Figure 18: Identification of apitopes within the RNB12 region using a RNB12 specific TCL generated from a healthy donor. The RNB12 specific T cells were cultured with BM14, a human cell line expressing human MHC class II molecules in presence of peptide. Black bars represent the stimulation in presence of fresh, but irradiated BM14 cells and white bars presence of fixed APCs. (See materials and methods). Before adding 3H-thymidine to the cultures, culture supernatant was collected and frozen. The supernatant was analysed for IFN gamma (A) to confirm the proliferative T cell response (B). TCL, T cell line; APC, antigen presenting cell; MHC class II, major histocompatibility complex class II; SI, stimulation index; OD, optical density.

Figure 19: Examples of Ex vivo tolerance induction by modified RNB5D modified peptides in DR3 mice according to the dose escalation schedule. 2-way ANOVA was used to measure overall treatment effects on T cell proliferation and p-values are written in the graphs. (* $p<0.05$; ** $p<0.01$; *** $p<0.001$; **** $p<0.0001$) Data represents mean ± SEM for the PBS-treated (black lines) and peptide treated mice (red lines). SI stimulation index. A: RNB5D-K1; B: RNB5D-K3; C: RNB5D-K16

Figure 20: Graph illustrating the apitope status of RNB5D modified peptides . An example of the response of a TSHR- and RNB-5-specific hybridoma clone, isolated from HLA-DR3 and HLA-DR4 mice immunized with TSHR/CFA, to RNB-5D modified peptides. The hybridoma clone was cultured with fresh (black bars) and fixed (white bars) APCs and 25 µg/ml antigen for 48 hours prior to determination of IL-2 production.

SUMMARY OF ASPECTS OF THE INVENTION

The present inventors have identified a number of peptides derived from TSHR which are useful in the prevention and/or treatment of GD.

Disclosed is a peptide which is capable of binding to an MHC molecule *in vitro* and being presented to a T cell without antigen processing, and which comprises all or a portion of the following Thyroid Stimulating Hormone Receptor (TSHR) peptides:

RNB_5: ISRIYVSIDVTLQQLESHSFYNLSKVTHI	(SEQ ID No 1)
RNB_4: LRTIPSHAFSNLPNISRIYVSIDVTLQQL	(SEQ ID No 2)
RNB_9: TGLKMFPDLTKVYSTDIFFILEITDNPYM	(SEQ ID No 3)
RNB_12: LTLKLYNNGFTSVQGYAFNGTKLDAVYL	(SEQ ID No 64)

In a first aspect, the present invention provides a peptide which is capable of binding to an MHC molecule in vitro and being presented to a T cell without antigen processing, which is selected from the following:

RNB_4K: NLPNISRIYVSIDVT (SEQ ID No. 62)

RNB_4K-GKK: KKGNLPNISRIYVSIDVTGKK (SEQ ID No. 63)

RNB_9B: GLKMFPDLTKVYSTD (SEQ ID No 18)

The peptide may be selected from the following TSHR peptides and derivatives thereof:

RNB_5D-GKK: KKGIYVSIDVTLQQLESHGKK	(SEQ ID No 12)
RNB_5D-KKK: KKKIYVSIDVTLQQLESHKKK	(SEQ ID No. 21)
RNB_5E-GKK: KKGYVSIDVTLQQLESHSGKK	(SEQ ID No 13)
RNB_5A: ISRIYVSIDVTLQQL	(SEQ ID No 6)
RNB_5B: SRIYVSIDVTLQQLE	(SEQ ID No 7)
RNB_5C: RIYVSIDVTLQQLES	(SEQ ID No 8)
RNB_5D: IYVSIDVTLQQLESH	(SEQ ID No 9)
RNB_5E: YVSIDVTLQQLESHS	(SEQ ID No 10)
RNB_5F: VSIDVTLQQLESHSF	(SEQ ID No 11)
RNB_5F-GKK: KKGVSIDVTLQQLESHSFGKK	(SEQ ID No 14)
RNB_4J-GKK: KKGSNLPNISRIYVSIDVGKK	(SEQ ID No 16)
RNB_4J: SNLPNISRIYVSIDV	(SEQ ID No 15)
RNB_4K: NLPNISRIYVSIDVT	(SEQ ID No. 62)
RNB_4K-GKK: KKGNLPNISRIYVSIDVTGKK	(SEQ ID No. 63)
RNB_9A: TGLKMFPDLTKVYST	(SEQ ID No 17)
RNB_9B: GLKMFPDLTKVYSTD	(SEQ ID No 18)
RNB_9C: LKMFPDLTKVYSTDI	(SEQ ID No 19)
RNB_9D: KMFPDLTKVYSTDIF	(SEQ ID No 20)
RNB_12A: LTLKLYNNGFTSVQG	(SEQ ID No. 65)
RNB_12B: TLKLYNNGFTSVQGY	(SEQ ID No. 66)
RNB_12B-KKK: KKK TLKLYNNGFTSVQGYKKK	(SEQ ID No. 67)

The peptide may comprise the RNB 5A, 5B, 5C, 5D, 5E, 5F, 4J, 4K, 9A, 9B, 9C, 9D, 12A or 12B sequence, or a variant thereof in which one or more amino acids has been replaced by another amino acid, such as K, which has been modified at one or both ends, for example by the introduction of "GKK" or "KKK" sequences.

The peptide may comprise the RNB-5D sequence, or a variant thereof in which one or more amino acids has been replaced by another amino acid, such as K, which has been modified at one or both ends, for example by the introduction of "GKK" or "KKK" sequences.

The present disclosure also provides a peptide which comprises the sequence:

KK-(G/K)-aa1-(RNB-5D peptide)-aa2-aa3-Z-(G/K)-KK

CLAIMS

1. A peptide which is capable of binding to an MHC molecule in vitro and being presented to a T cell without antigen processing, which is selected from the following:

RNB_4K: NLPNISRIYVSIDVT (SEQ ID No. 62)

RNB_4K-GKK: KKGNLPNISRIYVSIDVTGKK (SEQ ID No. 63)

RNB_9B: GLKMFPDLTKVYSTD (SEQ ID No 18)

2. A peptide which is capable of binding to an MHC molecule in vitro and being presented to a T cell without antigen processing, wherein the peptide is selected from the following group: KKGIYVSIDVTLQQLESHGKK (SEQ ID No 12), KKGKYVSIDVTLQQLESHGKK (SEQ ID No 22), KKGIKVSIDVTLQQLESHGKK (SEQ ID No 23), KKGIYKSIDVTLQQLESHGKK (SEQ ID No 24), KKGIYVSIDVKLQQLESHGKK (SEQ ID No 25), KKGIYVSIDVTLQKLESHGKK(SEQ ID No 26), KKGIYVSIDVTLQQKESHGKK (SEQ ID No 27), KKGIYVSIDVTLQQLKSHGKK (SEQ ID No 28), KKGIYVSIDVTLQQLEKHGKK (SEQ ID No 29), KKGIYVSIDVTLQQLESKGKK (SEQ ID No 30), KKGYVSIDVTLQQLEGKK (SEQ ID No 31), KKGYVSIDVKLQQLEGKK (SEQ ID No 32), KKGYVSIDVTLQKLEGKK (SEQ ID No 33), KKGYVSIDVTLQQKEGKK (SEQ ID No 34), KKGYVSIDVKLQKKEGKK (SEQ ID No 35), KKGIYVSIDVTLQQLEGKK (SEQ ID No 36), KKGIYVSIDVKLQQLEGKK (SEQ ID No 37), KKGIYVSIDVTLQKLEGKK (SEQ ID No 38), KKGIYVSIDVTLQQKEGKK (SEQ ID No 39), KKGIYVSIDVKLQKKEGKK (SEQ ID No 40), KKGTYVSIDVTLQQLEGKK (SEQ ID No 41), KKGTYVSIDVKLQQLEGKK (SEQ ID No 42), KKGTYVSIDVTLQKLEGKK (SEQ ID No 43), KKGTYVSIDVTLQQKEGKK (SEQ ID No 44), KKGTYVSIDVKLQKKEGKK (SEQ ID No 45), KKKIYVSIDVTLQQLESHKKK (SEQ ID No 21), KKKKYVSIDVTLQQLESHKKK (SEQ ID No 46), KKKIKVSIDVTLQQLESHKKK (SEQ ID No 47), KKKIYKSIDVTLQQLESHKKK (SEQ ID No 48), KKKIYVKIDVTLQQLESHKKK (SEQ ID No 49), KKKIYVSIDVKLQQLESHKKK (SEQ ID No 50), KKKIYVSIDVTLKQLESHKKK (SEQ ID No 51), KKKIYVSIDVTLQKLESHKKK (SEQ ID No 52), KKKIYVSIDVTLQQKESHKKK (SEQ ID No 53), KKKIYVSIDVTLQQLKSHKKK (SEQ ID No 54), KKKIYVSIDVTLQQLEKHKKK (SEQ ID No 55), KKKIYVSIDVTLQQLESKKKK (SEQ ID No 56), KKKYVSIDVTLQQLEKKK (SEQ ID No 57), KKKYVSIDVKLQQLEKKK (SEQ ID No 58), KKKYVSIDVTLQKLEKKK (SEQ ID No 59), KKKYVSIDVTLQQKEKKK (SEQ ID No 60), KKKYVSIDVKLQKKEKKK (SEQ ID No. 61).

3. A peptide according to claim 2, wherein the peptide is selected from the group consisting of:
KKGKYVSIDVTLQQLESHGKK (SEQ ID No. 22), KKGIYKSIDVTLQQLESHGKK (SEQ ID No. 24), KKGYVSIDVTLQQLEGKK (SEQ ID No. 31), KKGYVSIDVKLQQLEGKK (SEQ ID No. 32), KKGYVSIDVTLQKLEGKK (SEQ ID No. 33), KKGYVSIDVTLQQKEGKK (SEQ ID No. 34), KKGYVSIDVKLQKKEGKK (SEQ ID No. 35), KKGIYVSIDVKLQKKEGKK (SEQ ID No. 40), KKGTYVSIDVKLQQLEGKK (SEQ ID No. 42), KKGTYVSIDVKLQKKEGKK (SEQ ID No. 45), KKKKYVSIDVTLQQLESHKKK (SEQ ID No. 46), KKKIYKSIDVTLQQLESHKKK (SEQ ID No. 48), KKKIYVKIDVTLQQLESHKKK (SEQ ID No. 49), KKKYVSIDVTLQQLEKKK (SEQ ID No. 57), KKKYVSIDVKLQQLEKKK (SEQ ID No. 58), KKKYVSIDVTLQQKEKKK (SEQ ID No. 60), KKKYVSIDVKLQKKEKKK (SEQ ID No. 61).

4. A peptide according to claim 3, wherein the peptide is selected from the group consisting of: KKGIYKSIDVTLQQLESHGKK (SEQ ID No. 24), KKGYVSIDVKLQQLEGKK (SEQ ID No 32), KKGYVSIDVTLQKLEGKK (SEQ ID No. 33), KKGYVSIDVTLQQKEGKK (SEQ ID No. 34), KKGYVSIDVKLQKKEGKK (SEQ ID No. 35), KKGTYVSIDVKLQQLEGKK (SEQ Id No. 42), KKGTYVSIDVKLQKKEGKK (SEQ ID No. 45), KKKKYVSIDVTLQQLESHKKK (SEQ ID No. 46), KKKIYKSIDVTLQQLESHKKK (SEQ ID No. 48), KKKYVSIDVTLQQLEKKK (SEQ ID No. 57), KKKYVSIDVTLQQKEKKK (SEQ ID No. 60).

5. A peptide according to claim 3, wherein the peptide is selected from the group consisting of: KKGYVSIDVTLQKLEGKK (SEQ ID No. 32), KKGYVSIDVKLQKKEGKK (SEQ ID No. 34), KKKKYVSIDVTLQQLESHKKK (SEQ ID No. 46), KKKIYKSIDVTLQQLESHKKK (SEQ ID No. 48), KKKYVSIDVTLQQLEKKK (SEQ ID No. 57), KKKYVSIDVTLQQKEKKK (SEQ ID No. 60).

6. A composition comprising a plurality of peptides, including one or more peptide(s) according to any preceding claim.

7. A peptide according to any of claims 1 to 5, or a composition according to claim 6, for use in supressing or preventing the production of TSHR autoantibodies *in vivo*.

8. A peptide according to any of claims 1 to 5, or a composition according to claim 6, for use in treating and/or preventing Graves' Disease in a subject.

9. The use of a peptide according to any of claims 1 to 5, or a composition according to claim 6, in the manufacture of a medicament to suppress or prevent the production of TSHR autoantibodies *in vivo*, wherein said peptide or composition is to be administered to the subject.

10. The use of a peptide according to any of claims 1 to 85, or a composition according to claim 6, in the manufacture of a medicament to treat and/or prevent Graves' Disease in a subject, wherein said peptide or composition is to be administered to the subject.

11. The use according to claim 9 or 10, wherein the subject is HLA-DR3.

12. The use according to claim 9 or 10, wherein the subject in HLA-DR4.