Extensive Viral mimicry of human proteins in AIDS, multiple sclerosis and other autoimmune disorders, late-onset and familial Alzheimer’s disease and other genetic diseases

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Abstract

Peptide stretches within HIV-1 proteins display a striking homology to over 50 important components of the human immune and pathogen defence network. These include HLA-antigens, T-cell, Fc and cytokine receptors, CD molecules, lymphocyte antigens, proteins involved in B-Cell, T-cell, dendritic and natural killer cell, macrophage, mast cell and microglial function, lysosomal proteins, haematopoietic control, and also pathogen recognition pathways. The homologous peptides are in most cases highly immunogenic (B-cell epitope prediction), suggesting that antibodies to HIV-1 proteins could mount an autoimmune attack against multiple components of the immune system itself. HIV-1 proteins are also homologous to autoantigens in Alzheimer’s disease, chronic obstructive pulmonary disorder, multiple sclerosis, Myasthenia Gravis, Pemphigus Vulgaris, Sjogrens syndrome and systemic Lupus Erythmatosus, all of which have been associated with HIV-1 infection. This mimicry suggests that HIV-1/AIDS has a major autoimmune component and that HIV-1 antibodies could selectively target the immune system and autoantigens in other autoimmune disorders. This could radically change our conception of how HIV-1 acts, and perhaps lead to novel therapeutic strategies, which, counter intuitively might even involve the use of immunosuppressants in the early stages of the disease. Autoantigens from the human autoimmune diseases mentioned above also align with peptides from other viruses implicated as risk factors in each disease. Mutant peptides from Huntington’s disease and other polyglutamine disorders, and from cystic fibrosis also align with common viruses. The London APP717 V→I mutant in Familial Alzheimer’s disease converts the surrounding peptide to matches with Rhinoviruses causing the common cold and to the Norovirus responsible for vomiting sickness. Viral mimicry related autoimmunity may thus play a role in many autoimmune and even human genetic disorders. It is possible that this is a near universal phenomenon, reflecting the idea that viruses are responsible for the origin of higher forms of life, leaving behind a deadly legacy of viral-derived human proteins with homology to antigenic proteins in the current virome that may be responsible for most of our ills.

Introduction

The Human Immunodeficiency virus causes acquired immune deficiency syndrome (AIDS) by decreasing the capacity of the immune system to deal with opportunistic pathogens. The virus infects and kills CD4+ T-Lymphocytes which play an important role in regulation of immune defence and also targets B[cells,
natural killer cells, macrophages and microglia. It has already been noted that the HIV-1 envelope protein is homologous to several components of the immune system including HLA antigens, T cell receptors, Fas and immunoglobulins G and A, and also that autoimmune disorders are common in HIV-infected patients (Sjogrens syndrome, rheumatic disease and lupus, for example. HIV-1 has also been associated with myaesthenia gravis, multiple sclerosis and pemphigus, and can worsen symptoms in chronic obstructive pulmonary disease. HIV-1 infection can also cause dementia with Alzheimer’s disease-like pathology. These associations may be related to immune deficiency but could also reflect viral/antigen mimicry in these autoimmune disorders. Homology searches showed that all the autoantigens in these autoimmune diseases are homologous to short peptide stretches of diverse HIV-1 proteins, and that all HIV-1 proteins display this type of homology with important elements of the human immune and pathogen defence networks, suggesting that HIV-1 itself has an autoimmune component where antibodies to HIV-1 proteins may target crucial molecules within the immune system. This type of mimicry between viral and human proteins is observed for large number of other viruses, in most cases matching their reported implication in the relevant disease. It is common in many autoimmune disorders, and even in human genetic disorders where the mutant protein modifies the spectrum of viral matches to very common pathogens.

Methods

Homology searches, of HIV-1 proteins against human proteins and of human autoantigens against HIV-1 proteins were undertaken at the Uniprot BLAST server, using parameters designed to detect short consecutive peptide matches rather than overall homology. B-Cell epitopes were identified using the BepiPred server, which predicts the B-cell antigenicity of peptide sequences. Parameters were set to default (epitope predicted above an index of 0.35). Further homology searches were undertaken against all viral proteins in relation to autoantigens in autoimmune disorders and to mutant proteins in Alzheimer’s disease, Huntington’s disease and other polyglutamine disorders and in cystic fibrosis.

Results

The homology search results for each HIV-1 protein are shown in Tables 1 to 10 and summarised in Fig 1. It should be noted that all homologues (consecutive pentapeptides or more, or greater than 85% similarity) are recorded in these tables and that homology (for known proteins) is restricted to the classes shown in the tables and Fig 1. Homology of autoantigens with HIV-1 proteins from various autoimmune diseases is shown in Table 11 and Fig 1.

As can clearly be seen from the data in the various tables and from Fig 1, HIV-1 proteins are homologous to human proteins from every compartment of the immune system, including HLA-antigens, B- and T-cells, natural killer and dendritic cells, as well as macrophages, microglia and mast cells, and lysosomes which destroy foreign antigens and pathogens. A number of HIV-1 proteins are also homologous with proteins involved in haematopoiesis, which generates both red and white blood cells. Others are homologous to pathogen and pattern recognition pathways as well as to those implicated in responses to DNA damage, oxidative stress and to single stranded...
RNA/DNA (i.e. viral) binding. Homology to a thyroid hormone transporter was also observed. Thyroid hormones play an important role in preventing the decline in T- and B-cell efficiency in ageing.\textsuperscript{15,30}

Autoantigens from all the autoimmune disorders tested, Alzheimer’s disease, chronic obstructive pulmonary disorder, multiple sclerosis, Myasthenia Gravis, Pemphigus Vulgaris, Sjogrens syndrome and systemic Lupus Erythematosus are homologous to HIV-1 proteins (Table 11) and the homology searches detected two more involved in epidermolysis bullosa acquisita and systemic sclerosis.

The antigenicity of these matching peptides, as indexed by the B-Cell Epitope prediction index\textsuperscript{64} is shown in Figs 2 and 3. Most are above the cut-off level of 0.35 set as default by the BepiPred server, suggesting that cross-reactivity between human and viral homologues is likely.

Other viral infections have been implicated in a number of autoimmune disorders. The autoantigens in these disorders align with the respective viral risk factors (Table 12) and with many others, including phages infecting commensal bacteria, suggesting many potential viral contributors to autoimmune problems in a variety of disorders. The mutant proteins in Huntington’s disease and other polyglutamine repeat disorders as well as in cystic fibrosis also align with common viruses and phages (Table 12). The APP\textsuperscript{717} London mutation in Alzheimer’s disease\textsuperscript{39} is within a peptide liberated by beta- and gamma-secretase cleavage of APP as shown in Fig 4.\textsuperscript{18} The native APP form of this peptide is itself homologous to several viruses and phages, but the mutation converts the peptide to one matching over 30 strains of rhinoviruses that cause the common cold, as well as many strains of the Norovirus that is a frequent cause of vomiting sickness (Table 13).

Glycoprotein B of the Herpes simplex virus (HSV-1), shows homology to beta-amyloid, exactly matching a VGGVV c-terminal sequence\textsuperscript{93} that has been used as an epitope to label beta-amyloid in the Alzheimer’s disease brain.\textsuperscript{102} This pentapeptide, \textit{per se}, forms aggregates characterised by twisted ropes and banded fibrils.\textsuperscript{81} This is a characteristic of both beta-amyloid and of HSV-1 glycoprotein B peptide fragments containing this sequence. The viral glycoprotein B fragments form thioflavine T positive fibrils which accelerate beta-amyloid fibril formation, and are neurotoxic in cell culture.\textsuperscript{22}

Autoantibodies to beta-amyloid are common in the ageing population and in Alzheimer’s disease.\textsuperscript{90,111} As shown in Table 14, 69 viruses and phages contain this consensus VGGVV sequence, suggesting that Alzheimer’s disease may also be related to viral mimicry. HSV-1 and other Herpes viral infections have been implicated as risk factors in Alzheimer’s disease\textsuperscript{52,66} and HIV-1 is frequently associated with dementia with Alzheimer’s-related neuropathology\textsuperscript{32}.

Discussion.

All HIV-1 proteins show a high degree of homology to short peptide stretches of important proteins in most compartments of the immune system a phenomenon that is almost exclusively limited to proteins of the immune network. For the most part, these peptides are predicted to be highly immunogenic, suggesting that HIV-1/AIDS is an autoimmune disorder that targets a large and diverse spectrum of proteins in the immune and pathogen defence network. HIV-1 proteins are also homologous to autoantigens in a variety of autoimmune disorders that have been associated with HIV-1 infection. These homologous human proteins have important roles in almost every aspect of immune function (Fig 1) and autoantibodies to almost any would be
expected to disrupt the immune network. Antibodies to T-cell receptors and HLA-antigens have been reported in AIDS patients, along with many others, and a contribution of molecular mimicry and autoimmunity to AIDS pathogenesis has already been proposed 7,8,75,100,112. This survey shows how extensive this process could be and demonstrates a very selective targeting of the immune network. Certain autoantibodies may be beneficial in AIDS 47 and other disorders, for example beta-amyloid catalytic antibodies in Alzheimer’s disease 90. Certain proteins within this mimicry network are immunosuppressive, for example Sirutin (Table 1), the Fc receptor FCGR2B (Table 3) and the homoeobox protein ALX1 (Table 5) while others stimulate immune cell development or function, for example RET (Table 2) CD226 (Table 6) and Plexin B1 (Table 7). There may be ways of exploiting these differences in the design of potential therapies, for example vaccination to raise beneficial autoantibodies against the immunosuppressant proteins, or anti-antibody antibodies targeting the immunostimulant proteins. While totally counter intuitive, immunosuppressive therapies could also be of benefit in the early stages of infection.

Autoantigens in a variety of autoimmune disorders are homologous to proteins from other viruses that have been implicated as risk factors and to others that have not been suspected. Late-onset Alzheimer’s disease may also be added to the list of autoimmune disorders. Amyloid plaques in the brains of Alzheimer’s disease patients contain a variety of immune-related proteins 28,29,119 and Alzheimer’s disease neurones express the complement membrane attack complex, suggesting that complement related lysis as a response to beta-amyloid antigenicity may be responsible for neuronal death as already suggested 50,76.

Finally, even in human genetic disorders, including Huntington’s disease, and spinocerebellar ataxias or cystic fibrosis, mutant proteins align with common viral proteins. The London mutation in Familial Alzheimer’s disease converts the resultant peptide to one matching proteins from over 30 strains of Rhinovirus that cause the common cold, a potential unexpected cause of familial Alzheimer’s disease. Many of these diseases have symptoms related to the altered function of the mutant protein. Most have a degenerative component that could well be related to autoimmune attack triggered by complementary viral proteins, rather than to the mutant protein itself. Viral mimicry thus appears to be a universal phenomenon, that may be relevant to AIDS, autoimmune disorders, late-onset Alzheimer’s disease and even human genetic disorders.

Phages and viruses are the simplest form of “life”, as defined by the possession of DNA/RNA and a proteinaceous structure, and were long ago proposed as the origin of higher cellular organisms 23,45. While they may well be responsible for our existence, they appear to have left behind a legacy of viral derived human proteins that are homologous to many current viral antigens. There are currently 2463 viral genomes in the NCBI database, likely representing but a small percentage of those existing, and the likelihood of antigenic mimicry must be proportionately extensive. Viral related autoimmunity may thus be relevant to a large number of human ailments, a situation that has therapeutic implications in many diseases of autoimmune, polygenic and genetic origin, where pathogen elimination, vaccination and immunosuppression may be of benefit. Antibody arrays on the same scale as genome-wide association studies may also be envisaged to identify the most common culprits in these disorders.
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Table 1-10: Human proteins aligning with various HIV-1 proteins as indicated in the header of each table. Accession numbers are provided together with the amino acids aligning with the HIV-1 protein. Gaps are represented by – and conserved (similar properties) amino acids by +. The immune-related function for each human protein is also recorded where available. Gene symbols are in brackets after each definition. Proteins in bold show a mean antigenicity index of greater than the default value of 0.35 along their respective peptide matches (e.g. Fig 2).

Table 1: Human proteins aligning with the HIV-1 env protein.

| Human protein | Amino acid match env | Immune related function |
|---------------|----------------------|-------------------------|
| NP_001132986 dachshund homolog 2 isoform b (DACH2) | IQE-Q-QQEK-E-R—LEL | ? |
| EAW91766 Matrilin 2 (MATN2) | EL-K--VQQ---------+DNLLR—Q------KLS | ? |
| NP_114428 protein ITFG3 (Integrin) | ANVSTHI | ? |
| EAW52697 lymphocyte antigen 9, isoform (CD229) | LDITKW | Involved in T-Cell proliferation^{41} |
| NP_733751.2 histone-lysine N-methyltransferase (MLL3) | QQQDNL | Localised to a chromosomal region implicated in leukaemia^{114} |
| EAX09318 collagen, type VI, alpha 2 (COL6A2) | AIQAQQ+ | Autoantigen in epidermolysis bullosa acquisita^{122} |
| NP_066001 hypothetical protein (LOC57710) | QAQQHL | ? |
| BAF95000.1 tight junction protein ZO-1 (TJP1) | AIQ QQ L VW And QI N+ST And TVE NE And +QQQ N L | Binds to AMPA and NMDA glutamate receptors which are expressed in microglia^{66} |
| CAI15167.1 POU class 2 homeobox 1 OCT-1 protein (POU2F1) | SAAG T A AAT +T And AAT LTV And QQ Q NLL Q Q | Represses interferon alpha expression^{77} |
| Accession   | Description                                                                 | Domain | Notes                                                                 |
|------------|------------------------------------------------------------------------------|--------|----------------------------------------------------------------------|
| EAX08243   | zinc finger protein 198 (ZMYM2)                                               | QIANV T | ?                                                                   |
| EAW75084   | cleavage and polyadenylation factor subunit (PCF11).                          | GIVQ QD | ?                                                                   |
| EAW87998   | senataxin (SETX)                                                              | ELMK I+ | ?                                                                   |
| BAC76827   | X-linked PEST-containing transporter (SLC16A2)                               | QEA-QEQQE | Thyroid hormone transporter 117 Thyroxine plays a role in T-cell maintenance in Man and reverses the decline in immune function in ageing mice 15,30 |
| NP_036367  | sterol regulatory element-binding protein cleavage-activating protein (SCAP)  | ISIWD   | ?                                                                   |
| CAM14433.1 | crumbs homolog 2 (Drosophila) (CRB2)                                         | GCRG-PVC| ?                                                                   |
| Q6ZRI0     | Otogelin (OTOG)                                                               | QQLLN L| ?                                                                   |
| BAA86593.1 | KIAA1279 protein                                                              | TLMQN-QL| ?                                                                   |
| AAI57862   | Roundabout protein (ROBO1)                                                    | EAQEQQ | ROBO1 is involved in dendritic cell migration 44                     |
| NP_036370  | NAD-dependent deacetylase sirtuin-1 (SIRT1)                                  | EKNERT | Suppresses NF kappaBeta driven immune responses 99 and cyclooxygenase activity in macrophages 128  SIRT1 negatively regulates T-cell activation and this effect is blocked by HIV-1 tat binding to SIRT1 62 |
| BAH13573   | ets variant 5 (ETV5)                                                          | CRGRPV | Regulates immune synapse formation and T-cell activation 51         |
| NP_001103447| hypothetical protein LOC729830                                               | LL--IQAQQ LL| ?                                                                   |
| AAH28025   | integrator complex subunit 5 (INTS5)                                         | LL-LSVWG--LR| ?                                                                   |
| EAW66757   | galactosamine (N-acetyl)-6-sulfate sulfatase                                 | L-L-VLSAAG--MGA | Part of a lysosomal multienzyme complex 89 |
EAW78736: potassium voltage-gated channel, shaker-related subfamily, beta member 1 (KCNAB1)  LS—G—QLRAR-LAL  Microglial potassium channel related to brain inflammation 36
AAC39655 T-cell receptor delta chain TCRD  WG--I-IWDKL  T-Cell receptor

Table 2: Human proteins aligning with the HIV-1 p15 protein (vpr).

| Human protein | Amino acid match vpr | Immune related function |
|---------------|----------------------|-------------------------|
| Q5VST9 Isoform 5 of Obscurin | W-LE+LE-LKN-AVR | ? |
| Q9H4Z3 PDX1 C-terminal inhibiting factor 1 (PCIF1) | +QGP-REPH | ? |
| Q9BTX6 RET tyrosine kinase A8K6Z2; FLJ76670, highly similar to RET | LGQH+Y-TY | RET is expressed on B-cells T-cells and monocytes, plays an important role in B-cell development 118,120 |
| Q6Q0C0 Isoform 2 of E3 ubiquitin-protein ligase TRAF7 | LFIH-R-GCR | Regulates Toll-receptor signalling (TLR2) 125 |
| Q59F39 IL2-inducible T-cell kinase (ITK) | P-RE----W-L-L-EE +N | Expressed in T-cells Natural Killer cells and Mast cells: Regulates T cell receptor, CD28, CD2, chemokine receptor CXCR4, and FcepsilonR-mediated signaling pathways 98 |
| B3KUT9 Thymus-specific serine protease (EC3.4.-.-) PRSS16 | R-F-+I-LH-LGQ | Regulates the presentation of self peptides bound to MHC antigens 40 |

Table 3: Human proteins aligning with the HIV-1 p27 protein (nef).

| Human protein | Amino acid match nef | Immune related function |
|---------------|----------------------|-------------------------|
| Q15149 Isoform 8 of Plectin-1 (PLEC) | +EEEEVGF | Regulates leukocyte recruitment 2 |
| Q9Y5V3 Isoform 2 of Melanoma-associated antigen D1 (MAGED1) | PDWQ--P-P-+R | Involved in p75 neurotrophin receptor signalling and expressed in |
| Protein ID | Description                                                                 | Peptide Sequence | Notes                                                                 |
|-----------|-----------------------------------------------------------------------------|------------------|----------------------------------------------------------------------|
| D3DRW8    | CRA a LOC387647                                                            | KWS+SSV+ WP      | ?                                                                   |
| A2RUQ8    | Ubiquitin carboxyl-terminal hydrolase (USP37)                               | KL-P+EPDK-E--N G | No publications but members of this family are involved in ubiquitylation, a process that tags proteins for lysosomal destruction. |
| P31994    | Fc fragment of IgG, low affinity IIb, receptor (CD32) (FCGR2B)             | P-E-DK+---N----+ L+HP.+L----DD--R | The only inhibitory Fc Receptor: Prevents antigen presentation and is involved in immunosuppression as well as in macrophage proliferation. |
| Q9Y6R7    | IgGFc-binding protein (FCGBP)                                               | H---Y+P----Q+PGPG | Fc Receptors bind to antibodies bound to pathogens or infected cells. FCGBP is an autoantigen in progressive systemic sclerosis. |
| Q9Y4I6    | Protein tyrosine phosphatase receptor pi (PTPRN2)                           | ++ EEE--G+VT--+PLRP | Regulates B-Cell signalling and proliferation. |
| Q8TDW7    | Protocadherin (FAT3)                                                        | PQVP+RPM-Y       | No data                                                             |
| Q9UPG8    | Zinc finger protein PLAGL2                                                  | +A++EEEVG+ + P+  | Involved in acute myeloid leukemia (abnormal growth of white blood cells) |
| Q9P2F6    | Rho GTPase activating protein 20 (ARHGAP20)                                | KS-V+GWPTV       | ?                                                                   |
| Q9H44     | Lymphocyte antigen 75 variant (LY75) aka CD205                             | WI ++--D--Y++--P--R+P+TFG | Found in the spleen and lymph nodes and involved in antigen presentation. |
Table 4: Human proteins aligning with the HIV-1 p16 protein (vpu).

| Human protein                                                                 | Amino acid match vpu | Immune related function                                                                 |
|-------------------------------------------------------------------------------|----------------------|-----------------------------------------------------------------------------------------|
| Q9Y2T7 Y-box-binding protein 2 (YBX2)                                         | ERAEDSG              | Expressed in male and female germ cells<sup>43</sup>                                    |
| Q9Y487 V-type proton ATPase 116 kDa subunit a isoform 2 (ATP6V0A2)            | ERAEDSG              | Found in lysosomes. Important antigen processors<sup>121</sup>                          |
| Q96SA0 Putative uncharacterized protein                                        | +IDRLIE-AE           | ?                                                                                       |
| Q9BQ70 Transcription factor 25 (TCF25)                                        | IDR++ER EDS          | Inhibits serum response factor transcription<sup>12</sup>; SRF regulates the expression of an RNAase involved in immune modulation in macrophages<sup>55</sup> |
| P27449 V-type proton ATPase 16 kDa proteolipid subunit (ATP6VOC)              | I+AI LVVA++IA        | ?                                                                                       |
| B4DFG8 FLJ57916, highly similar to WD repeat domain phosphoinositide-interacting protein 4 | ALVVA+ ++SVW+       | ?                                                                                       |
| >SP:PRAF2_HUMAN O60831 PRA1 family protein 2 OS=Homo sapiens GN=PRAF2         | ALVVA+ ++SVW+        | Interacts with the CCR5 chemokine and HIV-1 receptor<sup>103</sup>                      |
| Q2M110 Histidine-rich calcium-binding protein No gene symbol                  | MGHH-PW              | ?                                                                                       |
| Q02388 Isoform 2 of Collagen alpha-1(VII) (COL7A1)                            | APWD-DD              | Autoantigen in epidermolysis bullosa acquisita<sup>122</sup>                           |
| Q5GJ7S Tumor necrosis factor alpha-induced protein 8-like 3 (TNFAIP8L3)      | DSG+SEGE             | TNF induced                                                                            |
| Q96J94 Isoform 3 of Piwi-like protein 1 (PIWIL1)                              | RQR++-RLID           | Expressed in haematopoetic                                                             |
| Human protein | Amino acid match rev | Immune related function |
|---------------|---------------------|------------------------|
| P08571 Monocyte differentiation antigen CD14 | P-P-+LP-+++ LTLD-N | Involved in dendritic cell apoptosis, an import mechanism regulating immunity to invading pathogens 42 |
| B7Z8R5 FLJ54826, highly similar to Homo sapiens solute carrier family 25 (mitochondrial carrier; Graves disease autoantigen) No gene symbol | Q---H----+RILG+Y-G---E +P | ? |
| B4E2R1 cDNA coiled-coil domain containing 129 CCDC129 | +L----EP+PLQ+P L | ? |
| A2A370 Dedicator of cytokinesis 8 (DOCK8) | SAE-VPLQ-PP++ | Plays a critical role in B-cell function 96 |
| Q15699 ALX homeobox protein 1 (ALX1) O95076 ALX3 Q9H161 ALX4 | +NRR++WR+R+R | ALX inhibits T-cell activation 106 |
| D3DQB0 Paired-like homeodomain transcription factor 1 PITX1 | +NRR +WR+R+R | PITX1 negatively regulates interferon alpha expression 77 |

Table 5: Human proteins aligning with the HIV-1 p19 protein (rev).
| O75364 Pituitary homeobox 3 (PITX3) |  |  |
| B3KY25 GC-rich sequence DNA-binding factor 1 (GCFC1) | R+ARR RRR+ RE+ |  |
| Q8NDA2 Hemicentin-2 (HMCN2) | C++DCGT G |  |
| Q68DH5 LMBR1 domain-containing protein 2 (LMBRD2) | NRRR-W+ER |  |

Table 6: Human proteins aligning with the HIV-1 p14 protein (tat).

| Human protein | Amino acid match tat | Immune related function |
|---------------|----------------------|-------------------------|
| A8K818_CD3e molecule, epsilon associated protein (CD3EAP) | MEPV+P-++P-+PG | CD3E is involved in T-cell activation 24 |
| Q15762 CD226 antigen | V--IT--- !---RR+RR---S---Q-+-+-+----+----G-P | Expressed in natural killer cells, monocytes and T-cells playing an important role in immune activation 31,124 |
| O14647 Isoform 2 of Chromodomain-helicase-DNA-binding protein 2 (CHD2) | KKCC-HC | Plays a role in DNA damage response and haematopoesis 84 |
| Q9UQ53 Isoform 2 of Alpha-1,3-mannosyl-glucoprotein 4-beta-N-acetylglucosaminyltransferase B (MGAT4B) | DPRL+PW | Adds sugar chains to interferon-gamma 37 |
| Q92766 Isoform 3 of Ras-responsive element-binding protein 1 (RREB1) | FHC-VCF | Suppresses the transcription of HLA-G , a molecule involved in immune tolerance 34 |
| Q02779 Mitogen-activated protein kinase kinase kinase 10 (MAP3K10; aka Mixed lineage kinase 2) | PRL+PWK | Involved in pathogen recognition receptor signalling in Jurkat T-lymphoma cells 27 |
| Q6NSK7 Ras and Rab interactor 3 (RIN3) | RGDPTGP | RIN3 is expressed in bone marrow cells 20 |
| Q6FI81 Isoform 3 of Anamorsin (CIAPIN1) | SQPK+AC-NCY | An antiapoptotic protein that controls haematopoesis 108 |
| Q9C0E4 Isoform 2 of Glutamate receptor-interacting protein 2 (GRIP2) | +RRQRRR-H++S | Interacts with glutamate (AMPA) receptors GRIA2 and GRIA3 which are
Table 7: Human proteins aligning with the HIV-1 p23 protein (vif).

| Human protein | Amino acid match vif | Immune related function |
|---------------|----------------------|-------------------------|
| Q8NDG7 Putative uncharacterized protein DKFZp434N172 | L+ PKKIK-P-+++-L-+W+P | ? |
| Q43157 Isoform 2 of Plexin-B1 (PLXNB1) | W+-K+-GHRGS--N++ | Involved in B- and T-cell activation $^8$ |
| B4DMT9 TBC1 domain family, member 15, (TBC1D15) | W+-K+-GHRGS--N+ | Involved in lysosomal regulation $^{91}$ |
| Q8N393 Zinc finger protein 786 (ZNF786) | +-++-GLHTGER +H | ? |
| B4E1Y7_HUMAN B4EY7 cDNA FLJ50947, highly similar to Atrial natriuretic peptide converting enzyme (CORIN) | PSVTKL-+--+P-++-H---++NG | Atrial natriuretic peptide controls the secretion of cytokines from macrophages: Dendritic cells and T-cells also express receptors for ANP $^{57,79}$ |
| Q9UH90 F-box only protein 40 (FBXO40) | V-++W+KKRYS | ? |

Table 8: Human proteins aligning with the HIV-1 gag-pol protein.

| Human protein | Amino acid match gag-pol: Immune related function |
|---------------|--------------------------------------------------|
| Q8NFP1 Pol protein (Fragment) | +P+NTPVF-IKKK |
| Human protein | Amino acid match gag | Immune related function |
|---------------|---------------------|------------------------|
| Q8NFP1 Pol protein | I—DN-S+T-----A------I-----IPYNPQ-Q-VV---+--LK-+I | |
| O15310 Polymerase | +--AFTIP+INN+-P+R+Q+VLPQG--SP-I-Q+ ++L+P R+++D—I--Y+ | |
| Q8NFP1 Pol protein | +P+NTPVF-iKKK | ? |
| Q14980 Isoform 2 of Nuclear mitotic apparatus protein 1 (NUMA1) | +E-ELELAENR++L-E | Autoantigen in Lupus and Sjogrens syndrome |
| Q8NSD6 Isoform 2 of Globoside alpha-1,3-N-acetylgalactosaminyltransferase 1 (GBGT1) | WETWW--+-QAT | Synthesises the Forsmann glycolipid that is involved in pathogen adherence to host cells |
| Q9NS56 E3 ubiquitin-protein ligase (TOPORS) | +PGGK+KYK +H+ | Binds to p53 and plays a role in growth suppression related to DNA damage |
| Q9BWF3 RNA-binding protein 4 (RBM4) | +-GC++CGKEGH–K+C | ? |

Table 9: Human proteins aligning with the HIV-1 gag protein.

| Human protein | Amino acid match gp120 | Immune related function |
|---------------|-------------------------|------------------------|
| A0T064 Staphylococcal-alpha-toxin-specific lambda light chain | GATPQDLNTML | Unpublished |
| P63128 HERV-K_6q14 provirus ancestral Gag-Pol polyprotein | +RQG-KEP+ D+V R---++++A+++---E+ +NANP+C+++K L | |
| P62633 Isoform 3 of Cellular nucleic acid-binding protein (CNBP) | C+NCGK-GH-AR+C---+++C+CG+-GH--KDCT+ | Binds to single-stranded DNA and RNA and to JC virus DNA |
| P63125 HERV-K_11q22 provirus ancestral Pro protein | RP+++I-G++-E- L+DTGAD+++++++P--W | |
| Q99575 Ribonucleases P/MRP protein subunit POP1 | RKKG-WK-G-EG | Autoantigen in connective tissue diseases |

Table 10: Human proteins aligning with the HIV-1 gp120 protein.
| **Disease and Autoantigen** | **HIV-1 Protein** | **Amino acid overlap** |
|----------------------------|------------------|----------------------|
| **Pemphigus vulgaris**     | ACR55549 vif protein | LRGSHTM |
| Desmoglein-3               | AAU89527 protease | PVTKTKTR |
| *Systemic lupus erythematosus* | ACD10671 envelope glycoprotein | AIVEKLR |
| X-ray repair complementing defective repair in Chinese hamster cells 6 XRCC6 (Ku70 antigen) | | |
| **Multiple sclerosis**     | CAC86080 pol protein | GR-L---RF-WG-------- |
| Myelin basic protein MBP 94 | ABJ99530 pol protein | QGK-R-LS-------S-----RF-W-- -GAEGQ |
| 94                         | ACO50234 pol protein (HIV-2) | GDDRGG--AP--RGS |
| 94                         | ACU55298 pol protein | GAEGQ-R-G |
| **Multiple sclerosis**     | AAC56235 envelope glycoprotein | + LPCRIP--N---M----EVG--- |
| MOG 94                     | AAC56235 envelope glycoprotein | Y-PP+++---------L-R+G |
| **Multiple Sclerosis**     | BAA76250 reverse transcriptase | FYTTG---QI-GD-K |
| PLP1 94                    | AAB07222 envelope glycoprotein | FYTTGA----VRQ |
| **Multiple sclerosis**     | ABO64827 envelope glycoprotein | LSTVIY-S |
| Myelin associated glycoprotein | ABO64827 envelope glycoprotein | LSTVIY-S |
| **Chronic obstructive pulmonary disorder** | AAL31352 vif protein (HIV-2) | IFP--GGACL |
| Elastin 38                 | ACJ37145 rev protein | TGTGVG--PQ |
| 38                         | ABA08289 envelope glycoprotein | FGLSP-F |

**Table 11 Autoantigens from human autoimmune disorders showing significant homology to HIV-1 proteins**

**Interleukin-31 receptor subunit alpha (IL31RA)**
progenitor cell proliferation

**D3DWB6 Ubiquitin carboxyl-terminal hydrolase (USP9X)**
Regulates TGFbeta and bone morphogenic protein signalling

**Q9NX61 Transmembrane protein 161A (TMEM161A)**
Increases resistance to oxidative stress, DNA damage and apoptosis
| Autoantigen | Viral Homolog | Sequence | Involvement |
|-------------|--------------|----------|-------------|
| Myasthenia Gravis | Nicotinic Acetylcholine receptor gamma subunit CHRNG | FDWQNC | ? |
| | | IVVNA | ? |
| Sjogrens syndrome | Lupus La protein SSB | R-R--RDY-G-VLRV | Anti nicotinic receptor antibodies isolated from myasthenia patients cross react with HSV-1 glycoprotein |
| Sjogrens syndrome | Lupus La protein SSB | EALTT | ? |
| Sjogrens syndrome | Lupus La protein SSB | DIVLEN | ? |
| Sjogrens syndrome | Lupus La protein SSB | NQEEERL | ? |
| Sjogrens syndrome | Lupus La protein SSB | TLFSALLI | ? |

Table 12

Viral proteins lining up with autoantigens from Chronic obstructive pulmonary disease, myasthenia gravis, multiple sclerosis, pemphigus vulgaris and lupus and to mutant proteins from polyglutamine repeat disorders (Huntington’s disease, Dentatorubropallidolysusian atrophy, Kennedy disease and Spinocerebellar ataxias) and from cystic fibrosis. APOE4 is included as an example of a risk factor in a number of polygenic diseases. Accession numbers and the aligning sequences are shown with references where the virus has been implicated in the relevant disease. The polyglutamine expansions also increase the antigenicity of the resultant peptide with each triplet QQQ addition.
NP_044050 Molluscum contagiosum virus subtype1
BAH15164 Serratia phage
CAM12729 Zucchini yellow mosaiccovirus
ADF28539 Human TMEV-like cardiovirus:
ACO92355 Saffold virus
ABD73306 Gremmeniella abietina type B RNA virus
NP_612874 Clostridium phage
BAA03030 Orgyia pseudotsugata single capsid nuclopolyhedrovirus
EBNA3 Epstein-Barr virus
D2XR26 Bacillus phage
9PARAQ84747 Human parainfluenza virus 1
C9WSX19 Norovirus dog

YP_164320 Pseudomonas phage
YP_003406894 Marseille virus
CAA24862.1 Human herpesvirus 4 (Epstein Barr)
P25939 Human herpesvirus 4 (Epstein Barr)
C9WSX19 Norovirus dog

Implicated 72

NP_00102025 2 myelin basic protein isoform 1

Implicated 61

AAB58805.1 Human herpesvirus 4 (Epstein Barr)

Implicated 72

AAR31274 Human herpesvirus 5 (Cytomegalovirus)

Implicated:
Seropositivity predicts a better outcome in Multiple Sclerosis (Beneficial virus?)

AAR31274 Human herpesvirus 5 (Cytomegalovirus)

Implicated:
Seropositivity predicts a better outcome in Multiple Sclerosis (Beneficial virus?)

APV71654.1 Human herpesvirus 5 (Cytomegalovirus)

Detected in MS tissue 88
NP_042301 Southern cowpea mosaic virus PGRSPLP
YP_143172 Acanthamoeba polyphaga mimivirus IGRFFGG
ABB22292 Ovine Herpesvirus 2 NP_065571 Alcelaphineherpes virus 1 FFKNIV
JC polyomavirus PRTPPP Seropositivity in some Multiple sclerosis patients

BAA00490 Ornithogalum mosaicvirus TQDENP
YP_003280846 Helicobasidium mompa endornavirus 1 DSIGRF
CAA32420 Simian rotavirus ARTAHY

YP_002117760 Pseudomonas phage IVTPRT
YP_164431 Bacillus phage GRASDY

NP_570206 Swinepoxvirus TLSKIF
ACV04605 Nakiwogovirus GRSPLP
YP_214645 Prochlorococcus phage LDSIGR

ACZ8140 Moussavirus TAHYGS

BAA77241 Broadbean wilt virus 2 RASDYK
NP_944019 Aeromonasphage AMELK
ADA81168 Staphylococcus phage VLGPLV
NP_690686 Bacillus phage LVALII
ABO87130 Hepatitis delta virus KDQDG

ADE60693 Rice stripe virus SRVVLH
ACA24946 Swine parainfluenzavirus 3 RDHSY
AAL89267 Shrimp whitespot syndrome virus NLHRTF
NP_569759 Mycobacterium phage ELLKDA+G

BAB83467 Chlorellavirus SATVTGGQ
CAG70345 Bovine viral diarrhea virus 1 VPPYYI

YP_001111042 Burkholderia phage And GITYA
FNTWT
| Accession | Description                                                                 | Query | Notes |
|-----------|------------------------------------------------------------------------------|-------|-------|
| AF310938  | Powassanvirus                                                                |       |       |
| NP_620108 | Langatvirus                                                                   |       |       |
| AAW33310  | Human adenovirus 4                                                            |       |       |
| ABO42303  | Avian metapneumovirus                                                         |       |       |
| ABU82778  | Human metapneumovirus                                                         |       |       |
| YP_002214563 | Mycobacterium phage Butterscotch     |       |       |
| YP_002214480 | Mycobacterium phage Troll4        |       |       |
| YP_655259  | Mycobacterium phage PBI1                                                      |       |       |
| YP_717772  | Synechococcus phage                                                           |       |       |
| YP_001129421 | Human herpes virus 8 (Kaposi’s sarcoma virus)                               |       |       |
| ABI35813  | Human metapneumovirus                                                         |       |       |
| YP_002241961 | Mycobacterium phage Gumball      |       |       |
| YP_001936156 | Mycobacterium phage Adjutor         |       |       |
| AAK69175  | Bovine viral diarrhea virus 1                                                |       |       |
| YP_717777  | Synechococcus phage syn9                                                      |       |       |
| ABB89216  | Human herpes virus 4 (Epstein Barr)                                          |       |       |
| AAS86764  | Zantedeschia mild mosaic virus                                                |       |       |
| AAQ96572  | Vibrio phage VP16C                                                            |       |       |
| YP_001468520 | Listeria phage A511            |       |       |
| YP_398993  | Enterobacteria phage                                                          |       |       |
| AAC5158   | Human herpesvirus 8 type M                                                    |       |       |
| AAR14310  | Lactococcus phage ul363                                                       |       |       |

Associated with relapse in multiple sclerosis

Query = Hinton’s disease, spinocerebellar ataxia, Dentatorubral-pallidoluysian atrophy, Kennedy disease

Implicated 72
| Accession   | Organism                          | Species                      | Accession   | Organism                          | Species                      |
|------------|----------------------------------|------------------------------|------------|----------------------------------|------------------------------|
| YP_001456769 | Corynebacterium phage           |                             | NP_116331  | T2 Tupaiid herpesvirus 1         |                             |
|            |                                 |                             | ACO25273   | Epizootic haematopoietic necrosis virus |                             |
|            |                                 |                             | AAL89066   | Shrimp white spot syndrome virus |                             |
|            |                                 |                             | YP_001218813 | Pseudomonas phage                |                             |
|            |                                 |                             | embCAA52472 | Human papillomavirus type 3      |                             |
|            |                                 |                             | CAA75466   | Human papillomavirus type 77     |                             |
|            |                                 |                             | AAA79432   | Human papillomavirus type 29     |                             |
|            |                                 |                             | CAA75466   | Human papillomavirus type 77     |                             |
|            |                                 |                             | AAL50729   | Human herpesvirus 6B             |                             |
|            |                                 |                             | AAA750183  | Human herpesvirus 6              |                             |
|            |                                 |                             | ADB84736   | Human herpesvirus 5              |                             |
|            |                                 |                             | ABQ51392   | Human rhinovirus sp.             |                             |
|            |                                 |                             | AAB59808   | Vaccinia virus                   |                             |
|            |                                 |                             | CAA53834   | Variola virus                    |                             |
|            |                                 |                             | YP_003090182 | Burkholderia phage KS9          |                             |
|            |                                 |                             | YP_001504144 | Enterococcus phage               |                             |
|            |                                 |                             | YP_098809   | Staphylococcus phage             |                             |
|            |                                 |                             | YP_002003602 | Escherichia phage rv5           |                             |
|            |                                 |                             | NP_046572   | Bacillus phage                   |                             |
|            |                                 |                             | YP_052931   | Palyam virus                     |                             |
|            |                                 |                             | BAA34933   | Chuzan virus                     |                             |
|            |                                 |                             | ABD63811    | Lactococcus phage                |                             |
|            |                                 |                             | YP_717768   | Synechococcus phage              |                             |
|            |                                 |                             | AAM4760     | Dendrolimus                      |                             |

Burkholderia infection has been related to Cystic fibrosis  

21,88
| Native | I | A | T | V | I | V | I | T | L | V |
|--------|---|---|---|---|---|---|---|---|---|---|
| Bacillus Phage NP 046589 | * | * | * | * | * |   |   |   |   |   |
| Rabies virus ACN38519 |   |   |   |   |   |   |   |   |   |   |
| Salmonella Phage YP 001742070 |   |   |   |   |   |   |   |   |   |   |
| Sendai Virus BAC79139 |   |   |   |   |   |   |   |   |   |   |

**Table 13** The effects of the London APP717 mutation on homology to viral proteins. Protein accession numbers are provided and amino acid matches are indicated by the asterisks or by the red letter of the mutant amino acid. Phages infecting commensal bacteria and common viruses (e.g., Rhinoviruses and Norovirus) are highlighted in bold.
| Virus/Phage/Strain                                                                 | I | A | T | V | I | I | T | L | V |
|----------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|---|
| **Aeromonas Phage YP_238915**                                                    |   |   |   |   |   |   | * |   |   |
| **Enterobacteria phage AC14704**                                                 |   |   |   |   |   |   | * | * | * |
| Human Coronavirus 229E CAA49377                                                   |   |   |   |   |   |   | * | * | * |
| Mossman Virus NP_958055                                                           |   |   |   |   |   |   | * |   |   |
| **Pseudomonas phage YP_418190**                                                  |   |   |   |   |   |   | * |   |   |
| SARS Coronavirus ACZ71766                                                          |   |   |   |   |   |   | * |   |   |
| **Staphylococcus phage**                                                          | * | * | * | * |   |   |   |   |   |
| YP_024500                                                                       |   |   |   |   |   |   |   |   |   |
| Aeromonas phage NP_932517,                                                        |   |   |   |   |   |   | * |   |   |
| Acanthamoeba polyphaga mimivirus                                                 |   |   |   |   |   |   | * |   |   |
| Flavobacterium Phage YP_112527                                                    |   |   |   |   |   |   | * |   |   |
| Mycobacterium Phage YP_002242149                                                  |   |   |   |   |   |   | * |   |   |
| Salmonella phages: Pseudocowpox ADC53802                                        |   |   |   |   |   |   | * |   |   |
| Uncultured Phage                                                                  |   |   |   |   |   |   | * |   |   |
| ADF97555 Paris Polyvirus X ABF74755                                               |   |   |   |   |   |   |   |   |   |
| **Lactococcus Phage P_002875673**                                                |   |   |   |   |   |   | * |   |   |
| **Pseudomonas Phage YP_003422512**                                               |   |   |   |   |   |   | * |   |   |
| Ralstonia Phage YP_001165297                                                      |   |   |   |   |   |   | * | * |   |
| Newcastle Disease virus ACZ72939                                                  |   |   |   |   |   |   | * |   |   |
| Human herpesvirus 5 (Cytomegalovirus)                                             |   |   |   |   |   |   | * | * |   |
| AAS48926                                                                         |   |   |   |   |   |   |   |   |   |
| SARS coronavirus AAY60778                                                          |   |   |   |   |   |   |   | * | * |
| Burkholderia phage YP_001111213                                                   |   |   |   |   |   |   |   | * | * |
| Enterobacteria phage YP_001837048                                                 |   |   |   |   |   |   |   | * | * |
| **Human rotavirus A BAF95721**                                                    |   |   |   |   |   |   |   | * | * |
| **Human parainfluenza virus ACZ95446**                                            |   |   |   |   |   |   |   | * | * |
| Human adenovirus 1 AP_000521                                                      |   |   |   |   |   |   |   | * | * |
| Lactate dehydrogenase-elevating virus NP_042576                                   |   |   |   |   |   |   |   | * | * |

**Mutant**

| Viruses/Phages                                                                 | I | A | T | V | I | I | T | L | V |
|--------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|---|
| **Rhinovirus 50 ACK37391 and >30 other Rhinovirus strains**                    |   |   |   |   |   |   | * | * | * |
| **Rhinovirus 38 ABF51189**                                                      |   |   |   |   |   |   | * | * | * |
| Virus PK224 ADF80719                                                             |   |   |   |   |   |   | * | * | * |
| Aeromonas phage NP_943894                                                        |   |   |   |   |   |   | * | * | * |
| **Enterobacteria phage SP ACY07251**                                             |   |   |   |   |   |   | * | * | * |
| **Enterobacteria phage F1 NP_695026 (and others)**                               |   |   |   |   |   |   | * | * | * |
| Listeria phage YP_002261439                                                      |   |   |   |   |   |   | * | * | * |
| Acanthamoeba polyphagamimivirus                                                 |   |   |   |   |   |   | * | * | * |
| YP_001427182                                                                    |   |   |   |   |   |   | * | * | * |
| Human herpesvirus 4 YP_401711                                                   |   |   |   |   |   |   | * | * | * |
| Human herpesvirus 5 AC891947                                                    |   |   |   |   |   |   | * | * | * |
| Aeromonas phage NP_943894                                                        |   |   |   |   |   |   | * | * | * |
| Lymphocystis disease virus NP_078753                                             |   |   |   |   |   |   | * | * | * |
| SARS coronavirus AAU93319                                                        |   |   |   |   |   |   | * | * | * |
| Vaccinia Virus NP_048189                                                         |   |   |   |   |   |   | * | * | * |
| **Staphylococcus phage YP_238539**                                               |   |   |   |   |   |   | * | * | * |
| Vibrio Phage NP_899546                                                           |   |   |   |   |   |   | * | * | * |
| Emiliania huxleyivirus CAZ69528                                                   |   |   |   |   |   |   | * | * | * |
| **Enterobacteria Phage ACT66763**                                                |   |   |   |   |   |   | * | * | * |
| **Human parainfluenza virus 1 CAA26576**                                         |   |   |   |   |   |   | * | * | * |
| Salmonella phage YP_003090232                                                    |   |   |   |   |   |   | * | * | * |
| Virus                      | Protein VVGGV                  | Disease                          | Seroprevalence                                      |
|---------------------------|-------------------------------|----------------------------------|-----------------------------------------------------|
| **Human Viruses**         |                               |                                  |                                                     |
| Dengue virus 1            | ACQ44424 Polyprotein          | Febrile tropical disease         | Endemic in some countries (eg 100% seroprevalence in Jamaica) 10 |
| Hepatitis C               | ACY65348 envelope protein 2: ADG28960 NS4A ABC58527 NS4B: ADC54771 Polyprotein | Hepatitis                        | An estimated 270-300 million people worldwide are infected with hepatitis C 1.8% (USA) 129 |
| Human adenovirus 8        | BAH18864 17.7kDa protein      | Keratoconjunctivitis             |                                                     |
| Human herpesvirus 1       | P08665 Envelope glycoprotein B: ABI63489 UL27 | Cold sores, mouth, throat, face, eye and CNS infection | 68% (USA) 101 |
| Human herpesvirus 2       | NP_04471 uracil-DNA glycosylase: BAG49514 Glycoprotein B AAA43846 Envelope glycoprotein B | Anogenital infections            | 16% in USA adults aged from 14-49: Higher in women (20.9%) and Afro-Americans (39%) 1 |
| Human herpesvirus 6       | AAA43846 Envelope glycoprotein B | Causes Roseola, a near-universal childhood disease | Approaching 100% 14 |
| Human herpesvirus 6B      | BAA78260 Envelope glycoprotein B | Acquired immune deficiency syndrome | Rare 0.02% (USA) 46 |
| Human immunodeficiency virus | ACQ42512 vif Protein          |                                  |                                                     |
| Lactate dehydrogenase-elevating virus | Polyprotein 1ab | Not well characterised | ? |
| --- | --- | --- | --- |
| Polyomavirus HPyv6 and 7 | ADE45477 VP2 | Human infection | No data on these strains but for other polyoma viruses can range from 9 to 69% \(^{56}\) |
| Yellow fever virus | NP_776003 Polyprotein : NS2A | Yellow Fever | 75% Nigeria \(^{87}\) |

### Phages infecting human bacteria and diseases associated with the bacteria

| Aeromonas phage | YP_238875 WAC | Gastroenteritis and wound infections |
| Enterobacteria phage | NP_037676 Tail length tape measure protein | Normal gut flora, many of which can cause gastrointestinal problems |
| Escherichia phage | Chain A, Ibv: YP_002003548 hypothetical protein ACU41726 GP233 YP_002014682 GP71 YP_655916 YP_655355 GP51 GP78 NP_818073 GP108 ACY76180 Hypothetical protein Tail fiber assembly protein | Many are harmless but can cause diarrhoea to dysentery |
| Mycobacterium Phage | ACU41726 GP233 YP_002014682 GP71 YP_655916 YP_655355 GP51 GP78 NP_818073 GP108 ACY76180 Hypothetical protein Tail fiber assembly protein | Pulmonary disease, Tuberculosis and leprosy |
| Prochlorococcus phage | ACY76180 Hypothetical protein | Marine cyanobacteria |
| Pseudomonas phage | TAILC_BPSK2 | Nosocomial hospital infections |
| Serratia phage KSP20 | TAILC_BPSK2 | Nosocomial hospital infections |
| Streptomyces phage | NP_958289 ORF9 | Antibiotic producing bacteria |
| Vibrio phage | AAQ96489 Hypothetical protein | Gastroenteritis, septicaemia |

### Other phages

| Azospirillum phage Halomonas phage | YP_001686888 Hypothetical protein YP_001686782 hypothetical protein HAPgp46 | Nitrogen fixing plant bacterium Salt water |
| Microcystis aeruginosa phage | YP_851126 hypothetical protein MalMM01_gp112 | Harmful blue-green algae |
| Prochlorococcus phage | ACY76180 hypothetical protein | Common marine cyanobacteria |
| Species/Type                                      | Accession(s)          | Protein(s)                                      | Host(s)                  |
|--------------------------------------------------|-----------------------|------------------------------------------------|--------------------------|
| Synechococcus phage                              | YP_003097380          | Tail fiber-like protein                        | Marine cyanobacteria     |
|                                                  | SRSM4_083              | Hypothetical protein                           |                          |
| **Agricultural Viruses**                         |                       |                                                |                          |
| Bovine herpesvirus 5 YP_003662471                | Envelope glycoprotein | Cattle                                         |
|                                                  | K                     |                                                |                          |
| Bovine herpesvirus type 2 P12641                 | Envelope glycoprotein | Cattle                                         |
|                                                  | B                     |                                                |                          |
| Bovine viral diarrhea virus CAD67689             | Hypothetical protein  | Cattle                                         |
|                                                  | lab                   |                                                |                          |
| Avian infectious bronchitis virus ACJ12832       | Polyprotein 1ab       | Poultry                                        |
|                                                  | lab                   |                                                |                          |
| Infectious bronchitis virus                      | Replicase polyprotein| Poultry                                        |
|                                                  | 1ab: InfB NSP3 Adrp    |                                                |                          |
|                                                  | Domain                |                                                |                          |
| Equid herpesvirus 1, 4 and 9 YP_002333504        | Tegument protein UL37 | Horse                                          |
|                                                  |                       |                                                |                          |
| Suid herpesvirus 1 YP_0053068                    | Tegument protein UL37 | Pigs                                           |
| Swinepox virus NP_570175                         | Kelch-like protein    | Pigs                                           |
| **Plant, Food and Environmental Viruses**        |                       |                                                |                          |
| Anguillid herpesvirus 1 YP_003358210             | ORF71                 | Eel                                            |
|                                                  | ADB93794              | Fish                                           |
| Viral hemorrhagic septicemia virus               | Polymerase: Large     | Fish                                           |
|                                                  | protein               |                                                |                          |
| Cherry necrotic rusty mottle mosaic virus ABZ89196| Replication protein  | Cherry                                         |
|                                                  |                       |                                                |                          |
| Radish mosaic virus BAG84603 Polyprotein         |                       | Radish                                         |
| Watermelon mosaic virus ACF60797 Polyprotein     |                       | Watermelon                                     |
| Ostreid herpesvirus 1 YP_024568ORF23             | Oyster                | Oyster                                         |
| Arabis mosaic virus BAF33582                     | Strawberry and raspberries |                                                |
| Viral hemorrhagic septicemia virus               | Polypeptide NTB       | Fish                                           |
|                                                  | binding domain        |                                                |                          |
| Shrimp white spot syndrome virus                 | ADB93794 Polymerase;  | Shrimp                                         |
|                                                  | Large protein         |                                                |                          |
| Antheraea pernyi nucleopolyhedrovirus ABQ12330  | ETM                   | Environment Insect Chinese Tuss Moth           |
| Murid herpesvirus 2 NP_064139                    | pR34                  | Environment Rodents                            |
| Allpahuayo virus NP_064139                       |                       | Environment Rodents                            |
| Organism                        | Protein/Component | Accession Number | Setting                                      |
|--------------------------------|-------------------|------------------|----------------------------------------------|
| *Helicobasidium mompa* endornavirus 1 | Nucleocapsid protein | YP_003280846     | Environment Root rot fungus                  |
| *Paramecium bursaria* Chlorella virus | YP_001498106 and others Hypothetical proteins |                  | Environmental Algae                          |
| *Archaecal BJ1 virus*           | YP_919057 hypothetical protein | BJ1_gp30        | Environmental                              |
| *West Caucasian bat virus*      | YP_919057         |                  | Environmental Bat                           |
| *Cyprinid herpesvirus 3*        | BAF48875          |                  | Family pet Goldfish                         |
| *Caviid herpesvirus 2*          | AAD11961          |                  | Zoo Marsupial                               |
| *Macropodid herpesvirus 1*      | Glycoprotein B    |                  | Zoo Marsupial                               |
| *Macropodid herpesvirus 2*      | Glycoprotein B    |                  | Zoo Monkey                                  |
| *Macacine herpesvirus 1*        | Glycoprotein B    |                  | Zoo Monkey                                  |
| *Cercopithecine herpesvirus 1, 2 and 16* | Envelope glycoprotein B |                  | Zoo Monkey                                  |
| *Papiine herpesvirus 2*         | AAA85650          |                  | Zoo Monkey                                  |
| *Chimpanzee alpha-1 herpesvirus*| BAE47051          |                  | Zoo Monkey                                  |
Figure 1:
The immune network localisation of the human proteins showing homology with HIV-1 proteins

Figure 2, 3
The B-cell epitope prediction profiles for the peptide matches between HIV-1 and human proteins. The prediction method calculates the antigenicity amino acid by amino acid allowing definition of the immunogenic spectrum along the length of the peptide \(^{64}\). Each bar within each set of histograms thus represents a single amino acid, derived from the alignments in tables 1 to 10. The default threshold predicting B-cell epitopes is 0.35.
Fig 4: The localisation of the APP\textsubscript{717} London mutation and of the beta- and gamma-secretase (\(\beta\) and \(\gamma\)) cleavage sites (\(\uparrow\)). The beta-amyloid sequence is highlighted in grey. The peptide used for homology searches is underlined.

\[\ldots \text{LTNIKTEIEEVKM} \uparrow\beta \text{DAEFRHDGVEVHQQKLVPFAEDVGSNKGAIIGLMVGVVY} \uparrow\gamma \text{IATIV}^{717} \text{ITLM} \uparrow\gamma \text{LKK} \ldots\]

**Mutation:** V→I

| A | C | D | E | F | G | H | I | K | L |
|---|---|---|---|---|---|---|---|---|---|
| Alanine | Cysteine | Aspartate | Glutamate | Phenylalanine | Glycine | Histidine | Isoleucine | Lysine | Leucine |
| M | N | P | Q | R | S | T | V | W | Y |
| Methionine | Asparagine | Proline | Glutamine | Arginine | Serine | Threonine | Valine | Tryptophan | Tyrosine |
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B-Cell epitope prediction
