tested for efficacy with approved drugs for Graves' disease, such as methimazole and methylprednisolone.

There is thus a need for alternative therapies for treating and preventing diseases associated with the production of TSHR autoantibodies, such as Graves' disease. Alternative therapies that are effective at treating Graves' disease and at alleviating or reducing the symptoms of the disease are thus needed. There is also a need for alternative models for assessing the potential efficacy of candidate Graves' disease therapies.

SUMMARY

The present inventors have found that a "cocktail" of two TSHR peptides is particularly effective in suppressing or preventing the production of TSHR autoantibodies *in vivo* and in treating Graves' disease.

Disclosed herein is a composition which comprises the following TSHR peptides:

(i) a peptide comprising the amino acid sequence KKKKYVSI DVTLQQLESH KKK (SEQ ID NO: 1); and

(ii) a peptide comprising the amino acid sequence GLKMFPDLTKVYSTD (SEQ ID NO: 2), and optionally an antithyroid agent and/or a β-blocker .

KKKKYVSI DVTLQQLESH KKK (SEQ ID NO: 1) is also referred to as RNB-5D-K1 herein. GLKMFPDLTKVYSTD (SEQ ID NO: 2) is also referred to as RNB-9B herein.

The composition according to the disclosure may be used in the therapeutic aspects of the disclosure described herein.

Disclosed herein is a peptide as described herein, and optionally an antithryoid agent and/or a β-blocker, or the composition as described herein, for use in therapy.

Disclosed herein is a peptide or composition as described herein, for use in suppressing or preventing the production of TSHR autoantibodies *in vivo*.

Disclosed herein is a peptide or composition as described herein for use in treating and/or preventing Graves' disease in a subject.

Disclosed herein is the use of a peptide or composition as described herein, in the manufacture of a medicament to suppress or prevent the production of TSHR autoantibodies *in vivo*.

Disclosed herein is the use of a peptide or composition as described herein, in the manufacture of a medicament to treat and/or prevent Graves' disease.

In an embodiment the present disclosure relates to a method for suppressing or preventing the production of TSHR autoantibodies in a subject, which comprises the step of administration of all or a part of a peptide of SEQ ID NO: 1 or a peptide with at least 60% sequence identity thereto, and all or a part of a peptide of SEQ ID NO:2 or a peptide with at least 60% sequence identity thereto, to the subject.

In an embodiment the present disclosure relates to a method for treating Graves' disease in a subject which comprises the step of administration of all or a part of a peptide of SEQ ID NO:1 or a peptide with at least 60% sequence identity thereto and all or a part of a peptide of SEQ ID NO:2 or a peptide with at least 60% sequence identity thereto to the subject.

In one embodiment, the composition does not include or comprise the following peptide:
RNB-4K-GKK: KKGNLPNISRIYVSIDVTGKK

A peptide composition according to the disclosure may comprise the amino acid sequences according to the disclosure as described herein.

In one embodiment the peptide composition comprises only the amino acid sequences according to the disclosure as described herein.

The subject may be HLA-DR3. The subject may be HLA-DR4.

The peptides of the disclosure as defined herein, or the composition of the disclosure, may be administered following a dose-escalation protocol.

Disclosed herein is a kit which comprises the following TSHR peptides:

(i) a peptide comprising the amino acid sequence KKKKYVSI DVTLQQLESH KKK (SEQ ID NO: 1); and

(ii) a peptide comprising the amino acid sequence GLKMFPDLTKVYSTD (SEQ ID NO: 2); and optionally an antithyroid agent and/or a β-blocker,
for simultaneous, separate or sequential administration.

The kit may be for the treatment or prevention of a condition involving the production of TSHR autoantibodies, such as Graves' Disease.

In an embodiment of the disclosure the peptides or composition of the invention is combined with a further therapeutic agent that is used in the treatment, prevention or management of Graves' Disease. For example, the peptides or composition may be combined with an antithyroid drug, or a β-blocker.

In an embodiment of the disclosure relates to an animal model for a disease associated with the production of TSHR antibodies, wherein the animal is transgenic for human HLA-DR3 and wherein levels of TSHR are increased in the animal relative to a suitable control animal.

In an embodiment the level of TSHR is increased by administration of a viral vector comprising a nucleic acid molecule encoding a TSHR peptide.

The disease associated with the production of TSHR antibodies may be Graves' Disease.

The TSHR may be human TSHR. For example the TSHR may be human TSHR A subunit or extracellular domain (ECD).

The viral vector may be an adenoviral vector or adenoviral construct.

The adenoviral vector or construct may be administered at three-week intervals. The adenoviral vector or construct may be administered in two or three sequential administrations.

CLAIMS

1. A composition which comprises the following Thyroid Stimulating Hormone Receptor (TSHR) peptides:
(i) a peptide comprising the amino acid sequence KKKKYVSIDVTLQQLESHKKK (SEQ ID NO: 1); and
(ii) a peptide comprising the amino acid sequence GLKMFPDLTKVYSTD (SEQ ID NO: 2), and optionally an antithyroid agent and/or a β-blocker.

2. The peptides as defined in claim 1, and optionally an antithyroid agent and/or a β-blocker, or the composition of claim 1, for use in therapy.

3. The peptides or composition according to claim 1 or claim 2, for use in suppressing or preventing the production of TSHR autoantibodies *in vivo*.

4. The peptides or composition according to claim 1 or claim 2, for use in treating and/or preventing Graves' Disease in a subject.

5. Use of the peptides or composition according to claim 1 or claim 2 in the manufacture of a medicament to suppress or prevent the production of TSHR autoantibodies *in vivo.*

6. Use of the peptides or composition according to claim 1 or claim 2 in the manufacture of a medicament to treat and/or prevent Graves' Disease.

7. The peptide or composition for use according to claim 3 or 4, or the use according to claim 5 or 6, wherein the subject is HLA-DR3.

8. The peptide or composition for use according to claim 3 or 4, or the use according to claim 5 or 6, wherein the subject is HLA-DR4.

9. The peptide or composition for use according to claim 3 or 4, or the use according to claim 5 or 6, in which the composition is to be administered following a dose-escalation protocol.

10. A kit which comprises the following TSHR peptides;
(i) a peptide comprising the amino acid sequence KKKKYVSIDVTLQQLESHKKK (SEQ ID NO: 1); and

(ii) a peptide comprising the amino acid sequence GLKMFPDLTKVYSTD (SEQ ID NO: 2); and optionally an antithyroid agent and/or a β-blocker, for simultaneous, separate or sequential administration.

11. The kit of claim 10 for simultaneous, separate or sequential administration in the prevention or treatment of Grave's Disease.