I Mamu-A and Mamu-B loci.	Electro-phoresis	28	918-924	2007
Washiyama M, Nishigaki K, Ahmed N, Kinpara S, Ishii Y, Kanzawa N, Masuda T, Kannagi M	IL-2 withdrawal induces HTLV-1 expression through p38 activation in ATL cell lines.	FEBS Lett	581	5207-5212	2007
Saeng-Aroon S, Yoshida LM, Ariyoshi K, Taguchi M, Pathipvanich P, Rojanawiwat A, Matsuda M, Kannagi M, Sawanpanyalert P, Sugiura W, Auwanit W	An efficient tool for surveying CRF01_AE HIV type 1 resistance in Thailand to combined stavudine-lamivudine-nevirapine treatment: mutagenically separated PCR targeting M184I/V.	AIDS Res Hum Retroviruses	23	1461-1468	2007
Song H, Nakayama EE, Likanonsakul S, Wasi C, Iwamoto A, Shioda T	A three-base-deletion polymorphism in the upstream non-coding region of human interleukin 7 (IL-7) gene could enhance levels of IL-7 expression.	Int J Immunogenet	34	107-113	2007
Wichukchinda N, Kitamura Y, Rojanawiwat A, Nakayama EE, Song H, Pathipvanich P, Auwanit W, Sawanpanyalert P, Iwamoto A, Shioda T, Ariyoshi K	The polymorphisms in DC-SIGNR affect susceptibility to HIV type 1 infection.	AIDS Res Hum Retroviruses	23	686-692	2007
Lwembe R, Ochieng W, Panikulam A, Mongoina CO, Palakudy T, Koizumi Y, Kageyama S, Yamamoto N, Shioda T, Musoke R, Owens M, Songok EM, Okoth FA, Ichimura H	Anti-retroviral drug resistance-associated mutations among non-subtype B HIV-1-infected Kenyan children with treatment failure.	J Med Virol	79	865-872	2007
Ohishi M, Shioda T, Sakuragi J	Retro-transduction by virus pseudotyped with glycoprotein of vesicular stomatitis virus.	Virology	362	131-138	2007
Koizumi Y, Kageyama S, Fujiyama Y, Miyashita M, Lwembe R, Ogino K, Shioda T, Ichimura H	RANTES -28G delays and DC-SIGN - 139C enhances AIDS progression in HIV type 1-infected Japanese hemophiliacs.	AIDS Res Hum Retroviruses	23	713-719	2007

Nakayama EE, Carpentier W, Costagliola D, Shioda T, Iwamoto A, Debre P, Yoshimura K, Autran B, Matsushita S, Theodorou I	Wild type and H43Y variant of human TRIM5alpha show similar anti-human immunodeficiency virus type 1 activity both in vivo and in vitro.	Immuno-genetics	59	511-515	2007
Song H, Nakayama EE, Yokoyama M, Sato H, Levy JA, Shioda T	A single amino acid of the human immunodeficiency virus type 2 capsid affects its replication in the presence of cynomolgus monkey and human TRIM5alphas.	J Virol	81	7280-7285	2007
Sakuragi J, Sakuragi S, Shioda T	Minimal region sufficient for genome dimerization in the human immunodeficiency virus type 1 virion and its potential roles in the early stages of viral replication.	J Virol	81	7985-7992	2007
Koh Y, Matsumi S, Das D, Amano M, Davis DA, Li J, Leschenko S, Baldridge A, Shioda T, Yarchoan R, Ghosh AK, Mitsuya H	Potent inhibition of HIV-1 replication by novel non-peptidyl small molecule inhibitors of protease dimerization.	J Biol Chem	282	28709-28720	2007
Liu H, Nakayama EE, Theodorou I, Nagai Y, Likanonsakul S, Wasi C, Debre P, Iwamoto A, Shioda T	Polymorphisms in CCR5 chemokine receptor gene in Japan.	Int J Immunogenet	34	325-335	2007
Louisirirotchanakul S, Sutthent R, Wasi C, Chuenchitra T, Nitayaphan S, Brown AE, Polonis VR, Nakayama EE, Shioda T, Liu H, Takebe Y	Host genetic analysis of HIV type 1 subtype CRF01_AE (E)-infected Thai patients with different rates of disease progression.	AIDS Res Hum Retroviruses	23	1605-1608	2007
Kinomoto M, Kanno T, Shimura M, Ishizaka Y, Kojima A, Kurata T, Sata T, Tokunaga K	All APOBEC3 family proteins differentially inhibit LINE-1 retrotransposition.	Nucleic Acids Res	35	2955-2964	2007
Hoshino S, Sun B, Konishi M, Shimura M, Segawa T, Hagiwara Y, Koyanagi Y, Iwamoto A, Mimaya J, Terunuma H, Kano S, Ishizaka Y	Vpr in plasma of HIV type 1-positive patients is correlated with the HIV type 1 RNA titers .	AIDS Res Hum Retroviruses	23	391-397	2007

Nakai-Murakami C, Shimura M, Kinomoto M, Takizawa Y, Tokunaga K, Taguchi T, Hoshino S, Miyagawa K, Sata T, Kurumizaka H, Yuo A, Ishizaka Y	HIV-1 Vpr induces ATM-dependent cellular signal with enhanced homologous recombination.	Oncogene	26	477-486	2007
Kameoka M, Kitagawa Y, Utachee P, Jinnopat P, Dhepakson P, Isarangkura-na-ayuthaya P, Tokunaga K, Sato H, Komano J, Yamamoto N, Oguchi S, Natori Y, Ikuta K	Identification of the suppressive factors for human immunodeficiency virus type-1 replication using the siRNA mini-library directed against host cellular genes.	Biochem Biophys Res Commun	359	729-734	2007
Futahashi Y, Komano J, Urano E, Aoki T, Hamatake M, Miyauchi K, Yoshida T, Koyanagi Y, Matsuda Z, Yamamoto N	Separate elements are required for ligand-dependent and -independent internalization of metastatic potentiator CXCR4.	Cancer Sci	98	373-379	2007
Miyano-Kurosaki N, Kira J, Barnor JS, Maeda N, Misawa N, Kawano Y, Tanaka Y, Yamamoto N, Koyanagi Y	Autonomous proliferation of HTLV-CD4+ T cell clones derived from human T cell leukemia virus type I (HTLV-I)-associated myelopathy patients.	Microbiol Immunol	51	235-242	2007
Takuya Y, Tsunetsugu-Yokota Y	Prospects for the therapeutic application of lentivirus-mediated gene therapy to HIV-1 infection.	Curr Gene Ther		in press	2008
Zhang LF, Okuma K, Tanaka R, Kodama A, Kondo K, Ansari AA, Tanaka Y	Generation of mature dendritic cells with unique phenotype and function by in vitro short-term culture of human monocytes in the presence of interleukin-4 and interferon-beta.	Exp Biol Med		in press	2008
Sato K, Aoki J, Misawa N, Daikoku E, Sano K, Tanaka Y, Koyanagi Y	Modulation of human immunodeficiency virus type 1 infectivity through incorporation of tetraspanin proteins.	J Virol	82	1021-1033	2008
Okuma K, Tanaka R, Ogura T, Ito M, Kumakura S, Yanaka M, Nishizawa M, Sugiura W, Yamamoto N, Tanaka Y	Interleukin-4-transgenic hu-PBL-SCID mice: a model for the screening of antiviral drugs and immunotherapeutic agents against X4 HIV-1 viruses.	J Infect Dis	197	134-141	2008

Harada S, Monde K, Tanaka Y, Kimura T, Maeda Y, Yusa K	Neutralizing antibodies decrease the envelope fluidity of HIV-1.	Virology	370	142-150	2008
Zhang LF, Okuma K, Tanaka R, Kodama A, Kondo K, Ansari AA, Tanaka Y	Generation of mature dendritic cells with unique phenotype and function by in vitro short-term culture of human monocytes in the presence of interleukin-4 and interferon-beta.	Exp Biol Med		in press	2008
Takahashi Y, Tanaka R, Yamamoto N, Tanaka Y	Enhancement of OX40-induced apoptosis by TNF co-activation in OX40-expressing T cell lines in vitro leading to decreased targets for HIV-1 production.	AIDS Res Hum Retroviruses		in press	2008
Koyanagi Y, Tanaka Y, Ito M, Yamamoto N	Humanized mice for human retrovirus infection.	Curr Top Microbiol Immunol		in press	2008
Yoshida T, Kawano Y, Sato K, Ando Y, Aoki J, Miura Y, Komano J, Tanaka Y, Koyanagi Y	A CD63 mutant inhibits T-cell tropic HIV-1 entry by disrupting CXCR4 trafficking to the plasma membrane.	Traffic		in press	2008
Wichukchinda N, Nakayama EE, Rojanawiwat A, Pathipvanich P, Auwanit W, Vongsheree S, Ariyoshi K, Sawanpanyalert P, Shioda T	Effects of CCR2 and CCR5 Polymorphisms on HIV-1 Infection in Thai Females.	J Acquir Immune Defic Syndr		in press	2008
Sugimoto C, Nakayama EE, Shioda T, Villinger F, Ansari AA, Yamamoto N, Suzuki Y, Nagai Y, Mori K	Impact of glycosylation on antigenicity of simian immunodeficiency virus SIV239: induction of rapid V1/V2-specific non-neutralizing antibody and delayed neutralizing antibody following infection with an attenuated deglycosylated mutant.	J Gen Virol	89	554-566	2008
Hosoya N, Miura T, Kawana-Tachikawa A, Koibuchi T, Shioda T, Odawara T, Nakamura T, Kitamura Y, Kano M, Kato A, Hasegawa M, Nagai Y, Iwamoto A	Comparison between Sendai virus and adenovirus vectors to transduce HIV-1 genes into human dendritic cells.	J Med Virol	80	373-382	2008

Kono K, Song H, Shingai Y, Shioda T, Nakayama EE	Comparison of anti-viral activity of rhesus monkey and cynomolgus monkey TRIM5alphas against human immunodeficiency virus type 2 infection.	Virology		in press	2008
Jun-ichi Sakuragi, Sayuri Sakuragi, Masahisa Ohishi, Tatsuo Shioda	A rapid recombination assay of HIV-1 using murine CD52 as a novel biomarker.	Microbes and Infection		in press	2008
Kitayama H, Miura Y, Ando Y, Hoshino S, Ishizaka Y, Koyanagi Y	Human immunodeficiency virus type 1 Vpr inhibits axonal outgrowth through induction of mitochondrial dysfunction.	J Virol	82	2528-2542	2008
Kitagawa Y, Kameoka M, Shoji-Kawata S, Iwabu Y, Mizuta H, Tokunaga K, Fujino M, Natori Y, Yura Y, Ikuta K	Inhibitory function of adapter-related protein complex 2 alpha 1 subunit in the process of nuclear translocation of human immunodeficiency virus type 1 genome.	Virology		in press	2008
Maeda T, Oyaizu N, Endo T, Odawara T, Nakamura T, Iwamoto A ,Fujii T	Pneumocystis jiroveci pneumonia in an AIDS patient: Unusual manifestation of multiple nodules with multiloculated cavities.	Eur J Radiol		in press	2008
Kitayama H, Miura Y, Ando Y, Koyanagi Y	Human immunodeficiency virus type 1 vulnerates nascent neuronal cells.	Microbiol Immunol		in press	2008