[Frontiers in Bioscience E3, 1385-1400, June 1, 2011]

Charting the peptide crossreactome between HIV-1 and the human proteome

Guglielmo Lucchese[1], Angela Stufano[1], Michele Calabro[1], Darja Kanduc[1]

[1]*Department of Biochemistry and Molecular Biology,Ernesto Quagliariello, University of Bari, Bari, Italy*

TABLE OF CONTENTS

1. ABSTRACT

This paper defines potential peptide cross-reactivity between HIV-1 and the human host. Specifically, the amino acid primary sequence of HIV-1, isolate CDC-451, was analyzed for potential immunopathological relationships with the human proteome. The results revealed that: 1) HIV-1 shares 50 heptapeptides and three octapeptides with the human proteome; 2) 34 of the 50 shared heptapeptides are experimentally validated epitopes targeted by immune responses following HIV-1 infection; 3) the viral heptapeptide epitopes are present in human proteins that, when altered, are associated with disease characteristics of acquired immunodeficiency syndrome (AIDS) such as CD4+ cell loss, encephalopathy, schizophrenia, myopathy, cardiovascular disorders, hypertension, corneal diseases, diarrhea, lymphoma, and bladder cancer; 4) at the pentapeptide level, the viral-versus-human overlap is extensive (14,227 matches), with the viral pentapeptides disseminated throughout 10,312 human proteins. The findings are discussed in relationship to HIV-1 escape from immune surveillance, adjuvant-induced HIV-1 immunogenicity, autoimmune cross-reactions following human hyperimmune responses against HIV-1, and AIDS.

2. INTRODUCTION

During recent decades, many studies have focused on the existence of extensive sequence similarity between HIV polyprotein and human proteins, including the sequence similarity between HIV envelope and neuroleukin protein (1), the numerous peptide similarities between HIV proteins and nuclear antigens, such as the 70 kDa component of RNP particles involved in mixed connective tissue disease, and the centromere CENP-B protein, related to scleroderma (2,3), the structural similarity between a HIV-1 sequence overlapping env gp41 and selenium-dependent glutathione peroxidases (4), and the significant sequence similarity between a HIV-1 encoded peptide and the DNA binding loop of nuclear factor kappa B, known to bind thioredoxin (5). Accordingly, HIV pathogenesis has been causally associated with such peptide sharing (i.e., with autoimmune phenomena due to molecular mimicry between viral and host proteins) (6–11). Neuropathogenesis (1, 12), subversion of the immune system (13), autoimmune thyroid disease (14), and immunologic thrombocytopenia (15, 16) are HIV-related pathologies that have been causally linked to molecular mimicry (8-10, 17). However, despite the numerous studies, any link between HIV pathogenesis and

HIV-induced immune response remains unclear. Moreover, currently, there is an enhanced effort in the clinical search for anti-HIV vaccines to be used in the prevention and therapy of HIV infection, notwithstanding the concern of inducing collateral autoimmune phenomena through cross reactions with the host proteome. A report of cardiolipin polyspecific autoreactivity by two broadly neutralizing HIV-1 antibodies is an example of such crossreactivity (18), and warns against indiscriminate immune-based approaches.

With the availability of the human proteome and access to public databases, we have examined the issue of HIV and molecular mimicry by a sequence-to-sequence analysis of viral versus human proteomes. Specifically, the current study addressed the following questions: i) How many human proteins harbor HIV peptide modules? ii) Can the potential cross-reactive risk between HIV-1 and Homo sapiens proteomes be quantified? iii) Based on peptide sharing data, might a relationship be drawn between viral-versus-human peptide sharing and HIV-induced AIDS?

3. METHODS

We used a HIV-1 sequence derived from an infectious clone of the US isolate CDC-451 as an experimental model. The HIV-1 sequence (Taxonomic Identifier: 11687, group M, subtype B, isolate CDC-451, polyprotein length: 1,682 aa) consisted of six proteins. Viral proteins, abbreviations, length, and UniProtKB/Swiss-Prot accession numbers are as follows: 1) Gag polyprotein, Gag, 500 aa (P05887-1), 2) Protein Vpr, viral protein R, 16 aa, (P05953), 3) protein Tat, transactivating regulatory protein, 101 aa (P05907), 4) Protein Rev, regulator of expression of viral proteins, 116 aa (P05865), 5) Protein Vpu, viral protein U, 81 aa (P08803), and 6) Envelope glycoprotein gp160, Env polyprotein, 868 aa (P05879).

The HIV-1 polyprotein sequence was dissected into 1,676 heptapeptides overlapped by six residues, *i.e*., they were each offset by one residue: MGARASV, GARASVL, ARASVLS, *etc*.Then, each viral heptapeptide was analyzed for exact matches with the human proteome using the Protein Information Resource perfect match program (pir.georgetown.edu/pirwww/search/peptide.shtml). The same procedure was applied when pentapeptides were used as probes in the matching analysis.

The human proteome consisted of 36,103 proteins and 15,697,964 occurrences of 10,431,975 unique 7-mers (20) at the time of analysis. Viral epitopes, functions of human proteins involved in the viral heptapeptide overlap, and potential disease associations were explored using the following publicly available resources: the HIV Molecular Immunology Database (http://www.hiv.lanl.gov/content/immunology), Universal Protein Resource (http://uniprot.org/uniprot), and PubMed (http://www.ncbi.nlm.nih.gov/omim).

4. RESULTS

In exploring the peptide commonality between HIV-1 and human proteins, as a first step, we carried out a systematic sequence-to-sequence peptide matching analysis of the viral polyprotein versus the human proteome at the heptapeptide level to quantitatively define the viral-versus-human overlap. Then, we searched the HIV Molecular Immunology Database (http://www.hiv.lanl.gov/content/immunology) for data on the immunoreactivity of the shared peptides to quantify the potential HIV-1 cross-reactivity risk in human immune responses. Finally, we analyzed the possible pathological impact of potential heptapeptide crossreactivity by examining the functional relevance of the human proteins involved in the viral epitope overlap. Table 1 presents the data obtained.

4.1. Theoretical and empirical values of the viral versus human heptapeptide overlap

Table 1 shows that HIV-1 shares 50 heptapeptides and three octapeptides with the human proteome, with a total of 52 human proteins involved in the overlap. As an immediate observation, the quantitation of the HIV-versus-human peptide overlap reveals a non-random nature of peptide sharing. Indeed, the human proteome is formed by 10,431,975 unique heptamers and 10,797,988 unique octamers, whereas the HIV proteome under analysis is formed by 1,676 unique heptamers and 1,675 unique octamers. Given 20 amino acids and the fact that amino acid composition has little or no effect on peptide frequencies (21), the theoretical probability p of a sequence of n amino acids occurring at random in two proteomes is 20^{-n} multiplied by the n-mers in the two proteomes, according to the equation: $p = 20^{-n}$ x the number of unique n-mers comprising the viral proteome x the number of unique n-mers comprising the human proteome.

Thus, the number of times a given viral 7- or 8-mer might occur at random in the human proteome (calculated on the basis of the unique viral and human 7- and 8-mers) is 13.6 and 0.7, respectively. Therefore, the measured extent of overlap (50 heptapeptides and three octapeptides) reported in Table 1 is roughly 3.7- and 4.3-fold higher, respectively, when compared with the theoretically expected values.

4.2. Quantifying the immune cross-reactivity risk between HIV-1 and human proteins

Following the numerical quantitation of the HIV-1-vs-human peptide overlap, we tried to quantify the potential immune cross-reactivity risk by asking whether the peptides shared between HIV-1 and the human proteins were endowed with immunoreactive potential. Specifically, we searched the HIV Molecular Immunology Database (http://www.hiv.lanl.gov/content/immunology) for experimentally validated epitope data. We found that 35 of the 50 shared heptapeptides were located in (or are) epitopes targeted by human humoral and/or cellular immune response(s) following HIV-1 infection. The viral epitopes are reported in Table 1 as heptapeptide sequences shown in boldface (22-92).

4.3. Analyzing the pathologies potentially associated to HIV-1 cross-reactivity

As a final step, we undertook a functional analysis of the human proteins hosting the viral heptapeptide epitopes (last

Table 1. HIV-1 versus human heptapeptide overlap: potential crossreactome

HIV-1 heptapeptide[1]: Protein	Aa pos	Sequence	Epitope Refs.[2]	Human protein(s) involved in the overlap[3]
Gag-Pol		**TLSGGEL**	2-25	**O75588** : H_YH95C04.1 protein
Gag-Pol	4	**EWEKIRL**	5-30	**TAM5A**: DBC1. Deleted in bladder cancer protein 1
Gag-Pol	6	ASRKLER		PECR: Peroxisomal trans-2-enoyl-CoA reductase
Gag-Pol	4	**RDTKEAL**	1-33	**TRN**: Striatin. Acts in dendritic Ca2+ signaling
Gag-Pol	9	**ALDKIEE**	4, 35	**O9NXH5**: Leucine-rich repeat flightless-interacting protein 2.
Gag-Pol	22	**GNSSQVS**	7, 36, 37	**THIK**: Peroxisomal 3-oxoacyl-CoA thiolase. Beta-ketothiolase
Gag-Pol	24	**SQVSQN**	2, 27, 35-39	**GUC2C**: Heat-stable enterotoxin receptor. STA receptor
Gag-Pol	56	**KVIEEKA**	7, 40-46	**RGS17**: Regulator of G-protein signaling 17
Gag-Pol	16	**PVHAGPI**	6, 37, 40, 47, 48	**PTPRE**: Receptor-type tyrosine-protein phosphatase epsilon
Gag-Pol	85	**RQGPKEP**	5, 40, 48-51	**O5T174**: Pre-B-cell leukemia transcription factor-interacting protein 1 (isoform 2). HPIP.
Gag-Pol	91	**PFRDYVD**	7, 40, 48, 50, 52, 53	**CPNE5**: Copine 5
Gag-Pol	92	**PRDYVDR**	7, 40, 48, 50, 52, 54	**CPNE5**: see previous entry
Gag-Pol	02	**TLRAEQA**	5	**O4UJ75**: Ankyrin repeat domain-containing protein 20A4 **O5TYW2**: Ankyrin repeat domain-containing protein 20A1 **O5VUR7**: Ankyrin repeat domain-containing protein 20A3
Gag-Pol	03	**LRAEQAS**	7, 50, 52, 56-58	**O8NE76**: Coiled-coil domain-containing protein 87. **CCDC87**
Gag-Pol	34	**KALGPAA**	0, 56, 59	**TMM24**: C2C2L. Transmembrane protein 24
Gag-Pol	35	**ALGPAAT**	2, 30, 59	**BGH3**: Transforming growth factor-beta-induced protein ig-h3 **TMM24**: see previous entry
Gag-Pol	36	**LGPAATL**	2, 30, 59, 60	**BGH3**: see previous entry
Gag-Pol	52	**PEPTAPP**	6, 31, 61-63	**CD5**: T cell surface glycoprotein CD5
Gag-Pol	72	QKQEPR		O53GP5: MOCOS. Molybdenum cofactor sulfurase
Gag-Pol	85	**LASLRSL**	6, 64-66	**GP125**: Probable G-protein coupled receptor 125
Gag-Pol	87	**LRSLFG**	6, 51, 67	**KIF1B**: Kinesin-like protein KIF1B
Tat	9	**RKKRRQR**	8-71	**SCN3A**: Sodium channel protein type 3 subunit alpha
Tat	8	EGDPTGP		RIN3: Ras interaction/interference protein 3
Tat	5	EEPKKEV		MAP1B: Microtubule-associated protein 1B
Tat	0	CVEREAE		LRC59: Leu-rich repeat-containing protein 59
Tat	1	YEREAET		NRG1: Pro-neuregulin-1, membrane-bound isoform . Pro-NRG1
Rev	6	IPPPKPE		O9H814: PHAX. Phosphorylated adapter RNA export protein.
Rev	8	**RRNRRRR**	1, 72	**CO4A**: Complement C4-A
Rev	1	**VPLQLPP**	6, 57, 66, 73, 74	**RHG05**: Rho GTPase-activating protein 5
Rev	4	**DLPPLER**	7, 36, 48, 75	**AMRA1**: Activating molecule in BECN1-regulated autophagy protein 1
Rev	1	LTLDCSE		O9C0D6: FH2 domain-containing protein 1
Rev	03	**LVESPAV**	8, 76-78	**PKD1**: Polycystin-1. Polycystic kidney disease 1 protein
Env gp160	7	**KEATTTL**	7, 37, 58, 79-81	**K0690**: RRP12-like protein. Ribosomal RNA processing 12
Env gp160	09	**TSVITQA**	7, 56, 80, 83, 84	**ATF7**: cAMP-dependent transcription factor ATF-7
Env gp160	45	**NGTGPCT**	5	**LRTM3**: Leu-rich repeat transmembrane neuronal protein 3
Env gp160	70	**ALLNGSL**	2, 85-88	**DGPIK4**: Dixin. DIX domain-containing protein 1
Env gp160	80	**CVVIRSE**	8	**RBL1**: Retinoblastoma-like protein 1. Tumor suppressor
Env gp160	03	**YEINCTR**	2, 82, 85, 89	**TNR6**: Tumor necrosis factor receptor superfamily, member 6
Env gp160	69	**AFNQSSG**	7	**ZN595**: Zinc finger protein 595
Env gp160	73	**ISGGDPE**	5, 87, 89	**O8NAP4**: cDNA FLJ35033 fis
Env gp160	89	**WWRSELY**	5, 85	**ACOT4**: Acyl-coenzyme A thioesterase 4
Env gp160	23	AVGMLGA		COX11: Cytochrome c oxidase assembly protein COX11
Env gp160	49	**LTVQARQ**	9, 90	**O8IVF2**: **AHNAK2.** Interacts with dysferlin
Env gp160	69	DQELLQL		DOT1L: Histone-lysine N-methyltransferase, H3 lys-79 specific O9BZE0: Zinc finger protein GLIS2
Env gp160	70	DELLQLD		CAPS1: Ca2+-binding protein
Env gp160	36	YRGPDRP		O8N7J0: CDNA FLJ25488 fis, clone CBR00232 O8TDX4: Nbla 3076 protein. **Specifically expressed in brain**
Env gp160	43	EGTEEGG		VGF: Neurosecretory protein VGF. Involved in synatogenesis
Env gp160	85	DLLLIVA		3A2: Anion exchange protein 2. **SLC4A2**
Env gp160	94	**VELLGRR**	7, 91, 92	**GTR5**: Glucose transporter type 5, small intestine. GLUT-5
Env gp160	21	NSAVSLV		RGR: RPE-retinal G protein-coupled receptor

[1] HIV-1 heptapeptides experimentally validated as epitopes are given in boldface. [2] References refer to experimentally validated heptapeptide epitopes [3] UniProt/Swiss entry, accession number, protein name and abbreviation from Universal Protein Resource. Proteins that, when altered, may be associated to AIDS pathologies (see text for refs), are given in boldface. Visit http://www.uniprot.org for further details on the human proteins involved in the viral overlap.

column in Table 1, entries in boldface). We found that, in general, the potential cross-reactivity risk related to the viral-versus-human epitopic peptide commonalities reported in Table 1 defines typical pathologies that occur in the course of HIV infection, such as immunosuppression, neurological disorders, myopathies, lipodystrophia, and malignancies.

4.3.1. HIV-1 heptapeptide cross-reactivity and immunosuppression

In addition to the well-known PEPTAPP peptide shared between HIV-1 Gag-Pol protein and the human T cell surface glycoprotein CD5 (26, 31, 61-63), a receptor that regulates T cell proliferation, we found the following cross-reactivities. 1) The Rev_{71-77}VPLQLPP epitope is present in human Rho GTPase-activating

protein 5. Rho GTPases have an essential role in human T cell development (93) and, clearly, a cross-immune reaction may contribute to destroying T cells. 2) The same observation holds for the occurrence of the Rev_{74-80}QLPPLER epitope in the human activating molecule in BECN1-regulated autophagy protein 1, a protein involved in the control of T cell homeostasis (94). 3) The Env $gp160_{303-310}$VEINCTR epitope is present in the human tumor necrosis factor receptor, also called CD95 (82). CD95 is expressed on $CD4^+$, $CD8^+$ and B cells. It is worth underlining that CD95, isoform 6, can block apoptosis.

It is logical to argue that altogether, immune cross-reactions with the above described T cell-related proteins may contribute to T cell loss and the consequent immunodeficiency characterizing HIV infection. Moreover, the Gag-Pol_{99-105}ALDKIEE sequence is present in leucine-rich repeat flightless-interacting protein 2, which positively regulates cytokine production in macrophages (95). Cross-reactivity with LRRFIP2 following virus infection might contribute to reducing host defenses, thus adding to AIDS-associated immunosuppression. Immunodeficiency might also be enhanced by an immune hit on the C4a anaphylatoxin complement**,** hosting the Rev_{38-44}RRNRRRR epitope, because alterations of CO4A are involved in inflammatory processes and primary immunodeficiency diseases (96).

4.3.2. HIV-1 heptapeptide cross-reactivity and neurological disorders

The Gag-Pol_{94-100}RDTKEAL epitopic sequence occurs in the human striatin protein and might explain the frequency of comorbid HIV infection and schizophrenia (97). In fact, striatin is preferentially expressed in brain neurons and may play a role in dendritic Ca^{2+} signaling (98). Of relevance, a **p**refrontal cortex shotgun proteome analysis revealed altered calcium homeostasis and immune system imbalance in schizophrenia, with striatin showing statistically significant differential expression (99). Moreover, striatin is involved in the activation of endothelial NO synthase (100). Hence, the alteration of striatin may also prevent NO formation, thus underlying the association between HIV infection and stiffness of the common carotid artery (101**).**

Another possible link between immune activation and schizophrenia might be represented by the Env $gp160_{270-276}$LLLNGSL epitope, which is common to the human dixin protein. Dixin is expressed ubiquitously, with higher expression in cardiac and skeletal muscles. Interestingly, dixin is a critical regulator of DISC1, the alteration of which has been associated with schizophrenia (102).

Neurological disorders might be related to potential cross-reactivity due to the presence of two consecutive overlapping viral epitopes, *i.e*., the Gag-$Pol_{291-298}$PFRDYVDR octapeptide in the human copine 5 protein. Copine 5 is expressed in both neural progenitor cells and in differentiated neurons during neural development, suggesting a role for CPNE5 in the development of the central nervous system (103). Alterations in CPNE5 might underlie the cognitive delay and the course of HIV-1-associated progressive encephalopathy in children (104, 105).

Env $gp160_{245-261}$NGTGPCT is found in the human leucine-rich repeat transmembrane neuronal protein 3 (LRTM3). In addition to a role in the development and maintenance of the vertebrate nervous system, LRTM3 is expressed almost exclusively in the nervous system, including regions affected during Alzheimer's disease, such as the dentate gyrus (106). An immune attack targeting the NGTGPCT sequence may determine inflammatory reactions at sites anatomically related to Alzheimer's disease, thus representing a pathogenic mechanism underlying the emerging intersection of HIV infection and Alzheimer's disease (107).

A potential neurological burden might be aggravated by the sharing of the Gag-$Pol_{487-493}$SLRSLFG epitope with the human kinesin-like protein KIF1B, isoform 2, expressed abundantly in the brain. It is worth recalling that the down-regulation of KIF1B has been associated specifically with sporadic amyotrophic lateral sclerosis (108). Thus, an immune reaction against KIF1B might underlie the suggested association between HIV and sporadic amyotrophic lateral sclerosis (109-111). Also, the Tat_{49-55}RKKRRQR epitope might play a role in amyotrophic lateral sclerosis because it is shared with the sodium channel protein type 3 subunit alpha, a protein that mediates the voltage-dependent sodium ion permeability of excitable membranes (112). Also, motor neuron disorders might be associated with the cross-reactivity derived from the presence of the Gag-$Pol_{156-162}$KVIEEKA epitope in the regulator of G-protein signaling 17, a protein that inhibits signal transduction by increasing the GTPase activity of G protein alpha subunits and is expressed predominantly in the cerebellum, cortex, and medulla. Alterations in GTPase activity have been related not only to amyotrophic lateral sclerosis (113), but also to malignancies. Indeed, neurofibromin 1 protein and tuberous sclerosis tumor suppressor complex regulate GTPase activities (114-116).

4.3.3. HIV-1 heptapeptide cross-reactivity and muscle diseases

Cross-reactivity between HIV and human ankyrin repeat domain containing protein occurs through the Gag-$Pol_{302-308}$TLRAEQA epitope. Alterations of ankyrin repeat domain-containing proteins are involved in muscle diseases (117), and may be a cause of HIV-associated myopathies (118). A role in myopathy genesis following HIV-1 infection might also be played by immune activation against the Env $gp160_{549-555}$LTVQARQ epitope, which is shared with the human **AHNAK2, a protein that i**nteracts with dysferlin. In dysferlinopathies, the reduction or absence of dysferlin is correlated with a secondary muscle-specific loss of AHNAK (119).

4.3.4. HIV-1 heptapeptide cross-reactivity and malignancies.

Regarding HIV-associated malignancies, potential cross-reactions might relate to the following

matches: 1) the Gag-Pol$_{285-292}$RQGPKEP epitope is shared with the human pre-B-cell leukemia transcription factor-interacting protein 1, which can inhibit the transcriptional activation of the oncogene E2A-Pbx (120); 2) the Gag-Pol$_{14-20}$RWEKIRL epitope is present in the human "deleted in bladder cancer protein 1" (DBC1). This sharing fits with recent reports that bladder cancer can be added to the list of cancers that may be encountered in patients living longer with chronic HIV infection (121); 3) Env gp160$_{209-215}$TSVITQA is present in the human cAMP-dependent transcription factor ATF-7, which binds the cAMP response element (consensus: 5'-GTGACGT(AG)(AG)-3'), a sequence present in many viral and cellular promoters. Moreover, it mediates the transcriptional activation exerted by the adenovirus oncoprotein E1 (122). ATF-7 is thought to support gene silencing by inducing histone H3-K9 trimethylation and may have a critical role in gene expression induced by social isolation stress (123); 4) the Env gp160$_{280-286}$EVVIRSE epitope is shared with the human tumor suppressor retinoblastoma-like protein 1, also known as p107, a protein with a critical role in suppressing tumor progression (124, 125).

4.3.5. HIV-1 cross-reactivity and other AIDS disorders: lipodystrophies, diarrhea, bone loss, corneal alterations, kidney disease, hypertension

The Gag-Pol$_{122-128}$GNSSQVS epitope is present in a human peroxisomal enzyme, 3-ketoacyl-CoA thiolase. Dysregulation of peroxisome function appears to be associated with the spectrum of biochemical changes seen in HIV associated lipodystrophies (126). Alterations in lipid metabolism might also derive from a cross-reaction between Env gp160$_{489-495}$NWRSELY and the human acyl-coenzyme A thioesterase 4, a protein that catalyzes the hydrolysis of acyl-CoAs into the free fatty acid and coenzyme A, so regulating the intracellular levels of acyl-CoAs, free fatty acids, and coenzyme A.

The Gag-Pol$_{124-130}$SSQVSQN epitope is present in the human intestinal guanylate cyclase C protein. This match may be of importance in AIDS syndrome, in light of two observations: 1) the binding of heat-stable enterotoxins to the intestinal receptor guanylyl cyclase C activates guanylyl cyclase and catalyzes the formation of cGMP, initiating a signaling cascade that opens the cystic fibrosis transmembrane conductance regulator chloride channel at the apical cell surface, thus causing secretory diarrhea, a leading cause of infectious diarrhea in humans (127). Thus, a HIV infection-induced humoral immune response targeting the SSQVSQN sequence may indicate the activation of guanylyl cyclase C and subsequent activation of the signaling cascade, leading to the secretory diarrhea status affecting HIV infected individuals (128, 129).

The Gag-Pol$_{216-222}$PVHAGPI peptide epitope is present in the human receptor-type tyrosine-protein phosphatase epsilon (PTPRE), a protein that regulates osteoclast formation (129). Cross-reactivity with PTPRE might relate to HIV-associated bone loss and alterations (130, 131).

Two consecutive overlapping viral epitopes, in the Gag-Pol$_{335-342}$ALGPAATL octapeptide, are present in the human transforming growth factor-beta-induced protein ig-h3 (BIGH3). This adhesion protein binds to type I, II, and IV collagens and is expressed highly in the corneal epithelium. Defects in BIGH3 cause corneal dystrophies (132). A cross-reaction with BIGH3 may underlie corneal alterations associated to HIV infection (133-135).

Cross reactivity between Rev$_{103-109}$LVESPAV and the human polycystic kidney disease 1 protein might contribute to one of the primary comorbid conditions affecting HIV-infected individuals, chronic kidney disease (136).

Env gp160$_{794-800}$VELLGRR is shared with a glucose transporter, GLUT-5, that functions primarily as a fructose transporter. Alterations of GLUT-5 are related to hypertension (137). Cross-reaction with GLUT-5 might contribute to the hypertension associated to HIV infection (138-141).

4.4. Analyzing sequence similarity of HIV-1 polyprotein to the human proteome at the pentapeptide level

We further analyzed the sequence similarity between the HIV polyprotein primary sequence and the human proteome to evaluate precisely the potential immunological cross-reactivity between viral and human proteins. To this aim, we used pentapeptides as scanning units. In fact, analyzing the sequence similarity between biological sequences in the immunological context equates to identifying the number of aligned epitopes with perfect sequence matching. In this case, immunological similarity analyses must consider the minimal length of an epitopic sequence (142, 143). As long ago as 1939, Landsteiner and van der Scheer demonstrated that a grouping of five amino acids could be an antigenic determinant (144). Since then, a number of scientific reports have validated five or six amino acids as the minimum size of the epitopic space characterizing humoral and cellular immune responses (147-151; reviewed in 152, 153), also exemplified by the HIV epitopes reported by Fiebig *et al.* (148). Based on these experimental reports, we defined immune epitopic peptide units as pentapeptides (143).

Thus, with the aim of obtaining a better definition of the potential cross-reactivity between HIV and the human host, the HIV-1 polyprotein sequence under analysis was dissected into 1,678 pentapeptides, each offset by one residue. Each viral pentapeptide was then used as a probe to scan the entire human proteome, searching for perfect matches. The data we obtained are presented in Figure 1, showing the number of matches with the human proteome for each HIV-1 pentapeptide and clearly documenting the existence of a massive viral-versus-human pentapeptide overlap. The pentapeptide identity profile of the HIV-1 polyprotein primary sequence versus the human proteome (*i.e.*, the number of times each HIV-1 pentapeptide is present in the human

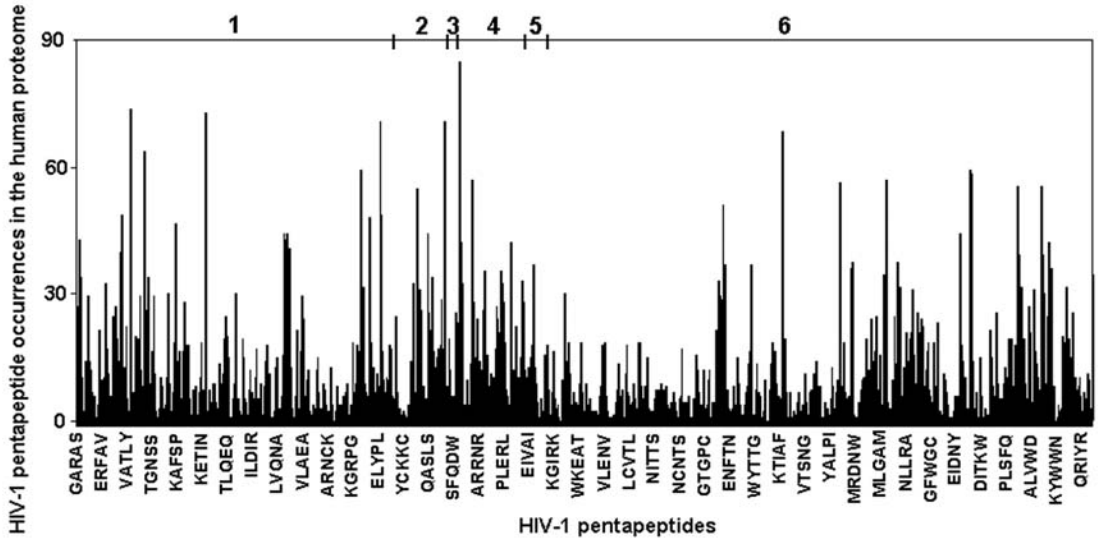

Figure 1. HIV-1 similarity profile *versus* the human proteome at the pentapeptide level. Columns indicate the number of the HIV-1 pentapeptide occurrences in the human proteome. Numbering 1 to 6 refers to the location of the 6 viral proteins along the analyzed HIV-1 polyprotein primary sequence. Viral proteins as detailed under Methods section. For further methodology details see also Refs. 152-154.

proteome) exhibits a range of behavior, with some HIV-1 polyprotein areas formed by pentapeptides matching a low number of human proteins, while others are formed by pentapeptides recurring in many different human proteins. As an example, the HIV-1 Env gp160$_{675-679}$LDKWA pentapeptide matches only a single human protein (kynureninase, UniProtKB/Swiss-Prot accession: D3DP79), whereas the HIV-1 Env gp160 $_{671-67}$5ELLQL pentapeptide occurs in 68 different human proteins. In parallel, multiple viral occurrences can also occur in the human proteins (*e.g.*, human titin shares 35 pentapeptides with HIV-1).

A snapshot of the HIV pentapeptide overlapping with the human proteome is reported in Table 2. Numerically, the viral 5-mers occurring in the human proteome (including multiple occurrences) amount to 14,227 and include proteins associated with the most crucial functions of the cell, from proliferation to apoptosis, from immune regulation to enzyme activity. Theoretically, the number of times a given pentamer from HIV-1 (isolate CDC-451, polyprotein length 1,682 aa) might occur at random in the human proteome (as calculated on the basis of the unique viral and human 5-mers) is 1,252. Therefore, the extent of overlap (14,227 matches) reported in Table 2 is roughly 11-fold higher than the expected value. Similar data were obtained by analyzing HIV-1, Taxonomy ID 11676 (data not shown).

The human proteins hosting HIV-1 pentapeptide(s) are listed in Table 3 (see Supplemental Data).

5. DISCUSSION

The current study demonstrated that: 1) HIV-1, isolate CDC-451, shares numerous perfect heptapeptide matches with human proteins; 2) most of the shared heptapeptides are part of epitopes immunologically recognized by a human immune response(s) following HIV-infection (*i.e.*, they have immune potential), and 3) the viral epitopes are present in human proteins that, when altered, are related to diseases characteristic of HIV-associated AIDS.

These data suggest that the constellation of diseases associated with HIV-infection may be related to anti-HIV immune responses. This hypothesis is supported by a pioneering study by Martinez *et al.* (154), who observed that AIDS-associated immunosuppression might be due to human anti-HIV immune responses, rather than to the pathogenicity of the virus. It was suggested that the basis of the immunosuppression could be molecular mimicries involving viral gp-110, CD4 molecules, antibodies, and CD4-acceptor sites. As a conclusion, the study remarked on the advantage of being a low responder subject (*i.e.*, a low producer of potentially harmful autoantibodies), and warned that anti-HIV vaccination might protect against infection but, at the same time, cause immunosuppression and disease. Using the current databases, our study scientifically validates the reasoning of Martinez *et al*. Successively, Victorino's group (155) reached a similar conclusion by comparing several immunological and viral variables during HIV-1 and HIV-2 infection, and found that immune activation, and not viremia, is closely linked to the extent of CD4 depletion in both infections.

Additionally, the current study provides a detailed picture of the phenetic commonalities between a HIV-1 strain and the human host. As discussed in the Introduction, numerous studies on the HIV-versus-human sequence similarity and potential cross-reactivity have

Table 2. Numerical description of the pentapeptide overlap between HIV-1 polyprotein and the human proteome[1]

Viral 5-mers	1,678
Viral 5-mers occurring in the human proteome (including multiple occurrences)	14,227
Human proteins involved in the viral overlap[1]	10,312
Expected number of viral 5-mer occurrences in the human proteome[3]	1,252

[1] Human proteome formed by 2,388,563 unique 5-mers (20). [2] The list of human proteins hosting viral 5-mer(s) is given in Supplemental Table 3. [3] Calculated as described in text

been reported (1-18, 20, 61, 62). Here, using the immune pentapeptide unit, we report for the first time a complete immune cross-reactivity map between HIV-1 and the human proteome. The present study demonstrates that the HIV-1 polyprotein analyzed presents thousands of pentapeptides (14,227) disseminated widely and repeatedly throughout the human proteome. Moreover, the human proteins involved in the viral overlap amount to 10,312; that is, about 32% of the human proteome contains viral pentamers. The implications of these data are profound, because pentapeptides are the minimal biological units exerting roles in immunobiology (151, 152). *De facto*, given the extent of the pentapeptide identity pattern between HIV-1 and humans, clearly, an anti-HIV immune response may explain the wide spectrum of autoimmune disease, as well as the complex array of autoantibodies towards the most disparate human targets in HIV/AIDS (156), definitely supporting the link described in Table 1 between the (auto)immune activation caused by HIV infection and AIDS.

However, the pentapeptide identity pattern between HIV-1 and humans poses the following unavoidable crucial question: what triggers the anti-HIV immune response in the high-responders HIV-infected subjects? As a matter of fact, when high degrees of immunological similarity (*i.e.*, identity at the level of immunobiological units) are present between microbial organisms and humans, the breaking of the immunotolerance mechanisms that avoid harmful self reactivity seems unlikely, because the sharing of epitopes with the host's molecules may rather represent an elective microbial mechanism to escape immune surveillance (157, 158). In fact, we and others (19, 20, 159, 160) have demonstrated that a number of viral proteomes, independent of their structural or pathogenic characteristics, present a high number of pentapeptide overlaps with the human proteome (19, 20) and, likewise, bacterial peptides are present throughout the human proteome (159, 160). As a logical conclusion, Kanduc (143, 161, 162) argued that the peptide identity platform unifying microbes and humans is at the root of the immune escape phenomenon (*i.e.*, the root of what the immunologists call the enigma of successful viral/bacterial escape from immune surveillance) (163-165). According to the relationship of high similarity-immune escape advocated by Kanduc (143, 162), vaccines containing the infectious agent are generally ineffective because they have scarce or no immunogenicity. To induce/increase an immune response, as a rule, vaccinology uses adjuvants (166), a highly heterogeneous group of chemical compounds which, through mechanisms not yet clear, bypass the host immunotolerance mechanisms and elicit hyperactivation of the immune system. Currently, aluminum salts and aluminum hydroxide are the most powerful (and used) adjuvants.

Consequently, to determine what triggers the anti-HIV immune response in the high-responders to the HIV-infection, we cannot help to recall that aluminum hydroxide has many applications in pharmaceuticals. In particular, it is an antacid, as well as an approved protectant used to heal and protect minor wounds, skin abrasions, skin tears and partial thickness pressure ulcers, and a component *par excellence* of ointments for treatment of hemorrhoids and nonhemorrhoidal anorectal conditions (such as fissure, abscess, skin tags, rectal prolapse, or pruritus ani) (167). In this regard, epidemiological studies aimed at analyzing a possible link between the use of aluminum-based compounds and immune activation following HIV infection are warranted. Also, the adjuvant action exerted by bacterial lipopolysaccharides (LPSs) has to be considered. LPSs act as adjuvants by inhibiting the induction of tolerance by nonimmunogenic tolerogenic antigens (168). Likewise, it is well known that bacteria are also frequent concomitant pathogens to HIV infection (169) and have been implicated in promoting HIV-1 pathogenesis through bacterial LPSs (170, 171). To conclude, it seems that the immune hyperactivation against the high-similarity tolerogenic HIV polyprotein and the successive progression to AIDS in specific cohorts of HIV-infected individuals might be specifically related to the presence of adjuvants of bacterial and/or chemical nature. Of note, our considerations would explain the highly context-dependent progression of HIV/AIDS and its secondary complications among patients (172-176).

Finally, this study joins other reports (18, 61) in suggesting that HIV antigen-based vaccines might have harmful outcomes in the prevention or treatment of HIV infection, and further supports Kanduc's suggestion (177, 178) that only epitopic peptides with low similarity to the human proteome may offer a basis for rational anti-HIV vaccines avoiding collateral adverse events (179, 180).

6. CONTRIBUTIONS

GL, AS, and MC have been involved in data analysis. DK conceived and designed the study, interpreted the data and wrote the manuscript. All authors have read and approved the final manuscript.

7. REFERENCES

1. MR Lee, DD Ho, ME Gurney: Functional interaction and partial homology between human immunodeficiency virus and neuroleukin. *Science* 237, 1047–1051 (1987)

2. A Douvas, S Sobelmen: Multiple overlapping homologies between two rheumatoid antigens and immunosuppressive viruses. *Proc Natl Acad Sci USA* 88, 6328–6332 (1991)

3. A Douvas, Y Takehana: Cross-reactivity between autoimmune anti-U1 snRNP antibodies and neutralizing epitopes of HIV-1 gp120/41. *AIDS Res Hum Retroviruses* 10, 253–262 (1994)

4. EW Taylor, A Bhat, RG Nadimpalli, W Zhang, J Kececioglu: HIV-1 encodes a sequence overlapping env gp41 with highly significant similarity to selenium-dependent glutathione peroxidases. *J Acquir Immune Defic Syndr Hum Retrovirol* 15, 393-394 (1997)

5. G Su, W Min, EW Taylor: An HIV-1 encoded peptide mimics the DNA binding loop of NF-kappaB and binds thioredoxin with high affinity. *Mutat Res* 579, 133-148 (2005)

6. RL Bjork Jr: HIV-1: seven facets of functional molecular mimicry. *Immunol Lett* 28, 91–95 (1991)

7. J Habeshaw, E Hounsell, A Dalgleish: Does the HIV envelope induce a chronic graftversus-host-like disease? *Immunol Today* 13, 207–210 (1992)

8. C Susal, M Kropelin, V Daniel, G Opelz: Molecular mimicry between HIV-1 and antigen receptor molecules: a clue to the pathogenesis of AIDS. *Vox Sang* 65:10–17 (1993)

9. JF Zagury, H Cantalloube, A Achour, YY Cho, L Fall, A Lachgar, V Chams, A Astgen, D Biou, O Picard, I Callebaut, JP Morton, A Burny, M Feldman, J Bernard, B Bizzini, D Zagury: Striking similarities between HIV-1 Env protein and the apoptosis mediating cell surface antigen Fas. Role in the pathogenesis of AIDS. *Biomed Pharmacother* 47, 331-335 (1993)

10. HM Cantalloube, CE Nahum, JF Zagury: Screening of protein sequences databanks by Automat for search of host sequences integration and/or autoimmune disorders induction by retroviruses. *Biomed Pharmacother* 48, 17-26 (1994)

11. RS Root-Bernstein: Antigenic complementarity among AIDS-associated infectious agents and molecular mimicry of lymphocyte proteins as inducers of lymphocytotoxic antibodies and circulating immune complexes. *J Clin Virol* 31, S16-25 (2004)

12. T Spehar, M Strand: Molecular mimicry between HIV-1 gp41 and an astrocyte isoform of alpha-actinin. *J Neurovirol* 1, 381-390 (1995)

13. PM Murphy: Viral exploitation and subversion of the immune system through chemokine mimicry. *Nat Immunol* 2, 116-122 (2001)

14. F Chen, SL Day, RA Metcalfe, G Sethi, MS Kapembwa, MG Brook, D Churchill, A de Ruiter, S Robinson, CJ Lacey, AP Weetman: Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease. *Medicine (Baltimore)* 84, 98-106 (2005)

15. Z Li, MA Nardi, S Karpatkin: Role of molecular mimicry to HIV-1 peptides in HIV-1-related immunologic thrombocytopenia. *Blood* 106, 572-576 (2005)

16. GH Tishkoff, LT Hunt: Unexpected molecular mimicry among peptides MHC class II, blood-clotting factor X, and HIV-1 envelope glycoprotein GP120. *Thromb Res* 98, 343-346 (2000)

17. N Veljkovic: Molecular mimicry of HIV gp120: Possible implications on prevention and therapy of AIDS. *Arch Oncol* 13, 126-130 (2005)

18. BF Haynes, J Fleming, EW St. Clair, H Katinger G Stiegler, R Kunert,J Robinson, RM Scearce, K Plonk, HF Staats, TL Ortel, H-X Liao, SM Alam: Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science* 308, 1906-1908 (2005)

19. C Natale, T Giannini, A Lucchese, D Kanduc: Computer-assisted analysis of molecular mimicry between human papillomavirus 16 E7 oncoprotein and human protein sequences. *Immunol Cell Biol* 78, 580-585 (2000)

20. D Kanduc, A Stufano, G Lucchese, A Kusalik: Massive peptide sharing between viral and human proteomes. *Peptides* 29, 1755-1766 (2008)

21. G Capone, G Novello, C Fasano, B Trost, M Bickis, A Kusalik, D Kanduc. The oligodeoxynucleotide sequences corresponding to never-expressed peptide motifs are mainly located in the non-coding strand. *BMC Bioinformatics* 11, 383 (2010)

22. NA Jones, X Wei, DR Flower, M Wong, F Michor, MS Saag, BH Hahn, MA Nowak, GM Shaw, P Borrow: Determinants of human immunodeficiency virus type 1 escape from the primary CD8+ cytotoxic T lymphocyte response. *J Exp Med* 200, 1243–1256 (2004)

23. U Malhotra, J Nolin, JI Mullins, MJ McElrath: Comprehensive epitope analysis of cross-clade Gagspecific T-cell responses in individuals with early HIV-1 infection in the US epidemic. *Vaccine* 25, 381–390 (2007)

24. X Gong, X Gui, Y Zhang, P Tien: Screening for CD8 cytotoxic T lymphocytes specific for Gag of human

immunodeficiency virus type 1 subtype B' Henan isolate from China and identification of novel epitopes restricted by the HLA-A2 and HLAA11 alleles. *J Gen Virol* 87, 151–158 (2006)

25. DE Kaufmann, PM Bailey, J Sidney, B Wagner, PJ Norris, MN Johnston, LA Cosimi, MM Addo, M Lichterfeld, M Altfeld, N Frahm, C Brander, A Sette, BD Walker, ES Rosenberg: Comprehensive analysis of human immunodeficiency virus type 1-specific CD4 responses reveals marked immunodominance of gag and nef and the presence of broadly recognized peptides. *J Virol* 78, 4463–4477 (2004)

26. WB Dyer, JJ Zaunders, FF Yuan, B Wang, JC Learmont, AF Geczy, NK Saksena, DA McPhee, PR Gorry, JS Sullivan: Mechanisms of HIV non-progression; robust and sustained CD4+ T-cell proliferative responses to p24 antigen correlate with control of viraemia and lack of disease progression after long-term transfusion-acquired HIV-1 infection. *Retrovirology* 5, 112 (2008)

27. S Zhai, Y Zhuang, Y Song, S Li, D Huang, W Kang, X Li, Q Liao, Y Liu, Z Zhao, Y Lu, Y Sun: HIV-1-specific cytotoxic T lymphocyte (CTL) responses against immunodominant optimal epitopes slow the progression of AIDS in China. *Curr HIV Res* 6, 335–350 (2008)

28. L Musey, Y Ding, J Cao, J Lee, C Galloway, A Yuen, KR Jerome, MJ McElrath: Ontogeny and specificities of mucosal and blood human immunodeficiency virus type 1-specific CD8+ cytotoxic T lymphocytes. *J Virol* 77, 291–300 (2003)

29. N Frahm, S Adams, P Kiepiela, CH Linde, HS Hewitt, M Lichterfeld, K Sango, NV Brown, E Pae, AGWurcel, M Altfeld, ME Feeney, TM Allen, T Roach, MA St. John, ES Daar, E Rosenberg, B Korber, F Marincola, BD Walker, PJR Goulder, C Brander: HLA-B63 presents HLA-B57/B58-restricted cytotoxic T-lymphocyte epitopes and is associated with low human immunodeficiency virus load. *J Virol* 79, 10218–10225 (2005)

30. M Daucher, DA Price, JM Brenchley, L Lamoreaux, JA Metcalf, C Rehm, E Nies-Kraske, E Urban, C Yoder, D Rock, J Gumkowski, MR Betts, MR Dybul, DC Douek: Virological outcome after structured interruption of antiretroviral therapy for human immunodeficiency virus infection is associated with the functional profile of virus-specific CD8+ T cells. *J Virol* 82, 4102– 4114 (2008)

31. PC Matthews, A Prendergast, A Leslie, H Crawford, R Payne, C Rousseau, M Rolland, I Honeyborne, J Carlson, C Kadie, C Brander, K Bishop, N Mlotshwa, JI Mullins, H Coovadia, T Ndung'u, BD Walker, D Heckerman, PJR Goulder: Central role of reverting mutations in HLA associations with human immunodeficiency virus set point. *J Virol* 82, 8548–8559 (2008)

32. DA Dilernia, L Jones, S Rodriguez, G Turk, AE Rubio, S Pampuro, M Gomez-Carrillo, C Bautista, G Deluchi, J Benetucci, MB Lasala, L Lourtau, MH Losso, H Perez, P Cahn, H Salomón: HLA-driven convergence of HIV-1 viral subtypes B and F toward the adaptation to immune responses in human populations. *PLoS ONE* 3, e3429 (2008)

33. A Milicic, CTT Edwards, S Hué, J Fox, H Brown, T Pillay, JW Drijfhout, JN Weber, EC Holmes, SJ Fidler, HT Zhang, RE Phillips: Sexual transmission of single human immunodeficiency virus type 1 virions encoding highly polymorphic multisite cytotoxic T-lymphocyte escape variants. *J Virol* 79, 13953–13962 (2005)

34. A Achour, O Picard, D Zagury, P Sarin, R Gallo, P Naylor, A Goldstein: Hgp-30, a synthetic analogue of human immunodeficiency virus p17, is a target for cytotoxic lymphocytes in hiv-infected individuals. *Proc Natl Acad Sci USA* 87, 7045– 7049 (1990)

35. B Wahren, J Rosen, E Sandstrom, T Mathiesen, S Modrow, H Wigzell: Hiv-1 peptides induce a proliferative response in lymphocytes from infected persons. *J Acquir Immune Defic Syndr* 4, 448–456 (1989)

36. TM Allen, M Altfeld, SC Geer, ET Kalife, C Moore, KM O'Sullivan, I DeSouza, ME Feeney, RL Eldridge, EL Maier, DE Kaufmann, MP Lahaie, L Reyor, G Tanzi, MN Johnston, C Brander, R Draenert, JK Rockstroh, H Jessen, ES Rosenberg, SA Mallal, BD Walker: Selective escape from CD8+ T-cell responses represents a major driving force of human immunodeficiency virus type 1 (HIV-1) sequence diversity and reveals constraints on HIV-1 evolution. *J Virol* 79, 13239–13249 (2005)

37. N Frahm, BT Korber, CM Adams, JJ Szinger, R Draenert, MM Addo, ME Feeney, K Yusim, K Sango, NV Brown, D SenGupta, A Piechocka-Trocha, T Simonis, FM Marincola, AG Wurcel, DR Stone, CJ Russell, P Adolf, D Cohen, T Roach, A StJohn, A Khatri, K Davis, J Mullins, PJR Goulder, BD Walker, C Brander: Consistent cytotoxic-T-lymphocyte targeting of immunodominant regions in human immunodeficiency virus across multiple ethnicities. *J Virol* 78, 2187–2200 (2004)

38. L Dorrell, BE Willcox, EY Jones, G Gillespie, H Njai, S Sabally, A Jaye, K DeGleria, T Rostron, E Lepin, A McMichael, H Whittle, S Rowland-Jones: Cytotoxic T lymphocytes recognize structurally diverse, clade-specific and crossreactive peptides in human immunodeficiency virus type-1 gag through HLA-b53. *Eur J Immunol* 31, 1747–1756 (2001)

39. A Buchacher, R Predl, K Strutzenberger, W Steinfellner, A Trkola, M Purtscher, G Gruber, C Tauer, F Steindl, A Jungbauer, H Katinger: Generation of human monoclonal antibodies against HIV-1 proteins; electrofusion and Epstein-Barr virus transformation for peripheral blood lymphocyte immortalization. *AIDS Res Hum Retroviruses* 10, 359-369 (1994)

40. L Gudmundsdotter, D Bernasconi, B Hejdeman, E Sandstrom, A Alaeus, K Lidman, B Ensoli, B Wahren, S

Buttò: Cross-clade immune responses to Gag p24 in patients infected with different HIV-1 subtypes and correlation with HLA class I and II alleles. *Vaccine* 26, 5182–5187 (2008)

41. P Kiepiela, AJ Leslie, I Honeyborne, D Ramduth, C Thobakgale, S Chetty, P Rathnavalu, C Moore, KJ Pfafferott, L Hilton, P Zimbwa, S Moore, T Allen, C Brander, MM Addo, M Altfeld, I James, S Mallal, M Bunce, LD Barber, J Szinger, C Day, P Klenerman, J Mullins, B Korber, HM Coovadia, BD Walker, PJR Goulder: Dominant influence of HLA-B in mediating the potential co-evolution of HIV and HLA. *Nature* 432, 769–775 (2004)

42. P Kiepiela, K Ngumbela, C Thobakgale, D Ramduth, I Honeyborne, E Moodley, S Reddy, C de Pierres, Z Mncube, N Mkhwanazi, K Bishop, M van der Stok, K Nair, N Khan, H Crawford, R Payne, A Leslie, J Prado, A Prendergast, J Frater, N McCarthy, C Brander, GH Learn, D Nickle, C Rousseau, H Coovadia, JI Mullins, D Heckerman, BD Walker, P Goulder: CD8+ T-cell responses to different HIV proteins have discordant associations with viral load. *Nat Med* 13, 46–53 (2007)

42. N Frahm, P. Kiepiela, S. Adams, C. H. Linde, H. S. Hewitt, K. Sango, M. E. Feeney, M. M. Addo, M. Lichterfeld,M. P Lahaie, E Pae, AG Wurcel, T Roach, MA St John, M Altfeld, FM Marincola, C Moore, S Mallal, M Carrington, D Heckerman, TM Allen, JI Mullins, B T Korber, PJR Goulder, BD Walker, C Brander: Control of human immunodeficiency virus replication by cytotoxic T lymphocytes targeting subdominant epitopes. *Nat Immunol* 7, 173–178 (2006)

43. DR Chopera, Z Woodman, K Mlisana, M Mlotshwa, DP Martin, C Seoighe, F Treurnicht, DA de Rosa, W Hide, SA Karim, CM Gray, C Williamson, CAPRISA 002 Study Team: Transmission of HIV-1 CTL escape variants provides HLA-mismatched recipients with a survival advantage. *PloS Pathog* 4:e1000033 (2008)

44. V Novitsky, N Rybak, MF McLane, P Gilbert, P Chigwedere, I Klein, S Gaolekwe, SY Chang, T Peter, I Thior, T Ndung'u, F Vannberg, BT Foley, R Marlink, TH Lee, M Essex: Identification of human immunodeficiency virus type 1 subtype C Gag-, Tat-, Rev-, and Nef-specific elispot-based cytotoxic T-lymphocyte responses for AIDS vaccine design. *J Virol* 75, 9210– 9228 (2001)

45. N Goonetilleke, S Moore, L Dally, N Winstone, I Cebere, A Mahmoud, S Pinheiro, G Gillespie, D Brown, V Loach, J Roberts, A Guimaraes-Walker, P Hayes, K Loughran, C Smith, J De Bont, C Verlinde, D Vooijs, C Schmidt, M Boaz, J Gilmour, P Fast, L Dorrell, T Hanke, AJ McMichael: Induction of multifunctional human immunodeficiency virus type 1 (HIV-1)-specific T cells capable of proliferation in healthy subjects by using a prime-boost regimen of DNA- and modified vaccinia virus Ankara-vectored vaccines expressing HIV-1 Gag coupled to CD8+ Tcell epitopes. *J Virol* 80, 4717–4728 (2006)

46. XG Yu, H Shang, MM. Addo, RL Eldridge, MN Phillips, ME Feeney, D Strick, C Brander, PJR Goulder, ES Rosenberg, BD Walker, M Altfeld: Important contribution of p15 Gag-specific responses to the total Gag-specific CTL responses. *AIDS* 16, 321–328 (2002)

47. S Wang, Y Sun, S Zhai, Y Zhuang, S Zhao, W Kang, X Li, D Huang, XG Yu, BD Walker, MA Altfeld: Identification of HLA-A11-restricted HIV-1-specific cytotoxic T-lymphocyte epitopes in China. *Curr HIV Res* 5, 119–128 (2007)

48. M Aidoo, S Sawadogo, EC Bile, C Yang, JN Nkengasong, JM McNicholl: Viral, HLA and T cell elements in cross-reactive immune responses to HIV-1 subtype A, CRF01_AE and CRF02_AG vaccine sequence in Ivorian blood donors. *Vaccine* 26, 4830–4839 (2008)

49. S McAdam, P Kaleebu, P Krausa, P Goulder, N French, B Collin, T Blanchard, J Whitworth, A McMichael, F Gotch: Cross-clade recognition of p55 by cytotoxic t lymphocytes in HIV-1 infection. *AIDS* 12, 571–579 (1998)

50. S Venturini, DE Mosier, DR Burton, P Poignard : Characterization of human immunodeficiency virus type 1 (HIV-1) Gag- and Gag peptide-specific CD4+ T-cell clones from an HIV-1-seronegative donor following in vitro immunization. *J Virol* 76, 6987–6999 (2002)

51. L Musey, Y Hu, L Eckert, M Christensen, T Karchmer, MJ McElrath: HIV-1 induces cytotoxic t lymphocytes in the cervix of infected women. *J Exp Med* 185, 293–303 (1997)

52. E Boritz, EL Rapaport, TB Campbell, JR Koeppe, CC Wilson: CD4+ T cell targeting of human immunodeficiency virus type 1 (HIV-1) peptide sequences present in vivo during chronic, progressive HIV-1 disease. *Virology* 361, 34–44 (2007)

53. MR Thakar, LS Bhonge, SK Lakhashe, U Shankarkumar, SS Sane, SS Kulkarni, BA Mahajan, RS Paranjape: Cytolytic T lymphocytes (CTLs) from HIV-1 subtype C-infected Indian patients recognize CTL epitopes from a conserved immunodominant region of HIV-1 Gag and Nef. *J Infect Dis* 192, 749–759 (2005)

54. PJ Goulder, C Brander, K Annamalai, N Mngqundaniso, U Govender, Y Tang, S He, KE Hartman, CA O'Callaghan, GS Ogg, MA Altfeld, ES Rosenberg, H Cao, SA Kalams, M Hammond, M Bunce, SI Pelton, SA Burchett, K McIntosh, HM Coovadia, BD Walker: Differential narrow focusing of immunodominant human immunodeficiency virus gag-specific cytotoxic T-lymphocyte responses in infected African and caucasoid adults and children. *J Virol* 74, 5679–5690 (2000)

55. J Lieberman, JA Fabry, DM Fong, GR Parkerson 3rd: Recognition of a small number of diverse epitopes dominates the cytotoxic T lymphocytes response to HIV

type 1 in an infected individual. *AIDS Res Hum Retroviruses* 13, 383–392 (1997)

56. MM Addo, XG Yu, A Rathod, D Cohen, RL Eldridge, D Strick, MN Johnston, C Corcoran, AG Wurcel, CA Fitzpatrick, ME Feeney, WR Rodriguez, N Basgoz, R Draenert, DR Stone, C Brander, PJR Goulder, ES Rosenberg, M Altfeld, BD Walker: Comprehensive epitope analysis of human immunodeficiency virus type 1 (HIV-1)-specific T-cell responses directed against the entire expressed HIV-1 genome demonstrate broadly directed responses, but no correlation to viral load. *J Virol* 77, 2081–2092 (2003)

57. S Zhao, S Zhai, Y Zhuang, S Wang, D Huang, W Kang, X Li, XG Yu, BD Walker, MA Altfeld, Y Sun: Inter-clade cross-reactivity of HIV-1-specific T cell responses in human immunodeficiency virus type 1 infection in China. *Curr HIV Res* 5, 251–259 (2007)

58. JR Bailey, TM Williams, RF Siliciano, JN Blankson: Maintenance of viral suppression in HIV-1- infected HLA-B*57+ elite suppressors despite CTL escape mutations. *J Exp Med* 203, 1357–1369 (2006)

59. JR Bailey, K O'Connell, HC Yang Y Han, J Xu, B Jilek, TM Williams, SC Ray, RF Siliciano, JN Blankson: Transmission of human immunodeficiency virus type 1 from a patient who developed AIDS to an elite suppressor. *J Virol* 82, 7395–7410 (2008)

60. JM Claverie, P Kourilsky, P Langlade-Demoyen, A Chalufour-Prochnicka, G Dadaglio, F Tekaia, F Plata, K Bougueleret: T-immunogenic peptides are constituted of rare sequence patterns. use in the identification of t epitopes in the human immunodeficiency virus gag protein. *Eur J Immunol* 18, 1547–1553 (1988)

61. AZ Maksyutov, AG Bachinskii, SI Bazhan: Searching for local similarities between HIV-1 and human proteins. application to vaccines. *Mol Biol* (Mosk) 36, 346–358 (2002)

62. AS De Groot, DS Rivera, JA McMurry, S Buus, W Martin: Identification of immunogenic HLA-B7 "Achilles' heel" epitopes within highly conserved regions of HIV. *Vaccine* 26, 3059–3071 (2008)

63. MJ Geels, SA Dubey, KAnderson, E Baan, M Bakker, G Pollakis, WA Paxton, JW Shiver, J Goudsmit: Broad cross-clade T-cell responses to Gag in individuals infected with human immunodeficiency virus type 1 non-B clades (A to G): Importance of HLA anchor residue conservation. *J Virol* 79, 11247–11258 (2005)

64. M Altfeld, TM Allen, XG Yu, MN Johnston, D Agrawal, BT Korber, DC Montefiori, DH O'Connor, BT Davis, P K Lee, EL Maier, JHarlow, PJR Goulder, C Brander, ES Rosenberg, BD Walker: HIV-1 superinfection despite broad CD8+ T-cell responses containing replication of the primary virus. *Nature* 420, 434–439 (2002)

65. CC Wilson, MJ Newman, BD Livingston, S MaWhinney, JE Forster, J Scott, RT Schooley, CA Benson: Clinical phase 1 testing of the safety and immunogenicity of an epitope-based DNA vaccine in human immunodeficiency virus type 1-infected subjects receiving highly active antiretroviral therapy. *Clin Vaccine Immunol* 15, 986–994 (2008)

66. SG Fonseca, A Coutinho-Silva, LAM Fonseca, AC Segurado, SL Moraes, H Rodrigues, J Hammer, EG Kallás, J Sidney, A Sette, J Kalil, E Cunha-Neto: Identification of novel consensus CD4 T-cell epitopes from clade B HIV-1 whole genome that are frequently recognized by HIV-1 infected patients. *AIDS* 20, 2263–2273 (2006)

67. FA Castelli, D Houitte, G Munier, N Szely, A Lecoq, JP Briand, S Muller, B Maillere: Immunoprevalence of the CD4+ T-cell response to HIV Tat and Vpr proteins is provided by clustered and disperse epitopes, respectively. *Eur J Immunol* 38, 2821–2831 (2008)

68. DM Noonan, A Gringeri, R Meazza, O Rosso, S Mazza, M Muca-Perja, H Le Buanec, RS Accolla, A Albini, S Ferrini: Identification of immunodominant epitopes in inactivated Tat-vaccinated healthy and HIV-1-infected volunteers. *J Acquir Immune Defic Syndr* 33, 47-55 (2003)

69. V Ovod, A Lagerstedt, A Ranki, FO Gombert, R Spohn, M Tahtinen, G Jung, KJ Krohn: Immunological variation and immunohistochemical localization of HIV-1 nef demonstrated with monoclonal antibodies. *AIDS* 6, 25–34 (1992)

70. IMM Schellens, C Kesmir, F Miedema, D van Baarle, JA M. Borghans: An unanticipated lack of consensus cytotoxic T lymphocyte epitopes in HIV-1 databases: The contribution of prediction programs. *AIDS* 22, 33–37 (2008)

71. A Ranki, M Nyberg, V Ovod, M Haltia, I Elovaara, R Raininko, H Haapasalo, K Krohn: Abundant expression of HIV nef and rev proteins in brain astrocytes in vivo is associated with dementia. *AIDS* 9, 1001–1008 (1995)

72. GJ Gorse, LR Baden, M Wecker, MJ Newman, G Ferrari, KJ Weinhold, BD Livingston, TL Villafana, H Li, E Noonan, ND Russell, HIV Vaccine Trials Network: Safety and immunogenicity of cytotoxic T-lymphocyte poly-epitope, DNA plasmid (EP HIV-1090) vaccine in healthy, human immunodeficiency virus type 1 (HIV-1)-uninfected adults. *Vaccine* 26, 215–223 (2008)

73. C Guillon, K Stankovic, Y Ataman-Önal, F Biron, B Verrier: Evidence for CTL-mediated selection of Tat and Rev mutants after the onset of the asymptomatic period during HIV type 1 infection. *AIDS Res Hum Retroviruses* 22, 1283– 1292 (2006)

74. MM Addo, XG Yu, ES Rosenberg, BD Walker, M Altfeld: Cytotoxic T-lymphocyte (CTL) responses

directed against regulatory and accessory proteins in HIV-1 infection. *DNA Cell Biol* 21, 671–678 (2002)

75. S Corbet, HV Nielsen, L Vinner, S Lauemoller, D Therrien, S Tang, G Kronborg, L Mathiesen, P Chaplin, S Brunak, S Buus, A Fomsgaard: Optimization and immune recognition of multiple novel conserved HLA-A2, human immunodeficiency virus type 1-specific CTL epitopes. *J Gen Virol* 84, 2409–2421 (2003)

76. M Thorn, S Tang, D Therrien, H Kløverpris, L Vinner, G Kronborg, J Gerstoft, S Corbet, A Fomsgaard: Sequence conservation of subdominant HLA-A2-binding CTL epitopes in HIV-1 clinical isolates and CD8+ T-lymphocyte cross-recognition may explain the immune reaction in infected individuals. *APMIS* 115, 757–768 (2007)

77. A Fomsgaard, L Vinner, D Therrien, LB Jørgensen, C Nielsen, L Mathiesen, C Pedersen, S Corbet: Full-length characterization of A1/D intersubtype recombinant genomesfrom a therapy-induced HIV type 1 controller during acute infection and his noncontrolling partner. *AIDS Res Hum Retroviruses* 24, 463–472 (2008)

78. RP Johnson, SA Hammond, A Trocha, RF Siliciano, BD Walker: Epitope specificity of mhc restricted cytotoxic t lymphocytes induced by candidate HIV-1 vaccine. *AIDS Res Hum Retroviruses* 10, S73–75 (1994)

79. G Dadaglio, A Leroux, P Langlade-Demoyen, EM Bahraoui, F Traincard, R Fisher, F Plata: Epitope recognition of conserved HIV envelope sequences by human cytotoxic T lymphocytes. *J Immunol* 147, 2302–2309 (1991)

80. ATL de Queiroz, LA Santos, DR Moreau, T de Oliveira, DI Watkins, B Galvão-Castro, LCJ Alcantara: Identification and characterization of previously described epitopes in HIV-1 subtypes B, C, F and BF in Brazil. *Braz J Infect Dis* 11, 27–30 (2007)

81. A Llano, N Frahm, C Brander, 2009. How to optimally define optimal cytotoxic T lymphocyte epitopes in HIV infection? In: HIV Molecular Immunology. (B Korber, C Brander, BF Haynes, R Koup, JP Moore, BD Walker, DI. Watkins, eds), Los Alamos National Laboratory, Theoretical Biology and Biophysics, Los Alamos, New Mexico, p. 3 (2009)

82. Z Moukrim, A Achour: Cytotoxic T lymphocytes specific for the synthetic VEINCTR peptide, a sequence found within the Fas molecule and env gp120 in the blood of HIV-1 seropositive individuals. *Cell Mol Biol* (Noisy-le-grand) 41, 439-44 (1995)

83. KV Sitz, S Ratto-Kim, AS Hodgkins, ML Robb, DL Birx: Proliferative responses to human immunodeficiency virus type 1 (HIV-1) gp120 peptides in HIV-1-infected individuals immunized with HIV-1 rgp120 or rgp160 compared with nonimmunized and uninfected controls. *J Infect Dis* 179, 817–824 (1999)

84. AM Geretti, CA Van Baalen, JC Borleffs, CA Van Els, AD Osterhaus: Kinetics and specificities of the T helper-cell response to gp120 in the asymptomatic stage of HIV-1 infection. *Scand J Immunol* 39, 355–362 (1994)

85. P Shankar, JA Fabry, DM Fong, J Lieberman: Three regions of HIV-1 gp160 contain clusters of immunodominant ctl epitopes. *Immunol Lett* 52, 23–30 (1996)

86. D Mirano-Bascos, M Tary-Lehmann, SJ Landry: Antigen structure influences helper T-cell epitope dominance in the human immune response to HIV envelope glycoprotein gp120. *Eur J Immunol* 38, 1231–1237 (2008)

87. AS De Groot, EA Bishop, B Khan, M Lally, L Marcon, J Franco, KH Mayer, CCJ Carpenter, W Martin: Engineering immunogenic consensus T helper epitopes for a cross-clade HIV vaccine. *Methods* 34, 476–487 (2004)

88. RD Schrier, JW Gnann, R Landes, C Lockshin, D Richman, A McCutchan, C Kennedy, MBA Oldstone, JA Nelson: T-cell recognition of HIV synthetic peptides in a natural infection. *J Immunol* 142, 1166–1176 (1989)

89. PN Nehete, SJ Schapiro, PC Johnson, KK Murthy, WC Satterfield, KJ Sastry: A synthetic peptide from the first conserved region in the envelope protein gp160 is a strong T-cell epitope in HIV-infected chimpanzees and humans. *Viral Immunol* 11, 147–158 (1998)

90. H Horton, C Havenar-Daughton, D Lee, E Moore, J Cao, J McNevin, T Andrus, H Zhu, A Rubin, T Zhu, C Celum, MJ McElrath: Induction of human immunodeficiency virus type 1 (HIV-1)-specific T-cell responses in HIV vaccine trial participants who subsequently acquire HIV-1 infection. *J Virol* 80, 9779–9788 (2006)

91. J Lieberman, JA Fabry, MC Kuo, P Earl, B Moss, PR Skolnik: Cytotoxic T lymphocytes from HIV-1 seropositive individuals recognize immunodominant epitopes in gp160 and reverse transcriptase. *J Immunol* 148, 2738–2747 (1992)

92. J Lieberman, JA Fabry, P Shankar, L Beckett, PR Skolnik: Ex vivo expansion of HIV type 1- specific cytolyticT cells from HIV type 1-seropositive subjects. *AIDS ResHum Retroviruses* 11, 257–271 (1995)

93. K Smits, V Iannucci, V Stove, P Van Hauwe, E Naessens, PJ Meuwissen, KK Ariën, M Bentahir, J Plum, B Verhasselt: Rho GTPase Cdc42 is essential

for human T-cell development. *Haematologica* 95, 367-375 (2010)

94. T Copetti, C Bertoli, E Dalla, F Demarchi, C Schneider: p65/RelA modulates BECN1 transcription and autophagy. *Mol Cell Biol* 29, 2594-2608 (2009)

95. P Dai, SY Jeong, Y Yu, T Leng, W Wu, Xie L, X Chen: Modulation of TLR signaling by multiple MyD88-interacting partners including leucine-rich repeat Fli-I-interacting proteins. *J Immunol* 182, 3450-3460 (2009)

96. FS Rosen, IUIS Scientific Committee: Primary immunodeficiency diseases report of an IUIS Scientific Committee. *Clin Exp Immunol* 118, S1–S28 (1999)

97. M De Hert, M Wampers, D Van Eyck, J Peuskens, T Franic, D Vidovic, K Van Herck, P Van Damme: Prevalence of HIV and hepatitis C infection among patients with schizophrenia. *Schizophr Res* 108, 307-308 (2009)

98. F Castets, M Bartoli, JV Barnier, G Baillat, P Salin, A Moqrich, JP Bourgeois, F Denizot, G Rougon, G Calothy, A Monneron: A novel calmodulin-binding protein, belonging to the WD-repeat family, is localized in dendrites of a subset of CNS neurons. *J Cell Biol* 134, 1051–1062 (1996)

99. D Martins-de-Souza, WF Gattaz, A Schmitt, C Rewerts, G Maccarrone, E Dias-Neto, CW Turck: Prefrontal cortex shotgun proteome analysis reveals altered calcium homeostasis and immune system imbalance in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 259, 151-163 (2009)

100. Q Lu, DC Pallas, HK Surks, WE Baur, ME Mendelsohn, RH Karas: Striatin assembles a membrane signaling complex necessary for rapid, nongenomic activation of endothelial NO synthase by estrogen receptor alpha. *Proc Natl Acad Sci USA* 101, 17126-17131 (2004)

101. EC Seaberg, L Benning, AR Sharrett, JM Lazar, HN Hodis, WJ Mack, MJ Siedner, JP Phair, LA Kingsley, RC Kaplan: Association between human immunodeficiency virus infection and stiffness of the common carotid artery. *Stroke* 41, 2163-2170 (2010)

102. KK Singh, X Ge, Y Mao, L Drane, K Meletis, BA Samuels, LH Tsai: Dixdc1 is a critical regulator of DISC1 and embryonic cortical development. *Neuron* 67, 33-48 (2010)

103. X Ding, Y Jin, Y Wu, Y Wu, H Wu, L Xiong, X Song, S Liu, W Fan, M Fan: Localization and cellular distribution of CPNE5 in embryonic mouse brain. *Brain Res* 1224, 20-28 (2008)

104. N Baillieu, J Potterton: The extent of delay of language, motor, and cognitive development in HIV-positive infants. *J Neurol Phys Ther* 32, 118-121 (2008)

105. S Sánchez-Ramón, C Cantó-Nogués, A Muñoz-Fernández: Reconstructing the course of HIV-1-associated progressive encephalopathy in children. *Med Sci Monit* 8, RA249-252 (2002)

106. J Majercak, WJ Ray, A Espeseth, A Simon, XP Shi, C Wolffe, K Getty, S Marine, E Stec, M Ferrer, B Strulovici, S Bartz, A Gates, M Xu, Q Huang, L Ma, P Shughrue, J Burchard, D Colussi, B Pietrak, J Kahana, D Beher, T Rosahl, M Shearman, D Hazuda, AB Sachs, KS Koblan, GR Seabrook, DJ Stone: LRRTM3 promotes processing of amyloid-precursor protein by BACE1 and is a positional candidate gene for late-onset Alzheimer's disease. *Proc Natl Acad Sci USA* 103, 17967-17972 (2006)

107. M Gisslén, J Krut, U Andreasson, K Blennow, P Cinque, BJ Brew, S Spudich, L Hagberg, L Rosengren, RW Price, H Zetterberg: Amyloid and tau cerebrospinal fluid biomarkers in HIV infection. *BMC Neurol* 9, 63 (2009)

108. M Pantelidou, SE Zographos, CW Lederer, T Kyriakides, MW Pfaffl, N Santama: Differential expression of molecular motors in the motor cortex of sporadic ALS. *Neurobiol Dis* 26, 577-589 (2007)

109. YJ Kim, Y Fan, P Laurie, JM Kim, J Ravits: No evidence of HIV pol gene in spinal cord tissues in sporadic ALS by real-time RT-PCR. *Amyotroph Lateral Scler* 11, 91-96 (2010)

110. AL McCormick, RH Jr Brown, ME Cudkowicz, A Al-Chalabi, JA Garson: Quantification of reverse transcriptase in ALS and elimination of a novel retroviral candidate. *Neurology* 70, 278-283 (2008)

111. DJ MacGowan, SN Scelsa, TE Imperato, KN Liu, P Baron, B Polsky: A controlled study of reverse transcriptase in serum and CSF of HIV-negative patients with ALS. *Neurology* 68, 1944-1946 (2007)

112. C Zona, M Pieri, I Carunchio: Voltage-dependent sodium channels in spinal cord motor neurons display rapid recovery from fast inactivation in a mouse model of amyotrophic lateral sclerosis. *J Neurophysiol* 96, 3314-3322 (2006)

113. S Hadano, CK Hand, H Osuga, Y Yanagisawa, A Otomo, RS Devon, N Miyamoto, J Showguchi-Miyata, Y Okada, R Singaraja, DA Figlewicz, T Kwiatkowski, BA Hosler, T Sagie, J Skaug, J Nasir, RH Brown Jr, SW Scherer, GA Rouleau, MR Hayden, JE Ikeda: A gene encoding a putative GTPase regulator is mutated in familial amyotrophic lateral sclerosis 2. *Nat Genet* 29, 166–173 (2001)

114. LQ Le, LF Parada: Tumor microenvironment and neurofibromatosis type I: connecting the GAPs. *Oncogene* 26, 4609-4616 (2007)

115. MV Johnston, A Ishida, WN Ishida, HB Matsushita,

A Nishimura, M Tsuji: Plasticity and injury in the developing brain. *Brain Dev* 31, 1-10 (2009)

116. R Shirakawa, S Fukai, M Kawato, T Higashi, H Kondo, T Ikeda, E Nakayama, K Okawa, O Nureki, T Kimura, T Kita, H Horiuchi: Tuberous sclerosis tumor suppressor complex-like complexes act as GTPase-activating proteins for Ral GTPases. *J Biol Chem* 284, 21580–21588 (2009)

117. JM Tee, MP Peppelenbosch: Anchoring skeletal muscle development and disease: the role of ankyrin repeat domain containing proteins in muscle physiology. *Crit Rev Biochem Mol Biol* 45, 318-330 (2010)

118. P Chariot, R Gherardi: Myopathy and HIV infection. *Curr Opin Rheumatol* 7, 497-502 (1995)

119. Y Huang, SH Laval, A van Remoortere, J Baudier, C Benaud, LV Anderson, V Straub, A Deelder, RR Frants, JT den Dunnen, K Bushby, SM van der Maarel: AHNAK, a novel component of the dysferlin protein complex, redistributes to the cytoplasm with dysferlin during skeletal muscle regeneration. *FASEB J* 21, 732-742 (2007)

120. C Abramovich, EA Chavez, PM Lansdorp, RK Humphries: Functional characterization of multiple domains involved in the subcellular localization of the hematopoietic Pbx interacting protein (HPIP). *Oncogene* 21, 6766-6771 (2002)

121. EM Gaughan, BJ Dezube, M Bower, DM Aboulafia, G Bohac, TP Cooley, L Pantanowitz: HIV-associated bladder cancer: a case series evaluating difficulties in diagnosis and management. *BMC Urol* 9, 10 (2009)

122. B Chatton, Bocco JL, Gaire M, Hauss C, Reimund B, Goetz J, Kedinger C: Transcriptional activation by the adenovirus larger E1a product is mediated by members of the cellular transcription factor ATF family which can directly associate with E1a. *Mol Cell Biol* 13, 561-570 (1993)

123. T Maekawa, S Kim, D Nakai, C Makino, T Takagi, H Ogura, K Yamada, B Chatton, S Ishii: Social isolation stress induces ATF-7 phosphorylation and impairs silencing of the 5-HT 5B receptor gene. *EMBO J* 29, 196-208 (2010)

124. M Santos, S Ruiz, MF Lara, C Segrelles, M Moral, AB Martínez-Cruz, C Ballestín, C Lorz, R García-Escudero, JM Paramio: Susceptibility of pRb-deficient epidermis to chemical skin carcinogenesis is dependent on the p107 allele dosage. *Mol Carcinog* 47, 815-821 (2008)

125. DL Burkhart, SE Wirt, AF Zmoos, MS Kareta, J Sage: Tandem E2F binding sites in the promoter of the p107 cell cycle regulator control p107 expression and its cellular functions. *PLoS Genet* 6, e1001003 (2010)

126. KJ Smith, HG Skelton: Peroxisomal proliferator-activated ligand therapy for HIV lipodystrophy. *Clin Exp Dermatol* 26, 155-161 (2001)

127. RO Scott, WR Thelin, SL Milgram: A novel PDZ protein regulates the activity of guanylyl cyclase C, the heat-stable enterotoxin receptor. *J Biol Chem* 277, 22934-22941 (2002)

128. ER Fernandes, C Pagliari, FF Tuon, HF de Andrade Jr, M Averbach, MI Duarte: Chronic colitis associated with HIV infection can be related to intraepithelial infiltration of the colon by CD8+ T lymphocytes. *Int J STD AIDS* 19, 524-528 (2008)

129. A Schmidt, SJ Rutledge, N Endo, EE Opas, H Tanaka, G Wesolowski, CT Leu, Z Huang, C Ramachandaran, SB Rodan, GA Rodan: Protein-tyrosine phosphatase activity regulates osteoclast formation and function: inhibition by alendronate. *Proc Natl Acad Sci USA* 93, 3068-3073 (1996)

130. A Bonjoch, M Figueras, C Estany, N Perez-Alvarez, J Rosales, L Del Rio, S di Gregorio, J Puig, G Gómez, B Clotet, E Negredo; the Osteoporosis Study Group: High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study. *AIDS* 24, 2827-2833 (2010)

131. S Arora, M Agrawal, L Sun, F Duffoo, M Zaidi, J Iqbal: HIV and bone loss. *Curr Osteoporos Rep* 8, 219-226 (2010)

132. P Ellies, G Renard, S Valleix, PY Boelle, P Dighiero: Clinical outcome of eight BIGH3-linked corneal dystrophies. *Ophthalmology* 109, 793-797 (2002)

133. S Gharai, P Venkatesh, R Tandon, S Garg: Peripheral ulcerative keratitis and central retinal vein occlusion as the initial manifestation of HIV infection. *Ocul Immunol Inflamm* 15, 407-409 (2007)

134. JE Thorne, KH Shah, DM Brown, GN Holland, DA Jabs: Posterior intracorneal opacities in patients with HIV infection. *Ocul Immunol Inflamm* 13, 25-31 (2005)

135. NR Acharya, ET Cunningham Jr: Corneal, anterior segment, and adnexal manifestations of human immunodeficiency virus. *Int Ophthalmol Clin* 38, 161-177 (1998)

136. MM Estrella, DM Fine: Screening for chronic kidney disease in HIV-infected patients. *Adv Chronic Kidney Dis* 17, 26-35 (2010)

137. AK Singh, H Amlal, PJ Haas, U Dringenberg, S Fussell, SL Barone, R Engelhardt, J Zuo, U Seidler, M Soleimani: Fructose-induced hypertension: essential role of chloride and fructose absorbing transporters PAT1 and Glut5. *Kidney Int* 74, 438-447 (2008)

138. LA Szczech: Hypertension and medication-related renal dysfunction in the HIV-infected patient. *Semin Nephrol* 21, 386-393 (2001)

139. HM Crane, C Grunfeld, RD Harrington, MM Kitahata: Lipoatrophy and lipohypertrophy are independently associated with hypertension. *HIV Med* 10, 496-503 (2009)

140. G Schillaci, GV De Socio, G Pucci, MR Mannarino, J Helou, M Pirro, E Mannarino: Aortic stiffness in untreated adult patients with human immunodeficiency virus infection. *Hypertension* 52, 308-313 (2008)

141. G Barbaro: Vascular injury, hypertension and coronary artery disease in human immunodeficiency virus infection. *Clin Ter* 159, 51-55 (2008)

142. AC May: Percent sequence identity; the need to be explicit. *Structure* 12, 737-738 (2004)

143. D Kanduc: Immunogenicity in peptide-immunotherapy: from self/nonself to similar/dissimilar sequences. *Adv Exp Med Biol* 640, 198-207 (2008)

144. K Landsteiner, J van der Scheer: On the serological specificity of peptides. III. *J Exp Med* 69, 705-719 (1939)

145. MJ Reddehase, JB Rothbard, UH Koszinowski: A pentapeptide as minimal antigenic determinant for MHC class I-restricted T lymphocytes. *Nature* 337, 651-653 (1989)

146. T Yamamura, JT Konola, H Wekerle, MB Lees: Monoclonal antibodies against myelin proteolipid protein: identification and characterization of two major determinants. *J Neurochem* 57, 1671-1680 (1991)

147. CW Stephen, DP Lane: Mutant conformation of p53. Precise epitope mapping using a filamentous phage epitope library. *J Mol Biol* 225, 577-583 (1992)

148. U Fiebig, M Schmolke, M Eschricht, R Kurth, J Denner: Mode of interaction between the HIV-1-neutralizing monoclonal antibody 2F5 and its epitope. *AIDS* 23, 887-895 (2009)

149. R Tiwari, J Geliebter, A Lucchese, A Mittelman, D Kanduc: Computational peptide dissection of Melan-a/MART-1 oncoprotein antigenicity. *Peptides* 25, 1865-1871 (2004)

150. A Stufano, D Kanduc: Proteome-based epitopic peptide scanning along PSA. *Exp Mol Pathol* 86, 36-40 (2009)

151. G Lucchese, A Stufano, D Kanduc: Proposing low-similarity peptide vaccines against Mycobacterium tuberculosis. *J Biomed Biotechnol* 832341 (2010)

152. D Kanduc: Protein information content resides in rare peptide segments. *Peptides* 31, 983-988 (2010)

153. G Lucchese, A Stufano, B Trost, A Kusalik, D Kanduc: Peptidology: short amino acid modules in cell biology and immunology. *Amino Acids* 33, 703-707(2007)

154. C Martínez-A, MA Marcos, A de la Hera, C Marquez, JM Alonso, ML Toribio, A Coutinho: Immunological consequences of HIV infection: advantage of being low responder casts doubts on vaccine development. *Lancet* 331, 454-457 (1988)

155. AE Sousa, J Carneiro, M Meier-Schellersheim, Z Grossman, RM Victorino: CD4 T cell depletion is linked directly to immune activation in the pathogenesis of HIV-1 and HIV-2 but only indirectly to the viral load. *J Immunol* 169, 3400-3406 (2002)

156. G Zandman-Goddard, Y Shoenfeld: HIV and autoimmunity. *Autoimmun Rev* 1, 329-337 (2002)

157. G Lucchese, A Stufano, D Kanduc: Proteome-guided search for influenza A B-cell epitopes. *FEMS Immunol Med Microbiol* 57, 88-92 (2009)

158. D Kanduc, L Tessitore, G Lucchese, A Kusalik, E Farber, FM Marincola: Sequence uniqueness and sequence variability as modulating factors of human anti-HCV humoral immune response. *Cancer Immunol Immunother* 57, 1215-1223 (2008)

159. B Trost, A Kusalik, G Lucchese, D Kanduc: Bacterial peptides are intensively present throughout the human proteome. *Self/Nonself* 1(1), 71–74 (2010)

160. B Trost, G Lucchese, A Stufano, M Bickis, A Kusalik, D Kanduc: No human protein is exempt from bacterial motifs. Not even one. *Self/Nonself* 1(4), 1-7 (2010)

161. D Kanduc: The self-nonself issue: a confrontation between proteomes. *Self/Nonself* 1(3), 255–258 (2010)

162. D Kanduc: Describing the hexapeptide identity platform between the influenza A H5N1 and Homo sapiens proteomes. *Biologics* 4, 245-261 (2010)

163. MB Oldstone: How viruses escape from cytotoxic T lymphocytes: molecular parameters and players. *Virology* 234, 179-185 (1997)

164. R Kiessling, G Pawelec, RM Welsh, JD Barry, S Ferrone: Have tumor cells learnt from microorganisms how to fool the immune system? Escape from immune surveillance of tumors and microorganisms: emerging mechanisms and shared strategies. *Mol Med Today* 6, 344-346 (2000)

165. W Kamp, MB Berk, CJ Visser, HS Nottet: Mechanisms of HIV-1 to escape from the host immune surveillance. *Eur J Clin Invest* 30, 740-746 (2000)

166. RL Coffman, A Sher, RA Seder: Vaccine adjuvants: putting innate immunity to work. *Immunity* 33, 492-503 2010

167. WS Pray: Nonprescription product therapeutics Lippincott Williams Wilkins, Philadelphia, Chapter 12, Hemorrhoids, 191-202 (2006)

168. T Yokochi, M Fukada, M Kawai, YH Zhang, GZ Jiang, K Takahashi: Novel adjuvant action of lipopolysaccharides that possess mannose homopolysaccharides as O-specific polysaccharides on immune responses to nonimmunogenic autoantigens in mice. *Infect Immun* 60, 4953-4956 (1992)

169. A Blanchard, L Montagnier, ML Gougeon: Influence of microbial infections on the progression of HIV disease. *Trends Microbiol* 5, 326-331 (1997)

170. O Equils, E Faure, L Thomas, Y Bulut, S Trushin, M Arditi: Bacterial lipopolysaccharide activates HIV long terminal repeat through Toll-like receptor 4. *J Immunol* 166, 2342-2347 (2001)

171. AA Chaves, RS Baliga, MJ Mihm, BL Schanbacher, A Basuray, C Liu, AC Cook, LW Ayers, JA Bauer: Bacterial lipopolysaccharide enhances cardiac dysfunction but not retroviral replication in murine AIDS: roles of macrophage infiltration and toll-like receptor 4 expression. *Am J Pathol* 168, 727-735 (2006)

172. K Goodkin, FL Wilkie, M Concha, CH Hinkin, S Symes, TT Baldewicz, D Asthana, RK Fujimura, D Lee, MH van Zuilen, I Khamis, P Shapshak, C Eisdorfer: Aging and neuro-AIDS conditions and the changing spectrum of HIV-1-associated morbidity and mortality. *J Clin Epidemiol* 54, S35-S43 (2001)

173. D Chattopadhya, UK Baveja, M Bose, A Kumar: Disease progression markers during asymptomatic phase of HIV-1 infected children with unimpaired CD4+ cell values: evaluation of repeat CD4+ cell evaluation vs. other immunological parameters. *J Trop Pediatr* 48, 340-347 (2002)

174. M Dean, M Carrington, C Winkler, GA Huttley, MW Smith, R Allikmets, JJ Goedert, SP Buchbinder, E Vittinghoff, E Gomperts, S Donfield, D Vlahov, R Kaslow, A Saah, C Rinaldo, R Detels, SJ O'Brien: Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study: Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. *Science* 273, 1856-1862 (1996)

175. M Moriuchi, H Moriuchi, W Turner, AS Fauci: Exposure to bacterial products renders macrophages highly susceptible to T-tropic HIV-1. *J Clin Invest* 102, 1540-1550 (1998)

176. D Goletti, D Weissman, RW Jackson, NM Graham, D Vlahov, RS Klein, Munsiff SS, Ortona L, Cauda R, AS Fauci: Effect of Mycobacterium tuberculosis on HIV replication: role of immune activation. *J Immunol* 157, 1271-1278 (1996)

177. D Kanduc: "Self-nonself" peptides in the design of vaccines. *Curr Pharm Des* 15, 3283-9 (2009)

178. D Kanduc: Epitopic peptides with low similarity to the host proteome: towards biological therapies without side effects. *Expert Opin Biol Ther* 9, 45-53 (2009)

179. D Kanduc, R Serpico, A Lucchese, Y Shoenfeld: Correlating low-similarity peptide sequences and HIV B-cell epitopes. *Autoimmun Rev* 7, 291-296 (2008)

180. A Lucchese, R Serpico, V Crincoli, Y Shoenfeld, D Kanduc: Sequence uniqueness as a molecular signature of HIV-1-derived B-cell epitopes. *Int J Immunopathol Pharmacol* 22, 639-646 (2009)

Key Words: HIV-1 proteome, human proteome, HIV-vs-human crossreactome, HIV-derived epitopes, HIV escape from immune surveillance, adjuvant-induced immune activation, crossreactivity-induced AIDS

Send correspondence to: Darja Kanduc, Dept. of Biochemestry & Molecular Biology, University of Bari, Bari, Italy. Tel: 390805443321 Fax: 390805443317, E-mail: d.kanduc@biologia.uniba.it

http://www.bioscience.org/current/volE3.htm