cyclophosphamide, cyclosporine, 2-chlorodeoxyadenosine; (3) immunomodulation with intravenous immunoglobulin; and (4) selective B-lymphocyte depletion with rituximab. Rituximab™ responders may require concurrent use of steroids and relapses may respond to retreatment.

Thus, all currently available methods for reducing alloantibody production associated with haemophilia A treatment, and autoantibody production in acquired haemophilia, 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 and to treat conditions such as haemophilia by administration of FVIII-derived peptides in order to reduce FVIII inhibitor antibodies.

SUMMARY OF ASPECTS OF THE INVENTION

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

In a first example ~~embodiment~~ of the first embodiment ~~aspect~~ of the disclosure ~~invention~~, the disclosure ~~invention~~ provides a peptide comprising the FVIII-derived sequence DNIMVTFRNQASRPY which has one of the following sequences:

Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys (SEQ ID No. 17)

Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Glu (SEQ ID No. 18)

Lys-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Glu-Lys (SEQ ID No. 19)

Lys-Glu-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys (SEQ ID No. 25)

Lys- Glu-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Glu (SEQ ID No. 26)

Lys- Glu-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Glu-Lys (SEQ ID No. 27)

Glu-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Lys (SEQ ID No. 29)

Glu-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Lys-Glu (SEQ ID No. 30) and

Glu-Lys-Gly-Asp-Asn-Ile-Met-Val-Thr-Phe-Arg-Asn-Gln-Ala-Ser-Arg-Pro-Tyr-Gly-Glu-Lys (SEQ ID No. 31).

In a second example ~~embodiment~~, the present disclosure ~~invention~~ provides a peptide comprising the FVIII-derived sequence PRCLTRYYSSFVNME which has one of the following sequences:

Lys-Lys-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Lys (SEQ ID No. 1)

Lys-Lys-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Glu (SEQ ID No. 2)

Lys-Lys-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Glu-Lys (SEQ ID No. 3)

Glu-Glu-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Lys (SEQ ID No. 5)

Glu-Glu-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Glu-Lys (SEQ ID No. 7)

Lys-Glu-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Lys (SEQ ID No. 9)

Lys- Glu-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Glu (SEQ ID No. 10)

Lys- Glu-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Glu-Lys (SEQ ID No. 11) and

Glu-Lys-Gly-Pro-Arg-Cys-Leu-Thr-Arg-Tyr-Tyr-Ser-Ser-Phe-Val-Asn-Met-Glu-Gly-Lys-Lys (SEQ ID No. 13).

In the first aspect, the present invention provides a peptide comprising the FVIII-derived sequence DNIMVTFRNQASRPY which peptide (a) has the formula

XXGDNIMVTFRNQASRPYGXX

wherein X is either Lysine or Glutamic acid; and
(b) has one of the following sequences:
KKGDNIMVTFRNQASRPYGKK (SEQ ID No. 17)

KKGDNIMVTFRNQASRPYGKE (SEQ ID No. 18)

KKGDNIMVTFRNQASRPYGEK (SEQ ID No. 19)

KEGDNIMVTFRNQASRPYGKK (SEQ ID No. 25)

KEGDNIMVTFRNQASRPYGKE (SEQ ID No. 26)

KEGDNIMVTFRNQASRPYGEK (SEQ ID No. 27)

EKGDNIMVTFRNQASRPYGKK (SEQ ID No. 29)

EKGDNIMVTFRNQASRPYGKE (SEQ ID No. 30) and

EKGDNIMVTFRNQASRPYGEK (SEQ ID No. 31).

In yet another first aspect, the present invention provides A peptide comprising the FVIII-derived sequence PRCLTRYYSSFVNME which peptide (a) has the formula

XXGPRCLTRYYSSFVNMEGXX

wherein X is either Lysine or Glutamic acid; and
(b) has one of the following sequences:

KKGPRCLTRYYSSFVNMEGKK (SEQ ID No. 1)

KKGPRCLTRYYSSFVNMEGKE (SEQ ID No. 2)

KKGPRCLTRYYSSFVNMEGEK (SEQ ID No. 3)

EEGPRCLTRYYSSFVNMEGKK (SEQ ID No. 5)

EEGPRCLTRYYSSFVNMEGEK (SEQ ID No. 7)

KEGPRCLTRYYSSFVNMEGKK (SEQ ID No. 9)

KEGPRCLTRYYSSFVNMEGKE (SEQ ID No. 10)

KEGPRCLTRYYSSFVNMEGEK (SEQ ID No. 11) and

EKGPRCLTRYYSSFVNMEGKK (SEQ ID No. 13).

In a second aspect, the present invention provides a composition comprising a plurality of peptides, including one or more peptide(s) according to the first aspect the invention.

The composition may comprise at least one peptide according to the first example ~~embodiment~~ and at least one peptide according to the second example ~~embodiment~~ of the first embodiment ~~aspect~~ of the disclosure ~~invention~~.

The composition may comprise a peptide having SEQ ID No. 1 and a peptide having SEQ ID No. 17.

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

In another aspect, the present invention provides a peptide as disclosed herein, or a composition as disclosed herein, for use in suppressing or preventing the production of factor VIII inhibitor antibodies *in vivo*.

The present disclosure ~~invention~~ 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.

In yet another aspect, the present invention provides the use of a peptide as disclosed herein, or a composition as disclosed herein, in the manufacture of a medicament to suppress or prevent the production of factor VIII inhibitor antibodies *in vivo* or in a subject.

The present disclosure ~~invention~~ also provides the use of such a peptide or composition in the manufacture of a medicament for treating haemophilia in a subject.

In yet another aspect, the present invention also provides the use of a peptide as disclosed herein, or a composition as disclosed herein, in the manufacture of a medicament for treating haemophilia A or acquired haemophilia in a subject.

Also disclosed is 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.

Alternatively the subject may have, or be 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.

DESCRIPTION OF THE FIGURES

Figure 1: Solubility of modified FVIII peptides

A total of 32 peptides were tested: 16 of which were based on the FVIII peptide PRCLTRYYSSFVNME ("PRCLT") (SEQ ID No. 1,2,3,4,5,6,7,8,9,10,11,12,13); and 16 of which were based on the FVIII peptide DNIMVTFRNQASRPY ("DNIMV") (SEQ ID No. 17,18,19,20,21,22,23,245,26,27,28,29,30,31,32). Their solubility was tested relative to an unrelated control peptide (4Y) which is known to be sufficiently soluble for application as a tolerising antigen. In the diagram, green represents a peptide which is at least as soluble as 4Y, orange represents a peptide which is not quite as soluble as 4Y but is fairly close, and red represents a peptide which is not as soluble as 4Y. Peptides coded green were as soluble as control peptide 4Y, peptides coded red were poorly soluble, and one peptide coded amber had intermediate solubility.

8. The use of a peptide according to claim 1 or 2, or a composition according to any of claims 3 to 5, in the manufacture of a medicament for treating haemophilia in a subject.

9. The use according to claim 7 or 8, wherein the subject has haemophilia A, and is undergoing, or is about to undergo, factor VIII replacement therapy and/or FVIII by-passing therapy.

10. The use according to claim 7 or 8, wherein the subject has, or is at risk from contracting, acquired haemophilia.

11. The use according to any of claims 7 to 10, wherein the subject is HLA-DR2.

8. The use of a peptide according to claim 1 or 2, or a composition according to any of claims 3 to 5, in the manufacture of a medicament for treating haemophilia A or acquired haemophilia in a subject.

9. The use according to claim 7 or 8, wherein the subject has haemophilia A, and is undergoing, or is about to undergo, factor VIII replacement therapy and/or FVIII by-passing therapy.

10. The use according to claim 7 or 8, wherein the subject has, or is at risk from contracting, acquired haemophilia.

11. The use according to any of claims 7 to 10, wherein the subject is HLA-DR2.