INFLUENZA PEPTIDE SEQUENCES AND VACCINE COMPOSITIONS

The invention concerns peptide sequences, compositions comprising the peptide sequences, and in particular influenza vaccines comprising the sequences and the compositions, and uses of the sequences. The present invention is especially concerned with vaccines that are protective against a plurality of influenza virus strains, including existing viruses across different species (e.g. protective against both human and avian influenza) as well as future viruses that have mutated from existing viruses (such as a future mutated form of avian flu that is readily transmissible from human to human, which could potentially give rise to an influenza pandemic).

The defence against disease is critical for the survival of all animals, and the defence mechanism employed for this purpose is the animal immune system. Understanding the immune system is therefore a key to understanding the development of new and more sophisticated treatments for humans and animals alike.

The mechanism of operation of the immune system has been under investigation for many years. The system is composed of a number of cell types and a variety of molecules, making it extremely complex. Even after many years of study, the full extent of the immune system components, and their interaction with each other, is imperfectly understood.

Many years ago it was recognised that a person who recovers from a particular disease may acquire some protection in future against that disease, but not against a disease which that person has not yet contracted. This fundamental aspect of the immune system was interpreted at that time by considering that the immune system acquired a kind of ‘memory’ against certain pathogens once exposure to such pathogens had taken place, that memory being specific to a certain disease.

Gradually, it became known that exposure to less harmful variants of a pathogen could induce protection against more harmful variants (e.g. exposure to cowpox to protect against smallpox, or exposure to an inactivated anthrax to protect against live anthrax). Thus, the idea of vaccination against a disease arose.

It is now known that the immune system has at least two divisions: innate immunity and adaptive immunity. The innate system is fully functional before a pathogen enters the system, whilst the adaptive system is switched on after the pathogen enters the system. It then develops an attack specific to the pathogen. The innate system comprises a number of components, including phagocytes such as macrophages, which (as the name suggests) 'eat' or engulf foreign bodies such as pathogens.

Typically, but not exclusively, the present invention is concerned with the adaptive immune system, and unless specifically indicated otherwise, 'immune system' in the present context refers to the adaptive immune system.

In order to understand more fully how the immune system functions, the role of its individual components must be carefully considered. In respect of the adaptive immune system, it is well known that immunity against pathogens is provided by the action of lymphocytes, which constitute the most common cell type in the immune system. There are two types of lymphocyte: the B lymphocyte and the T lymphocyte. These are generally termed B cells and T cells respectively.

B cells have the ability to develop into plasma cells, which manufacture antibodies. Antibodies are very important components of the animal immune system. They are produced in response to some signature portion of the invading pathogen (an antigen of the pathogen – antigens here being defined as any foreign substance recognised by the immune system) and are usually specific to that pathogen. However, if two pathogens are very similar, or at least contain the same antigen, then antibodies produced against one can nevertheless be effective against the other (they may 'cross-react'). This explains why inoculation with cowpox may protect against smallpox. It is important to realise that the antibodies 'recognise' only a small portion of the antigenic molecule of the pathogen rather than the pathogen as a whole. These portions are termed epitopes.

T cells do not possess or produce antibodies. Instead, they recognise fragments (i.e. epitopes) of the foreign antigen complexed with major histocompatibility complex (MHC) (or in the

case of humans, human leucocyte antigen (HLA)) via a specialised receptor known as TCR (T cell receptor). T cells are themselves divisible into subsets which can have either a regulatory function or an effector function. The effector cells are involved with 'effecting' the removal of foreign substances. For example, cytotoxic T cells (CTL) are effector cells that are able to kill infected cells, as well as other unwanted species such as tumour cells. Regulatory T cells, on the other hand, play a role in helping effector T and B cells to become more effective. Due to this function, these regulatory T cells are often termed 'helper' T cells. Other regulatory T cells, termed 'suppressor' T cells, are thought to inhibit immune responses, but these are less well understood. Regulatory T cells may also interact with components of the innate immune system to boost their activity.

In a normal healthy individual, the lymphocytes in the immune system remain in an inactive 'resting' state until an immune response is triggered. When an immune response is required, the lymphocytes become activated, proliferate and begin to carry out their designated functions. For example, any resting T cell displaying on its surface a TCR that recognises an epitope of the invading pathogen complexed with a MHC molecule is activated, proliferates (this being termed clonal expansion) and the resulting offspring start to actively carry out their predetermined effector functions required to combat the invading organisms.

When the immune response is completed, (i.e. the pathogens and/or infected cells have been eliminated) the lymphocytes revert to a resting state once again. This resting state is not, however, equivalent to the initial inactive resting state. Activated, but resting lymphocytes, can be rapidly recruited and induced to proliferate in response to an infection by the same, or closely related, pathogen at a later time.

This ability of activated resting lymphocytes, to deliver a faster and more powerful response following a second encounter with an invading pathogen, effectively provides the immune system with 'memory'. The exploitation of the immune system's memory is the basis for all long-term immunoprophylactic drugs (e.g. vaccines) and remains the goal of much long-term immunotherapeutic drug development.

In order for cells to perform their functions within the complex systems of an animal, the cells need to have 'receptors' on their surfaces. These receptors are capable of 'recognising' specific substances that control various essential processes such as activation, proliferation and adherence to other cells or substrates. For example, in the case of the immune system, the receptors on T and B cells allow them not only to recognise antigen but also to interact with each other and thus regulate their activities. Without these receptors, the cells would lack an essential means of communication and would be unable to act effectively in the concerted way that is essential for the immune system of a multicellular organism.

In order to be able to specifically recognise and deal with the wide range of pathogens present in the environment, the immune system has developed two types of highly variable antigen receptor on lymphocytes: antibodies in B cells and T cell receptors, or TCRs, in T cells.

There are a great many different possible antigen receptors present in the body, to enable the immune system to recognise a wide variety of invading pathogens. In fact there are approximately 10^{12} different B cells and T cell receptors in an individual. Each individual B cell has only one type of receptor, and so to deal with a particular pathogen, a B cell having the 'best fitting' receptor for an antigen of that pathogen must be selected. This process is termed 'clonal selection'. In theory, only a single clone may respond (a monoclonal response) or several (an oligoclonal response) or many (a polyclonal response) depending on the number of antigens/epitopes exhibited by the pathogen, and the specificity of the various selected B cells to these antigen/epitopes.

There is a major difference between the types of antigen that can be recognised by B cells and T cells. As far as it is known, only the receptors on the surface of B lymphocytes (i.e. antibodies) are capable of directly recognising antigens such as proteins on viruses and bacteria, or foreign molecules dissolved in body fluid. Antibodies can also be produced in a soluble form by the B cells when they are activated and develop into plasma cells. The antibodies are also termed immunoglobulins (abbreviated to Ig). T cell receptors, on the other hand, recognise only short peptides, also known as T cell epitopes, on the surface of cells of the body. These T-cell epitopes are produced by degradation of larger proteins that are either self (i.e. naturally occurring body proteins) or non-self (i.e. derived from foreign

organisms infecting the body). Only those derived from foreign proteins, i.e. antigens, are normally capable of inducing an immune response in the body. Once produced, these epitopes are bound to a special type of molecule, the MHC (major histocompatibility complex) and the resulting complex is then presented on the cell surface for binding the T cell receptor.

It should be clear that due to the destructive nature of the immune response, the response has to act only against foreign pathogens, not against the body's own cells or proteins. Thus, the immune system needs to distinguish between 'self' and 'non-self'. It has been proposed that although clones of lymphocytes reacting against self are produced, they are deleted before any reaction can occur. This process is termed 'clonal deletion'. It has also been proposed that any self-reacting lymphocytes could be retained but only in a 'switched-off' state. This mechanism is termed 'clonal anergy'. Whatever the process considered, it remains unclear what is the exact underlying mechanism allowing lymphoid tissues, such as the thymus, to identify individual T cell clones reacting against self from the pool of T lymphocytes reacting only against non-self. The present inventors have now investigated more fully the mechanism of self/non-self discrimination, which has led to the development of the present invention. The inventors have now established a method of predicting the immunogenicity of a substance such as a peptide, which has enabled quicker identification of immunogenic peptide sequences within large proteins.

It has been known for many years that the major histocompatibility complex (MHC) plays a key role in the immune system of animals. The MHC molecules enable T cells to recognise antigens, as has already been discussed above. There are three general types of MHC molecule, class I, class II and class III. Class I and class II MHC molecules are glycoproteins that are present on the surface of the cell, whilst class III are usually soluble molecules present inside the cell. There are a large number of different types of MHC molecule. For example in humans (where MHC is termed HLA, human leukocyte antigen) there are several hundreds of different alleles of the genes coding for MHC molecules, meaning that in the human population there are many different types of HLA. The MHC of different species is typically named according to different conventions, thus MHC for mouse is termed H-2, for rat RT1 and for rabbit RLA. The different gene regions coding for different MHC molecules

in an individual are usually individually named, such as HLA-A, HLA-C or the like in humans.

The MHC molecule is a critical immune system molecule, since it is this molecule that presents the epitopes of the antigens to the immune system. For example, if a T cell is to respond to a particular pathogen, the pathogen must have a least one antigen (such as a protein) that has at least one epitope (such as a peptide portion of the protein) that can bind to an MHC molecule on the surface of a cell and thus interact with a T cell which binds to the MHC-peptide complex. Thus, the immune response is dependent on the ability of the MHC to bind to an epitope. If there is no epitope that the MHC will bind to, or if there is no T cell which will bind to the MHC-peptide complex, then no immune response will occur.

In respect of 'self' proteins, however, one of several epitopes may be able to bind to the MHC molecule and hence potentially induce an immune response. On these occasions a specific "signal" must be provided for the self-reacting lymphocyte clones to be deleted or "switched off".

Since, as indicated above, both self and foreign (i.e. non-self) peptides can bind to MHC molecules, the binding of various peptides to MHC molecules has received particular scrutiny in the immunology field. Many investigations have sought to calculate or predict the strength of binding between certain MHC (particularly HLA and H-2) types and peptide sequences, to try to account for immune responses, or the lack of them (i.e. the "signal" required for discrimination between self and foreign). Examples of these include the following:

Altuvia Y, Schueler O, Margalit H. 1995. "Ranking potential binding peptides to MHC molecules by a computational threading approach". J. Mol. Biol., 249:244–250.

Altuvia Y, Sette A, Sidney J, Southwood S, Margalit H. 1997. "A structure-based algorithm to predict potential binding peptides to MHC molecules with hydrophobic binding pockets". Hum. Immunol. 58:1–11.

G.E. Meister, C.G.P. Roberts, J.A. Berzofsky, A.S. De Groot, “Two novel T cell epitope prediction algorithms based on MHC-binding motifs; comparison of predicted and published epitopes from Mycobacterium tuberculosis and HIV protein sequences” Vaccine, 13:581-591, (1995).

Gulukota K, Sidney J, Sette A, DeLisi C. 1997. “Two complementary methods for predicting peptides binding major histocompatibility complex molecules”. J. Mol. Biol. 267:1258–1267.

Pamer EG, Harty JT, Bevan MJ. “Precise prediction of a dominant class I MHC-restricted epitope of Listeria monocytogenes”. Nature 1991; 353: 852 –855.

Parker KC, Bednarek MA, Coligan JE. 1994. “Scheme for ranking potential HLA-A2 binding peptides based on independent binding of individual peptide side-chains”. J. Immunol. 152:163–175.

Rammensee HG, Friede T, Stevanoviic S. 1995. “MHC ligands and peptide motifs: First listing”. Immunogenetics 41:178–228.

Ruppert J, Sidney J, Celis E, Kubo RT, Grey HM, Sette A. 1993. “Prominent role of secondary anchor residues in peptide binding to HLA-A2.1 molecules”. Cell 74:929–937.

Schueler-Furman O, Elber R, Margalit H. 1998. “Knowledge-based structure prediction of MHC class I bound peptides: A study of 23 complexes”. Fold Des. 3:549–564.

Sette A, Buus S, Appella E, Smith JA, Chesnut R, Miles C, Colon SM, Grey HM. 1989. “Prediction of major histocompatibility complex binding regions of protein antigens by sequence pattern analysis”. Proc. Natl. Acad. Sci. USA 86:3296–3300.

Sette A, Sidney J, del Guercio MF, Southwood S, Ruppert J, Dahlberg C, Grey HM, Kubo RT. 1994a. “Peptide binding to the most frequent HLA-A class I alleles measured by quantitative molecular binding assays”. Mol. Immunol. 31:813–822.

Sette A, Vitiello A, Reherman B, Fowler P, Nayersina R, Kast WM, Melief CJM, Oseroff C, Yuan L, Ruppert J, et al. 1994b. “The relationship between class I binding affinity and immunogenicity of potential cytotoxic T cell epitopes”. J. Immunol. 153:5586–5592.

Stefan Stevanovic (2002): “Structural basis of immunogenicity”, Transplant Immunology 10 133–136

Sturniolo T, Bono E, Ding J, Raddrizzani L, Tuereci O, Sahin U, Braxenthaler M, Gallazzi F, Protti MP, Sinigaglia F, Hammer J. 1999. “Generation of tissue-specific and promiscuous HLA ligand databases using DNA microarrays and virtual HLA class II matrices”. Nat. Biotechnol. 17:555–561.

T. Sudo, N. Kamikawaji, A. Kimura, Y. Date, C.J. Savoie, H. Nakashima, E. Furuichi, S. Kuhara, and T. Sasazuki, “Differences in MHC Class I self peptide repertoires among HLA-A2 subtypes.” J. Immunol.: 155: 4749-4756, (1995).

T. Tana, N. Kamikawaji, C.J.Savoie, T. Sudo, Y. Kinoshita, T. Sasazuki, “A HLA binding motif-aided peptide epitope library: A novel library design for the screening of HLA-DR4-restricted antigenic peptides recognized by CD4+ T cells.” J. Human Genet., 43:14-21 (1998).

K. Falk, *et al.* “Allele-specific motifs revealed by sequencing of self-peptides eluted from MHC molecules”, Nature, Vol. 351, 290-297 (1991).

T Elliott *et al.* “Peptide-induced conformational change of the class I heavy chain”, Nature, Vol. 351, 402-407, (1991).

P. Parham, “Deconstructing the MHC”, Nature, Vol. 360, 300-301, (1992).

Hwai-Chen Guo *et al.*, “Different length peptides bind to HLA-Aw68 similarly at their ends but bulge out in the middle”, Nature, Vol. 360, 364-367, (1992).

Y. Chen *et al.* "Naturally processed peptides longer than nine amino acid residues bind to the class I MHC molecule HLA-A2.1 with high affinity and in different conformations", J. Immunol., 152, 2874-2881, (1994).

D. F. Hunt *et al.* "Characterization of peptides bound to the class I MHC molecule HLA-A2.1 by mass spectrometry", Science, Vol. 255, 1261-1263, (1992).

Generally, the prior art attempts to predict the immunogenicity of particular peptides by calculating the strength of binding between that peptide and the known binding environment of a particular MHC molecule. The binding environment involves a 'pocket' in the MHC molecule that is adapted to accept a peptide of a certain length (such as 7-15 amino acids). The structure of the pocket may already be known from previous X-ray crystallographic studies. This strength may be calculated mathematically using appropriate algorithms for atomic and molecular interaction. Alternatively, the prior art may attempt to 'score' the binding strength of a peptide based upon motifs existing in the peptide, such as particular amino acids being present at particular positions in a peptide of a certain length, e.g. a proline present at position 3 in an 8-amino acid peptide binding to a particular known HLA molecule. Generally these approaches have met with limited success.

The present inventors believe that they have improved upon the above theories from a better understanding of how T cells reacting against self-substances such as self-proteins are identified prior to their elimination (clonal deletion) or silencing (clonal anergy). Accordingly, the inventors have been able to identify specific immunogenic peptide sequences that may provide protection against specific pathogens, and have developed vaccines to these pathogens, using the identified sequences. In the case of the present invention, the inventors have developed peptides useful in influenza vaccines eliciting a T cell response.

Previously, influenza vaccines have been developed by identifying an existing influenza virus strain and then producing a vaccine specific to that virus. Generally, the vaccines have been based upon a B cell (antibody) response, the antibody being reactive with the surface antigens (i.e. Hemagglutinin and Neuraminidase) of the specific influenza virus strain against which it

has been developed. Typically, the surface proteins comprising the antigens are variable from one influenza virus strain to the next, since mutation of the virus to produce a new virus tends to occur in the surface proteins. The consequence of this is that conventional influenza vaccines generally protect only against one specific virus strain, and will not protect against a new strain that results from a mutation. Thus, a new vaccine is required for protection against an emerging strain. The clear problem with this approach is that there is a period of time between emergence of the new virus strain, and development of the vaccine, during which there is no protection available against the virus. If the virus is particularly harmful, this can lead to many millions of deaths, as occurred in the major influenza pandemics of the last century.

It has been known for some time that cytotoxic T lymphocytes may provide an immune response to influenza virus strains. Recent studies have shown that a CTL response in humans may be directed towards multiple epitopes. It has been suggested that there is a dominant response to the HLA-A2 restricted M-1 58-66 epitope. Such studies include A.C. Boon *et al*, J. Virol, Jan. 2002, 582-90; S. Tamura *et al* Jpn. J. Infect. Dis., Dec. 2004, 236-47; G. Deliyannis *et al* J. Virol., May 2002, 4212-21; C. Gianfrani *et al* Hum. Immunol., May 2000, 438-52; and J. Jameson *et al* J. Immunol., Jun. 1999, 7578-83.

There has recently also been investigation into specific immunogenic peptides that might be useful in developing an influenza vaccine eliciting a T cell response. Typically, such work has involved investigation of CTL response to test influenza peptides, e.g. in transgenic mice. The tested peptides tend to be short sequences that might be reactive to one MHC (or HLA) type, and are taken from a specific test influenza strain. For example, in Vaccine, 2005, 5231-44, N. Hu *et al* disclose testing wild type M1 58-66 peptide in HLA Tg mice expressing HLA-A2, -B7 or –B27. The results show that the peptide is an influenza epitope recognised by transgenic mice expressing HLA-A2. In Clin. Exp. Immunol., October 2005, 45-52, A.C. Boon *et al* disclose M1 58-66 and NP 44-52 influenza A peptides as epitopes recognised in HLA-A*0101 and HLA-A*0201 individuals. In Cell Immunol., April 2005, 110-123, E. Cheuk *et al* disclose NP 383-391 influenza A peptide as an epitope recognised in HLA-B27/H2 class I-deficient mice. Using epitope prediction programs, the authors identified three more B27 restricted influenza A epitopes, BP-2 702-710, PB-1 571-579 and

PB-2 368-376. In J. Immunol., Feb 2004, 2453-60, A.C. Boon *et al* disclose human CTL clones specific for natural variants of the HLA-B*3501-restricted epitope in NP 418-426. In J. Immunother., Jan-Feb 2003, 41-6, A. Trojan *et al* disclose the HLA-A3-restricted 9-mer RLEDVFAGK which is capable of inducing specific CTL reactivity. HLA-A2 restricted influenza A virus matrix peptide GILGFVFTL is also disclosed. In J. Gen. Virol., July 2001, 1749-55, S. Tourdot *et al* identify a murine D(k) restricted epitope derived from the influenza virus strain A/PR/8/34 polymerase protein PB-1, corresponding to amino acid residues 349-357 (ARLGKGYMF). In J. Immunol., April 2001, 4627-33, G.T. Belz *et al* identify an immunogenic peptide (SSYRRPVGI) from influenza polymerase protein PB-1, corresponding to amino acid residues 703-711 and a mimotope (ISPLMVAYM) from PB-2 polymerase. PCT/US2005/002954 discloses CTL epitopes comprising NP 265-273, having the sequence ILRGSVAHK, and also epitopes comprising NP 305-313. Finally, US 6,740325 discloses two CTL epitopes: NP 335-350, and NP 380-393.

Further studies have shown that data from transgenic mice provide a reliable model for the investigation of CTL responses in humans. In Int. Immunol., Apr. 1995, 597-605, S. Man *et al* have shown that the dominant influenza A epitope recognised by HLA-A2.1-restricted cytotoxic T lymphocytes from HLA-A2.1 transgenic mice was the matrix protein 1 (M-1) peptide epitope that is immunodominant in human CTL responses. Further studies in this area have been conducted by E.J. Bernhard *et al* (J. Exp. Med., Sep 1998, 1157-62) and E. Cheuk *et al* (J. Immunol., Nov 2002, 5571-80).

However, although known epitopes have been studied extensively, none has yet been satisfactory for forming the basis of an influenza vaccine that is capable of protecting against more than a single strain of influenza virus. Moreover, vaccines based upon these single epitopes, even if they were to provide some protection, would likely be specific for a particular HLA, making them ineffective in a large proportion of the human population.

Thus, a significant problem with known vaccines, whether relying on a B-cell or T-cell response is that they only protect against an existing virus strain, and do not provide protection against possible future strains that might develop. With the emergence of the highly dangerous H5N1 strain in the avian population, the need for a vaccine in advance of a

human pandemic based upon a subsequent mutation of the H5N1 strain has become more acute. Moreover, vaccines based upon known peptides eliciting T-cell responses may not be effective in large sections of the population.

Accordingly, it is an aim of the present invention to solve the problems associated with the known prior art as set out above. It is a further aim of the present invention to provide a polypeptide that is capable of eliciting a CTL immune response in vertebrates against a plurality of influenza strains and/or in a plurality of individuals expressing differing MHCs (HLAs). It is a further aim of the present invention to provide an influenza vaccine using the polypeptide of the invention. Preferably the vaccine is capable of protection against a plurality of influenza strains and/or is effective in a plurality of individuals expressing differing MHCs (HLAs).

Accordingly, the present invention provides a polypeptide having no more than 100 amino acids, which polypeptide comprises one or more sequences having at least 60% homology with any of SEQ ID 1-6, or comprises two or more epitopes having 7 amino acids or more, each epitope having at least 60% homology with a sub-sequence of any of SEQ ID 1-6 that has the same length as the epitope:

SEQ ID 1 DLEALMEWLKTRPILSPLTKGILGFVFTLTVP
SEQ ID 2 LLYCLMVMYLNPGNYSMQVKLGTLCALCEKQASHS
SEQ ID 3 DLIFLARSALILRGSVAHKSC
SEQ ID 4 PGIADIEDLTLLARSMVVVRP
SEQ ID 5 LLIDGTASLSPGMMMGMFNMLSTVLGVSILNLGQ
SEQ ID 6 IIGILHLILWILDRLFFKCIYRLF

wherein, the polypeptide is immunogenic in a vertebrate expressing a major histocompatibility complex (MHC) allele, and wherein the polypeptide is not a complete influenza virus protein.

Thus, the polypeptide is one that may comprise the whole of (or may comprise at least two 7 or more residue parts of) any of the above sequences, but cannot have more than 100 amino

acid residues in total. The polypeptide must also be immunogenic in a vertebrate expressing an MHC (HLA in humans) allele. An immunogenic polypeptide is understood in the present context to mean a polypeptide that elicits an immune response in a vertebrate, such as by binding to a vertebrate MHC and causing it to react with a cytotoxic T cell lymphocyte. One method for determining whether a polypeptide possesses immunogenicity is set out in Experiment 1 below. However, the present invention may not be limited to such methods, and the skilled person may select any known method for determining immunogenicity, as desired.

As mentioned above, the polypeptide may be one comprising two 7 or more residue epitopes that react with one or more MHCs and so elicit a broad CTL response. The response may be in a single individual or may be in at least two different individuals (and the individuals may be of the same species or different species). Thus, the polypeptide may comprise at least two different 7 or more residue epitopes, each of which individually provides a response to a different subject. An epitope in the context of the present invention is a part of a polypeptide which is capable of binding to a vertebrate MHC in a vertebrate, preferably eliciting an immune response, such as by causing the MHC-epitope complex to react with a CTL. One method for determining whether a polypeptide is or contains an epitope is set out in Experiment 1 below. However, the present invention may not be limited to such methods, and the skilled person may select any known method for determining whether a polypeptide is or contains an epitope, as desired.

The present inventors have found that the above sequences comprise a plurality of CTL epitopes, which may afford protection against influenza for a wide variety of vertebrates in a population. In addition, the inventors have analysed all known influenza virus strain sequences across all species, and have found that the specified sequences are remarkably conserved across all known influenza virus strains. As such, these sequences are very unlikely to be significantly altered in new strains resulting from mutation of existing strains. Accordingly, the epitopes within these sequences that provide protection are highly likely to be present in unchanged form in new strains, since mutation does not normally occur in these regions. Consequently, these epitopes provide excellent opportunity not only for providing protection against existing influenza strains (such as the H5N1 strain of ‘bird flu’), but also

protecting against as yet unknown strains (such as a mutated form of H5N1 that could pass easily from human to human and form the basis of a pandemic).

As discussed above, the sequences have been identified after analysis of all known influenza virus strain sequences across all species. The sequences are thus consensus sequences developed from the above analysis. Despite being consensus sequences, the sequences in some cases correspond exactly to natural sequences in some of the known influenza virus strains. Due to the remarkable conservation in the sequences across all viruses in all species, the consensus sequences, even when differing from actual sequences, only differ in a small number of residues, and thus contain many smaller epitopes (8-mers, 9-mers, 10-mers or the like.) for which there are no differences from natural sequences. The above consensus sequences as a whole thus contain many effective epitopes that are the same as the natural epitopes, as well as effective epitopes that differ only slightly from natural epitopes. It will be apparent to the skilled person that the invention extends not only to the consensus sequences and their epitopes, but also to the corresponding actual sequences in any influenza virus strains. Thus, sequences with some homology to the consensus sequences are also within the scope of the invention. Such homology allows substitution of, for example, up to 3 amino acids in an 8-mer epitope (62.5% homology) or in a 9–mer, 10-mer, or 11-mer epitope. It is preferred that no more than 10 such substitutions are identifiable in a sequence of the invention corresponding to the full sequences of SEQ ID 1-6 (66.6% homology for a 30-mer). Such substitutions are preferably conservative substitutions in line with known substitution schemes.

Having in mind that the invention extends from the consensus sequence to the corresponding natural sequences, then the invention also provides a polypeptide having no more than 100 amino acids, which polypeptide comprises one or more sequences defined by the following amino acid residues of an influenza virus protein, or comprises two or more epitopes having 7 amino acids or more from a sequence defined by the following amino acid residues of an influenza virus protein:

residues 36-75	of an M1 protein (preferably from an influenza A strain)
residues 124-158	of an M1 protein (preferably from an influenza B strain)

residues 255-275 of an NP protein (preferably from an influenza A strain)
residues 306-326 of an NP protein (preferably from an influenza B strain)
residues 395-428 of a PB1 protein
residues 32-55 of an M2 protein

wherein, the polypeptide is immunogenic in a vertebrate expressing a major histocompatibility complex (MHC) allele, and wherein the polypeptide is not a complete influenza virus protein.

The sequence numbering referred to in the present invention is defined according to well-recognised principles. Thus, the numbering begins at 1 from the recognised translation initiation codon (ATG). This corresponds to a Methionine (M), for the segment of the Influenza genome coding for the protein of interest. In other words, it begins at 1 in respect of the Methionine shown as the first amino acid in the protein sequence of interest as used and defined by the databases in which the sequences have been set forth (i.e. GenBank, SwissProt, or the like.).

The present invention will be described in more detail by way of example only with reference to the following Figures, in which:

Figure 1A to 1F show IFN-γ production by primary splenocyte cultures of FLU-v and NRP vaccinated mice stimulated with Con A (10 μg/ml), soluble Lysozyme (5 μg/ml), purified soluble polypeptides (P1 (Figure 1A), P2 (Figure 1B), P3 (Figure 1C), P4 (Figure 1D), P5 (Figure 1E) and P6 (Figure 1F); 5 μg/ml) and HLA-matched T1 (T1) and mismatched JURKAT (Ju) human cells transfected with either Lysozyme, P1, P2, P3, P4, P5 or P6 according to the protocol described in Example 1 below (splenocyte to transfected cell ratio is 10:1). IFN-γ production is represented as the differential between the level of production in response to the antigen considered minus the IFN-γ produced in response to either soluble Lysozyme or the corresponding cell transfected with Lysozyme. Background levels of Lysozyme mediated production of IFN-γ were for soluble antigen 25 ± 10 pg/ml, for antigen in T1 316 ± 43 pg/ml, and for antigen in Jurkat 19 ± 6 pg/ml;

Figure 2 shows IFN-γ production by primary splenocyte cultures of FLU-v and NRP vaccinated mice stimulated with Con A (10 μg/ml), soluble Lysozyme (5 μg/ml), purified soluble FLU-v polypeptide preparation (P1, P2, P3, P4, P5 and P6 all together at 5 μg/ml) and HLA-matched T1 (T1) and mismatched JURKAT (Ju) human cells either infected with influenza strains A/New_Caledonia/20/99, A/NYMC/X-147 or B/Johannesburg/5/99 or transfected with Lysozyme according to the protocol described in Example 1 below (splenocyte to infected/transfected cell ratio is 10:1); IFN-γ production is represented as the differential between the level of production in response to the antigen considered minus the IFN-γ produced in response to either soluble Lysozyme or the corresponding cell transfected with Lysozyme; background levels of Lysozyme mediated production of IFN-γ were for soluble antigen 25 ± 10 pg/ml, for antigen in T1 316 ± 43 pg/ml, and for antigen in Jurkat 19 ± 6 pg/ml; and

Figures 3A and 3B show survival of animals following a lethal challenge with Influenza A/PR/8/34; animals were immunised subcutaneously with either FLU-v or NRP-v on days 1 and 15 and on day 20 all were challenged intranasally with 45 μl of the virus ($5x10^7$ pfu per dose) under anaesthesia; animals in Fig 3A were inoculated intraperitoneally with 100 μg of rat anti-mouse CD8 sera on days 19 and 22; animals in Fig 3B were inoculated intraperitoneally with an irrelevant rat sera on days 19 and 22; the arrow indicates the date of intranasal challenge whilst the diamonds indicate the date animals were inoculated with the anti-CD8 sera.

The polypeptide described above typically comprises one or more (preferably two or more) epitopes. These epitopes are preferably T cell epitopes, such as cytotoxic T lymphocyte (CTL) epitopes. Generally the polypeptide is immunogenic to an influenza virus strain, and preferably to a plurality of influenza virus strains. In the present context, a polypeptide immunogenic to an influenza virus strain is understood to mean a polypeptide that is part of an influenza virus protein and that elicits an immune system response, such as by exhibiting CTL reactivity when bound to an MHC. One method for determining whether a polypeptide possesses such immunogenicity is set out in Experiment 1 below. However, the present invention may not be limited to such methods, and the skilled person may select any known method for determining immunogenicity, as desired.

In the present invention, the polypeptide comprises two or more sequences as described above. Typically, two, three, four, five or more such sequences may be present in the polypeptide, if desired. The more such epitopes are present, the greater the breadth of protection afforded within a population of humans and/or animals individuals with differing HLAs or MHCs.

The polypeptide according to the present invention may also comprise one or more further sequences that are not epitopes, if desired. Typically the further sequences are from one or more influenza virus proteins. These sequences may be situated between two or more of the sequences (the epitopes) described above, or may be situated at one or both ends of the polypeptide. The presence of such further sequences should not affect the function of the polypeptide, provided that the polypeptide as a whole does not become too large, interfering with the presentation of the epitopes in the vertebrate's immune system. In specific embodiments of the invention, when the polypeptide is homologous to SEQ ID 1, the further sequences are preferably one or more from an influenza M1 protein (preferably from an influenza A strain), when the polypeptide is homologous to SEQ ID 2, the further sequences are preferably one or more from an influenza M1 protein (preferably from an influenza B strain), when the polypeptide is homologous to SEQ ID 3, the further sequences are preferably one or more from an influenza NP protein (preferably from an influenza A strain), when the polypeptide is homologous to SEQ ID 4, the further sequences are preferably one or more from an influenza NP protein (preferably from an influenza B strain), when the polypeptide is homologous to SEQ ID 5, the further sequences are preferably one or more from an influenza PB1 protein, and when the polypeptide is homologous to SEQ ID 6, the further sequences are preferably one or more from an influenza M2 protein.

In the most preferred embodiments, the further sequences from the above-mentioned proteins are ones within the following consensus sequences, or ones having at least 60% homology with a sequence within the following consensus sequences:

M1 Influenza A Consensus – SEQ ID 7

MSLLTEVETYVLSIVPSGPLKAEIAQRLEDVFAGKNTDLEALMEWLKTRPILSPLTKG
ILGFVFTLTVPSERGLQRRRFVQNALNGNGDPNNMDKAVKLYRKLKREITFHGAKEI
ALSYSAGALASCMGLIYNRMGAVTTEVAFGLVCATCEQIADSQHRSHRQMVATTNP
LIKHENRMVLASTTAKAMEQMAGSSEQAAEAMEIASQARQMVQAMRTVGTHPSSS
TGLRDDLLENLQTYQKRMGVQMQRFK

M1 Influenza B Consensus – SEQ ID 8

MSLFGDTIAYLLSLTEDGEGKAELAEKLHCWFGGKEFDLDSALEWIKNKRCLTDIQK
ALIGASICFLKPKDQERKRRFITEPLSGMGTTATKKKGLILAERKMRRCVSFHEAFEIA
EGHESSALLYCLMVMYLNPGNYSMQVKLGTLCALCEKQASHSHRAHSRAARSSVP
GVRREMQMVSAMNTAKTMNGMGKGEDVQKLAEELQSNIGVLRSLGASQKNGEGI
AKDVMEVLKQSSMGNSALVKKYL

NP Influenza A Consensus– SEQ ID 9

MASQGTKRSYEQMETDGDRQNATEIRASVGKMIDGIGRFYIQMCTELKLSDYEGRLI
QNSLTIEKMVLSAFDERRNRYLEEHPSAGKDPKKTGGPIYRRVDGKWMRELVLYDK
EEIRRIWRQANNGEDATAGLTHMMIWHSNLNDATYQRTRALVRTGMDPRMCSLMQ
GSTLPRRSGAAGAAVKGIGTMVMELIRMIKRGINDRNFWRGENGRKTRSAYERMCN
ILKGKFQTAAQRAMVDQVRESRNPGNAEIEDLIFLARSALILRGSVAHKSCLPACVY
GPAVSSGYDFEKEGYSLVGIDPFKLLQNSQVYSLIRPNENPAHKSQLVWMACHSAAF
EDLRLLSFIRGTKVSPRGKLSTRGVQIASNENMDNMGSSTLELRSGYWAIRTRSGGN
TNQQRASAGQISVQPTFSVQRNLPFEKSTVMAAFTGNTEGRTSDMRAEIIRMMEGAK
PEEVSFRGRGVFELSDEKATNPIVPSFDMSNEGSYFFGDNAEEYDN

NP Influenza B Consensus– SEQ ID 10

MSNMDIDGINTGTIDKTPEEITSGTSGTTRPIIRPATLAPPSNKRTRNPSPERATTSSEA
DVGRKTQKKQTPTEIKKSVYNMVVKLGEFYNQMMVKAGLNDDMERNLIQNAHAV
ERILLAATDDKKTEFQKKKNARDVKEGKEEIDHNKTGGTFYKMVRDDKTIYFSPIRI
TFLKEEVKTMYKTTMGSDGFSGLNHIMIGHSQMNDVCFQRSKALKRVGLDPSLISTF
AGSTLPRRSGATGVAIKGGGTLVAEAIRFIGRAMADRGLLRDIKAKTAYEKILLNLK
NKCSAPQQKALVDQVIGSRNPGIADIEDLTLLARSMVVVRPSVASKVVLPISIYAKIP
QLGFNVEEYSMVGYEAMALYNMATPVSILRMGDDAKDKSQLFFMSCFGAAYEDLR
VLSALTGTEFKPRSALKCKGFHVPAKEQVEGMGAALMSIKLQFWAPMTRSGGNEV
GGDGGSGQISCSPVFAVERPIALSKQAVRRMLSMNIEGRDADVKGNLLKMMNDSM
AKKTNGNAFIGKKMFQISDKNKTNPVEIPIKQTIPNFFFGRDTAEDYDDLDY

PB1 Influenza Consensus– SEQ ID 11

MDVNPTLLFLKVPAQNAISTTFPYTGDPPYSHGTGTGYTMDTVNRTHQYSEKGKWT
TNTETGAPQLNPIDGPLPEDNEPSGYAQTDCVLEAMAFLEESHPGIFENSCLETMEVV
QQTRVDKLTQGRQTYDWTLNRNQPAATALANTIEVFRSNGLTANESGRLIDFLKDV
MESMDKEEMEITTHFQRKRRVRDNMTKKMVTQRTIGKKKQRVNKRGYLIRALTLN
TMTKDAERGKLKRRAIATPGMQIRGFVYFVETLARSICEKLEQSGLPVGGNEKKAKL
ANVVRKMMTNSQDTELSFTITGDNTKWNENQNPRMFLAMITYITKNQPEWFRNILSI
APIMFSNKMARLGKGYMFESKRMKLRTQIPAEMLASIDLKYFNESTRKKIEKIRPLLI
DGTASLSPGMMMGMFNMLSTVLGVSILNLGQKKYTKTTYWWDGLQSSDDFALIVN
APNHEGIQAGVDRFYRTCKLVGINMSKKKSYINKTGTFEFTSFFYRYGFVANFSMEL
PSFGVSGINESADMSIGVTVIKNNMINNDLGPATAQMALQLFIKDYRYTYRCHRGDT
QIQTRRSFELKKLWDQTQSKAGLLVSDGGPNLYNIRNLHIPEVCLKWELMDEDYRG
RLCNPLNPFVSHKEIESVNNAVVMPAHGPAKSMEYDAVATTHSWIPKRNRSILNTSQ
RGILEDEQMYQKCCNLFEKFFPSSSYRRPVGISSMVEAMVSRARIDARIDFESGRIKK
EEFSEIMKICSTIEELRRQKK

M2 Influenza Consensus– SEQ ID 12

MSLLTEVETPIRNEWGCRCNDSSDPLVVAASIIGILHLILWILDRLFFKCIYRLFKHGL
KRGPSTEGVPESMREEYRKEQQNAVDADDSHFVSIELE

The homology referred to above in respect of these sequences is preferably 75%, 85%, 95% or substantially 100%.

In the present invention, the influenza strain may not be especially limited, and the polypeptides may be immunogenic against, and/or derived from, any known influenza strain. Preferably, however, the relevant strain is an Influenza A or Influenza B strain. Future influenza strains that have mutated from any of these existing strains may also be ones against which the polypeptides are immunogenic, or from which the polypeptides are derived.

The proteins within which the sequences defining the polypeptides of the present invention are situated are selected from M1, NP, PB and M2 proteins from any influenza virus strain (especially A and B strains) (the consensus sequences of which for all analysed sequences, or alternatively the positions of which within the protein, are described above). The following specific proteins were analysed by the inventors, and preferably the influenza virus proteins referred to in the invention are selected from these specific proteins, or mutations from these proteins. Thus, the specific sequences homologous to SEQ ID 1-6 described above are preferably the ones at the appropriate positions within the following proteins. Similarly, the sequences of the present invention defined by the residue positions within proteins from any influenza strain, namely residues 36-75 of M1 protein (especially infuenza A M1), residues 124-158 of M1 protein (especially in influenza B M1), residues 255-275 of NP protein (especially in influenza A NP), residues 306-326 of NP protein (especially in influenza B NP), residues 395-428 of PB1 protein, and residues 32-55 of M2 protein, are preferably those within the following specific proteins. The list is in the form |version number (gi number)|database identification (e.g. gb for GenBank)|NCBI accession number|optional further information (e.g. the accession number of the nucleotide sequence from which the protein sequence is derived). The sequences and corresponding influenza strains from which they derive can all be found from the public NCBI protein database, which may be accessed online at the following URL address http://www.ncbi.nlm.nih.gov/entrez/query/static/help/helpdoc.html#Protein. The protein database contains sequence data from the translated coding regions from DNA sequences in GenBank, EMBL, and DDBJ as well as protein sequences submitted to Protein Information

Resource (PIR), SWISS-PROT, Protein Research Foundation (PRF), and Protein Data Bank (PDB) (sequences from solved structures).

M1 proteins

|27530653|dbj|BAC54009.1|; |27530634|dbj|BAC53998.1|; |53829719|gb|AAU94746.1|; |53829716|gb|AAU94744.1|; |53829713|gb|AAU94742.1|; |53829710|gb|AAU94740.1|; |53829707|gb|AAU94738.1|; |53829704|gb|AAU94736.1|; |53829701|gb|AAU94734.1|; |53829698|gb|AAU94732.1|; |53829695|gb|AAU94730.1|; |53829692|gb|AAU94728.1|; |53829689|gb|AAU94726.1|; |53829686|gb|AAU94724.1|; |53829683|gb|AAU94722.1|; |8486160|ref|NP_056664.1|; |30466242|ref|NP_848689.1|; |30349250|gb|AAP22121.1|; |30466211|ref|NP_848672.1|; |30349219|gb|AAP22104.1|; |4761025|gb|AAD29208.1|AF100392_1|; |4761022|gb|AAD29206.1|AF100391_1|; |4761019|gb|AAD29204.1|AF100390_1|; |4761016|gb|AAD29202.1|AF100389_1|; |4761013|gb|AAD29200.1|AF100388_1|; |4761010|gb|AAD29198.1|AF100387_1|; |4761007|gb|AAD29196.1|AF100386_1|; |4761004|gb|AAD29194.1|AF100385_1|; |4761001|gb|AAD29192.1|AF100384_1|; |4760998|gb|AAD29190.1|AF100383_1|; |4760995|gb|AAD29188.1|AF100382_1|; |4760992|gb|AAD29186.1|AF100381_1|; |4760989|gb|AAD29184.1|AF100380_1|; |4760986|gb|AAD29182.1|AF100379_1|; |4760983|gb|AAD29180.1|AF100378_1|; |4760980|gb|AAD29178.1|AF100377_1|; |4760977|gb|AAD29176.1|AF100376_1|; |4760974|gb|AAD29174.1|AF100375_1|; |4760971|gb|AAD29172.1|AF100374_1|; |12862823|dbj|BAB32623.1|; |12862820|dbj|BAB32621.1|; |12862817|dbj|BAB32619.1|; |5702096|gb|AAD47140.1|; |51340785|gb|AAU01001.1|; |50059438|gb|AAT69451.1|; |50059400|gb|AAT69429.1|; |50059419|gb|AAT69440.1|; |325196|gb|AAA67100.1|; |325202|gb|AAA43726.1|; |138823|sp|P03489|VMT1_INBLE|; |138824|sp|P06816|VMT1_INBSI|; |138822|sp|P13880|VMT1_INBAD|; |138821|sp|P13879|VMT1_INBAC|; |325198|gb|AAA66416.1|; |325194|gb|AAA66414.1|; |9049382|dbj|BAA99399.1|; |5764368|gb|AAD51265.1|AF153257_1|; |76443315|gb|ABA42441.1|; |76443312|gb|ABA42439.1|; |76443309|gb|ABA42437.1|; |76443306|gb|ABA42435.1|; |76443303|gb|ABA42433.1|; |21636455|gb|AAM70003.1|AF457712_1|; |21636450|gb|AAM70000.1|AF457710_1|; |21636434|gb|AAM69991.1|AF457703_1|; |21636416|gb|AAM69981.1|AF457695_1|; |21636398|gb|AAM69971.1|AF457687_1|; |21636378|gb|AAM69960.1|AF457678_1|; |9802291|gb|AAF99672.1|AF258523_1|; |9802288|gb|AAF99670.1|AF258522_1|; |5764374|gb|AAD51269.1|AF153259_1|; |5805289|gb|AAD51928.1|AF144306_1|; |5764371|gb|AAD51267.1|AF153258_1|; |71655384|gb|AAZ38740.1|; |71655379|gb|AAZ38738.1|; |71655371|gb|AAZ38736.1|; |71655356|gb|AAZ38734.1|; |71655345|gb|AAZ38732.1|; |71655341|gb|AAZ38730.1|; |71655320|gb|AAZ38728.1|; |73852957|ref|YP_308671.1|; |73912688|ref|YP_308854.1|; |28849409|gb|AAO52887.1|AF509044_1|; |5732422|gb|AAD49093.1|AF156470_2|; |5732419|gb|AAD49091.1|AF156469_2|; |5732416|gb|AAD49089.1|AF156468_2|; |28194354|gb|AAO33517.1|AF474058_1|; |28194351|gb|AAO33515.1|AF474057_1|; |28194348|gb|AAO33513.1|AF474056_1|; |28194345|gb|AAO33511.1|AF474055_1|; |28194342|gb|AAO33509.1|AF474054_1|; |28194339|gb|AAO33507.1|AF474053_1|; |28194336|gb|AAO33505.1|AF474052_1|; |28194333|gb|AAO33503.1|AF474051_1|; |28194330|gb|AAO33501.1|AF474050_1|; |28194327|gb|AAO33499.1|AF474049_1|; |28849451|gb|AAO52908.1|AF509065_1|; |28849449|gb|AAO52907.1|AF509064_1|;

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|37785163|gb|AAO46420.1|; |37785160|gb|AAO46418.1|; |37785157|gb|AAO46416.1|;
|37785154|gb|AAO46414.1|; |37785151|gb|AAO46412.1|; |37785145|gb|AAO46408.1|;
|37785142|gb|AAO46406.1|; |37785139|gb|AAO46404.1|; |37785136|gb|AAO46402.1|;
|37785133|gb|AAO46400.1|; |37785130|gb|AAO46398.1|; |37785127|gb|AAO46396.1|;
|37785124|gb|AAO46394.1|; |37785121|gb|AAO46392.1|; |37785118|gb|AAO46390.1|;
|37785115|gb|AAO46388.1|; |37785112|gb|AAO46386.1|; |37785109|gb|AAO46384.1|;
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|37785097|gb|AAO46376.1|; |37785094|gb|AAO46374.1|; |37785091|gb|AAO46372.1|;
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|37785079|gb|AAO46364.1|; |37785076|gb|AAO46362.1|; |37785073|gb|AAO46360.1|;
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|37785061|gb|AAO46352.1|; |37785058|gb|AAO46350.1|; |37785055|gb|AAO46348.1|;
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|324322|gb|AAA43294.1|; |325068|gb|AAA43674.1|; |324395|gb|AAA43344.1|;
|324371|gb|AAA43316.1|; |324334|gb|AAA43302.1|; |324316|gb|AAA43290.1|;
|324310|gb|AAA43286.1|; |324299|gb|AAA43277.1|;
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|324948|gb|AAA43635.1|; |324946|gb|AAA43634.1|; |324944|gb|AAA43633.1|;
|324942|gb|AAA43632.1|; |133503|sp|P27153|RRP1_DHVI1|; |279899|pir|A60008|;
|279898|pir|B60011|; |67089|pir|P1IV61|; |77917350|gb|ABB05224.1|;
|77917331|gb|ABB05213.1|; |77917312|gb|ABB05202.1|; |77869502|gb|ABB05191.1|;
|77863505|gb|ABB05013.1|; |77863486|gb|ABB05002.1|; |77863467|gb|ABB04991.1|;
|77863448|gb|ABB04980.1|; |77863429|gb|ABB04969.1|; |77863410|gb|ABB04958.1|;
|77863391|gb|ABB04947.1|; |77863372|gb|ABB04936.1|; |77863353|gb|ABB04925.1|;
|77863334|gb|ABB04914.1|; |77861881|gb|ABB04379.1|; |77861862|gb|ABB04368.1|;
|77861843|gb|ABB04357.1|; |77861824|gb|ABB04346.1|; |77861805|gb|ABB04335.1|;
|77861786|gb|ABB04324.1|; |77861767|gb|ABB04313.1|; |77861748|gb|ABB04302.1|;
|77861729|gb|ABB04291.1|; |77747474|gb|ABB03153.1|; |77747455|gb|ABB03142.1|;
|77747436|gb|ABB03131.1|; |77747416|gb|ABB03120.1|; |77747397|gb|ABB03109.1|;
|77747378|gb|ABB03098.1|; |77747359|gb|ABB03087.1|; |77747340|gb|ABB03076.1|;
|77747319|gb|ABB03065.1|; |77747300|gb|ABB03054.1|; |77747281|gb|ABB03043.1|;
|77747262|gb|ABB03032.1|; |77747243|gb|ABB03021.1|; |77747224|gb|ABB03010.1|;
|77747205|gb|ABB02999.1|; |77747186|gb|ABB02988.1|; |77747165|gb|ABB02977.1|;
|77747146|gb|ABB02966.1|; |77747127|gb|ABB02955.1|; |77747108|gb|ABB02944.1|;
|77747087|gb|ABB02932.1|; |77747068|gb|ABB02921.1|; |77747049|gb|ABB02910.1|;
|77747003|gb|ABB02899.1|; |77746984|gb|ABB02888.1|; |77746965|gb|ABB02877.1|;
|77746946|gb|ABB02866.1|; |77746927|gb|ABB02855.1|; |77746906|gb|ABB02844.1|;
|77746887|gb|ABB02833.1|; |77746868|gb|ABB02822.1|; |77746849|gb|ABB02811.1|;
|77746830|gb|ABB02800.1|; |77746811|gb|ABB02789.1|; |66733937|gb|AAY52743.1|;
|66733935|gb|AAY52742.1|; |66733933|gb|AAY52741.1|; |66733931|gb|AAY52740.1|;
|66733929|gb|AAY52739.1|; |66733927|gb|AAY52738.1|; |66733925|gb|AAY52737.1|;
|66733923|gb|AAY52736.1|; |66733921|gb|AAY52735.1|; |66733919|gb|AAY52734.1|;

|66733917|gb|AAY52733.1|; |66733915|gb|AAY52732.1|; |66733913|gb|AAY52731.1|; |66733911|gb|AAY52730.1|; |66733909|gb|AAY52729.1|; |66733907|gb|AAY52728.1|; |66733905|gb|AAY52727.1|; |66733903|gb|AAY52726.1|; |66733901|gb|AAY52725.1|; |66733899|gb|AAY52724.1|; |66733897|gb|AAY52723.1|; |66733895|gb|AAY52722.1|; |66733893|gb|AAY52721.1|; |66733891|gb|AAY52720.1|; |66733889|gb|AAY52719.1|; |66733887|gb|AAY52718.1|; |66733885|gb|AAY52717.1|; |66733883|gb|AAY52716.1|; |13925401|gb|AAK49363.1|AF258827_1|; |13274640|gb|AAK18014.1|AF258823_1|; |13274638|gb|AAK18013.1|AF258822_1|; |50296446|gb|AAT73499.1|; |8307775|gb|AAF74316.1|AF084266_1|; |8307773|gb|AAF74315.1|AF084265_1|; |8307771|gb|AAF74314.1|AF084264_1|; |73852949|ref|YP_308665.1|; |71013490|dbj|BAE07199.1|; |54610035|gb|AAV35116.1|; |54299856|gb|AAV32652.1|; |54299842|gb|AAV32644.1|; |13925398|gb|AAK49362.1|AF258826_1|; |13925395|gb|AAK49361.1|AF258825_1|; |13925392|gb|AAK49360.1|AF258824_1|; |13925389|gb|AAK49359.1|AF258821_1|; |13925386|gb|AAK49358.1|AF258820_1|; |13925383|gb|AAK49357.1|AF258819_1|; |13925380|gb|AAK49356.1|AF258818_1|; |13925377|gb|AAK49355.1|AF258817_1|; |13925374|gb|AAK49354.1|AF258816_1|; |47156561|gb|AAT12168.1|; |47156559|gb|AAT12167.1|; |47156557|gb|AAT12166.1|; |47156555|gb|AAT12165.1|; |47156553|gb|AAT12164.1|; |47156551|gb|AAT12163.1|; |47156549|gb|AAT12162.1|; |47156547|gb|AAT12161.1|; |47156545|gb|AAT12160.1|; |47156543|gb|AAT12159.1|; |47156541|gb|AAT12158.1|; |47156539|gb|AAT12157.1|; |47156537|gb|AAT12156.1|; |47156535|gb|AAT12155.1|; |47156533|gb|AAT12154.1|; |47156531|gb|AAT12153.1|; |47156529|gb|AAT12152.1|; |47156527|gb|AAT12151.1|; |47156525|gb|AAT12150.1|; |47156523|gb|AAT12149.1|; |47156521|gb|AAT12148.1|; |1430831|emb|CAA67498.1|; |19422189|gb|AAL87925.1|AF455727_1|; |19422183|gb|AAL87922.1|AF455724_1|; |19422181|gb|AAL87921.1|AF455723_1|; |14532423|gb|AAK64188.1|; |13661046|emb|CAC37002.1|; |5805279|gb|AAD51923.1|; |57916067|gb|AAW59406.1|; |57916013|gb|AAW59396.1|; |57915966|gb|AAW59388.1|; |47716769|gb|AAT37561.1|; |58531173|dbj|BAD89344.1|; |58531153|dbj|BAD89333.1|; |58531135|dbj|BAD89323.1|; |58531117|dbj|BAD89313.1|; |58531085|dbj|BAD89303.1|; |50956624|gb|AAT90830.1|; |50296498|gb|AAT73525.1|; |50296468|gb|AAT73510.1|; |50296462|gb|AAT73507.1|; |50296458|gb|AAT73505.1|; |50296456|gb|AAT73504.1|; |50296454|gb|AAT73503.1|; |50296452|gb|AAT73502.1|; |50296450|gb|AAT73501.1|; |50296448|gb|AAT73500.1|; |50296444|gb|AAT73498.1|; |50296440|gb|AAT73496.1|; |50296438|gb|AAT73495.1|; |50296436|gb|AAT73494.1|; |50296432|gb|AAT73492.1|; |50296430|gb|AAT73491.1|; |50296428|gb|AAT73490.1|; |50296416|gb|AAT73484.1|; |50296414|gb|AAT73483.1|; |50296412|gb|AAT73482.1|; |37963694|gb|AAR05984.1|; |37963692|gb|AAR05983.1|; |37963696|gb|AAR05985.1|; |38524562|dbj|BAD02360.1|; |38524542|dbj|BAD02349.1|; |24286097|gb|AAN46833.1|; |61612044|gb|AAX47280.1|; |61612038|gb|AAX47279.1|; |71000178|dbj|BAE07153.1|; |30025725|gb|AAP04506.1|; |70905275|gb|AAZ14161.1|; |70905273|gb|AAZ14160.1|; |70905271|gb|AAZ14159.1|; |70905269|gb|AAZ14158.1|; |70905267|gb|AAZ14157.1|; |70905265|gb|AAZ14156.1|; |70905263|gb|AAZ14155.1|; |70905261|gb|AAZ14154.1|; |70905259|gb|AAZ14153.1|; |70905257|gb|AAZ14152.1|; |70905255|gb|AAZ14151.1|; |70905253|gb|AAZ14150.1|; |3335435|gb|AAC32096.1|; |3335415|gb|AAC32085.1|; |56548870|gb|AAV97600.1|; |56548868|gb|AAV97599.1|; |56548866|gb|AAV97598.1|; |56548864|gb|AAV97597.1|; |56424948|gb|AAV91207.1|; |56424946|gb|AAV91206.1|; |56424942|gb|AAV91204.1|; |50542650|gb|AAT78590.1|; |50365727|gb|AAT76165.1|; |47834828|gb|AAT39049.1|; |47834824|gb|AAT39047.1|; |47834822|gb|AAT39046.1|; |47834814|gb|AAT39042.1|;

|47834812|gb|AAT39041.1|; |40732896|emb|CAF04464.1|; |14275693|emb|CAC40038.1|; |13383273|dbj|BAB39508.1|; |13383271|dbj|BAB39507.1|; |13661044|emb|CAC37001.1|; |28823019|gb|AAO46859.1|; |28822828|gb|AAO46858.1|; |28822609|gb|AAO46857.1|; |28822076|gb|AAO46856.1|; |28821871|gb|AAO46855.1|; |28821644|gb|AAO46854.1|; |28821462|gb|AAO46853.1|; |28821280|gb|AAO46852.1|; |28821223|gb|AAO46851.1|; |27462113|gb|AAO15325.1|AF225521_1|; |27462111|gb|AAO15324.1|AF225520_1|; |27462109|gb|AAO15323.1|AF225519_1|; |27462107|gb|AAO15322.1|AF225518_1|; |21359664|gb|AAM49557.1|AF468839_1|; |20068025|emb|CAC84758.1|; |20068023|emb|CAC84686.1|; |20068021|emb|CAC84757.1|; |20068019|emb|CAC84756.1|; |20068017|emb|CAC84755.1|; |20068015|emb|CAC84754.1|; |20068007|emb|CAC84750.1|; |19697848|gb|AAL31425.1|; |19697846|gb|AAL31424.1|; |19697836|gb|AAL31419.1|; |19422195|gb|AAL87928.1|AF455730_1|; |19422193|gb|AAL87927.1|AF455729_1|; |19422191|gb|AAL87926.1|AF455728_1|; |19422187|gb|AAL87924.1|AF455726_1|; |19422185|gb|AAL87923.1|AF455725_1|; |16076717|gb|AAL14089.1|AF222819_1|; |16076715|gb|AAL14088.1|AF222818_1|; |13661048|emb|CAC37003.1|; |8452850|gb|AAF75122.1|AF115293_1|; |8452848|gb|AAF75121.1|AF115292_1|; |323669|gb|AAA42968.1|; |133517|sp|P16508|RRP1_IAMAN|; |133523|sp|P03430|RRP1_IAWIL|; |2506782|sp|P16506|RRP1_IAKOR|; |133527|sp|P16512|RRP1_IAZTF|; |133526|sp|P16510|RRP1_IAZON|; |133525|sp|P16509|RRP1_IAZH3|; |133524|sp|P16514|RRP1_IAWIS|; |133522|sp|P16513|RRP1_IATKM|; |133521|sp|P16511|RRP1_IASIN|; |133518|sp|P16507|RRP1_IAME8|; |133512|sp|P18882|RRP1_IAKIE|; |133511|sp|P16505|RRP1_IAHTE|; |133510|sp|P16504|RRP1_IAHLO|; |133509|sp|P16503|RRP1_IAGU2|; |133506|sp|P16502|RRP1_IABEI|; |6647779|sp|Q82571|RRP1_IAFOM|; |6647775|sp|O91741|RRP1_IAKIT|; |6647773|sp|O89749|RRP1_IACKH|; |133531|sp|P19703|RRP1_INCJJ|; |133520|sp|P03431|RRP1_IAPUE|; |133519|sp|P03432|RRP1_IANT6|; |133505|sp|P21426|RRP1_IAANN|; |401026|sp|P31341|RRP1_IAVI7|; |133516|sp|P26121|RRP1_IALE3|; |133515|sp|P26120|RRP1_IALE2|; |133514|sp|P26119|RRP1_IALE1|; |133508|sp|P26118|RRP1_IADUN|; |34733402|gb|AAQ81638.1|; |34733400|gb|AAQ81637.1|; |9863938|gb|AAG01228.1|AF216740_1|; |9863920|gb|AAG01218.1|AF216732_1|; |9863902|gb|AAG01208.1|AF216724_1|; |9863883|gb|AAG01198.1|AF216716_1|; |324980|gb|AAA43647.1|; |324970|gb|AAA43646.1.

The preferred influenza strains referred to in the present invention, for example against which the present polypeptides should be immunogenic, are those containing these specific proteins. The above accesion numbers specify explicitly the identity of the strain in addition to the specific protein sequence.

In some preferred embodiments the polypeptide according to the present invention may comprise one or more sequences as described above and having at least 60% homology with a consensus sequence over known human and avian influenza virus strains (or two or more epitopes of 7 amino acids or more having at least 60% homology with such a sequence). In

further preferred embodiments the polypeptide may comprise one or more sequences as described above and having at least 60% homology with a consensus sequence over known human influenza virus strains (or two or more epitopes of 7 amino acids or more having at least 60% homology with such a sequence).

The percent homology of a first polypeptide sequence to a second polypeptide sequence, as referred to in the context of the present invention, is defined as the number of amino acid residues in the second sequence that match in both position and identity to those in the first sequence, divided by the total number of amino acid residues in the second polypeptide (both first and second polypeptides must have the same number of amino acid residues) and multiplied by 100. In the present invention, it is preferred that the polypeptide homology to the defined sequences is 75% or more, 85% or more, 95% or more or 100% (or substantially 100%).

The epitopes within the sequences defined above may not be especially limited, provided that they contain 7 amino acid residues or more. Preferably the epitopes are of a length that is appropriate for CTL epitopes in a particular vertebrate species, such as in a human, having a specific MHC. Typically the epitopes contain 8, 9, 10, or 11 amino acid residues, but may contain more if desired. Generally an appropriate epitope is one which is a CTL epitope in a vertebrate such as a human.

Typically, the polypeptide comprises between 7 and 100 amino acids, and preferably from 8-50 amino acids. The size should not be so great that useful epitopes suffer from competition with non-protective epitopes in the immune system (for this reason full proteins are not included), nor should the size be so small that only a very narrow range of protection is offered. More preferred ranges are from 8-40 amino acids, 15-40 amino acids and 15-35 amino acids. The most preferred length is from 20-35 amino acid residues. It is particularly preferred that the polypeptide consists of (or substantially consists of) a sequence selected from the sequences at the positions defined above in the specific list of proteins set out above.

In addition to the polypeptides described above, which should not be larger than 100 amino acid residues in length, the invention also provides multi-epitope immunogenic polypeptides

comprising two or more polypeptides of the present invention. These multi-epitope polypeptides may not be limited in size. Thus, they extend not only to the polypeptides having from 7-100 amino acid residues as outlined above, but also to larger polypeptides, provided that these larger polypeptides comprise two or more units, each unit consisting of a polypeptide of the invention. Thus, a polypeptide having 100 repeating units of a 7-mer according to the present invention is encompassed by the present invention, as is a polypeptide having, say 52 units of one 8-mer epitope, and 23 units of a second 10-mer epitope. Polypeptides of this type will not suffer from the competition problems associated with similar length polypeptides that comprise only one or two epitopes. For the avoidance of doubt, the multi-epitope polypeptide may comprise multiple copies of the same epitope, or single copies of a plurality of different epitopes, or multiple copies of 2 or more epitopes.

Also provided by the invention is a polypeptide composition comprising two or more different polypeptides as defined above. Thus, the polypeptide composition may comprise any number of polypeptides of the present invention together in the same mixture or formulation. The presence of a plurality of polypeptides together is useful since each may elicit its own immune response, widening the protective effect of the composition. It is particularly preferred that the composition contains all of the sequences of SEQ ID 1-6 either each in a separate peptide or several in a smaller number of peptides (e.g. 3 combined in one larger peptide and the other three 3 in another larger peptide, or the like.).

The invention also provides a polypeptide construct, which construct comprises a polypeptide as defined above and a carrier. The construct may be formed by combining two or more epitopes and/or a polypeptide as defined above with the carrier. The carrier may be a molecule, such as an adjuvant and/or an excipient. Combining in this context means either mixing together, or attaching together (e.g. via a covalent linkage).

The present invention further provides a polypeptide as defined above for use in medicine. Also provided is a medicament or vaccine composition against influenza, comprising a polypeptide as defined above, and one or more appropriate excipients and/or adjuvants, or a polypeptide construct as defined above and optionally one or more appropriate excipients and/or adjuvants (if the carrier part of the construct is itself an excipient or adjuvant, then a

further excipient or adjuvant may not be needed). The excipient or adjuvant may not be especially limited, and any excipients or adjuvants used in medicaments and vaccines may be employed. The medicament or vaccine composition may be produced according to any known method appropriately adapted to the present invention, such as by mixing a polypeptide of the invention with an appropriate excipient.

A method of producing a polypeptide as defined above is also provided by the invention. The method may not be especially limited, and typically comprises joining two or more epitopes to form the polypeptide. The polypeptide may, however, be synthesised by direct chemical synthesis (e.g. incorporating one amino acid at a time until the full polypeptide is formed) or by recombinant methods. Such general methods are well known to the skilled person and may be adapted to the present invention as desired. In some instances, the polypeptide of the present invention may comprise additional amino acid sequences at one or both termini to help in synthesis of the polypeptide. These additional sequences are preferably from 1-5 amino acids in length. Typically 3 amino acids are involved. For example, in one preferred embodiment, SEQ ID 6 comprises the amino acids AAS immediately prior to the IIG part of the sequence.

The invention still further provides use of a polypeptide or composition as defined above, in the manufacture of a medicament or vaccine, effective in the treatment or prevention of influenza. Also provided is a method of treating or preventing influenza, which method comprises administering a polypeptide, a composition, a medicament or a vaccine as defined above to a vertebrate. The method of administration may not be especially limited, and may comprise subcutaneous, intramuscuscular, intra-venous, intra-dermal, or intra-nasal administration, or may be administered orally (e.g. in the form of a pill or a liquid preparation), or may be in the form of a suppository, if desired. The form of such administration preparations may not be especially limited, and known forms may be employed with appropriate modifications that will be apparent to the skilled person. The dosage may not be especially limited and may range from 1 μg to 100 g of the polypeptide per individual, depending upon the size, weight and species of the individual involved.

The invention may be applied to any vertebrate, since the immune systems of vertebrates operate in a related manner. Typically, the vertebrate referred to in the present context is a mammal, bird, a reptile or a fish. It is especially preferred that the vertebrate is a human, a domestic animal (such as a dog or a cat), a farm animal (such as a pig or a horse), a bovine animal (such as cattle, or a cow), or fowl (such as a domestic bird, a farm bird, or a game bird). When the vertebrate is a bird, it is preferably a chicken, a turkey, a duck, or a goose.

Examples of human MHCs (HLAs) that may be employed with the present invention include the following:

HLA-A

A*010101, A*010102, A*010103, A*0102, A*0103, A*0104N, A*0106, A*0107, A*0108, A*0109, A*0110, A*02010101, A*02010102L, A*020102, A*020103, A*020104, A*020105, A*020106, A*020107, A*020108, A*020109, A*020110, A*020111, A*0202, A*020301, A*020302, A*0204, A*0205, A*020601, A*020602, A*020603, A*0207, A*0208, A*0209, A*0210, A*0211, A*0212, A*0213, A*0214, A*0215N, A*0216, A*021701, A*021702, A*0218, A*0219, A*022001, A*022002, A*0221, A*0222, A*0224, A*0225, A*0226, A*0227, A*0228, A*0229, A*0230, A*0231, A*0232N, A*0233, A*0234, A*023501, A*023502, A*0236, A*0237, A*0238, A*0239, A*0240, A*0241, A*0242, A*0243N, A*0244, A*0245, A*0246, A*0247, A*0248, A*0249, A*0250, A*0251, A*0252, A*0253N, A*0254, A*0255, A*0256, A*0257, A*0258, A*0259, A*0260, A*0261, A*0262, A*0263, A*0264, A*0265, A*0266, A*0267, A*0268, A*0269, A*0270, A*0271, A*0272, A*0273, A*03010101, A*03010102N, A*03010103, A*030102, A*030103, A*0302, A*0303N, A*0304, A*0305, A*0306, A*0307, A*0308, A*0309, A*0310, A*0311N, A*0312, A*0313, A*0314, A*110101, A*110102, A*1102, A*1103, A*1104, A*1105, A*1106, A*1107, A*1108, A*1109, A*1110, A*1111, A*1112, A*1113, A*1114, A*1115, A*1116, A*1117, A*1118, A*1119, A*2301, A*2302, A*2303, A*2304, A*2305, A*2306, A*2307N, A*2308N, A*2309, A*2310, A*2311N, A*2312, A*24020101, A*24020102L, A*240202, A*240203, A*240204, A*240205, A*240206, A*240301, A*240302, A*2404, A*2405, A*2406, A*2407, A*2408, A*2409N, A*2410, A*2411N, A*2413, A*2414, A*2415, A*2417, A*2418, A*2419, A*2420, A*2421, A*2422, A*2423, A*2424, A*2425, A*2426, A*2427, A*2428, A*2429, A*2430, A*2431, A*2432, A*2433,

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HLA-B

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HLA-C

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HLA-E

E*0101, E*010301, E*010302, E*010303, E*0104.

HLA-F

F*010101, F*010102.

HLA-G

G*010101, G*010102, G*010103, G*010104, G*010105, G*010106, G*010107, G*010108, G*0102, G*0103, G*010401, G*010402, G*010403, G*0105N, G*0106.

HLA-DRA

DRA*0101, DRA*010201, DRA*010202.

HLA-DRB1

DRB1*010101, DRB1*010102, DRB1*010103, DRB1*010201, DRB1*010202, DRB1*010203, DRB1*010204, DRB1*0103, DRB1*0104, DRB1*0105, DRB1*0106,

DRB1*0107, DRB1*0108, DRB1*0109, DRB1*0110, DRB1*0111, DRB1*030101, DRB1*030102, DRB1*030201, DRB1*030202, DRB1*0303, DRB1*0304, DRB1*030501, DRB1*030502, DRB1*0306, DRB1*0307, DRB1*0308, DRB1*0309, DRB1*0310, DRB1*0311, DRB1*0312, DRB1*0313, DRB1*0314, DRB1*0315, DRB1*0316, DRB1*0317, DRB1*0318, DRB1*0319, DRB1*0320, DRB1*0321, DRB1*0322, DRB1*0323, DRB1*0324, DRB1*0325, DRB1*0326, DRB1*0327, DRB1*0328, DRB1*040101, DRB1*040102, DRB1*0402, DRB1*040301, DRB1*040302, DRB1*0404, DRB1*040501, DRB1*040502, DRB1*040503, DRB1*040504, DRB1*0406, DRB1*040701, DRB1*040702, DRB1*040703, DRB1*0408, DRB1*0409, DRB1*0410, DRB1*0411, DRB1*0412, DRB1*0413, DRB1*0414, DRB1*0415, DRB1*0416, DRB1*0417, DRB1*0418, DRB1*0419, DRB1*0420, DRB1*0421, DRB1*0422, DRB1*0423, DRB1*0424, DRB1*0425, DRB1*0426, DRB1*0427, DRB1*0428, DRB1*0429, DRB1*0430, DRB1*0431, DRB1*0432, DRB1*0433, DRB1*0434, DRB1*0435, DRB1*0436, DRB1*0437, DRB1*0438, DRB1*0439, DRB1*0440, DRB1*0441, DRB1*0442, DRB1*0443, DRB1*0444, DRB1*0445, DRB1*0446, DRB1*0447, DRB1*0448, DRB1*0449, DRB1*0450, DRB1*070101, DRB1*070102, DRB1*0703, DRB1*0704, DRB1*0705, DRB1*0706, DRB1*0707, DRB1*0708, DRB1*080101, DRB1*080102, DRB1*080201, DRB1*080202, DRB1*080203, DRB1*080302, DRB1*080401, DRB1*080402, DRB1*080403, DRB1*080404, DRB1*0805, DRB1*0806, DRB1*0807, DRB1*0808, DRB1*0809, DRB1*0810, DRB1*0811, DRB1*0812, DRB1*0813, DRB1*0814, DRB1*0815, DRB1*0816, DRB1*0817, DRB1*0818, DRB1*0819, DRB1*0820, DRB1*0821, DRB1*0822, DRB1*0823, DRB1*0824, DRB1*0825, DRB1*0826, DRB1*0827, DRB1*0828, DRB1*0829, DRB1*090102, DRB1*090103, DRB1*0902, DRB1*0903, DRB1*100101, DRB1*100102, DRB1*110101, DRB1*110102, DRB1*110103, DRB1*110104, DRB1*110105, DRB1*1102, DRB1*1103, DRB1*110401, DRB1*110402, DRB1*1105, DRB1*110601, DRB1*110602, DRB1*1107, DRB1*110801, DRB1*110802, DRB1*1109, DRB1*1110, DRB1*1111, DRB1*111201, DRB1*111202, DRB1*1113, DRB1*1114, DRB1*1115, DRB1*1116, DRB1*1117, DRB1*1118, DRB1*1119, DRB1*1120, DRB1*1121, DRB1*1122, DRB1*1123, DRB1*1124, DRB1*1125, DRB1*1126, DRB1*112701, DRB1*112702, DRB1*1128, DRB1*1129, DRB1*1130, DRB1*1131, DRB1*1132, DRB1*1133, DRB1*1134, DRB1*1135, DRB1*1136, DRB1*1137,

DRB1*1138, DRB1*1139, DRB1*1140, DRB1*1141, DRB1*1142, DRB1*1143, DRB1*1144, DRB1*1145, DRB1*1146, DRB1*1147, DRB1*1148, DRB1*1149, DRB1*1150, DRB1*1151, DRB1*1152, DRB1*1153, DRB1*1154, DRB1*120101, DRB1*120102, DRB1*120201, DRB1*120202, DRB1*120302, DRB1*1204, DRB1*1205, DRB1*1206, DRB1*1207, DRB1*1208, DRB1*1209, DRB1*1210, DRB1*130101, DRB1*130102, DRB1*130103, DRB1*130201, DRB1*130202, DRB1*130301, DRB1*130302, DRB1*1304, DRB1*1305, DRB1*1306, DRB1*130701, DRB1*130702, DRB1*1308, DRB1*1309, DRB1*1310, DRB1*1311, DRB1*1312, DRB1*1313, DRB1*131401, DRB1*131402, DRB1*1315, DRB1*1316, DRB1*1317, DRB1*1318, DRB1*1319, DRB1*1320, DRB1*1321, DRB1*1322, DRB1*1323, DRB1*1324, DRB1*1325, DRB1*1326, DRB1*1327, DRB1*1328, DRB1*1329, DRB1*1330, DRB1*1331, DRB1*1332, DRB1*1333, DRB1*1334, DRB1*1335, DRB1*1336, DRB1*1337, DRB1*1338, DRB1*1339, DRB1*1340, DRB1*1341, DRB1*1342, DRB1*1343, DRB1*1344, DRB1*1345, DRB1*1346, DRB1*1347, DRB1*1348, DRB1*1349, DRB1*1350, DRB1*1351, DRB1*1352, DRB1*1353, DRB1*1354, DRB1*1355, DRB1*1356, DRB1*1357, DRB1*1358, DRB1*1359, DRB1*1360, DRB1*1361, DRB1*1362, DRB1*1363, DRB1*1364, DRB1*1365, DRB1*140101, DRB1*140102, DRB1*1402, DRB1*140301, DRB1*140302, DRB1*1404, DRB1*140501, DRB1*140502, DRB1*1406, DRB1*140701, DRB1*140702, DRB1*1408, DRB1*1409, DRB1*1410, DRB1*1411, DRB1*1412, DRB1*1413, DRB1*1414, DRB1*1415, DRB1*1416, DRB1*1417, DRB1*1418, DRB1*1419, DRB1*1420, DRB1*1421, DRB1*1422, DRB1*1423, DRB1*1424, DRB1*1425, DRB1*1426, DRB1*1427, DRB1*1428, DRB1*1429, DRB1*1430, DRB1*1431, DRB1*1432, DRB1*1433, DRB1*1434, DRB1*1435, DRB1*1436, DRB1*1437, DRB1*1438, DRB1*1439, DRB1*1440, DRB1*1441, DRB1*1442, DRB1*1443, DRB1*1444, DRB1*1445, DRB1*1446, DRB1*1447, DRB1*1448, DRB1*150101, DRB1*150102, DRB1*150103, DRB1*150104, DRB1*150105, DRB1*150201, DRB1*150202, DRB1*150203, DRB1*1503, DRB1*1504, DRB1*1505, DRB1*1506, DRB1*1507, DRB1*1508, DRB1*1509, DRB1*1510, DRB1*1511, DRB1*1512, DRB1*1513, DRB1*1514, DRB1*1515, DRB1*1516, DRB1*160101, DRB1*160102, DRB1*160201, DRB1*160202, DRB1*1603, DRB1*1604, DRB1*160501, DRB1*160502, DRB1*1607, DRB1*1608.

HLA-DRB2-9

DRB2*0101, DRB3*010101, DRB3*01010201, DRB3*01010202, DRB3*010103, DRB3*010104, DRB3*0102, DRB3*0103, DRB3*0104, DRB3*0105, DRB3*0106, DRB3*0107, DRB3*0108, DRB3*0109, DRB3*0110, DRB3*0111, DRB3*0201, DRB3*020201, DRB3*020202, DRB3*020203, DRB3*020204, DRB3*0203, DRB3*0204, DRB3*0205, DRB3*0206, DRB3*0207, DRB3*0208, DRB3*0209, DRB3*0210, DRB3*0211, DRB3*0212, DRB3*0213, DRB3*0214, DRB3*0215, DRB3*0216, DRB3*0217, DRB3*0218, DRB3*0219, DRB3*030101, DRB3*030102, DRB3*0302, DRB3*0303, DRB4*01010101, DRB4*0102, DRB4*01030101, DRB4*01030102N, DRB4*010302, DRB4*010303, DRB4*010304, DRB4*0104, DRB4*0105, DRB4*0106, DRB4*0107, DRB4*0201N, DRB4*0301N, DRB5*010101, DRB5*010102, DRB5*0102, DRB5*0103, DRB5*0104, DRB5*0105, DRB5*0106, DRB5*0107, DRB5*0108N, DRB5*0109, DRB5*0110N, DRB5*0111, DRB5*0112, DRB5*0113, DRB5*0202, DRB5*0203, DRB5*0204, DRB5*0205, DRB6*0101, DRB6*0201, DRB6*0202, DRB7*010101, DRB7*010102, DRB8*0101, DRB9*0101.

HLA-DQA1

DQA1*010101, DQA1*010102, DQA1*010201, DQA1*010202, DQA1*0103, DQA1*010401, DQA1*010402, DQA1*0105, DQA1*0106, DQA1*0107, DQA1*0201, DQA1*030101, DQA1*0302, DQA1*0303, DQA1*040101, DQA1*040102, DQA1*0402, DQA1*0403N, DQA1*0404, DQA1*050101, DQA1*050102, DQA1*0502, DQA1*0503, DQA1*0504, DQA1*0505, DQA1*060101, DQA1*060102, DQA1*0602.

HLA-DQB1

DQB1*020101, DQB1*020102, DQB1*0202, DQB1*0203, DQB1*030101, DQB1*030102, DQB1*030201, DQB1*030202, DQB1*030302, DQB1*030303, DQB1*0304, DQB1*030501, DQB1*030502, DQB1*030503, DQB1*0306, DQB1*0307, DQB1*0308, DQB1*0309, DQB1*0310, DQB1*0311, DQB1*0312, DQB1*0313, DQB1*0401, DQB1*0402, DQB1*050101, DQB1*050102, DQB1*050201, DQB1*050202, DQB1*050301, DQB1*050302, DQB1*0504, DQB1*060101, DQB1*060102, DQB1*060103, DQB1*0602, DQB1*0603, DQB1*060401, DQB1*060402, DQB1*060501, DQB1*060502, DQB1*0606, DQB1*0607, DQB1*0608, DQB1*0609, DQB1*0610,

DQB1*061101, DQB1*061102, DQB1*0612, DQB1*0613, DQB1*0614, DQB1*0615, DQB1*0616, DQB1*0617, DQB1*0618, DQB1*0619, DQB1*0620, DQB1*0621, DQB1*0622, DQB1*0623.

HLA-DPA1

DPA1*010301, DPA1*010302, DPA1*010303, DPA1*0104, DPA1*0105, DPA1*0106, DPA1*0107, DPA1*0108, DPA1*020101, DPA1*020102, DPA1*020103, DPA1*020104, DPA1*020105, DPA1*020106, DPA1*020201, DPA1*020202, DPA1*020203, DPA1*0203, DPA1*0301, DPA1*0302, DPA1*0303, DPA1*0401.

HLA-DPB1

DPB1*010101, DPB1*010102, DPB1*010103, DPB1*0102, DPB1*020102, DPB1*020103, DPB1*020104, DPB1*020105, DPB1*020106, DPB1*0202, DPB1*0203, DPB1*030101, DPB1*030102, DPB1*0302, DPB1*040101, DPB1*040102, DPB1*0402, DPB1*0501, DPB1*0601, DPB1*0801, DPB1*0901, DPB1*1001, DPB1*110101, DPB1*110102, DPB1*1301, DPB1*1401, DPB1*1501, DPB1*1601, DPB1*1701, DPB1*1801, DPB1*1901, DPB1*200101, DPB1*200102, DPB1*2101, DPB1*2201, DPB1*2301, DPB1*2401, DPB1*2501, DPB1*260101, DPB1*260102, DPB1*2701, DPB1*2801, DPB1*2901, DPB1*3001, DPB1*3101, DPB1*3201, DPB1*3301, DPB1*3401, DPB1*3501, DPB1*3601, DPB1*3701, DPB1*3801, DPB1*3901, DPB1*4001, DPB1*4101, DPB1*4401, DPB1*4501, DPB1*4601, DPB1*4701, DPB1*4801, DPB1*4901, DPB1*5001, DPB1*5101, DPB1*5201, DPB1*5301, DPB1*5401, DPB1*5501, DPB1*5601, DPB1*5701, DPB1*5801, DPB1*5901, DPB1*6001, DPB1*6101N, DPB1*6201, DPB1*6301, DPB1*6401N, DPB1*6501, DPB1*6601, DPB1*6701, DPB1*6801, DPB1*6901, DPB1*7001, DPB1*7101, DPB1*7201, DPB1*7301, DPB1*7401, DPB1*7501, DPB1*7601, DPB1*7701, DPB1*7801, DPB1*7901, DPB1*8001, DPB1*8101, DPB1*8201, DPB1*8301, DPB1*8401, DPB1*8501, DPB1*8601, DPB1*8701, DPB1*8801, DPB1*8901, DPB1*9001, DPB1*9101, DPB1*9201, DPB1*9301, DPB1*9401, DPB1*9501, DPB1*9601, DPB1*9701, DPB1*9801, DPB1*9901.

HLA-DMA

DMA*0101, DMA*0102, DMA*0103, DMA*0104.

HLA-DMB

DMB*0101, DMB*0102, DMB*0103, DMB*0104, DMB*0105, DMB*0106.

HLA-DOA

DOA*010101, DOA*01010201, DOA*01010202, DOA*01010203, DOA*010103, DOA*01010401, DOA*01010402, DOA*010105.

HLA-DOB

DOB*01010101, DOB*01010102, DOB*010102, DOB*010201, DOB*010202, DOB*0103, DOB*01040101, DOB*01040102.

MHC Class I

H-2Db, H-2Dd, H-2Dk, H-2Dq, H-2Kb, H-2Kd, H-2Kk, H-2Ld, H-2M3, H-2Ad, H-2Ag7, H-2Ak, H2-Ab, H-2Ed, H-2Ek, H-2Bxk, H-2F, H-2I, H-2P, H-2R, H-2S, H-2Sxd, H-2T4, H-2U.

MHC Class II

I-Ab, I-Ad, I-Ag7, I-Ak, I-Ap, I-Aq, I-Ar, I-As, I-Au, I-Av, I-Ea, I-Eb, I-Ed, I-Ek, I-Es, I-Eu, H-2Q, H-2Qa-2, H-2Qa-2a, Qa-1a, Qa-1b.

The invention may not be limited to such MHC and HLA molecules, and can be adapted to newly discovered such molecules, if desired, simply by establishing the reactivity of substances such as peptides with the molecules. This can be readily achieved using known techniques that are standard in the field. Particularly preferred HLA alleles for use with the present invention include the following:

HLA Class I

HLA A	HLA B	HLA Cw
A*6802	B*5801	Cw*1701
A*6801	B*5701	Cw*1601
A*6601	B*5501	Cw*1502
A*3303	B*5201	Cw*1402
A*3301	B*5101	Cw*1203
A*3201	B*5001	Cw*0802
A*310102	B*4901	Cw*0801
A*3002	B*4501	Cw*0704
A*3001	B*4403	Cw*0703
A*2902	B*4402	Cw*0702
A*2608	B*4101	Cw*0701
A*2601	B*4002	Cw*0602
A*2501	B*4001	Cw*0501
A*2402	B*3901	Cw*0401
A*2301	B*3801	Cw*0304
A*1101	B*3701	Cw*0303
A*0302	B*3503	Cw*0202
A*0301	B*3501	Cw*0102
A*0205	B*2705	
A*0201	B*1801	
A*0101	B*1501	
	B*1402	
	B*1401	
	B*1302	
	B*0801	
	B*0705	
	B*0702	

HLA Class II

HLA DPB	HLA DQA	HLA DQB	HLA DRB
DPB1*1701	DQA1*0505	DQB1*0604	DRB1*1601
DPB1*1301	DQA1*0501	DQB1*0603	DRB1*1501
DPB1*1001	DQA1*0401	DQB1*0602	DRB1*1401
DPB1*0601	DQA1*0303	DQB1*0503	DRB1*1302
DPB1*0501	DQA1*0302	DQB1*0502	DRB1*1301
DPB1*0402	DQA1*0301	DQB1*0501	DRB1*1201
DPB1*0401	DQA1*0201	DQB1*0402	DRB1*1104
DPB1*0301	DQA1*0104	DQB1*0303	DRB1*1101
DPB1*0201	DQA1*0103	DQB1*0302	DRB1*0801
DPB1*0101	DQA1*0102	DQB1*0301	DRB1*0701
	DQA1*0101	DQB1*0202	DRB1*0404
		DQB1*0201	DRB1*0401
			DRB1*0301
			DRB1*0103
			DRB1*0102
			DRB1*0101

The most preferred alleles according to the invention are the following:

HLA-A*0201, HLA-A*0206, HLA-A*0301, HLA-A*1101, HLA-A*2402, HLA-A*3401, HLA-B*0702, HLA-B*0801, HLA-B*1301, HLA-B*27, HLA-B*4002, HLA-B*5101, HLA-Cw*03, HLA-cW*07

HLA-DRB1*0301, HLA-DRB1*0401, HLA-DRB1*0701, HLA-DRB1*1501, HLA-DRB1*1104, HLA-DRB1*1101, HLA-DRB4*0101

HLA-DQA1*01, HLA-DQA1*02, HLA-DQA1*05

HLA-DQB1*03, HLA-DQB1*04, HLA-DQB1*05, HLA-DQB1*06

HLA-DPA1*01, HLA-DPA1*02

HLA-DPB1*02, HLA-DPB1*04

The invention will now be described by way of example only, with reference to the following specific embodiments.

EXAMPLES

EXPERIMENT 1 – Reactivity of polypeptides against influenza antigens

The purpose of the study was to demonstrate the reactivity of the above-described influenza polypeptides and their ability to induce a specific Th1-type cytokine response against naturally processed and presented influenza proteins in the context of human HLA (HLA A*0201).

As background to the experiments, it is useful to understand that Th1 and Th2 responses are defined by the pattern of cytokines produced by the T helper cells involved in them. That, however, does not mean that the remaining lymphocytes (T and B cells) involved in those specific responses do not also produce cytokines that help drive the characteristic pattern of response in which they are involved. In this way, a Th1-like response is characterised by the production of IFN-γ and IL-2, leading to the stimulation of a CD8+ CTL response and an associated (in mice) IgG2a antibody response. The IFN-γ response can be produced both by the CD4+ T helper 1 cells as well as by the CD8+ T cells that also form part of it. In this case the IFN-γ component of the response produced by the CD8+ T cells was investigated. That was because the experiment was primarily investigating CD8+ T cell epitopes and it was desirable to prove that the response seen was caused by those cells. Since CD8+ T cells react to epitopes only on MHC class I molecules, human cells that share with the transgenic mouse only one MHC class I molecule (i.e. HLA-A*0201) were used. A Th2-like response is characterised by the production of IL-4 and IL-10, leading to the stimulation of an IgGE, IgG1 and (in mice) IgG2b antibody response. Both responses are antagonistic with IFN-γ and IL-10 downregulating the production of each other.

All the experiments described below were carried out in duplicate.

Materials and methods

Peptides and recombinant proteins

All the polypeptides used in this study (i.e. P1: M1A amino acid (aa) 36 to 75 (SEQ ID 1); P2: M1B aa 124 to 158 (SEQ ID 2); P3: NPA aa 255 to 275 (SEQ ID 3); P4: NPB aa 306 to 326 (SEQ ID 4); P5: PB1 aa 395 to 428 (SEQ ID 5); P6: M2 aa 32 to 55 (SEQ ID 6) and NRP: a control non-relevant polypeptide) were synthesised by Fmoc chemistry and resuspended in 10 % DMSO in PBS.

Cell lines and viruses

The T1 and JURKAT cell lines are human lymphoblastoid lines derived from HLA-A*0201 bearing and non-bearing individuals respectively. T1 was maintained in IMDM medium (Invitrogen) whilst JURKAT was maintained in RPMI-1640 medium (Sigma) containing 10 mM HEPES and 1 mM sodium pyruvate. Both media were supplemented with 50 IU/50 mg/ml of penicillin/streptomycin (Sigma) and, as complete medium, 10 % FCS. Cell cultures were maintained at 37ºC in a humidified atmosphere of 5 % CO_2.

Primary splenocytes were maintained in IMDM medium (Invitrogen) supplemented with 0.02 mM β-mercaptoethanol (Sigma), 50 IU/50 mg/ml of penicillin/streptomycin (Sigma) and 10 % FCS (Sigma) at 37ºC in a humidified atmosphere of 5 % CO_2.

Influenza A strains New_Caledonia/20/99, NYMC/X-147 and Influenza B strain Johannesburg/5/99 were obtained from NIBSC as lyophilised stocks and used for the infection of syngeneic (T1) and allogeneic (JURKAT) human cell lines.

Preparation of target cells for cytokine analysis

Cell cultures in exponential phase were harvested by centrifugation (250 g, 5 min) and resuspended at a density of 10^6 cells/ml in serum-free medium. Aliquots of the cell suspensions were transfected with a range of polypeptide antigens at a concentration of 5 μg per 10^6 cells using Lipofectin (Invitrogen) according to the manufacturer's instructions and incubated in complete medium for 8-10 hours before Mytomicin C (MMC) treatment. Alternatively, aliquots of the cell suspensions were infected with a range of live Influenza

virus (MOI of 5-10) for one hour, washed twice in serum free medium and incubated in complete medium for 24 hours before MMC treatment.

For MMC treatment, cells were harvested by centrifugation (250 g, 5 min) and resuspended in serum-free IMDM medium containing 50 μg/ml of Mitomycin C (Sigma). After 45 min incubation at 37ºC, the cell suspensions were washed four times in serum-free IMDM medium (250 g, 5 min) and finally resuspended in complete IMDM medium.

Immunisations

Seven to ten week old C57BL/6-Tg(HLA-A2.1)1Enge/J mice (HLA-A*0201 transgenic on a C57/BL6 background, Jackson Labs) were immunised subcutaneously with a 200 μl dose of the antigen preparation per mouse. In the test group, each dose of the antigen preparation contained 60 nmol of an equimolar mixture of all six peptides (10 nmol each) prepared in IFA (Sigma) according to the manufacturer's instructions (FLU-v preparation). In the control group, each dose of the antigen preparation contained an equivalent dose of the non-relevant polypeptide prepared in IFA (Sigma) according to the manufacturer's instructions (NRP preparation).

On day 14 post-immunisation, all animals received a booster immunisation using the same doses and route of delivery as used originally. Finally, on day 21 or 22, all animals were culled and their spleens collected.

The immunisation protocol can be represented schematically as follows:

Scheme 1 - innoculation

FLU-v = combination of P1 P2 P3 P4 P5 & P6



Immunise mouse with FLU-v

Harvest splenocytes after 21 or 22 days - any immune reaction will have caused amplification in mouse T cells reactive to correctly presented epitopes within P1-P6, which will become activated and/or proliferate. If peptides are correctly presented by both mouse MHC and human HLA, T cells reactive to epitopes presented in each of these contexts may be present (antigen presenting cells, APCs, in the transgenic mice will express both mouse MHC and human HLA). The harvested splenocytes may comprise significant quantities of activated/proliferated T cells, along with smaller quantities of other cells, such as antigen presenting cells (APCs)

Obtain splenocytes containing:

1. mouse T-cells
   - (a) HLA T cells in amplified quantities, reactive to APC(HLA)-P1 (or APC(HLA)-P2 etc.)
   - (b) MHC T cells, non-reactive to APC(HLA)-P1 (or APC(HLA)-P2 etc.)
2. mouse antigen presenting cells (APCs)
   - (a) APC(HLA)-
   - (b) APC(MHC)-

Statistical analysis

Statistically significant differences in the IFN-γ response to different antigens between FLU-v and NRP vaccinated animals were established through non-parametric Mann-Whitney analysis of the samples. Differences were considered statistically significant if the p value was below 0.05.

Cytokine ELISA

Mouse spleens belonging to the same experimental group were pooled, gently pressed through cell strainers and red blood cells removed by treatment with red cell lysis buffer (nine parts 0.16 M NH_4Cl and one part of 0.17 M Tris, pH 7.2). Splenocyte suspensions from each experimental group were plated in 24-well plates at a density of 4×10^6 cells/well containing a range of polypeptide antigens (5 μg/ml) or, alternatively, MMC treated cell lines

(splenocyte to cell (S:C) ratio 10:1) either transfected with polypeptide antigens or infected with different live Influenza virus as described above.

After 4 days incubation at 37ºC, the supernatant was collected and analysed for IFN-γ and IL-4 by a sandwich cytokine ELISA according to the manufacturer's protocol (Pharmingen). The lower detection limits for the assay were 9.77 pg/ml for IL-4 and 39.06 pg/ml for IFN-γ.

Results

Each individual polypeptide peptide described in this patent application (including P1, P2, P3, P4, P5 and P6 tested in this example) has been defined as containing T cell epitopes reactive in multiple human HLA molecules, amongst them HLA-A*0201. The aim of this study is, therefore, to assess the ability of the above described polypeptides to induce a specific multi-antigen Th1-like immune (i.e. IFN-γ mediated) response as well as the ability of this response to specifically react to naturally processed and presented Influenza antigens from several non-related strains pathogenic to humans in the context of infected human HLA A*0201 bearing cells.

Reactivity of peptide 1

Upon internal processing of the polypeptide by the antigen presenting cells (APCs) of the transgenic mice, the contained CD8+ T cell specific epitopes would be presented in the surface of the APC in association with the HLA-A*0201 molecules where they would proceed to activate naïve CD8+ T cells and induce a P1 specific Th1-like immune response.

To confirm this, HLA-A*0201 bearing (T1) and non-bearing (JURKAT) human cell lines were intracellularly loaded with P1 by means of a lipid vehicle (Lipofectin, INVITROGEN). Splenocytes from animals immunised with the influenza polypeptide preparation (FLU-v) were found to produce significantly increased levels of IFN-γ compared to splenocytes from NRP immunised animals when co-cultured with MMC treated HLA-A*0201 bearing human cells (T1) transfected with P1, but not when co-cultured with non-HLA-A*0201 bearing human cells (JURKAT) treated in the same way (see Figure 1A, the data for which is presented in Table 1 below).

Table 1

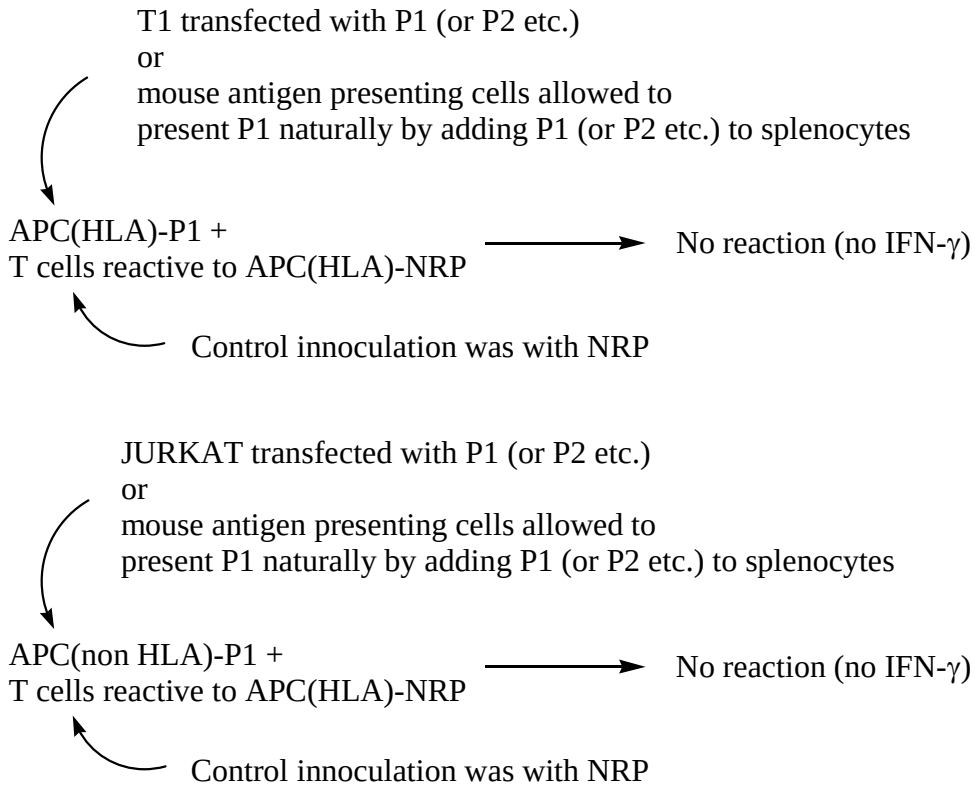
Δ IFN-γ to Lys (pg/ml)	FLU-v	NRP
Con A	2395.6 ± 45.9	2257.5 ± 29.8
FLU Peptide 1 (sol)	119.3 ± 7.1	< 39
T1-FLU pep 1 (pro)	228.4 ± 16.6	55.8 ± 7
Ju-FLU pep 1 (pro)	< 39	51.2 ± 1.6

Note:

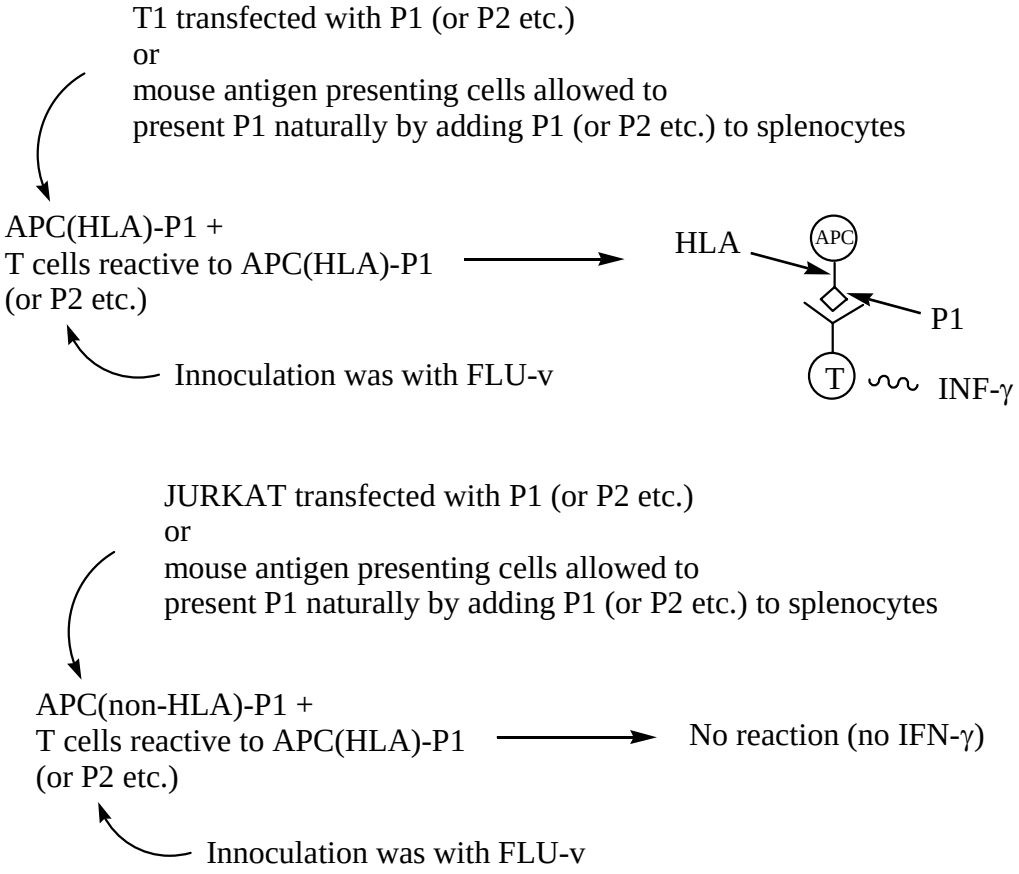
"Lys" means the negative control background upon which all values are calculated. "Sol" means soluble peptide presented to the primary splenocyte population. "Pro" means that the peptide is being presented complexed with the cell's HLA molecules following internal processing and loading of the resulting epitopes on to the MHC molecules. Values represent average ± standard error of the Δ IFN-γ to Lys (pg/ml).

The experiment can be represented schematically as follows:

Scheme 2 – control test for T1 and JURKAT



Scheme 3 – FLU-v test results for T1 and JURKAT



As the transgenic mice used in these experiments do not bear any other human HLA and the ability of its CD8+ T cells to specifically recognise P1-derived epitopes in the context of other human HLAs which they have never encountered is low, these results clearly show that the observed IFN-γ response is specifically caused by primed CD8+ T cells recognising P1-derived epitopes in association with HLA-A*0201 molecules.

It is also important to note that no IL-4 response was detected against the P1 transfected cells in either FLU-v or NRP immunised animals (data not shown). Since IL-4 production is antagonistic to IFN-γ production and hence to the creation of antigen specific CD8+ T cell responses, the lack of IL-4 production in both groups clearly shows that immunisation with FLU-v induces a specific Th1-like response to the P1 component of the preparation.

A significantly increased level in IFN-γ production is also observed in the FLU-v compared to the NRP immunised groups when soluble P1 antigen is simply added to the splenocyte culture (in the absence of T1 or JURKAT cells). However, the overall level of this IFN-γ response is lower than that observed when the antigen was presented via the HLA-A*0201 bearing T1 cells. The explanation for this observation is that P1 was defined on the basis of containing epitopes that are primarily reactive in the context of human and not mouse HLAs. The transgenic mice here used contain a full complement of mouse MHC molecules in addition to the HLA-A*0201 molecules, hence the soluble P1 captured by the APC population present in the primary splenocyte cultures can also be processed into the mouse MHC Class I and II pathways (Peachman KK, Rao M, Alving CR, Palmer DR, Sun W, Rothwell SW. "Human dendritic cells and macrophages exhibit different intracellular processing pathways for soluble and liposome-encapsulated antigens." *Immunobiology*. 2005;210(5):321-33), which mediate H-2D restricted CD8+ and CD4+ T cell responses respectively. As a result, if P1 contained multiple murine epitopes, it would be expected that the IFN-γ response to soluble P1 would be equal or greater to that observed for the case of human cell mediated presentation as a much larger pool of CD4+ and CD8+ T cells would be able to react to the stimulus. As this is not observed and the level of an immune response *in vitro* is primarily determined by the availability of antigen, it clearly follows that the P1-specific CD8+ T lymphocytes detected in the T1 co-culture experiments would simply be unable to respond at the same level due to the reduced amount of antigen being presented to them in the correct HLA-A*0201 context.

Reactivity of peptide 2

Splenocytes from animals immunised with the FLU-v have been found to produce significantly increased levels of IFN-γ compared to splenocytes from NRP immunised animals when co-cultured with MMC treated HLA-A*0201 bearing human cells (T1) transfected with P2, but not when co-cultured with non-HLA-A*0201 bearing human cells (JURKAT) treated in the same way (see Figure 1B, the data for which is set out in Table 2 below). As it was the case for P1, these results clearly show that the observed IFN-γ response is specifically caused by CD8+ T cells recognising P2-derived epitopes in association with HLA-A*0201 molecules. Similarly, as IL-4 production is antagonistic to IFN-γ production and hence to the development of CD8+ T cells, the lack of an IL-4 response against P2

transfected cells in either FLU-v or NRP immunised animals (data not shown) clearly shows that FLU-v immunisation induces a P2-specific Th1-like response.

Table 2

Δ IFN-γ to Lys (pg/ml)	FLU-v	NRP
Con A	2395.6 ± 45.9	2257.5 ± 29.8
FLU Peptide 2 (sol)	976.9 ± 24.1	468.4 ±14.7
T1-FLU pep 2 (pro)	372.9 ± 6.4	154.5 ± 10.7
Ju-FLU pep 2 (pro)	< 39	< 39

Note:

"Lys" means the negative control background upon which all values are calculated. "Sol" means soluble peptide presented to the primary splenocyte population. "Pro" means that the peptide is being presented complexed with the cell's HLA molecules following internal processing and loading of the resulting epitopes on to the MHC molecules. Values represent average ± standard error of the Δ IFN-γ to Lys (pg/ml).

A significantly increased IFN-γ production was also observed in the FLU-v compared to NRP immunised groups when P2 was simply added to the splenocyte culture. In contrast to P1, however, the overall level of the IFN-γ response was greater to the soluble antigen than to that presented by the HLA-A*0201 bearing cells. This observation would indicate that P2 harbours not only strong HLA-A*0201 epitopes but also strong mouse (H-2D) epitopes.

Reactivity of peptides 3, 4 and 5

As was the case for P2, significantly increased IFN-γ production can be observed between FLU-v and NRP immunised groups when P3, P4 and P5 are simply added to the culture as well as when they are presented via HLA-matched transfected human cells lines (T1), but not when they are presented via HLA-mismatched (JURKAT) human cell lines (see Figures 1C, 1D and 1E, the data for which is set out in Tables 3-5 below). In all three cases, the increment in IFN-γ production is greater when splenocytes are co-cultured with transfected human cells rather than when soluble antigen is simply added to the medium. These results, due to the

same arguments developed for the case of P2, indicate that P3, P4 and P5 contain a number of strong mouse T cell epitopes in addition to the human ones.

Table 3

Δ IFN-γ to Lys (pg/ml)	FLU-v	NRP
Con A	2395.6 ± 45.9	2257.5 ± 29.8
FLU Peptide 3 (sol)	1734.1 ± 57.2	268.0 ± 11.0
T1-FLU pep 3 (pro)	587.5 ± 14.9	< 39
Ju-FLU pep 3 (pro)	148.5 ± 3.0	146.5 ± 17.6

Table 4

Δ IFN-γ to Lys (pg/ml)	FLU-v	NRP
Con A	2395.6 ± 45.9	2257.5 ± 29.8
FLU Peptide 4 (sol)	1170.5 ± 27.8	693.8 ± 5.6
T1-FLU pep 4 (pro)	229.9 ± 35.2	84.6 ± 11.6
Ju-FLU pep 4 (pro)	< 39	< 39

Table 5

Δ IFN-γ to Lys (pg/ml)	FLU-v	NRP
Con A	2395.6 ± 45.9	2257.5 ± 29.8
FLU Peptide 5 (sol)	1067.7 ± 7.3	220.5 ± 6.6
T1-FLU pep 5 (pro)	405.6 ± 11.8	< 39
Ju-FLU pep 5 (pro)	< 39	< 39

Note:

“Lys” means the negative control background upon which all values are calculated. “Sol” means soluble peptide presented to the primary splenocyte population. “Pro” means that the peptide is being presented complexed with the cell’s HLA molecules following internal processing and loading of the resulting epitopes on to the MHC molecules. Values represent average ± standard error of the Δ IFN-γ to Lys (pg/ml).

Finally, as all three peptides fail to induce the production of IL-4 (data not shown), it is clear that the immune response induced by vaccination with the FLU-v preparation induces a Th1-like response to each of these three polypeptides.

Reactivity of peptide 6

As was the case for P1, significantly increased IFN-γ production can be observed between FLU-v and NRP immunised groups when P6 is simply added to the culture as well as when it is presented via HLA-matched transfected human cells lines (T1), but not when it is presented via HLA-mismatched (JURKAT) human cell lines (see Figure 1F, the data for which is set out in Table 6 below). Again as for P1, the greater response is observed to the soluble antigen, indicating that P6 does not contain strong H-2D epitopes. As the causes for these observations have already been explained for the case of P1 they shall not be developed further here and one shall refer to that earlier section.

Table 6

Δ IFN-γ to Lys (pg/ml)	FLU-v	NRP
Con A	2395.6 ± 45.9	2257.5 ± 29.8
FLU Peptide 6 (sol)	496.2± 11.8	105.5 ± 7.0
T1-FLU pep 6 (pro)	1210.5 ± 11.5	817.6 ± 8.9
Ju-FLU pep 6 (pro)	< 39	< 39

Note:

"Lys" means the negative control background upon which all values are calculated. "Sol" means soluble peptide presented to the primary splenocyte population. "Pro" means that the peptide is being presented complexed with the cell's HLA molecules following internal processing and loading of the resulting epitopes on to the MHC molecules. Values represent average ± standard error of the Δ IFN-γ to Lys (pg/ml).

The failure of stimulation with P6 to induce any IL-4 production (data not shown), clearly show that the immune response induced by FLU-v vaccination induces a Th1-like response to P6.

Reactivity of FLU-v to non-related influenza strains

The experiments described up to this point clearly show that immunisation with FLU-v induces a specific CD8+ T cell IFN-γ response against each of the six constituent polypeptides. However, as these polypeptides were defined as containing reactive CD8+ T cell epitopes subject to a low level of sequence variability within the influenza virus population analysed, it was also desirable to establish whether FLU-v vaccinated mice were capable of recognising, and hence inducing a specific Th1-like immune response, T cell epitopes naturally processed and presented following infection with different non-related strains of influenza. Such analysis provides a clear indication of the potential efficacy of the FLU-v polypeptide mixture as an influenza vaccine which, by virtue of targeting T cell epitopes of low sequence variability across the human and animal influenza population, would provide protection against all current strains as well as those which may arise in the future from spontaneous recombination between highly pathogenic animal strains with current human strains.

For this analysis, primary splenocyte cultures of transgenic animals inmmunised with FLU-v or NRP were co-cultured with several influenza infected HLA-A*0201 bearing (T1) and non-bearing (JURKAT) human cells. The three influenza strains used for infection (A/New_Caledonia/20/99, A/NYMC/X-147 and B/Johannesburg/5/99) are all pathogenic to humans and were obtained from the Influenza WHO repository, based at NIBSC (UK). As an antigen specific positive control an equimolar soluble preparation of the six polypeptides added to the primary splenocyte preparation was used.

Splenocytes from FLU-v vaccinated animals produced a significantly higher level of IFN-γ compared to those of NRP vaccinated animals when co-cultured with MMC treated influenza infected HLA-A*0201 bearing human cells (T1) transfected, but not when co-cultured with non-HLA-A*0201 bearing human cells (JURKAT) treated in the same way (see Figure 2, the data for which is set out in Table 7 below). No IL-4 response was detected in any of the vaccinated mice against either the soluble polypeptide antigen or the Influenza infected cells (data not shown). These results clearly show that the observed IFN-γ response is specifically caused by primed CD8+ T cells recognising epitopes contained in the FLU-v preparation and

which are also naturally processed and presented in association with HLA-A*0201 molecules in influenza infected human cells.

Table 7

Δ IFN-γ to Lys (pg/ml)	FLU-v	NRP
Con A	2395.6 ± 45.9	2257.5 ± 29.8
FLU peptide mix (sol)	1440.2 ± 44.9	678.3 ± 29.2
T1-Flu A/NC/20/99	2146.4 ± 23.7	1282.1 ± 4.8
Ju-Flu A/NC/20/99	1246.9 ± 48.8	1206.4 ± 10.9
T1-Flu A/NYMC/X147	1949.4 ± 37.9	1101 ± 5.9
Ju-Flu A/NYMC/X147	1342.3 ± 14.5	1248.6 ± 8.3
T1-Flu B/Johannesburg/5/99	1769.0 ± 33.6	1196.0 ± 16.2
Ju-Flu B/Johannesburg/5/99	257.6 ± 3.0	257.0 ± 8.3

Note:

"Lys" means the negative control background upon which all values are calculated. "Sol" means soluble peptide presented to the primary splenocyte population. "Pro" means that the peptide is being presented complexed with the cell's HLA molecules following internal processing and loading of the resulting epitopes on to the MHC molecules. T1 is the HLA-A*0201-bearing human cell line. "Ju" refers to JURKAT which is the HLA-A*0201 non-bearing human cell line. A/NC/20/99 (i.e. A/New_Caledonia/20/99), A/NYMC/X-147 and B/Johannesburg/5/99 are, respectively, the two influenza A and one influenza B strains used for infection of the human cell lines. Values represent average ± standard error of the Δ IFN-γ to Lys (pg/ml).

Interestingly, the background production of IFN-γ for all influenza infected groups was greater than observed when similar analysis were carried out using purified polypeptide antigen. This observation, however, most likely reflects the inability of MMC treatment to fully inactivate the virus present in the cell preparation. This, in turn, would result in viable Influenza virus infecting susceptible mouse cells in the primary splenocyte cultures, thus leading to a primary response *in vitro*. This interpretation is sustained by the observation that most influenza virus strains used induced the same level of background IFN-γ response

independently of the human cell line infected and the vaccinated group considered. The only exception to this rule is the much reduced background IFN-γ production observed in JURKAT cells infected with B/Johannesburg/5/99. However, as even in this case IFN-γ production for both FLU-v and NRP vaccinated animals is equivalent, it would appear that the observed difference is caused more by the reduced susceptibility of JURKAT cells to infection by Influenza B/Johannesburg/5/99, than by any cause intrinsically associated to the different vaccination regimes. Whatever the case, this observation, does not detract from the clear fact that vaccination with FLU-v leads to the specific recognition of naturally processed influenza epitopes presented in association with HLA-A*0201 molecules following infection of human cells with several non-related strains of infectious influenza virus. Therefore, FLU-v constitutes an effective candidate vaccine preparation for protection against multiple influenza strains, thus obviating the need for the current yearly re-vaccination protocols.

EXPERIMENT 2 – protective effect of polypeptides in mice

The purpose of this study was to demonstrate that low dose immunisation with the identified Influenza conserved T cell polyepitope peptides (FLU-v) induces protection, mediated by CD8+ T cells, against lethal challenge with the influenza virus.

Materials and methods

Peptides, antisera and virus:

The candidate vaccine preparation (FLU-v) tested in this study is composed of several peptides (i.e. P1: M1A amino acid (aa) 36 to 75 (SEQ ID 1); P2: M1B aa 124 to 158 (SEQ ID 2); P3: NPA aa 255 to 275 (SEQ ID 3); P4: NPB aa 306 to 326 (SEQ ID 4); P5: PB1 aa 395 to 428 (SEQ ID 5); P6: M2 aa 32 to 55 (SEQ ID 6)) which were all synthesised by Fmoc chemistry and resuspended in DMSO in PBS (the concentration of DMSO in the final preparation was less than 5%). Lysozyme (Sigma) denatured by boiling was used as the control non relevant preparation (NRP-v).

Purified rat anti-mouse CD8 IgG2a (clone YTS169.4) was obtained from AbD Serotec (UK) whilst the infectious virus Influenza A/PR/8/34 were obtained from NIBSC as lyophilised standard stock.

Immunisations

On day 1, seven to ten week old C57BL/6-Tg(HLA-A2.1)1Enge/J mice (HLA-A*0201 transgenic on a C57/BL6 background, Jackson Labs) were immunised subcutaneously at the base of the tail with a 200 μl dose of the antigen preparation emulsified in IFA (Sigma). In the test group (n = 14), each dose of the antigen preparation contained 60 nmol of an equimolar mixture of all six peptides (10 nmol each) whilst in the control group (n = 14), each dose of the antigen preparation contained an equivalent dose of the non-relevant polypeptide.

On day 15 all animals received a booster immunisation using the same doses and route of delivery as used originally.

On Day 16 both the test and control groups were split into two equal subgroups (n = 7 each; i.e. Ctrol-1, Ctrol-2, Test-1 and Test-2).

On Day 19, all animals in the Ctrol-1 and Test-1 groups received a 200 μl intraperitoneal injection of rat anti-mouse-CD8 sera (100 μg) whilst all animals in the Ctrol-2 and Test-2 groups received an equivalent injection of unrelated sera.

The following day (Day 20), all groups were challenged intranasally under anaesthesia with a large lethal dose (approximately $1.5x10^7$ pfu) of Influenza A/PR/8/34.

On day 22, animals were again intraperitoneally injected with either rat anti-mouse-CD8 or unrelated sera as described above.

From day 20 all animals were monitored daily for symptoms of influenza (e.g. sneezing and pyrexia) as well as weight loss.

All animals still alive on day 27 were culled and the study was terminated.

Results

In order to assess the efficacy of the FLU-v preparation as a candidate Influenza vaccine it was desirable to set up a challenge study in NRP-v and FLU-v immunised animals using the Influenza A/PR/8/34 strain. Typically, an intranasal dose of approximately $1.5x10^7$ pfu will kill non-immunised C57BL/6-Tg(HLA-A2.1)1Enge/J mice on day 4 or 5 after challenge (data not shown).

As shown in Fig. 3A, most animals immunised with either the FLU-v or NRP-v peptide preparations, but subject to CD8 depletion, had succumbed to infection by Influenza A/PR/8/34 by day 7 after intranasal challenge (71% vs 100% respectively). In contrast, as shown in Fig. 3B and in the absence of CD8 depletion, animals immunised with the FLU-v preparation showed a significant reduction ($p < 0.05$) in their mortality rate compared to animals immunised with the NRP-v preparation (28% vs 100%).

The results of this study clearly indicate that vaccination with the FLU-v peptide preparation, even at a low level dose of each of its constituent active peptides (10 nmol), induces a significant level of protection against lethal challenge with Influenza. These peptides, as indicated earlier, where identified *in silico* primarily by their T cell reactivity within the context of Human HLA Class I. The results corroborate the fact that CD8+ T cells stimulated by vaccination with the FLU-v peptide preparation play a significant role in conferring protection against Influenza infection.

Claims

1. A polypeptide having no more than 50 amino acids, which polypeptide comprises one or more sequences having at least 85% homology with SEQ ID NO: 2, or comprises two or more epitopes having 7 amino acids or more, each epitope having at least 85% homology with a sub-sequence of SEQ ID NO: 2 that has the same length as the epitope:

   SEQ ID 2 LLYCLMVMYLNPGNYSMQVKLGTLCALCEKQASHS

   Wherein the polypeptide is immunogenic in a vertebrate expressing a major histocompatibility complex (MHC) allele.

2. A polypeptide according to claim 1, further comprising one or more sequences having at least 85% homology with any of SEQ ID NOS: 3, 4, 5, or 6, or further comprising two or more epitopes having 7 amino acids or more, each epitope having at least 85% homology with a sub-sequence of any of SEQ ID NOS: 3, 4, 5, or 6 that has the same length as the epitope.

3. A polypeptide having no more than 50 amino acids, which polypeptide comprises one or more sequences defined by the following amino acid residues of an influenza virus protein, or comprises two or more epitopes having 7 amino acids or more from a sequence defined by the following amino acid residues of an influenza virus protein:

   residues 124-158 of an Ml protein

   wherein the polypeptide is immunogenic in a vertebrate expressing a major histocompatibility complex (MHC) allele.

4. A polypeptide according to claim 3, further comprising one or more sequences defined by the following amino acid residues of an influenza virus protein, or further comprising two or more epitopes having 7 amino acids or more from a sequence defined by any of the following amino acid residues of an influenza virus protein:

   residues 255-275 of an NP protein
   residues 306-326 of an NP protein
   residues 395-428 of an PB 1 protein
   residues 32-55 of an M2 protein

5. A polypeptide according to any of claims 1-4, which polypeptide comprises a cytotoxic T lymphocyte (CTL) epitope.

6. A polypeptide according to any preceding claim, comprising 2, 3, 4, 5 or more epitopes.

7. A polypeptide according to any preceding claim, which is immunogenic to an epitope within any of the sequences of SEQ ID NOS: 2-6.

8. A polypeptide according to any preceding claim, which is immunogenic to an influenza virus strain.

9. A polypeptide according to claim 8, which is immunogenic to a plurality of influenza virus strains.

10. A polypeptide according to any preceding claim, further comprising one or more further sequences from an influenza virus protein.

11. A polypeptide according to any one of claims 2 or 4-9, wherein when the polypeptide is at least 85% homologous to SEQ ID NO: 2, the protein is an influenza M1 protein, when the polypeptide is at least 85% homologous to SEQ ID NO: 3, the protein is an influenza NP protein, when the polypeptide is at least 85% homologous to SEQ ID NO: 4, the protein is an influenza NP protein, when the polypeptide is at least 85% homologous to SEQ ID NO: 5, the protein is an influenza PB 1 protein, and when the polypeptide is at least 85% homologous to SEQ ID NO: 6, the protein is an influenza M2 protein.

12. A polypeptide according to any preceding claim, wherein said homology is substantially 100%.

13. A polypeptide according to any preceding claim, wherein the epitope comprises 8, 9, 10 or 11 amino acids or more.

14. A polypeptide according to any preceding claim, having from 8-40 amino acid residues.

15. A polypeptide according to any preceding claim comprising from 15-35 amino acid residues.

16. An immunogenic multi-epitope polypeptide, which multi-epitope polypeptide comprises two or more polypeptides wherein the polypeptides comprise one or more sequences having at least 85% homology with any of SEQ ID NO: 2, or which multi-epitope polypeptide comprises two or more epitopes having 7 amino acids or more, each epitope having at least 85% homology with a sub-sequence of any of SEQ ID NO: 2 that has the same length as the epitope:

    SEQ ID 2 LLYCLMVMYLNPGNYSMQVKLGTLCALCEKQASHS

    wherein, the multi-epitope polypeptide is immunogenic in a vertebrate expressing a major histocompatibility complex (MHC) allele.

17. An immunogenic multi-epitope polypeptide according to claim 16, which further comprises all of the polypeptides of SEQ ID NOS: 3, 4, and 6, or comprises a polypeptide for each of SEQ ID NOS: 3, 4, and 6 having at least 85% homology for that sequence.

18. An immunogenic multi-epitope polypeptide according to claim 16, which further comprises all of the polypeptides of SEQ ID NOS: 3-6, or comprises a polypeptide for each of SEQ ID NOS: 3-6, having at least 85% homology for that sequence.

19. An immunogenic multi-epitope polypeptide, which multi epitope polypeptide comprises two or more polypeptides wherein each polypeptide comprise one or more sequences defined by the following amino acid residues of an influenza virus protein, or which multi-epit[[i]]ope polypeptide comprises two or more epitopes having 7 amino acids or more from a sequence

defined by the following amino acid residues of an influenza virus protein:

residues 124-158 of an M1 protein

wherein, the polypeptide is immunogenic in a vertebrate expressing a major histocompatibility complex (MHC) allele.

20. An immunogenic multi-epitope polypeptide according to claim 19, which further comprises all of the sequences defined by the following amino acid residues of an influenza virus protein:

    residues 255-275 of an NP protein
    residues 306-326 of an NP protein
    residues 32-55 of an M2 protein

21. An immunogenic multi-epitope polypeptide according to claim 19, which further comprises all of the sequences defined by the following amino acid residues of an influenza virus protein:

    residues 255-275 of an NP protein
    residues 306-326 of an NP protein
    residues 395-428 of an PBI protein
    residues 32-55 of an M2 protein

22. A polypeptide composition comprising two or more polypeptides as defined in any preceding claim.

23. A polypeptide composition according to claim 22, in which polypeptides having sequences of SEQ ID NOS: 2, 3, 4, and 6 are all present.

24. A polypeptide composition according to claim 22, in which polypeptides having sequences of SEQ ID NOS: 2-6 are all present, or in which all of the sequences defined by the following amino acid residues of an influenza virus protein are present:

    residues 124-158 of an M1 protein
    residues 255-275 of an NP protein
    residues 306-326 of an NP protein
    residues 395-428 of an PB I protein
    residues 32-55 of an M2 protein

25. A polypeptide, or polypeptide composition, as defined in any preceding claim for use in medicine.

26. A method of producing a polypeptide as defined in any preceding claim, which method comprises combining two or more epitopes to form the polypeptide.

27. A polypeptide construct, which construct comprises a polypeptide as defined in any

preceding claim and a carrier.

28. A method of producing a polypeptide construct as defined in claim 27, which method comprises combining two or more epitopes and/or a polypeptide with the carrier.

29. A polypeptide construct or a method according to claim 27 or claim 28, wherein the carrier is a molecule.

30. A polypeptide construct or a method according to any of claims 27-29, wherein the carrier comprises an adjuvant and/or an excipient.

31. A medicament or vaccine composition against influenza, comprising a polypeptide, or polypeptide composition, as defined in any of claims 1-25, and an appropriate excipient and/or adjuvant.

32. A medicament or vaccine composition against influenza, comprising a polypeptide construct as defined in claim 27, claim 29 or claim 30 and optionally an appropriate excipient and/or adjuvant.

33. A method of producing a medicament or vaccine composition as defined in claim 31, which method comprises mixing a polypeptide, or a polypeptide composition, as defined in any of claims 1-25 with an appropriate excipient and/or adjuvant.

34. Use of a polypeptide, a polypeptide composition, a polypeptide construct or a medicament or vaccine composition as defined in any of claims 1-25, 27 and 29-32 in the manufacture of a medicament or vaccine, effective in the treatment or prevention of influenza.

35. Use according to claim 34, wherein the medicament or vaccine composition is suitable for administration to a vertebrate.

36. Use according to claim 35, wherein the vertebrate is selected from a mammal, a bird, a reptile and a fish.

37. Use according to claim 36, wherein the vertebrate is a human, a domestic animal, or a farm animal, a bovine animal, or is fowl.

38. Use according to claim 37, wherein the vertebrate is selected from a chicken, a duck, a goose, a pig, a horse, a cow, a dog, or a cat.

39. A polypeptide, polypeptide construct, method, medicament, vaccine or use according to any preceding claim, wherein the influenza is an influenza A strain.

40. A polypeptide, polypeptide construct, method, medicament, vaccine or use according to any of claims 1-38, wherein the influenza is an influenza B strain.