have shortcomings. There is therefore a need for improved methods to address the issue of anti-FVIII antibodies in haemophilia A and acquired haemophilia.

The present inventors have found that it is possible to prevent FVIII inhibitor antibody formation by pre-tolerising the patient with FVIII-derived peptides.

SUMMARY OF ASPECTS OF THE INVENTION

The first aspect of the present invention, therefore, relates to a peptide which consists of the sequence EDNIMVTFRNQASR. Also disclosed is a peptide, at least part of the sequence of which is derivable from FVIII, which is capable of inducing or restoring tolerance to FVIII.

Also disclosed is~~In a first embodiment, the present invention provides~~ a peptide comprising one of the following FVIII-derived sequences:

GTLMVFFGNVDSSGI
TQTLHKFILLFAVFD
SLYISQFIIMYSLDG
PPIIARYIRLHPTHY
PPLLTRYLRIHPQSW
MHTVNGYVNRSLPGL
LGQFLLFCHISSHQH
DTLLIIFKNQASRPY
PRCLTRYYSSFVNME
TENIQRFLPNPAGVQ
DNIMVTFRNQASRPY
RYLRIHPQSWVHQIA

with one or more of the following modifications:

(i) removal of one or more hydophobic amino acid(s);

(ii) replacement of one or more hydrophobic amino acid(s) with charged hydrophilic amino acid(s); and

(iii) insertion of a charged amino acid at one or both terminus(i)

which modified peptide is capable of binding to an MHC class II molecule without further antigen processing and being recognised by a factor VIII specific T cell.

The "parent" (unmodified) peptide may be PRCLTRYYSSFVNME or DNIMVTFRNQASRPY

Also disclosed is~~In a second embodiment the present invention provides~~ a peptide comprising the sequence

$X(aa)_n$-core sequence -$(aa)_m$

wherein X is a charged hydrophilic residue;

aa is an amino acid;

n is an integer between 0 and 5;

m is an integer between 0 and 5; and

the "core sequence" is selected from the following group of FVIII-derived peptides: LYISQFIIM

FIIMYSLDG

IARYIRLHP

LIIFKNQAS

LTRYYSSFV

MVTFRNQAS

LRIHPQSWV

which peptide is capable of binding to an MHC class II molecule without further antigen processing and being recognised by a factor VIII specific T cell.

For example, the peptide may comprise the sequence

XDNIMVTFRNQAS.

Also disclosed is~~In a third embodiment, the present invention provides~~ a peptide comprising the sequence:

$Y(aa)_n$-core sequence-$(aa)_mZ$

wherein Y and Z are charged amino acids having reverse polarity;

aa is an amino acid;

n is an integer between 0 and 5;

m is an integer between 0 and 5; and

the "core sequence" is selected from the following group of FVIII-derived peptides:

LYISQFIIM

FIIMYSLDG

IARYIRLHP

LIIFKNQAS

LTRYYSSFV

MVTFRNQAS

LRIHPQSWV

which peptide is capable of binding to an MHC class II molecule without further antigen processing and being recognised by a factor VIII specific T cell.

For example, the peptide may comprise the sequence:

YDNIMVTFRNQASZ

In the example~~third embodiment~~, for example, Y may be a positively charged amino acid and Z may be a negatively charged amino acid. Alternatively, Y may be a negatively charged amino acid and Z may be a positively charged amino acid.

A charged, hydrophilic amino acid may, for example be D, E, K, H or R. A positively charged amino acid may, for example be K, H or R. A negatively charged amino acid may, for example be D or E.

The peptide of the first aspect of the invention may, for example, comprise or consist of the sequence EDNIMVTFRNQASR.

In a second aspect, the present invention provides a composition, such as a pharmaceutical composition comprising one or more peptide(s) of the first aspect of the invention. The composition may comprise a plurality of peptides wholly or partly derivable from FVIII which are capable of inducing or restoring tolerance to FVIII.

The composition may be in the form of a kit, in which the plurality of peptides are provided separately for separate, subsequent, sequential or simultaneous administration.

The peptide or a composition of the ~~invention~~disclosure may be for use in suppressing, reducing, or preventing the development of factor VIII inhibitor antibodies.

The present ~~invention~~disclosure also provides the use of such a peptide or composition in the manufacture of a medicament to suppress, reduce or prevent the development of factor VIII inhibitor antibodies.

The present ~~invention~~disclosure also provides a method for suppressing, preventing or reducing the development of Factor VIII inhibitor antibodies in a subject, which comprises the step of administration of such a peptide or composition to the subject.

The subject may be deficient in FVIII. In particular the subject may have haemophilia A, and may be, or be about to, undergo factor VIII replacement therapy.

In another aspect, the present invention provides a peptide as defined herein, or a composition as defined herein, for use in treating haemophilia in a subject.

Alternatively the subject may have, or be at risk from contracting, acquired haemophilia.

In yet another aspect, the present invention provides a peptide as defined herein or composition as defined herein for use in treating haemophilia in a subject as defined herein, wherein the subject

(a) has haemophilia A, and is undergoing, or is about to undergo, factor VIII replacement therapy; or

(b) has, or is at risk from contracting, acquired haemophilia.

Factor VIII inhibitors are found more frequently in individuals expressing HLA-DR2. The subject treated by the method of the invention may therefore be HLA-DR2 positive.

In yet another aspect, the present invention provides a peptide as defined herein or composition as defined herein for use in treating haemophilia in a subject as defined herein, wherein the subject is HLA-DR2.

DESCRIPTION OF THE FIGURES

Figure 1: Recall responses for lymph node cells (LNC) from FVIII+DR2+ mice primed with rhFVIII/CFA

a) LNC proliferation to FVIII peptides 1-6

b) LNC proliferation to FVIII peptides 7-12

c) LNC proliferation to FVIII peptides 1, 3 and 11

Figure 2: Representative examples of FVIII+DR2+ T cell hybridoma clones specific for FVIII-derived peptides

Figure 3: Recall responses for LNC from FVIII-DR2+ mice primed with rhFVIII/CFA

Figure 4: Representative examples of FVIII-DR2+ T cell hydridoma clones specific for FVIII-derived peptides

Figure 5: FVIII-/- clones specific for a) DNIMV and b) PRCLT