US008298769B2

(12) **United States Patent**
Smith et al.

(10) **Patent No.: US 8,298,769 B2**
(45) **Date of Patent: *Oct. 30, 2012**

(54) **EPITOPE REGIONS OF A THYROTROPHIN (TSH) RECEPTOR, USES THEREOF AND ANTIBODIES THERETO**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 307 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/488,074**

(22) PCT Filed: **Aug. 21, 2002**

(86) PCT No.: **PCT/GB02/03831**

§ 371 (c)(1),
(2), (4) Date: **Jun. 17, 2004**

(87) PCT Pub. No.: **WO03/018632**

PCT Pub. Date: **Mar. 6, 2003**

(65) **Prior Publication Data**

US 2005/0118638 A1 Jun. 2, 2005

(30) **Foreign Application Priority Data**

Aug. 23, 2001 (GB) 0120649.9
Jul. 1, 2002 (GB) 0215212.2

(51) **Int. Cl.**
G01N 33/53 (2006.01)

(52) **U.S. Cl.** **435/7.1**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention is concerned with epitope regions of thyrotrophin (TSH) receptor, uses thereof and antibodies thereto.

15 Claims, 52 Drawing Sheets

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                MRPTPLLQLALLLALPRSLGGKGCPSPPCECHQEDDFRVT  Majority

  1 MRPADLLQLVLLLDLPRDLGGMGCSSPPCECHQEEDFRVT  HTSHR.PRO
  1 MSLTPLLQLALVLALPRSLRGKGCPSPPCECHQEDDFRVT  PTSHR.PRO
  1 MRPTPLLRLALFLVLPSSLGGERCPSPPCECRQEDDFRVT  BTSHR.PRO
  1 MRQTPLLQLALLLSLPRSLGGKGCPSPPCECHQEDDFRVT  CTSHR.PRO
  1 MRPPPLLHLALLLALPRSLGGKGCPSPPCECHQEDDFRVT  DTSHR.PRO
  1 MRPGSLLLLVLLLALSRSLRGKECASPPCECHQEDDFRVT  MTSHR.PRO
  1 MRPGSLLQLTLLLALPRSLWGRGCTSPPCECHQEDDFRVT  RTSHR.PRO
  1 MRPTPLLRLALLLVLPSSLWGERCPSPPCECRQEDDFRVT  STSHRP.PRO

    CKDIHRIPSLPPSTQTLKFIETHLKTIPSRAFSNLPNISR  Majority

 41 CKDIQRIPSLPPSTQTLKLIETHLRTIPSHAFSNLPNISR  HTSHR.PRO
 41 CKDIHSIPPLPPNTQTLKFIETHLKTIPSRAFSNLPNISR  PTSHR.PRO
 41 CKDIQSIPSLPPSTQTLKFIETHLKTIPSRAFSNLPNISR  BTSHS.PRO
 41 CKDIHRIPSLPPSTQTLKFIETHLKTIPSRAFSNLPNISR  CTSHR.PRO
 41 CKDIHRIPTLPPSTQTLKFIETQLKTIPSRAFSNLPNISR  DTSHR.PRO
 41 CKELHRIPSLPPSTQTLKLIETHLKTIPSLAFSSLPNISR  MTSHR.PRO
 41 CKELHQIPSLPPSTQTLKLIETHLKTIPSLAFSSLPNISR  RTSHS.PRO
 41 CKDIQRIPSLPPSTQTLKFIETHLKTIPSRAFSNLPNISR  STSHRP.PRO

    IYLSIDATLQQLESHSFYNLSKMTHIEIRNTRSLTYIDPG  Majority

 81 IYVSIDVTLQQLESHSFYNLSKVTHIEIRNTRNLTYIDPD  HTSHR.PRO
 81 IYLSIDATLQQLESQSFYNLSKMTHIEIRNTRSLTYINPG  PTSHR.PRO
 81 IYLSIDATLQQLESHSFYNLSKVTHIEIRNTRSLTYIDSG  BTSHR.PRO
 81 IYLSIDATLQRLESHSFYNLSKMTHIEIRNTRSLTYIDPG  CTSHR.PRO
 81 IYLSIDATLQRLESHSFYNLSKMTHIEIRNTRSLTSIDPD  DTSHR.PRO
 81 IYLSIDATLQRLEPHSFYNLSKMTHIEIRNTRSLTYIDPD  MTSHR.PRO
 81 IYLSIDATLQRLEPHSFYNLSKMTHIEIRNTRSLTYIDPD  RTSHR.PRO
 81 IYLSIDATLQQLESHSFYNLSKVTHIEIRNTRSLTYIDSG  STSHRP.PRO

    ALKELPLLKFLGIFNTGLRVFPDLTKVYSTDVFFILEITD  Majority

121 ALKELPLLKFLGIFNTGLKMFPDLTKVYSTDIFFILEITD  HTSHR.PRO
121 ALKDLPLLKFLGIFNTGLRIFPDLTKVYSTDVFFILEITD  PTSHR.PRO
121 ALKELPLLKFLGIFNTGLRVFPDLTKIYSTDVFFILEITD  BTSHR.PRO
121 ALKELPLLKFLGIFNTGLGVFPDLTKVYSTDVFFILEITD  CTSHR.PRO
121 ALKELPLLKFLGIFNTGLGVFPDVTKVYSTDVFFILEITD  DTSHR.PRO
121 ALTELPLLKFLGIFNTGLRIFPDLTKIYSTDIFFILEITD  MTSHR.PRO
121 ALTELPLLKFLGIFNTGLRIFPDLTKIYSTDVFFILEITD  RTSHR.PRO
121 ALKELPLLKFLGIFNTGLRVFPDLTKIYSTDVFFILEITD  STSHRP.PRO

    NPYMTSIPANAFQGLCNETLTLKLYNNGFTSIQGHAFNGT  Majority

161 NPYMTSIPVNAFQGLCNETLTLKLYNNGFTSVQGYAFNGT  HTSHR.PRO
161 NPYMTSIPANAFQGLCNETLTLKLYNNGFTSVQGHAFNGT  PTSHR.PRO
161 NPYMTSIPANAFQGLCNETLTLKLYNNGFTSIQGHAFNGT  BTSHR.PRO
161 NPYMTSIPANAFQGLCNETLTLKLYNNGFTSIQGHAFNGT  CTSHR.PRO
161 NPYMASIPANAFQGLCNETLTLKLYNNGFTSIQGHAFNGT  DTSHR.PRO
161 NPYMTSVPENAFQGLCNETLTLKLYNNGFTSVQGHAFNGT  MTSHR.PRO
161 NPYMTSVPENAFQGLCNETLTLKLYNNGFTSIQGHAFNGT  RTSHR.PRO
161 NPYMTSVPANAFQGLSNETLTLKLYNNGFTSIQGHAFNGT  STSHRP.PRO
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FIG. 1

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    ATGAGGCCGACGCCCCTGCTGCAGCTGGCGCTGCTTCTCG  Majority

 1  ATGAGGCAGACGCCCCTGCTGCAGCTGGCGTTACTTCTCT  CAT.SEQ
 1  ATGCGGCCGACGCCCCTCCTGCGGCTGGCGCTGTTTCTGG  COW.SEQ
 1  ATGAGGCCGCCGCCCCTGCTGCACCTGGCGCTGCTTCTCG  DOG.SEQ
 1  ATGAGGCCAGGGTCCCTGCTGCTGCTTGTTCTGCTGCTCG  MOUSE.SEQ
 1  ATGAGTCTGACGCCCCTGTTGCAGCTGGCGCTCGTTCTCG  PTSHR.SEQ
 1  ATGAGGCCAGGGTCCCTGCTCCAGCTCACTCTGCTGCTCG  RAT.SEQ
 1  ATGCGGCCGACGCCCCTCCTGCGGTTGGCGCTGCTTCTGG  SHEEP.SEQ
 1  ATGAGGCCGGCGGACTTGCTGCAGCTGGTGCTGCTGCTCG  HTSHR.SEQ

    CCCTGCCCAGGAGCCTGGGGGGGAAGGGGTGTCCGTCTCC  Majority

41  CCCTGCCCAGGAGCCTGGGGGGGAAAGGGTGTCCGTCTCC  CAT.SEQ
41  TCCTGCCCAGCAGCCTCGGTGGGGAGAGGTGTCCGTCTCC  COW.SEQ
41  CCCTGCCCAGGAGCCTGGGGGGGAAGGGGTGTCCTTCTCC  DOG.SEQ
41  CCCTGTCCAGGAGCCTGCGGGGCAAAGAGTGTGCGTCTCC  MOUSE.SEQ
41  CCCTGCCCAGGAGCCTCAGGGGGAAAGGGTGTCCGTCTCC  PTSHR.SEQ
41  CCCTGCCCAGGAGCCTCTGGGGCAGAGGGTGTACTTCTCC  RAT.SEQ
41  TCCTGCCCAGCAGCCTCTGGGGGGAGAGGTGTCCGTCTCC  SHEEP.SEQ
41  ACCTGCCCAGGGACCTGGGCGGAATGGGGTGTTCGTCTCC  HTSHR.SEQ

    GCCCTGCGAGTGCCACCAGGAGGACGACTTCAGAGTCACC  Majority

81  GCCCTGCGAGTGTCACCAGGAAGATGACTTCAGAGTCACC  CAT.SEQ
81  GCCCTGCGAATGCCGCCAGGAGGACGACTTCAGAGTCACC  COW.SEQ
81  CCCCTGTGAGTGCCACCAGGAGGATGACTTCAGAGTCACC  DOG.SEQ
81  ACCCTGTGAGTGTCACCAGGAGGACGACTTCAGAGTCACC  MOUSE.SEQ
81  GCCCTGCGAATGCCACCAGGAGGACGACTTCAGAGTCACC  PTSHR.SEQ
81  ACCCTGCGAATGCCACCAGGAGGACGACTTCAGAGTCACC  RAT.SEQ
81  GCCCTGCGAATGCCGCCAGGAGGACGACTTCAGAGTCACC  SHEEP.SEQ
81  ACCCTGCGAGTGCCATCAGGAGGAGGACTTCAGAGTCACC  HTSHR.SEQ

    TGCAAGGATATCCACCGCATCCCCAGCTTACCGCCCAGCA  Majority

121  TGCAAGGATATTCACCGTATCCCCAGCCTACCGCCCAGCA  CAT.SEQ
121  TGCAAGGACATCCAGAGCATCCCTAGCTTACCCCCCAGCA  COW.SEQ
121  TGCAAGGATATCCACCGCATCCCCACCCTACCACCCAGCA  DOG.SEQ
121  TGCAAGGAGCTCCACCGAATCCCCAGCCTGCCGCCCAGCA  MOUSE.SEQ
121  TGCAAGGATATCCACAGCATCCCCCCCTTACCACCCAATA  PTSHR.SEQ
121  TGCAAGGAACTCCACCAAATCCCCAGCCTACCGCCCAGCA  RAT.SEQ
121  TGCAAGGACATCCAGCGCATCCCTAGCTTACCCCCCAGCA  SHEEP.SEQ
121  TGCAAGGATATTCAACGCATCCCCAGCTTACCGCCCAGTA  HTSHR.SEQ

    CGCAGACTCTGAAGTTTATAGAGACTCATCTGAAAACCAT  Majority

161  CGCAGACTCTGAAATTTATAGAGACTCATCTGAAAACCAT  CAT.SEQ
161  CGCAGACCCTGAAGTTTATAGAGACTCATCTGAAAACCAT  COW.SEQ
161  CGCAGACTCTGAAGTTTATAGAGACTCAGCTGAAAACCAT  DOG.SEQ
161  CCCAGACTCTGAAGCTCATCGAGACTCATCTGAAGACCAT  MOUSE.SEQ
161  CTCAGACACTAAAGTTTATAGAGACTCATCTGAAAACCAT  PTSHR.SEQ
161  CCCAGACTCTGAAGCTCATCGAGACTCACCTGAAGACCAT  RAT.SEQ
161  CGCAGACCCTGAAGTTTATAGAGACTCATCTGAAAACCAT  SHEEP.SEQ
161  CGCAGACTCTGAAGCTTATTGAGACTCACCTGAGAACTAT  HTSHR.SEQ
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FIG. 2

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     TCCCAGTCGTGCATTTTCAAATCTGCCCAATATTTCCAGG  Majority

201  TCCCAGTCGTGCATTTTCAAATCTGCCCAATATTTCCAGG  CAT.SEQ
201  TCCCAGTCGTGCGTTCTCAAATCTGCCCAATATTTCCAGG  COW.SEQ
201  TCCCAGTCGTGCATTTTCAAATCTGCCCAATATTTCCAGG  DOG.SEQ
201  ACCCAGTCTTGCATTTTCGAGTCTGCCCAATATTTCCAGG  MOUSE.SEQ
201  CCCCAGTCGTGCATTTTCAAATCTGCCCAATATTTCCAGG  PTSHR.SEQ
201  TCCCAGTCTTGCCTTTTCGAGCCTGCCCAATATTTCCAGG  RAT.SEQ
201  TCCCAGTCGTGCGTTCTCAAATTTGCCCAATATTTCCAGG  SHEEP.SEQ
201  TCCAAGTCATGCATTTTCTAATCTGCCCAATATTTCCAGA  HTSHR.SEQ

     ATCTACTTGTCAATAGATGCAACTCTGCAGCGGCTGGAAT  Majority

241  ATCTACTTGTCAATAGATGCAACTCTGCAGCGACTGGAAT  CAT.SEQ
241  ATCTACTTGTCAATAGATGCAACTCTGCAGCAGCTGGAAT  COW.SEQ
241  ATCTACTTGTCAATAGATGCAACTCTGCAGCGGCTGGAAT  DOG.SEQ
241  ATCTATTTATCTATAGATGCAACTCTGCAGCGGCTGGAAC  MOUSE.SEQ
241  ATCTACCTGTCAATAGATGCAACTCTACAGCAGCTGGAAT  PTSHR.SEQ
241  ATCTATCTATCCATAGATGCCACTCTGCAGCGACTGGAGC  RAT.SEQ
241  ATCTACTTGTCAATAGATGCGACTTTGCAGCAACTGGAAT  SHEEP.SEQ
241  ATCTACGTATCTATAGATGTGACTCTGCAGCAGCTGGAAT  HTSHR.SEQ

     CACATTCCTTCTACAATTTG                      Majority

281  CACATTCCTTCTACAATTTG                      CAT.SEQ
281  CACATTCCTTCTACAATTTA                      COW.SEQ
281  CACATTCCTTCTACAATTTA                      DOG.SEQ
281  CACATTCTTTCTACAATTTG                      MOUSE.SEQ
281  CACAGTCCTTCTACAATTTG                      PTSHR.SEQ
281  CACATTCTTTCTACAATTTG                      RAT.SEQ
281  CACATTCCTTCTACAATTTA                      SHEEP.SEQ
281  CACACTCCTTCTACAATTTG                      HTSHR.SEQ
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FIG. 2CONT'D

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     TKLDAVYLNKNKYLTAIDKDAFGGVYSGFTLLDVSYTSVT  Majority

200  TKLDAVYLNKNKYLTVIDKDAFGGVYSGPSLLDVSQTSVT  HTSHR.PRO
200  TKLDAVYLNKNKYLTVIDKDAFGGVFSGPTLLDVSYTSVT  PTSHR.PRO
200  TKLDAVYLNKNKYLTVIGQDAFAGVYSGPTLLDISYTSVT  BTSHR.PRO
200  TKLDAVYLNKNKYLTAIDQDAFGGVYSGPTLLDVSYTSVT  CTSHR.PRO
200  TKLDAVYLNKNKYLSAIDKDAFGGVYSGPTLLDVSYTSVT  DTSHR.PRO
200  TKLDAVYLNKNKYLTAIDNDAFGGVYSGPTLLDVSSTSVT  MTSHR.PRO
200  TKLDAVYLNKNKYLTAIDKDAFGGVYSGPTLLDVSSTSVT  RTSHR.PRO
200  TKLDAVYLNKNKYLTVIDQDAFAGVYSGPTLLDISYTSVT  STSHRP.PRO

     ALPSKGLEHLKELIARNTWTLKKLPLSPSFLHLTRADLSY  Majority

240  ALPSKGLEHLKELIARNTWTLKKLPLSLSFLHLTRADLSY  HTSHR.PRO
240  ALPPKGLEHLKELIARNTWTLKKLPLSLSFLHLTRADLSY  PTSHR.PRO
240  ALPSKGLEHLKELIARNTWTLRKLPLSLSFLHLTRADLSY  BTSHS.PRO
240  ALPSKGLEHLKELIARNTWTLKKLPLTLSFLHLTRADLSY  CTSHR.PRO
240  ALPSKGLEHLKELIARNTWTLKKLPLSLSFLHLTRADLSY  DTSHR.PRO
240  ALPSKGLEHLKELIAKDTWTLKKLPLSLSFLHLTRADLSY  MTSHR.PRO
240  ALPSKGLEHLKELIAKNTWTLKKLPLSLSFLHLTRADLSY  RTSHS.PRO
240  ALPSKGLEHLKELIARNTWTLKKLPLSLSFLHLTRADLSY  STSHRP.PRO

     PSHCCAFKNQKKIRGILESLM                     Majority

280  PSHCCAFKNQKKIRGILESLM                     HTSHR.PRO
280  PSHCCAFKNQKKIRGILESLM                     PTSHR.PRO
280  PSHCCAFKNQKKIRGILQSLM                     BTSHR.PRO
280  PSHCCAFKNQKKIRGILESFM                     CTSHR.PRO
280  PSHCCAFKNQKKIRGILESLM                     DTSHR.PRO
280  PSHCCAFKNQKKIRGILESLM                     MTSHR.PRO
280  PSHCCAFKNQKKIRGILESLM                     RTSHR.PRO
280  PSHCCAFKNQKNIRGILQSLM                     STSHRP.PRO
```

FIG. 3

```
     TCTTACACCAGTGTCACTGCCCTTCCATCCAAAGGCCTGG  Majority

700  TCTTACACCAGTGTCACTGCCCTGCCATCCAAAGGCCTGG  CAT.SEQ
700  TCTTATACCAGTGTCACAGCCCTACCATCCAAAGGCCTGG  COW.SEQ
700  TCTTACACCAGTGTTACTGCCCTGCCATCCAAAGGCCTGG  DOG.SEQ
700  TCTTCCACCAGCGTCACTGCCCTTCCTTCCAAAGGCCTGG  MOUSE.SEQ
700  TCTTATACCAGTGTTACTGCCCTGCCACCCAAAGGCCTGG  PTSHR.SEQ
700  TCTTCCACCAGCGTTACTGCTCTTCCTTCCAAAGGCCTGG  RAT.SEQ
700  TCTTATACCAGTGTCACTGCCCTACCATCCAAAGGCCTGG  SHEEP.SEQ
700  TCTCAAACCAGTGTCACTGCCCTTCCATCCAAAGGCCTGG  HTSHR.SEQ

     AGCACCTGAAGGAACTGATACCAAGAAACACTTGGACTCT  Majority

740  AGCACCTGAAGGAATTGATAGCAAGAAACACTTGGACTCT  CAT.SEQ
740  AACACCTGAAGGAATTGATAGCAAGAAACACTTGGACTCT  COW.SEQ
740  AGCATCTAAAGGAGCTGATAGCAAGAAACACTTGGACTCT  DOG.SEQ
740  AGCACCTCAAAGAACTGATCGCAAAAGACACCTGGACTCT  MOUSE.SEQ
740  AACACCTGAAGGAACTGATAGCAAGAAATACTTGGACTCT  PTSHR.SEQ
740  AGCACCTCAAAGAGCTGATCGCGAAGAACACCTGGACTCT  RAT.SEQ
740  AACACCTGAAGGAATTGATAGCAAGAAACACTTGGACTCT  SHEEP.SEQ
740  AGCACCTGAAGGAACTGATAGCAAGAAACACCTGGACTCT  HTSHR.SEQ

     AAAGAAACTTCCACTTTCCTTGAGTTTCCTTCACCTCACA  Majority

780  AAAGAAACTTCCACTTACCTTGAGTTTCCTTCACCTCACA  CAT.SEQ
780  AAGGAAACTTCCTCTTTCCTTGAGTTTCCTTCACCTCACA  COW.SEQ
780  AAAGAAACTCCCACTTTCCTTGAGTTTCCTTCACCTTACA  DOG.SEQ
780  CAAAAAGCTCCCGCTGTCGTTGAGTTTCCTCCACCTCACT  MOUSE.SEQ
780  AAAGAAACTTCCACTGTCCTTGAGTTTCCTTCACCTCACA  PTSHR.SEQ
780  CAAAAAGCTCCCCCTGTCCTTGAGCTTCCTCCACCTCACT  RAT.SEQ
780  AAAGAAACTTCCTCTTTCCTTGAGTTTCCTTCACCTCACA  SHEEP.SEQ
780  TAAGAAACTTCCACTTTCCTTGAGTTTCCTTCACCTCACA  HTSHR.SEQ

     CGGGCTGACCTTTCTTATCCAAGCCACTGCTGTGCTTTTA  Majority

820  CGGGCTGACCTTTCTTATCCAAGCCACTGCTGTGCTTTTA  CAT.SEQ
820  CGGGCTGACCTTTCTTATCCGAGCCACTGCTGCGCTTTTA  COW.SEQ
820  CGGGCTGACCTTTCTTATCCAAGCCACTGCTGTGCTTTTA  DOG.SEQ
820  CGGGCTGACCTCTCTTACCCGAGCCACTGCTGCGCTTTTA  MOUSE.SEQ
820  CGAGCTGACCTTTCTTATCCAAGCCACTGCTGTGCTTTTA  PTSHR.SEQ
820  CGGGCTGACCTCTCTTACCCAAGTCACTGCTGTGCTTTTA  RAT.SEQ
820  CGGGCTGACCTTTCTTATCCGAGCCACTGCTGTGCTTTTA  SHEEP.SEQ
820  CGGGCTGACCTTTCTTACCCAAGCCACTGCTGTGCCTTTA  HTSHR.SEQ

     AGAATCAGAAGAAAATCAGACCAATCCTTGACTCTTTAAT  Majority

860  AGAATCAGAAGAAAATCAGAGGAATCCTTGAGTCCTTCAT  CAT.SEQ
860  AGAATCAGAAGAAAATCAGAGGAATCCTTCAGTCTTTAAT  COW.SEQ
860  AGAATCAGAAGAAAATCAGAGGAATCCTTGAGTCCTTAAT  DOG.SEQ
860  AGAACCAGAAGAAAATCAGGGGAATCCTGGAGTCTTTGAT  MOUSE.SEQ
860  AGAATCAGAAGAAGATCAGAGGAATCCTTGAGTCTTTAAT  PTSHR.SEQ
860  AGAACCAGAAGAAAATCAGGGGAATCCTAGAGTCTTTGAT  RAT.SEQ
860  AGAATCAGAAGAATATCAGAGGAATCCTTCAGTCTTTAAT  SHEEP.SEQ
860  AGAATCAGAAGAAAATCAGAGGAATCCTTGAGTCCTTGAT  HTSHR.SEQ
```

FIG. 4

```
    KELIARNTWTLKKLPLSLSFLHLTRADLSYPSHCCAFKNQ  Majority

250 KELIARNTWTLKKLPLSLSFLHLTRADLSYPSHCCAFKNQ  HTSHR.PRO
250 KELIARNTWTLKKLPLSLSFLHLTRADLSYPSHCCAFKNQ  PTSHR.PRO
250 KELIARNTWTLRKLPLSLSFLHLTRADLSYPSHCCAFKNQ  BTSHR.PRO
250 KELIARNTWTLKKLPLTLSFLHLTRADLSYPSHCCAFKNQ  CTSHR.PRO
250 KELIARNTWTLKKLPLSLSFLHLTRADLSYPSHCCAFKNQ  DTSHR.PRO
250 KELIAKDTWTLKKLPLSLSFLHLTRADLSYPSHCCAFKNQ  MTSHR.PRO
250 KELIAKNTWTLKKLPLSLSFLHLTRADLSYPSHCCAFKNQ  RTSHR.PRO
250 KELIARNTWTLKKLPLSLSFLHLTRADLSYPSHCCAFKNQ  STSHRP.PRO

    KKIRGILESLMCNESSIRSLRQRKSVNALNGPFYQEYEED  Majority

290 KKIRGILESLMCNESSMQSLRQRKSVNALNSPLHQEYEEN  HTSHR.PRO
290 KKIRGILESLMCNESSIRSLRQRKSVNAVNGPFYQEYEED  PTSHR.PRO
290 KKIRGILQSLMCNESSIRGLRQRKSASALNGPFYQEYEDX  BTSHS.PRO
290 KKIRGILESFMCNDSSIRSLRQRKSVNALNGPFDQEYEEY  CTSHR.PRO
290 KKIRGILESLMCNESSIRSLRQRKSVNTLNGPFDQEYEEY  DTSHR.PRO
290 KKIRGILESLMCNESSIRNLRQRKSVNILRGPIYQEYEED  MTSHR.PRO
290 KKIRGILESLMCNESSIRNLRQRKSVNVMRGPVYQEYEEG  RTSHS.PRO
290 KNIRGILQSLMCNESSIWGLRQRKSASALNGPFYQEYEED  STSHRP.PRO

    LDGSSAGYKENSKFQDTHSNSHYYVFFEEQEDEIIGFGQE  Majority

330 LGDSIVGYKEKSKFQDTHNNAHYYVFFEEQEDEIIGFGQE  HTSHR.PRO
330 LGDTSVGNKENSKFQDTHSNSHYYVFFEEQEDEIIGFGQE  PTSHR.PRO
330 LGDGSAGYKENSKFQDTQSNSHYYVFFEEQEDEIIGFGQQ  BTSHR.PRO
330 LGDSHAGYKDNSKFQDTRSNSHYYVFFEEQXDEILGFGQE  CTSHR.PRO
330 LGDSHAGYKDNSQFQDTDSNSHYYVFFEEQEDEILGFGQE  DTSHR.PRO
330 PGDNSVGYKQNSKFQESPSNSHYYVFFEEQEDEVVGFGQE  MTSHR.PRO
330 LGDNHVGYKQNSKFQEGPSNSHYYVFFEEQEDEIIGFGQE  RTSHR.PRO
330 LGDGSAGYKENSKFQDTHSNSHYYVFFEDQEDEIIGFGQE  STSHRP.PRO

    LKNPQEETLQAFDSHYDYTVCGGSEDMVCTPKSDEFNPCE  Majority

370 LKNPQEETLQAFDSHYDYTICGDSEDMVCTPKSDEFNPCE  HTSHR.PRO
370 LKNPQEETLQAFDSHYDYTVCGGSEDMVCTPKSDEFNPCE  PTSHR.PRO
370 LKNPQEETLQAFDSHYDYTVCGGSEDMVCTPKSDEFNPCE  BTSHR.PRO
370 LKNPQEETLQAFDSHYDYTVCGGNEDMVCTPKSDEFNPCE  CTSHR.PRO
370 LKNPQEETLQAFDSHYDYTVCGGNEDMVCTPKSDEFNPCE  DTSHR.PRO
370 LKNPQEETLQAFESHYDYTVCGDNEDMVCTPKSDEFNPCE  MTSHR.PRO
370 LKNPQEETLQAFDSHYDYTVCGDNEDMVCTPKSDEFNPCE  RTSHR.PRO
370 LKNPQEETLQAFDNHYDYTVCGGSEEMVCTPKSDEFNPCE  STSHRP.PRO

    DIMGYKFLRIVVWFVSLLALLGNVFVLVILLTSHYKLTVP  Majority

410 DIMGYKFLRIVVWFVSLLALLGNVFVLLILLTSHYKLNVP  HTSHR.PRO
410 DIMGYRFLRIVVWFVSLLALLGNVFVLVILLTSHYKLTVP  PTSHR.PRO
410 DIMGYKFLRIVVWFVSLLALLGNVFVLVILLTSHYKLTVP  BTSHR.PRO
410 DIMGYKFLRIVVWFVSLLALLGNVFVLIILLTSHYKLTVP  CTSHR.PRO
410 DIMGYKFLRIVVWFVSLLALLGNVFVLIVLLTSHYKLTVP  DTSHR.PRO
410 DIMGYRFLRIVVWFVSLLALLGNIFVLLILLTSHYKLTVP  MTSHR.PRO
410 DIMGYKFLRIVVWFVSPMALLGNVFVLFVLLTSHYKLTVP  RTSHR.PRO
410 DIMGYKFLRIVVWFVSLLALLGNVFVLVILLTSHYKLTVP  STSHRP.PRO
```

FIG. 5

```
    GGAACTGATAGCAAGAAACACTTGGACTCTAAAGAAACTT  Majority

750 GGAATTGATAGCAAGAAACACTTGGACTCTAAAGAAACTT  CAT.SEQ
750 GGAATTGATAGCAAGAAACACTTGGACTCTAAGGAAACTT  COW.SEQ
750 GGAGCTGATAGCAAGAAACACTTGGACTCTAAAGAAACTC  DOG.SEQ
750 AGAACTGATCGCAAAAGACACCTGGACTCTCAAAAAGCTC  MOUSE.SEQ
750 GGAACTGATAGCAAGAAATACTTGGACTCTAAAGAAACTT  PTSHR.SEQ
750 AGAGCTGATCGCGAAGAACACCTGGACTCTCAAAAAGCTC  RAT.SEQ
750 GGAATTGATAGCAAGAAACACTTGGACTCTAAAGAAACTT  SHEEP.SEQ
750 GGAACTGATAGCAAGAAACACCTGGACTCTTAAGAAACTT  HTSHR.SEQ

    CCACTTTCCTTGAGTTTCCTTCACCTCACACGGGCTGACC  Majority

790 CCACTTACCTTGAGTTTCCTTCACCTCACACGGGCTGACC  CAT.SEQ
790 CCTCTTTCCTTGAGTTTCCTTCACCTCACACGGGCTGACC  COW.SEQ
790 CCACTTTCCTTGAGTTTCCTTCACCTTACACGGGCTGACC  DOG.SEQ
790 CCGCTGTCGTTGAGTTTCCTCCACCTCACTCGGGCTGACC  MOUSE.SEQ
790 CCACTGTCCTTGAGTTTCCTTCACCTCACACGAGCTGACC  PTSHR.SEQ
790 CCCCTGTCCTTGAGCTTCCTCCACCTCACTCGGGCTGACC  RAT.SEQ
790 CCTCTTTCCTTGAGTTTCCTTCACCTCACACGGGCTGACC  SHEEP.SEQ
790 CCACTTTCCTTGAGTTTCCTTCACCTCACACGGGCTGACC  HTSHR.SEQ

    TTTCTTATCCAAGCCACTGCTGTGCTTTTAAGAATCAGAA  Majority

830 TTTCTTATCCAAGCCACTGCTGTGCTTTTAAGAATCAGAA  CAT.SEQ
830 TTTCTTATCCGAGCCACTGCTGCGCTTTTAAGAATCAGAA  COW.SEQ
830 TTTCTTATCCAAGCCACTGCTGTGCTTTTAAGAATCAGAA  DOG.SEQ
830 TCTCTTACCCGAGCCACTGCTGCGCTTTTAAGAACCAGAA  MOUSE.SEQ
830 TTTCTTATCCAAGCCACTGCTGTGCTTTTAAGAATCAGAA  PTSHR.SEQ
830 TCTCTTACCCAAGTCACTGCTGTGCTTTTAAGAACCAGAA  RAT.SEQ
830 TTTCTTATCCGAGCCACTGCTGTGCTTTTAAGAATCAGAA  SHEEP.SEQ
830 TTTCTTACCCAAGCCACTGCTGTGCCTTTAAGAATCAGAA  HTSHR.SEQ

    GAAAATCAGAGGAATCCTTGAGTCTTTAATGTGTAATGAG  Majority

870 GAAAATCAGAGGAATCCTTGAGTCCTTCATGTGTAATGAC  CAT.SEQ
870 GAAAATCAGAGGAATCCTTCAGTCTTTAATGTGTAACGAG  COW.SEQ
870 GAAAATCAGAGGAATCCTTGAGTCCTTAATGTGTAATGAA  DOG.SEQ
870 GAAAATCAGGGGAATCCTGGAGTCTTTGATGTGTAATGAG  MOUSE.SEQ
870 GAAGATCAGAGGAATCCTTGAGTCTTTAATGTGTAATGAG  PTSHR.SEQ
870 GAAAATCAGGGGAATCCTAGAGTCTTTGATGTGTAATGAG  RAT.SEQ
870 GAATATCAGAGGAATCCTTCAGTCTTTAATGTGTAACGAG  SHEEP.SEQ
870 GAAAATCAGAGGAATCCTTGAGTCCTTGATGTGTAATGAG  HTSHR.SEQ

    AGCAGTATTCGGAGCCTGCGTCAGAGAAAATCTGTGAATG  Majority

910 AGCAGTATTCGGAGCCTGCGTCAGAGAAAATCTGTGAATG  CAT.SEQ
910 AGCAGTATTCGGGGCCTGCGTCAGAGAAAATCCGCAAGTG  COW.SEQ
910 AGCAGTATTCGGAGCCTGCGCCAGAGAAAATCTGTGAATA  DOG.SEQ
910 AGCAGTATCCGGAACCTTCGTCAAAGGAAATCAGTGAACA  MOUSE.SEQ
910 AGCAGTATTCGGAGCCTGCGTCAGAGAAAATCTGTGAATG  PTSHR.SEQ
910 AGTAGTATCCGGAACCTGCGTCAAAGAAAGTCAGTGAACG  RAT.SEQ
910 AGCAGTATTTGGGGCCTGCGTCAGAGAAAATCCGCGAGTG  SHEEP.SEQ
910 AGCAGTATGCAGAGCTTGCGCCAGAGAAAATCTGTGAATG  HTSHR.SEQ
```

FIG. 6

```
     CTTTGAATGGTCCCTTCTACCAGGAATATGAAGAGGATCT  Majority

 950 CTTTGAATGGTCCCTTCGACCAGGAATATGAAGAGTATCT  CAT.SEQ
 950 CTTTGAATGGTCCCTTCTACCAGGAATATGAGGATNNNCT  COW.SEQ
 950 CTTTGAATGGCCCCTTTGACCAGGAATATGAAGAGTATCT  DOG.SEQ
 950 TCTTGAGGGGTCCCATCTACCAGGAATATGAAGAAGATCC  MOUSE.SEQ
 950 CTGTAAATGGTCCCTTTTACCAAGAATATGAAGAGGATCT  PTSHR.SEQ
 950 TCATGAGGGGTCCCGTCTACCAGGAATATGAAGAAGGTCT  RAT.SEQ
 950 CTTTGAATGGTCCCTTCTACCAGGAATATGAAGAGGATCT  SHEEP.SEQ
 950 CCTTGAATAGCCCCCTCCACCAGGAATATGAAGAGAATCT  HTSHR.SEQ

     GGGTGACAGCAGTGTTGGGTACAAGGAAAACTCCAAGTTC  Majority

 990 AGGTGACAGCCATGCTGGATATAAGGACAACTCTAAGTTC  CAT.SEQ
 990 GGGTGATGGCAGTGCTGGGTACAAGGAGAACTCCAAGTTC  COW.SEQ
 990 GGGTGACAGCCATGCTGGGTACAAGGACAACTCTCAGTTC  DOG.SEQ
 990 GGGTGACAACAGTGTTGGGTACAAACAAAACTCCAAGTTC  MOUSE.SEQ
 990 GGGCGACACGAGTGTTGGGAATAAGGAAAACTCCAAGTTC  PTSHR.SEQ
 990 GGGTGACAACCATGTTGGGTACAAACAAAACTCCAAGTTC  RAT.SEQ
 990 GGGTGATGGCAGTGCTGGGTACAAGGAGAACTCCAAGTTC  SHEEP.SEQ
 990 GGGTGACAGCATTGTTGGGTACAAGGAAAAGTCCAAGTTC  HTSHR.SEQ

     CAGGATACCCATAGCAACTCTCATTATTATGTCTTCTTTG  Majority

1030 CAGGATACTCGCAGCAACTCTCATTATTATGTCTTCTTTG  CAT.SEQ
1030 CAAGATACCCAAAGCAACTCTCATTACTATGTCTTCTTTG  COW.SEQ
1030 CAGGATACCGATAGCAATTCTCATTATTATGTCTTCTTCG  DOG.SEQ
1030 CAGGAGAGCCCAAGCAACTCTCACTATTACGTCTTCTTTG  MOUSE.SEQ
1030 CAGGATACCCATAGCAACTCCCATTACTACGTCTTCTTTG  PTSHR.SEQ
1030 CAGGAGGGCCCAAGCAACTCTCACTATTACGTCTTCTTTG  RAT.SEQ
1030 CAAGATACCCACAGCAACTCTCATTACTATGTCTTCTTTG  SHEEP.SEQ
1030 CAGGATACTCATAACAACGCTCATTATTACGTCTTCTTTG  HTSHR.SEQ

     AAGAACAAGAGGATGAGATCATTGGTTTTGG            Majority

1070 AAGAACAANNNGACGAGATCCTTGGTTTTGG            CAT.SEQ
1070 AGGAGCAAGAAGATGAGATCATCGGTTTTGG            COW.SEQ
1070 AAGAACAAGAAGATGAGATCCTCGGTTTTGG            DOG.SEQ
1070 AAGAACAAGAGGATGAGGTCGTTGGTTTCGG            MOUSE.SEQ
1070 AAGAACAAGAGGATGAGATCATTGGTTTTGG            PTSHR.SEQ
1070 AAGAACAAGAGGACGAGATCATCGGTTTCGG            RAT.SEQ
1070 AGGATCAAGAAGATGAGATCATCGGTTTTGG            SHEEP.SEQ
1070 AAGAACAAGAGGATGAGATCATTGGTTTTGG            HTSHR.SEQ
```

FIG. 6CONT'D

```
SHYYVFFEEQEDEIIGFGQELKNPQEETLQAFDSHYDYTV  Majority

AHYYVFFEEQEDEIIGFGQELKNPQEETLQAFDSHYDYTI  CAT.SEQ
SHYYVFFEEQEDEIIGFGQELKNPQEETLQAFDSHYDYTV  COW.SEQ
SHYYVFFEEQEDEIIGFGQQLKNPQEETLQAFDSHYDYTV  DOG.SEQ
SHYYVFFEEQXDEILGFGQELKNPQEETLQAFDSHYDYTV  MOUSE.SEQ
SHYYVFFEEQEDEILGFGQELKNPQEETLQAFDSHYDYTV  PTSHR.SEQ
SHYYVFFEEQEDEVVGFGQELKNPQEETLQAFESHYDYTV  RAT.SEQ
SHYYVFFEEQEDEIIGFGQELKNPQEETLQAFDSHYDYTV  SHEEP.SEQ
SHYYVFFEDQEDEIIGFGQELKNPQEETLQAFDNHYDYTV  HTSHR.SEQ

CGGSEDMVCTPKSDEFNPCEDIMGYKFLRIVVWFVSLLAL  Majority

CGDSEDMVCTPKSDEFNPCEDIMGYKFLRIVVWFVSLLAL  CAT.SEQ
CGGSEDMVCTPKSDEFNPCEDIMGYRFLRIVVWFVSLLAL  COW.SEQ
CGGSEDMVCTPKSDEFNPCEDIMGYKFLRIVVWFVSLLAL  DOG.SEQ
CGGNEDMVCTPKSDEFNPCEDIMGYKFLRIVVWFVSLLAL  MOUSE.SEQ
CGGNEDMVCTPKSDEFNPCEDIMGYKFLRIVVWFVSLLAL  PTSHR.SEQ
CGDNEDMVCTPKSDEFNPCEDIMGYRFLRIVVWFVSLLAL  RAT.SEQ
CGDNEDMVCTPKSDEFNPCEDIMGYKFLRIVVWFVSPMAL  SHEEP.SEQ
CGGSEEMVCTPKSDEFNPCEDIMGYKFLRIVVWFVSLLAL  HTSHR.SEQ

LGNVFVLVILLTSHYKLTVPRFLMCNLAFADFCMGMYLLL  Majority

LGNVFVLLILLTSHYKLNVPRFLMCNLAFADFCMGMYLLL  CAT.SEQ
LGNVFVLVILLTSHYKLTVPRFLMCNLAFADFCMGMYLLL  COW.SEQ
LGNVFVLVILLTSHYKLTVPRFLMCNLAFADFCMGLYLLL  DOG.SEQ
LGNVFVLIILLTSHYKLTVPRFLMCNLAFADFCMGMYLLL  MOUSE.SEQ
LGNVFVLIVLLTSHYKLTVPRFLMCNLAFADFCMGMYLLL  PTSHR.SEQ
LGNIFVLLILLTSHYKLTVPRFLMCNLAFADFCMGVYLLL  RAT.SEQ
LGNVFVLFVLLTSHYKLTVPRFLMCNLAFADFCMGVYLLL  SHEEP.SEQ
LGNVFVLVILLTSHYKLTVPRFLMCNLAFADFCMGLYLLL  HTSHR.SEQ

IASVDLYTHSEYYNHAIDWQTGPGCNTAGFF           Majority

IASVDLYTHSEYYNHAIDWQTGPGCNTAGFF           CAT.SEQ
IASVDLYTQSEYYNHAIDWQTGPGCNTAGFF           COW.SEQ
IASVDLYTQSEYYNHAIDWQTGPGCNTAGFF           DOG.SEQ
IASVDLYTHSEYYNHAIDWQTGPGCNAAGFF           MOUSE.SEQ
IASVDLYTHSEYYNHAIDWQTGPGCNTAGFF           PTSHR.SEQ
IASVDLYTHSEYYNHAIDWQTGPGCNTAGFF           RAT.SEQ
IASVDLYTHTEYYNHAIDWQTGPGCNTAGFF           SHEEP.SEQ
IASVDLYTQSEYYNHAIDWQTGPGCNTAGFF           HTSHR.SEQ
```

FIG. 7

```
GCCAAGAGCTCAAAAACCCCCAGGAAGAGACCCTCCAGGC  Majority

GCCAGGAGCTTAAAAACCCACAAGAAGAGACCCTACAGGC  CAT.SEQ
GCCAACAGCTCAAAAACCCCCAGGAGGAGACCCTGCAGGC  COW.SEQ
GGCAGGAGCTTAAAAACCCACAGGAAGAGACCCTCCAGGC  DOG.SEQ
GCCAAGAGCTCAAAAATCCTCAGGAAGAGACTCTCCAAGC  MOUSE.SEQ
GCCAAGAGCTCAAAAACCCCCAGGAAGAGACCCTCCAGGC  PTSHR.SEQ
GCCAAGAGCTCAAAAATCCTCAGGAAGAGACTCTCCAAGC  RAT.SEQ
GCCAAGAGCTTAAAAACCCCCAGGAGGAGACCCTGCAGGC  SHEEP.SEQ
GCCAGGAGCTCAAAAACCCCCAGGAAGAGACTCTACAAGC  HTSHR.SEQ

CTTTGACAGCCATTATGACTACACCGTGTGTCGGGGCAGT  Majority

CTTCGATAGCCATTATGACTACACTGTGTGTGGAGGCAAT  CAT.SEQ
CTTTGACAGCCATTACGACTATACCGTGTGTGGGGGCAGT  COW.SEQ
CTTTGATAGCCATTATGACTACACTGTGTGTGGTGGCAAT  DOG.SEQ
CTTCGAGAGCCACTATGACTACACGGTGTGTGGGGACAAC  MOUSE.SEQ
CTTTGACAGCCATTACGACTACACCGTGTGTGGGGGCAGT  PTSHR.SEQ
CTTCGACAGCCACTATGACTACACTGTGTGTGGGGACAAC  RAT.SEQ
CTTTGACAACCATTACGACTATACCGTGTGCGGGGGGAGT  SHEEP.SEQ
TTTTGACAGCCATTATGACTACACCATATGTGGGGACAGT  HTSHR.SEQ

GAGGACATGGTGTGTACCCCCAAGTCAGATCAGTTCAACC  Majority

GAAGACATGGTGTGTACTCCCAAGTCAGATGAGTTCAACC  CAT.SEQ
GAGGACATGGTGTGTACCCCCAAGTCGGATGAGTTCAACC  COW.SEQ
GAAGACATGGTGTGTACTCCTAAGTCAGATGAGTTCAACC  DOG.SEQ
GAGGACATGGTGTGTACCCCCAAGTCGGACGAGTTTAACC  MOUSE.SEQ
GAAGACATGGTGTGCACCCCCAAGTCAGATGAGTTCAACC  PTSHR.SEQ
GAGGACATGGTGTGTACCCCCAAGTCAGACGAGTTTAACC  RAT.SEQ
GAGGAGATGGTGTGTACCCCCAAGTCGGATGAGTTCAACC  SHEEP.SEQ
GAAGACATGGTGTGTACCCCCAAGTCCGATGAGTTCAACC  HTSHR.SEQ

CCTGTGAAGACATCATGGGCTACAAGTTCCTGAGAATTGT  Majority

CCTGTGAAGACATAATGGGCTACAAGTTCCTGAGAATTGT  CAT.SEQ
CCTGTGAGGACATCATGGGCTACAAGTTCCTGAGAATCGT  COW.SEQ
CCTGTGAAGACATAATGGGCTACAAGTTCCTGAGGATTGT  DOG.SEQ
CCTGTGAAGATATCATGGGCTACAGGTTCCTGAGAATCGT  MOUSE.SEQ
CCTGTGAAGACATAATGGGCTACAGGTTCCTGAGAATCGT  PTSHR.SEQ
CCTGTGAAGATATCATGGGCTACAAGTTCCTGAGAATCGT  RAT.SEQ
CCTGTGAGGACATCATGGGCTACAAGTTCCTGAGAATTGT  SHEEP.SEQ
CGTGTGAAGACATAATGGGCTACAAGTTCCTGAGAATTGT  HTSHR.SEQ

GGTGTGGTTTGTTAGTCTGCTGGCTCTCCTGGGCAATGTC  Majority

GGTGTGGTTTGTTAGTCTGCTGGCTCTCCTGGGCAATGTC  CAT.SEQ
GGTGTGGTTTGTGAGTCTGCTGGCTCTCCTGGGCAACGTC  COW.SEQ
GGTGTGGTTTGTTAGTCTGCTGGCTCTCCTGGGCAATGTC  DOG.SEQ
GGTGTGGTTTGTCAGTCTGCTGGCTCTCCTGGGCAATATC  MOUSE.SEQ
GGTGTGGTTCGTTAGCCTGCTGGCTCTCCTGGGCAATGTC  PTSHR.SEQ
GGTATGGTTTGTCAGTCCGATGGCTCTCCTGGGCAACGTC  RAT.SEQ
GGTGTGGTTTGTGAGTCTGCTGGCTCTCCTGGGCAACGTC  SHEEP.SEQ
GGTGTGGTTCGTTAGTCTGCTGGCTCTCCTGGGCAATGTC  HTSHR.SEQ
```

FIG. 8

4D7 - HC

DVQLKHSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGL
INPYTGGTNYNQKFKGKAKLTVDKSSSTAFMELLSLTSEDSAVYYCARDG
NLDYWGQGTTLTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPE
PVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVA
HPASKTKVD

FIG. 9

4D7 - HC

DVQLKHSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGL 50
PCR primer CDR I

INPYTGGTNYNQKFKGKAKLTVDKSSSTAFMELLSLTSEDSAVYYCARDG 100
CDR II CDR III

NLDYWGQGTTLTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPE 150
constant region

PVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVA 200

HPASKTKVD 209
PCR primer

FIG. 10

4D7 - LC

SIVMSQSPASLAVSLGQRATISCRASETVDNYGFSFMHWFQQIPGQPPKL
LIYAASNQGSGVPARFSGSGSGTDFSLNIHPMEEDDTAMYFCQQSKEVPY
TFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINV
KWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEA
THKTSTSPIVKSFNRNEC

FIG. 11

4D7 - LC

SIVMSQSPASLAVSLGQRATISCRASETVDNYGFSFMHWFQQIPGQPPKL 50
PCR primer CDR I

LIYAASNQGSGVPARFSGSGSGTDFSLNIHPMEEDDTAMYFCQQSKEVPY 100
CDR II CDR III

TFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINV 150
constant region

KWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEA 200

THKTSTSPIVKSFNRNEC 218
PCR primer

FIG. 12

16E5 - HC

DVQLVQSGPELVKPGASVKMSCKASGYSFTGYNMHWVKQSHGKSLEWIGY
IDPYNGATSYNQKFEDKATLTVDKSSSTAYMQLNSLTSEDSAVYYCARRW
DWDPYAMDYWGQGTSVTVSSAKTTAPSVYPLAPVCGDTSGSSVTLGCLVK
GYFPEPVTLTWNSGSLSSGVHTSPAVLQSDLYTLSSSVTVTSSTWPSQSI
TCNVAHPASKTKVD

FIG. 13

16E5 - HC

DVQLVQSGPELVKPGASVKMSCKASGYSFTGYNMHWVKQSHGKSLEWIGY 50
PCR primer CDR I

IDPYNGATSYNQKFEDKATLTVDKSSSTAYMQLNSLTSEDSAVYYCARRW 100
CDR II

DWDPYAMDYWGQGTSVTVSSAKTTAPSVYPLAPVCGDTSGSSVTLGCLVK 150
CDR III constant region

GYFPEPVTLTWNSGSLSSGVHTSPAVLQSDLYTLSSSVTVTSSTWPSQSI 200

TCNVAHPASKTKVD 214
PCR primer

FIG. 14

16E5 - LC

DILLTQSPAILSVSPGERVSFSCRASQSIGTSIHWYQQRTNGSPRLLIKY
ASESISGIFSRFSGSGSGTDFTLTINSVESEDIADYYCQQSNRWPLTFGA
GTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI
DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKT
STSPIVKSFNRNEC

FIG. 15

16E5 - LC

DILLTQSPAILSVSPGERVSFSCRASQSIGTSIHWYQQRTNGSPRLLIKY 50
PCR primer CDR I

ASESISGIFSRFSGSGSGTDFTLTINSVESEDIADYYCQQSNRWPLTFGA 100
CDR II CDR III

GTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI 150
constant region

DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKT 200

STSPIVKSFNRNEC 214
PCR primer

FIG. 16

17D2 - HC

DVQIQQSGPELVKPGASVKMSCKASGYSFTAYNMHWVKQTHGKSLEWIGY
IDPYSGATSYHQKFKGKATLTVDKSSSTAYMRLNSLTSEDSAVYYCARRW
DWDPYAMDYWGQGTSVTVSSAKTTPPSVYPLAPGCGDTTGSSVTLGCLVK
GYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSAWPSQTV
TCSVAHPASNTTVD

FIG. 17

17D2 - HC

DVQIQQSGPELVKPGASVKMSCKASGYSFTAYNMHWVKQTHGKSLEWIGY 50
PCR primer CDR I

IDPYSGATSYHQKFKGKATLTVDKSSSTAYMRLNSLTSEDSAVYYCARRW 100
CDR II

DWDPYAMDYWGQGTSVTVSSAKTTPPSVYPLAPGCGDTTGSSVTLGCLVK 150
CDR III constant region

GYFPESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSAWPSQTV 200

TCSVAHPASNTTVD 214
PCR primer

FIG. 18

17D2 - LC

SVEMSQSPAILSVSPGERISFSCRASQSIGTSIHWYQQRTNGSPRLLIKY
ASASISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQSNSWPLTFGA
GTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI
DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKT
STSPIVKSFNRNEC

FIG. 19

17D2 - LC

SVEMSQSPAILSVSPGERISFSCRASQSIGTSIHWYQQRTNGSPRLLIKY 50
PCR primer CDR I

ASASISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQSNSWPLTFGA 100
CDR II CDR III

GTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI 150
constant region

DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKT 200

STSPIVKSFNRNEC 214
PCR primer

FIG. 20

14D3 - HC

DVQMQQPGPELVKPGASLKMSCKASGYSFTGYNMHWVKQSHGKSLEWIGY
IDPYSGATSYNQKFEGKATLTVDKSSSTAYMQLNSLTSEDSAVYYCARRW
DWDPYAMDYWGQGTSVTVSSAKTTAPSVYPLAPVCGDTSGSSVTLGCLVK
GYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI
TCNVAHPASNTKVD

FIG. 21

14D3 - HC

DVQMQQPGPELVKPGASLKMSCKASGYSFTGYNMHWVKQSHGKSLEWIGY 50
PCR primer CDR I

IDPYSGATSYNQKFEGKATLTVDKSSSTAYMQLNSLTSEDSAVYYCARRW 100
CDR II

DWDPYAMDYWGQGTSVTVSSAKTTAPSVYPLAPVCGDTSGSSVTLGCLVK 150
CDR III constant region

GYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSI 200

TCNVAHPASNTKVD 214
PCR primer

FIG. 22

14D3 - LC

NILMTQSPAILSVSPGERVSFACRASQSIGTSIHWYQQRTNGSPRLLIKY
ASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQTNRWPLTFGA
GTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI
DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKT
STSPIVKSFNRNEC

FIG. 23

14D3 - LC

NILMTQSPAILSVSPGERVSFACRASQSIGTSIHWYQQRTNGSPRLLIKY 50
PCR primer CDR I

ASESISGIPSRFSGSGSGTDFTLSINSVESEDIADYYCQQTNRWPLTFGA 100
CDR II CDR III

GTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI 150
constant region

DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKT 200

STSPIVKSFNRNEC 214
PCR primer

FIG. 24

4D7 - HC

gacgtccagctgaagcactcaggacctgagctggtgaagcctggagcttc
aatgaagatatcctgtaaggcttctggttactcattcactggctacacca
tgaactgggtgaagcagagccatggaaagaaccttgagtggattggactt
attaatccttacactggtggtactaactacaaccagaagttcaagggcaa
ggccaaattaactgtagacaagtcatccagcacagccttcatggagctcc
tcagtctgacatctgaggactctgcagtctattactgtgcaagagatggt
aaccttgactactggggccaaggcaccactctcacagtctcctcagccaa
aacgacacccccatctgtctatccactggcccctggatctgctgcccaaa
ctaactccatggtgaccctgggatgcctggtcaagggctatttccctgag
ccagtgacagtgacctggaactctggatccctgtccagcggtgtgcacac
cttcccagctgtcctgcagtctgacctctacactctgagcagctcagtga
ctgtcccctccagcacctggcccagcgagaccgtcacctgcaacgttgcc
cacccagccagcaagaccaaggtcgac

FIG. 25

4D7 - HC

gacgtccagctgaagcactcaggacctgagctggtgaagcctggagcttc 50
PCR primer

aatgaagatatcctgtaaggcttctggttactcattcactggctacacca 100
CDR I

tgaactgggtgaagcagagccatggaaagaaccttgagtggattggactt 150

attaatccttacactggtggtactaactacaaccagaagttcaagggcaa 200
CDR II

ggccaaattaactgtagacaagtcatccagcacagccttcatggagctcc 250

tcagtctgacatctgaggactctgcagtctattactgtgcaagagatggt 300
CDR III

aaccttgactactggggccaaggcaccactctcacagtctcctcagccaa 350

aacgacaccccatctgtctatccactggccctggatctgctgcccaaa 400
constant region

ctaactccatggtgaccctgggatgcctggtcaagggctatttccctgag 450

ccagtgacagtgacctggaactctggatccctgtccagcggtgtgcacac 500

cttcccagctgtcctgcagtctgacctctacactctgagcagctcagtga 550

ctgtcccctccagcacctggcccagcgagaccgtcacctgcaacgttgcc 600

cacccagccagcaagaccaaggtcgac 627
PCR primer

FIG. 26

4D7 - LC

agcattgtgatgtcacagtcgccagcttctttggctgtgtctctagggca
gagggccaccatctcctgcagagccagcgaaactgttgataattatggct
ttagttttatgcactggttccaacagataccgggacagccacccaaactc
ctcatctatgctgcatccaaccaaggatccggggtccctgccaggtttag
tggcagtgggtctgggacagacttcagcctcaacatccatcctatggagg
aggatgatactgcaatgtatttctgtcagcaaagtaaggaggttccgtac
acgttcggaggggggaccaagctggaaataaaacgggctgatgctgcacc
aactgtatccatcttcccaccatccagtgagcagttaacatctggaggtg
cctcagtcgtgtgcttcttgaacaacttctaccccaaagacatcaatgtc
aagtggaagattgatggcagtgaacgacaaaatggcgtcctgaacagttg
gactgatcaggacagcaaagacagcacctacagcatgagcagcaccctca
cgttgaccaaggacgagtatgaacgacataacagctatacctgtgaggcc
actcacaagacatcaacttcacccattgtcaagagcttcaacaggaatga
gtgt

FIG. 27

4D7 - LC

agcattgtgatgtcacagtcgccagcttctttggctgtgtctctagggca 50
PCR primer

gagggccaccatctcctgcagagccagcgaaactgttgataattatggct 100
CDR I

ttagttttatgcactggttccaacagataccgggacagccacccaaactc 150

ctcatctatgctgcatccaaccaaggatccggggtccctgccaggtttag 200
CDR II

tggcagtgggtctgggacagacttcagcctcaacatccatcctatggagg 250

aggatgatactgcaatgtatttctgtcagcaaagtaaggaggttccgtac 300
CDR III

acgttcggaggggggaccaagctggaaataaaacgggctgatgctgcacc 350
constant region

aactgtatccatcttcccaccatccagtgagcagttaacatctggaggtg 400

cctcagtcgtgtgcttcttgaacaacttctaccccaaagacatcaatgtc 450

aagtggaagattgatggcagtgaacgacaaaatggcgtcctgaacagttg 500

gactgatcaggacagcaaagacagcacctacagcatgagcagcaccctca 550

cgttgaccaaggacgagtatgaacgacataacagctatacctgtgaggcc 600

actcacaagacatcaacttcacccattgtcaagagcttcaacaggaatga 650
PCR primer

gtgt 654

FIG. 28

16E5 - HC

gacgtccagttggtgcaatctggacctgagctggtgaagcctggagcttc
agtgaagatgtcctgcaaggcttctggttactcattcactggctacaaca
tgcactgggtgaagcagagccatggaaagagccttgagtggattgggtat
attgatccttacaatggtgctactagctacaaccagaaattcgaggacaa
ggccacattgactgtagacaaatcttccagcacagcctacatgcagctca
acagcctgacatctgaggactctgcagtctattactgtgcaagaagatgg
gactgggacccttatgctatggactactggggtcaaggaacctcagtcac
cgtctcctcagccaaaacaacagccccatcggtctatccactggcccctg
tgtgtggagatacaagtggctcctcggtgactctaggatgcctggtcaag
ggttatttccctgagccagtgaccttgacctggaactctggatccctgtc
cagtggtgtgcacacctccccagctgtcctgcagtctgacctctacaccc
tcagcagctcagtgactgtaacctcgagcacctggcccagccagtccatc
acctgcaatgtggcccacccggccagcaagaccaaggtcgac

FIG. 29

16E5 - HC

gacgtccagttggtgcaatctggacctgagctggtgaagcctggagcttc 50
PCR primer

agtgaagatgtcctgcaaggcttctggttactcattcactggctacaaca 100
CDR I

tgcactgggtgaagcagagccatggaaagagccttgagtggattgggtat 150

attgatccttacaatggtgctactagctacaaccagaaattcgaggacaa 200
CDR II

ggccacattgactgtagacaaatcttccagcacagcctacatgcagctca 250

acagcctgacatctgaggactctgcagtctattactgtgcaagaagatgg 300
CDR III

gactgggacccttatgctatggactactggggtcaaggaacctcagtcac 350

cgtctcctcagccaaaacaacagccccatcggtctatccactggcccctg 400
constant region

tgtgtggagatacaagtggctcctcggtgactctaggatgcctggtcaag 450

ggttatttccctgagccagtgaccttgacctggaactctggatccctgtc 500

cagtggtgtgcacacctccccagctgtcctgcagtctgacctctacaccc 550

tcagcagctcagtgactgtaacctcgagcacctggcccagccagtccatc 600

acctgcaatgtggcccacccggccagcaagaccaaggtcgac 642
PCR primer

FIG. 30

16E5 - LC

gacatcttgctgactcagtctccagccatcctgtctgtgagtccaggaga
aagagtcagtttctcctgcagggccagtcagagcattggcacaagcatac
actggtatcagcaaagaacaaatggttctccaaggcttctcataaagtat
gcttctgagtccatctctgggatattttctaggtttagtggcagtggatc
agggacagattttactcttaccatcaacagtgtggagtctgaagatattg
cagattattactgtcaacaaagtaataggtggccgctcacgttcggagct
gggaccaagctggagctgaaacgggctgatgctgcaccaactgtatccat
cttcccaccatccagtgagcagttaacatctggaggtgcctcagtcgtgt
gcttcttgaacaacttctaccccaaagacatcaatgtcaagtggaagatt
gatggcagtgaacgacaaaatggcgtcctgaacagttggactgatcagga
cagcaaagacagcacctacagcatgagcagcaccctcacgttgaccaagg
acgagtatgaacgacataacagctatacctgtgaggccactcacaagaca
tcaacttcacccattgtcaagagcttcaacaggaatgagtgt

FIG. 31

16E5 - LC

gacatcttgctgactcagtctccagccatcctgtctgtgagtccaggaga 50

PCR primer

aagagtcagtttctcctgcagggccagtcagagcattggcacaagcatac 100

CDR I

actggtatcagcaaagaacaaatggttctccaaggcttctcataaagtat 150

gcttctgagtccatctctgggatattttctaggtttagtggcagtggatc 200

CDR II

agggacagattttactcttaccatcaacagtgtggagtctgaagatattg 250

cagattattactgtcaacaaagtaataggtggccgctcacgttcggagct 300

CDR III

gggaccaagctggagctgaaacgggctgatgctgcaccaactgtatccat 350

constant region

cttcccaccatccagtgagcagttaacatctggaggtgcctcagtcgtgt 400

gcttcttgaacaacttctaccccaaagacatcaatgtcaagtggaagatt 450

gatggcagtgaacgacaaaatggcgtcctgaacagttggactgatcagga 500

cagcaaagacagcacctacagcatgagcagcaccctcacgttgaccaagg 550

acgagtatgaacgacataacagctatacctgtgaggccactcacaagaca 600

tcaacttcacccattgtcaagagcttcaacaggaatgagtgt 642

PCR primer

FIG. 32

17D2 - HC

gacgtccagatccagcagtctgggcctgagctggtgaagcctggagcttc
agtgaagatgtcctgcaaggcttctggttactcattcactgcctacaaca
tgcactgggtgaagcagacccatggaaagagccttgagtggattggttat
attgatccttacagtggtgctactagctaccaccagaaattcaagggcaa
ggccacattgactgttgacaaatcttccagcacagcctacatgcgcctca
acagcctgacatctgaggactctgcagtctattactgtgcaagaagatgg
gactgggacccttatgctatggactactggggtcaaggaacctcagtcac
cgtctcctcagccaaaacaacacccccatcagtctatccactggcccctg
ggtgtggagatacaactggttcctccgtgactctgggatgcctggtcaag
ggctacttccctgagtcagtgactgtgacttggaactctggatccctgtc
cagcagtgtgcacaccttcccagctctcctgcagtctggactctacacta
tgagcagctcagtgactgtcccctccagcgcctggccaagtcagaccgtc
acctgcagcgttgctcacccggccagcaacaccacggtcgac

FIG. 33

17D2 - HC

gacgtccagatccagcagtctgggcctgagctggtgaagcctggagcttc 50
PCR primer

agtgaagatgtcctgcaaggcttctggttactcattcactgcctacaaca 100
CDR I

tgcactgggtgaagcagacccatggaaagagccttgagtggattggttat 150

attgatccttacagtggtgctactagctaccaccagaaattcaagggcaa 200
CDR II

ggccacattgactgttgacaaatcttccagcacagcctacatgcgcctca 250

acagcctgacatctgaggactctgcagtctattactgtgcaagaagatgg 300

gactgggaccttatgctatggactactggggtcaaggaacctcagtcac 350
CDR III

cgtctcctcagccaaaacaacacccccatcagtctatccactggcccctg 400
constant region

ggtgtggagatacaactggttcctccgtgactctgggatgcctggtcaag 450

ggctacttccctgagtcagtgactgtgacttggaactctggatccctgtc 500

cagcagtgtgcacaccttcccagctctcctgcagtctggactctacacta 550

tgagcagctcagtgactgtcccctccagcgcctggccaagtcagaccgtc 600

acctgcagcgttgctcacccggccagcaacaccacggtcgac 642
PCR primer

FIG. 34

17D2 - LC

agcgttgagatgtcacagtcgccagccatcctgtctgtgagtccaggaga
aagaatcagtttctcctgcagggccagtcagagcattggcacaagcatac
actggtatcagcaaagaacaaatggttctccaaggcttctcattaagtat
gcttctgcgtctatctctgggatcccttccaggtttagtggcagtggatc
agggacagattttactcttagcatcaacagtgtggagtctgaagatattg
cagattattactgtcaacaaagtaatagctggccgctcacgttcggtgct
gggaccaagctggagctgaaacgggctgatgctgcaccaactgtatccat
cttcccaccatccagtgagcagttaacatctggaggtgcctcagtcgtgt
gcttcttgaacaacttctaccccaaagacatcaatgtcaagtggaagatt
gatggcagtgaacgacaaaatggcgtcctgaacagttggactgatcagga
cagcaaagacagcacctacagcatgagcagcaccctcacgttgaccaagg
acgagtatgaacgacataacagctatacctgtgaggccactcacaagaca
tcaacttcacccattgtcaagagcttcaacaggaatgagtgt

FIG. 35

17D2 - LC

agcgttgagatgtcacagtcgccagccatcctgtctgtgagtccaggaga 50
PCR primer

aagaatcagtttctcctgcagggccagtcagagcattggcacaagcatac 100
CDR I

actggtatcagcaaagaacaaatggttctccaaggcttctcattaagtat 150

gcttctgcgtctatctctgggatcccttccaggtttagtggcagtggatc 200
CDR II

agggacagattttactcttagcatcaacagtgtggagtctgaagatattg 250

cagattattactgtcaacaaagtaatagctggccgctcacgttcggtgct 300
CDR III

gggaccaagctggagctgaaacgggctgatgctgcaccaactgtatccat 350
constant region

cttcccaccatccagtgagcagttaacatctggaggtgcctcagtcgtgt 400

gcttcttgaacaacttctaccccaaagacatcaatgtcaagtggaagatt 450

gatggcagtgaacgacaaaatggcgtcctgaacagttggactgatcagga 500

cagcaaagacagcacctacagcatgagcagcaccctcacgttgaccaagg 550

acgagtatgaacgacataacagctatacctgtgaggccactcacaagaca 600

tcaacttcacccattgtcaagagcttcaacaggaatgagtgt 642
PCR primer

FIG. 36

14D3 - HC

gacgtccagatgcagcagcctgggcctgagctggtgaagcctggagcttc
actaaagatgtcctgcaaggcttctggttactcattcactggctacaaca
tgcactgggtgaagcagagccatggaaagagccttgagtggattggatat
attgatccttacagtggtgctactagctacaaccagaaattcgagggcaa
ggccacattgactgtagacaaatcttccagcacagcctacatgcagctca
acagcctgacatctgaggactctgcagtctattactgtgcaagaagatgg
gactgggacccttatgctatggactactggggtcaaggaacctcagtcac
cgtctcctcagccaaaacaacagccccatcggtctatccactggcccctg
tgtgtggagatacaagtggctcctcggtgactctaggatgcctggtcaag
ggttatttccctgagccagtgaccttgacctggaactctggatccctgtc
cagtggtgtgcacaccttcccagctgtcctgcagtctgacctctacaccc
tcagcagctcagtgactgtaacctcgagcacctggcccagccagtccatc
acctgcaatgtggcccacccagccagcaacaccaaggtcgac

FIG. 37

14D3 - HC

gacgtccagatgcagcagcctgggcctgagctggtgaagcctggagcttc 50
PCR primer

actaaagatgtcctgcaaggcttctggttactcattcactggctacaaca 100
CDR I

tgcactgggtgaagcagagccatggaaagagccttgagtggattggatat 150

attgatccttacagtggtgctactagctacaaccagaaattcgagggcaa 200
CDR II

ggccacattgactgtagacaaatcttccagcacagcctacatgcagctca 250

acagcctgacatctgaggactctgcagtctattactgtgcaagaagatgg 300
CDR III

gactgggaccctatgctatggactactggggtcaaggaacctcagtcac 350

cgtctcctcagccaaaacaacagccccatcggtctatccactggccctg 400
constant

tgtgtggagatacaagtggctcctcggtgactctaggatgcctggtcaag 450

ggttatttccctgagccagtgaccttgacctggaactctggatccctgtc 500

cagtggtgtgcacaccttcccagctgtcctgcagtctgacctctacaccc 550

tcagcagctcagtgactgtaacctcgagcacctggcccagccagtccatc 600

acctgcaatgtggcccacccagccagcaacaccaaggtcgac 642
PCR primer

FIG. 38

14D3 - LC

aacattctgatgacacagtctccagccatcttgtctgtgagtccaggaga
aagagtcagtttcgcctgcagggccagtcagagcattggcacaagcatac
actggtatcagcaaagaacaaatggttctccaaggcttctcataaagtat
gcttctgagtctatctctgggatcccttccaggtttagtggcagtggatc
agggacagattttactcttagcatcaacagtgtggagtctgaagatattg
cagattattactgtcaacaaactaataggtggccgctcacgttcggtgct
gggaccaagctggagctgaaacgggctgatgctgcaccaactgtatccat
cttcccaccatccagtgagcagttaacatctggaggtgcctcagtcgtgt
gcttcttgaacaacttctaccccaaagacatcaatgtcaagtggaagatt
gatggcagtgaacgacaaaatggcgtcctgaacagttggactgatcagga
cagcaaagacagcacctacagcatgagcagcaccctcacgttgaccaagg
acgagtatgaacgacataacagctatacctgtgaggccactcacaagaca
tcaacttcacccattgtcaagagcttcaacaggaatgagtgt

FIG. 39

14D3 - LC

aacattctgatgacacagtctccagccatcttgtctgtgagtccaggaga 50
PCR primer

aagagtcagtttcgcctgcagggccagtcagagcattggcacaagcatac 100
CDR I

actggtatcagcaaagaacaaatggttctccaaggcttctcataaagtat 150

gcttctgagtctatctctgggatcccttccaggtttagtggcagtggatc 200
CDR II

agggacagattttactcttagcatcaacagtgtggagtctgaagatattg 250

cagattattactgtcaacaaactaataggtgggcgctcacgttcggtgct 300
CDR III

gggaccaagctggagctgaaacgggctgatgctgcaccaactgtatccat 350
constant region

cttcccaccatccagtgagcagttaacatctggaggtgcctcagtcgtgt 400

gcttcttgaacaacttctaccccaaagacatcaatgtcaagtggaagatt 450

gatggcagtgaacgacaaaatggcgtcctgaacagttggactgatcagga 500

cagcaaagacagcacctacagcatgagcagcaccctcacgttgaccaagg 550

acgagtatgaacgacataacagctatacctgtgaggccactcacaagaca 600

tcaacttcacccattgtcaagagcttcaacaggaatgagtgt 642
PCR primer

FIG. 40

3B3 - HC

DVQLQQPGAELVKPGASVKLSCTTSGVNIKDTYMHWMKQRPEQGLEWIGR
IDPANGNTKYDPKFRGKATITADTSSNTVYVQLRSLTSEDTAVYYCAYDG
YWGQGTLVTVSAAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVT
VTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPA
SSTKVD

FIG. 41

3B3 - HC

DVQLQQPGAELVKPGASVKLSCTTSGVNIKDTYMHWMKQRPEQGLEWIGR 50
PCR primer
CDR I

IDPANGNTKYDPKFRGKATITADTSSNTVYVQLRSLTSEDTAVYYCAYDG 100
CDR II
CDR III

YWGQGTLVTVSAAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVT 150
constant region

VTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPA200
PCR primer

SSTKVD 206

FIG. 42

3B3 - LC

NIVMTQTPASLAVSLGQRATISCRASESVDSYGNNFMHWYQQKPGQSPRL
LIYRASNLESGIPARFSGSGSRTDFTLTTNPVEADDVATYYCQQSHKDPL
TFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINV
KWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEA
THKTSTSPIVKSFKANEC

FIG. 43

3B3 - LC

NIVMTQTPASLAVSLGQRATISCRASESVDSYGNNFMHWYQQKPGQSPRL 50
PCR primer CDR I

LIYRASNLESGIPARFSGSGSRTDFTLTTNPVEADDVATYYCQQSHKDPL 100
CDR II CDR III

TFGAGTKLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINV 150
constant region

KWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEA 200

THKTSTSPIVKSFKANEC 218
PCR primer

FIG. 44

3C7 - HC

DVQLKHSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLDWIGL
INPYNGGTSYDQKFKGKATLTVDKSSSTAYMELLSLTSEDSAVYYCARDG
LMDYWGQGTSVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPE
PVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVA
HPASKTKVD

FIG. 45

3C7 - HC

DVQLKHSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLDWIGL 50
PCR primer CDR I

INPYNGGTSYDQKFKGKATLTVDKSSSTAYMELLSLTSEDSAVYYCARDG 100
CDR II

LMDYWGQGTSVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPE 150
CDR III constant region

PVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVA 200

HPASKTKVD 209
PCR primer

FIG. 46

3C7 - LC

DIVMTQTPASLAVSLGQRATIFCRASQSVDYNGISYMHWFQQKPGQPPKL
LIYAASNLESGIPARFSGSGSGTDFTLNIHPVEEEDAATYYCQQSFEDPH
TFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINV
KWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEA
THKTSTSPIVKSFNRNEC

FIG. 47

3C7 - LC

DIVMTQTPASLAVSLGQRATIFCRASQSVDYNGISYMHWFQQKPGQPPKL 50
PCR primer CDR I

LIYAASNLESGIPARFSGSGSGTDFTLNIHPVEEEDAATYYCQQSFEDPH 100
CDR II CDR III

IFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINV 150
constant region

KWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEA 200

THKTSTSPIVKSFNRNEC 218
PCR primer

FIG. 48

2B4 - HC

DVQLQQSGTVLARPGASVRMSCKASGYSFTRYWIHWLKQRPGQGLEWIGA
IFPGNRDTSYNQRFKGKAEVTAVTSASTAYLDLSSLTNEDSAVYYCTRWP
YYGSIYVNFDYWGQGTTLTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCL
VKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSE
TVTCNVAHPASSTKVD

FIG. 49

2B4 - HC

DVQLQQSGTVLARPGASVRMSCKASGYSFTRYWIHWLKQRPGQGLEWIGA 50
PCR primer CDR I

IFPGNRDTSYNQRFKGKAEVTAVTSASTAYLDLSSLTNEDSAVYYCTRWP 100
CDR II

YYGSIYVNFDYWGQGTTLTVSSAKTTPPSVYPLAPGSAAQTNSMVTLGCL 150
CDR III constant region

VKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSE 200

TVTCNVAHPASSTKVD 216
PCR primer

FIG. 50

2B4 - LC

DIVMTQSPLSLPVSLGDQASISCRTSQNLVHRNGNTYLHWYLQKPGQSPK
LLIYKISNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQGTHVP
PTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDIN
VKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCE
ATHKTSTSPIVKSFNRNEC

FIG. 51

2B4 - LC

DIVMTQSPLSLPVSLGDQASISCRTSQNLVHRNGNTYLHWYLQKPGQSPK 50
PCR primer
CDR I

LLIYKISNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQGTHVP 100
CDR II CDR III

PTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDIN 150
constant region

VKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCE 200

ATHKTSTSPIVKSFNRNEC 219
PCR primer

FIG. 52

3B3 - HC

gacgtccagctccagcagcctggagcagagcttgtgaagccaggggcctc
agtcaagttgtcctgcaccacttctggcgtcaacattaaagacacctata
tgcactggatgaagcagaggcctgaacagggcctggagtggattggaagg
attgatcctgcgaatggtaatactaaatatgacccgaaattccggggcaa
ggccactataacagcagacacatcctccaacacggtctacgtgcaactca
gaagcctgacatctgaggacactgccgtctattactgtgcctatgatggt
tactggggccaagggactctggtcactgtctctgcagccaaaacgacacc
cccatctgtctatccactggcccctggatctgctgcccaaactaactcca
tggtgaccctgggatgcctggtcaagggctatttccctgagccagtgaca
gtgacctggaactctggatccctgtccagcggtgtgcacaccttcccagc
tgtcctgcagtctgacctctacactctgagcagctcagtgactgtcccct
ccagcacctggcccagcgagaccgtcacctgcaacgttgcccacccggcc
agcagcaccaaggtcgac

FIG. 53

3B3 - HC

gacgtccagctccagcagcctggagcagagcttgtgaagccaggggcctc 50
PCR primer

agtcaagttgtcctgcaccacttctggcgtcaacattaaagacacctata 100
CDR I

tgcactggatgaagcagaggcctgaacagggcctggagtggattggaagg 150

attgatcctgcgaatggtaatactaaatatgacccgaaattccggggcaa 200
CDR II

ggccactataacagcagacacatcctccaacacggtctacgtgcaactca 250

gaagcctgacatctgaggacactgccgtctattactgtgcctatgatggt 300
CDR III

tactggggccaagggactctggtcactgtctctgcagccaaaacgacacc 350
constant region

cccatctgtctatccactggcccctggatctgctgcccaaactaactcca 400

tggtgaccctgggatgcctggtcaagggctatttccctgagccagtgaca 450

gtgacctggaactctggatccctgtccagcggtgtgcacaccttcccagc 500

tgtcctgcagtctgacctctacactctgagcagctcagtgactgtcccct 550

ccagcacctggcccagcgagaccgtcacctgcaacgttgcccacccggcc 600
PCR primer

agcagcaccaaggtcgac 618

FIG. 54

3B3 - LC

aacattgtgatgacccaaactccagcctctttggctgtgtctctagggca
gagggccaccatatcctgcagagccagtgaaagtgttgatagttatggca
ataattttatgcactggtaccagcagaaaccaggacagtcacccagactc
ctcatctatcgtgcatccaacctagaatctgggatccctgccaggttcag
tggcagtgggtctaggacagacttcaccctcaccactaatcctgtggagg
ctgatgatgttgcaacctattactgtcagcaaagtcataaggatccgctc
acgttcggtgctgggaccaagctggagctgaaacgggctgatgctgcacc
aactgtatccatcttcccaccatccagtgagcagttaacatctggaggtg
cctcagtcgtgtgcttcttgaacaacttctaccccaaagacatcaatgtc
aagtggaagattgatggcagtgaacgacaaaatggcgtcctgaacagttg
gactgatcaggacagcaaagacagcacctacagcatgagcagcaccctca
cgttgaccaaggacgagtatgaacgacataacagctatacctgtgaggcc
actcacaagacatcaacttcacccattgtcaagagcttcaaggaacatga
gtgt

FIG. 55

3B3 - LC

aacattgtgatgacccaaactccagcctctttggctgtgtctctagggca 50
PCR primer

gagggccaccatatcctgcagagccagtgaaagtgttgatagttatggca 100
CDR I

ataattttatgcactggtaccagcagaaaccaggacagtcacccagactc 150

ctcatctatcgtgcatccaacctagaatctgggatccctgccaggttcag 200
CDR II

tggcagtgggtctaggacagacttcaccctcaccactaatcctgtggagg 250

ctgatgatgttgcaacctattactgtcagcaaagtcataaggatccgctc 300
CDR III

acgttcggtgctgggaccaagctggagctgaaacgggctgatgctgcacc 350
constant region

aactgtatccatcttcccaccatccagtgagcagttaacatctggaggtg 400

cctcagtcgtgtgcttcttgaacaacttctaccccaaagacatcaatgtc 450

aagtggaagattgatggcagtgaacgacaaaatggcgtcctgaacagttg 500

gactgatcaggacagcaaagacagcacctacagcatgagcagcaccctca 550

cgttgaccaaggacgagtatgaacgacataacagctatacctgtgaggcc 600

actcacaagacatcaacttcacccattgtcaagagcttcaacaggaatga 650
PCR primer

gtgt 652

FIG. 56

3C7 - HC

gacgtccagctgaagcatcaggacctgagctggtgaagcctggagcttca
atgaagatatcctgcaaggcttctggttactcattcactggctacaccat
gaactgggtgaagcagagccatggaaagaaccttgagtggattggactta
ttaatccttacaatggtggtactagctacgaccagaagttcaagggcaag
gccacattaactgtagacaagtcatccagcacagcctacatggagctcct
cagtctgacatctgaggactctgcagtctattactgtgcaagagatggcc
tgatggactactggggtcaaggaacctcagtcaccgtctcctcagccaaa
acgacacccccatctgtctatccactggcccctggatctgctgcccaaac
taactccatggtgaccctgggatgcctggtcaagggctatttccctgagc
cagtgacagtgacctggaactctggatccctgtccagcggtgtgcacacc
ttcccagctgtcctgcagtctgacctctacactctgagcagctcagtgac
tgtcccctccagcacctggcccagcgagaccgtcacctgcaacgttgccc
acccggccagcaagaccaaggtcgac

FIG. 57

3C7 - HC

gacgtccagctgaagcatcaggacctgagctggtgaagcctggagcttca 50

PCR primer

atgaagatatcctgcaaggcttctggttactcattcactggctacaccat 100

CDR I

gaactgggtgaagcagagccatggaaagaaccttgagtggattggacttta 150

CDR II

ttaatccttacaatggtggtactagctacgaccagaagttcaagggcaag 200

gccacattaactgtagacaagtcatccagcacagcctacatggagctcct 250

cagtctgacatctgaggactctgcagtctattactgtgcaagagatggcc 300

CDR III

tgatggactactggggtcaaggaacctcagtcaccgtctcctcagccaaa 350

constant region

acgacaccccatctgtctatccactggcccctggatctgctgcccaaac 400

taactccatggtgaccctgggatgcctggtcaagggctatttccctgagc 450

cagtgacagtgacctggaactctggatccctgtccagcggtgtgcacacc 500

ttcccagctgtcctgcagtctgacctctacactctgagcagctcagtgac 550

tgtcccctccagcacctggcccagcgagaccgtcacctgcaacgttgccc 600

acccggccagcaagaccaaggtcgac 626

PCR primer

FIG. 58

3C7 - LC

gatattgtgatgacccaaactccagcttctttggctgtgtctctaggaca
gagagccactatcttctgcagagccagccagagtgtcgattataatggaa
ttagttatatgcactggttccaacagaaaccaggacagccacccaaactc
ctcatctatgctgcatccaacctagaatctgggatccctgccaggttcag
tggcagtgggtctgggacagacttcaccctcaacatccatcctgtggagg
aggaagatgctgcaacctattactgtcagcaaagttttgaggatccgcac
acgttcggaggggggaccaagctggaaataaaacgggctgatgctgcacc
aactgtatccatcttcccaccatccagtgagcagttaacatctggaggtg
cctcagtcgtgtgcttcttgaacaacttctaccccaaagacatcaatgtc
aagtggaagattgatggcagtgaacgacaaaatggcgtcctgaacagttg
gactgatcaggacagcaaagacagcacctacagcatgagcagcaccctca
cgttgaccaaggacgagtatgaacgacataacagctatacctgtgaggcc
actcacaagacatcaacttcacccattgtcaagagcttcaacaggaatga
gtgt

FIG. 59

3C7 - LC

gatattgtgatgacccaaactccagcttctttggctgtgtctctaggaca 50
PCR primer

gagagccactatcttctgcagagccagccagagtgtcgattataatggaa 100
CDR I

ttagttatatgcactggttccaacagaaaccaggacagccacccaaactc 150

ctcatctatgctgcatccaacctagaatctgggatccctgccaggttcag 200
CDR II

tggcagtgggtctgggacagacttcaccctcaacatccatcctgtggagg 250

aggaagatgctgcaacctattactgtcagcaaagttttgaggatccgcac 300
CDR III

acgttcggaggggggaccaagctggaaataaaacgggctgatgctgcacc 350
constant region

aactgtatccatcttcccaccatccagtgagcagttaacatctggaggtg 400

cctcagtcgtgtgcttcttgaacaacttctaccccaaagacatcaatgtc 450

aagtggaagattgatggcagtgaacgacaaaatggcgtcctgaacagttg 500

gactgatcaggacagcaaagacagcacctacagcatgagcagcaccctca 550

cgttgaccaaggacgagtatgaacgacataacagctatacctgtgaggcc 600

actcacaagacatcaacttcacccattgtcaagagcttcaacaggaatga 650
PCR primer

gtgt 654

FIG. 60

2B4 - HC

gacgtccagctgcagcagtctgggactgtgctggcaaggcctggggcttc
cgtgaggatgtcctgcaaggcttctggctacagctttaccaggtactgga
tacactggttaaaacagaggcctggacagggtctagaatggattggtgct
atttttcctggaaatcgtgataccagttacaaccagaggttcaagggcaa
ggccgaagtgactgcagtcacatccgccagcactgcctacttggacctca
gtagcctgacaaatgaggactctgcggtctattactgtacaagatggcct
tactatggttccatctacgttaactttgactactggggccaaggcaccac
tctcacagtctcctcagccaaaacgacacccccatctgtctatccactgg
cccctggatctgctgcccaaactaactccatggtgaccctgggatgcctg
gtcaagggctatttccctgagccagtgacagtgacctggaactctggatc
cctgtccagcggtgtgcacaccttcccagctgtcctgcagtctgacctct
acactctgagcagctcagtgactgtcccctccagcacctggcccagcgag
accgtcacctgcaacgttgcccacccagccagcagcaccaaggtcgac

FIG. 61

2B4 - HC

gacgtccagctgcagcagtctgggactgtgctggcaaggcctggggcttc 50

PCR primer

cgtgaggatgtcctgcaaggcttctggctacagctttaccaggtactgga 100

CDR I

tacactggttaaaacagaggcctggacagggtctagaatggattggtgct 150

attttcctggaaatcgtgataccagttacaaccagaggttcaagggcaa 200

CDR II

ggccgaagtgactgcagtcacatccgccagcactgcctacttggacctca 250

gtagcctgacaaatgaggactctgcggtctattactgtacaagatggcct 300

tactatggttccatctacgttaactttgactactggggccaaggcaccac 350

CDR III

tctcacagtctcctcagccaaaacgacaccccatctgtctatccactgg 400

constant region

ccctggatctgctgcccaaactaactccatggtgaccctgggatgcctg 450

gtcaagggctatttccctgagccagtgacagtgacctggaactctggatc 500

cctgtccagcggtgtgcacaccttcccagctgtcctgcagtctgacctct 550

acactctgagcagctcagtgactgtcccctccagcacctggcccagcgag 600

accgtcacctgcaacgttgcccacccagccagcagcaccaaggtcgac 648

PCR primer

FIG. 62

2B4 - LC

gatattgtgatgacccagtctcctctctccctgcctgtcagtcttggaga
tcaagcctccatctcttgcagaactagtcagaaccttgtacacaggaatg
gaaacacctatttacattggtacctgcagaagccaggccagtctccaaag
ctcctgatttacaaaatttccaaccgattttctggggtcccagacaggtt
cagtggcagtggatcagggacagatttcacactcaagatcagcagagtgg
aggctgaggatctgggagtttatttctgctctcaaggtacacatgttcct
ccgacgttcggtggaggcaccaagctggaaatcaaacgggctgatgctgc
accaactgtatccatcttcccaccatccagtgagcagttaacatctggag
gtgcctcagtcgtgtgcttcttgaacaacttctaccccaaagacatcaat
gtcaagtggaagattgatggcagtgaacgacaaaatggcgtcctgaacag
ttggactgatcaggacagcaaagacagcacctacagcatgagcagcaccc
tcacgttgaccaaggacgagtatgaacgacataacagctatacctgtgag
gccactcacaagacatcaacttcacccattgtcaagagcttcaacaggaa
tgagtgt

FIG. 63

2B4 - LC

gatattgtgatgacccagtctcctctctccctgcctgtcagtcttggaga 50
PCR primer

tcaagcctccatctcttgcagaactagtcagaaccttgtacacaggaatg 100
CDR I

gaaacacctatttacattggtacctgcagaagccaggccagtctccaaag 150

ctcctgatttacaaaatttccaaccgattttctggggtcccagacaggtt 200
CDR II

cagtggcagtggatcagggacagatttcacactcaagatcagcagagtgg 250

aggctgaggatctgggagtttatttctgctctcaaggtacacatgttcct 300
CDR III

ccgacgttcggtggaggcaccaagctggaaatcaaacgggctgatgctgc 350
constant region

accaactgtatccatcttcccaccatccagtgagcagttaacatctggag 400

gtgcctcagtcgtgtgcttcttgaacaacttctaccccaaagacatcaat 450

gtcaagtggaagattgatggcagtgaacgacaaaatggcgtcctgaacag 500

ttggactgatcaggacagcaaagacagcacctacagcatgagcagcaccc 550

tcacgttgaccaaggacgagtatgaacgacataacagctatacctgtgag 600

gccactcacaagacatcaacttcacccattgtcaagagcttcaacaggaa 650
PCR primer

tgagtgt 657

FIG. 64

EPITOPE REGIONS OF A THYROTROPHIN (TSH) RECEPTOR, USES THEREOF AND ANTIBODIES THERETO

The present invention is concerned with epitope regions of a thyrotrophin (TSH) receptor, uses thereof and antibodies thereto.

Thyrotrophin or thyroid stimulating hormone (TSH) is a pituitary hormone which plays a key role in regulating the function of the thyroid. Its release is stimulated by the hormone TRH formed in the hypothalamus and controls the formation and release of the important thyroid hormones thyroxine (T4) and tri-iodothyronine (T3). On the basis of a feedback mechanism, the thyroid hormone content of the serum controls the release of TSH. The formation of T3 and T4 by the thyroid cells is stimulated by TSH by a procedure in which the TSH released by the pituitary binds to the TSH receptor of the thyroid cell membrane.

In certain pathological conditions, various types of autoantibodies against this TSH receptor can also be formed. Depending on the type of these autoantibodies, either inhibition of the formation and release of T3 and T4 may occur at the TSH receptor owing to the shielding of the TSH molecules, or, on the other hand, these thyroid hormones may be released in an uncontrolled manner because the anti-TSH receptor autoantibodies mimic the action of the TSH and stimulate the synthesis and release of thyroid hormones.

Autoimmune thyroid disease (AMD) is the most common autoimmune disease affecting different populations worldwide. A proportion of patients with AITD, principally those with Graves' disease, have autoantibodies to the TSH receptor substantially as hereinbefore described. The autoantibodies bind to the TSH receptor and usually mimic the actions of TSH, stimulating the thyroid gland to produce high levels of thyroid hormones. These autoantibodies are described as having stimulating activity. In some patients, autoantiodies bind to the TSH receptor but do not stimulate thyroid hormone production and are described as having blocking activity [J Sanders, Y Oda, S-A Roberts, M Maruyama, J Furmaniak, B Rees Smith "Understanding the thyrotrophin receptor function-structure relationship." Baillière's Clinical Endocrinology and Metabolism. Ed. T F Davies 1997 11(3): 451-479. Pub. Baillière Tindall, London].

Measurements of TSH receptor autoantibodies are important in the diagnosis and management of AMTD, particularly Graves' disease. Currently three types of assays are used to measure TSH receptor autoantibodies:

(a) competitive binding assays which measure the ability of TSH receptor autoantibodies to inhibit the binding of TSH to preparations of TSH receptor;

(b) bioassays which measure the ability of TSH receptor autoantibodies to stimulate cells expressing the TSH receptor in culture; and

(c) immunoprecipitation of TSH receptor preparations with TSH receptor autoantibodies.

Measurement of TSH receptor autoantibodies using such assays are described in references J Sanders, Y Oda, S-A Roberts, M Maruyama, J Furmaniak, B Rees Smith "Understanding the thyrotrophin receptor function-structure relationship." Baillière's Clinical Endocrinology and Metabolism. Ed. T F Davies 1997 11(3): 451-479. Pub. Baillière Tindall, London, and J Sanders, Y Oda, S Roberts, A Kiddie, T Richards, J Bolton, V McGrath, S Walters, D Jaskólski, J Furmaniak, B Rees Smith "The interaction of TSH receptor autoantibodies with ^{125}I-labelled TSH receptor." Journal of Clinical Endocrinology and Metabolism 1999 84(10):3797-3802.

There are, however, a number of limitations associated with the use of the above described currently available assays for measuring TSH receptor autoantibodies. The competitive assays of type (a) which are available in different formats are generally sensitive, relatively easy to perform and adaptable for routine use. However, competitive radioreceptor assays known to date for detecting TSH receptor autoantibodies have fundamental disadvantages of a practical nature which can be ascribed to the fact that the binding ability of TSH receptor preparations generally react very sensitively to changes in the receptor or in a biomolecule bound by it. The binding of biomolecules which are peptides or protein in nature, for example hormones or autoantibodies, to receptors is as a rule very complicated in nature, and the specific binding between receptor and biomolecule is very much more sensitive to structural alterations, in particular of the receptor, than is the case with a usual antigen/antibody binding pair which is the basis of most immunoassays in which receptors are involved. Attempts to immobilise and/or to label the TSH receptor have as a rule led to structural alterations which have greatly impaired the functionality of the receptor.

As far as bioassays of the type mentioned in (b) are concerned, these tend to be expensive, time-consuming, require highly skilled staff and are essentially unsuitable for routine use.

With respect to the direct immunoprecipitation assays of type (c), currently available such immunoprecipitation assays do not in practice have the required sensitivity for TSH receptor autoantibody detection.

The present invention alleviates the problems hitherto associated with the prior art detection of TSH receptor autoantibodies. More particularly, the present invention provides diagnostic methods and kits for screening for TSH receptor autoantibodies, with improved sensitivity compared to prior art diagnostic methods and kits, and which, if desired, allow the use of one or more competitive binding partners or competitors for a TSH receptor in competitive assays of the type described above. In particular the present invention is concerned with the use of one or more identified epitope regions of TSH receptor in diagnostic methods and kits for screening for TSH receptor autoantibodies.

There is provided by the present invention, therefore, for use in diagnosis or therapy of autoimmune disease associated with an immune reaction to a TSH receptor, a polypeptide sequence comprising part or all of the primary structural conformation (that is a continuous sequence of amino acid residues) of one or more TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

(in particular said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and/or the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one

or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments);

wherein autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) with said polypeptide sequence, so as to enable said diagnosis or therapy.

More particularly, there is provided by the present invention for use in diagnosis or therapy of autoimmune disease associated with an immune reaction to a TSH receptor, a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;

amino acid numbers 246 to 260 of a TSH receptor;

amino acid numbers 260 to 363 of a TSH receptor; and

amino acid numbers 380 to 418 of a TSH receptor;

(in particular said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and/or the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments);

wherein autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies) with said polypeptide sequence, so as to enable said diagnosis or therapy.

Alternatively, there is provided by the present invention for use in diagnosis or therapy of autoimmune disease associated with an immune reaction to a TSH receptor, a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;

amino acid numbers 246 to 260 of a TSH receptor;

amino acid numbers 260 to 363 of a TSH receptor; and

amino acid numbers 380 to 418 of a TSH receptor;

(in-particular said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and/or the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments);

wherein lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes) with said polypeptide sequence, so as to enable said diagnosis or therapy.

The present invention further provides for use in diagnosis or therapy of autoimmune disease associated with an immune reaction to a TSH receptor, a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;

amino acid numbers 246 to 260 of a TSH receptor;

amino acid numbers 260 to 363 of a TSH receptor; and

amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and/or the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments);

wherein autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) with said polypeptide sequence, so as to enable said diagnosis or therapy.

More particularly, the present invention further provides for use in diagnosis or therapy of autoimmune disease associated with an immune reaction to a TSH receptor, a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;

amino acid numbers 246 to 260 of a TSH receptor;

amino acid numbers 260 to 363 of a TSH receptor; and

amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid

numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and/or the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments);

wherein autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies) with said polypeptide sequence, so as to enable said diagnosis or therapy.

The present invention further provides for use in diagnosis or therapy of autoimmune disease associated with an immune reaction to a TSH receptor, a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and/or the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments);

wherein lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes) with said polypeptide sequence, so as to enable said diagnosis or therapy.

More preferably, it is generally preferred that such diagnostic or therapeutic use employs a polypeptide sequence or sequences comprising, consisting of or consisting essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 32 to 41 of a TSH receptor;
amino acid numbers 36 to 42 of a TSH receptor;
amino acid numbers 247 to 260 of a TSH receptor;
amino acid numbers 277 to 296 of a TSH receptor; and
amino acid numbers 381 to 385 of a TSH receptor;

(in particular said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and/or the primary structural conformation of amino acid numbers 247 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 247 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments).

In particular, it is generally preferred according to the present invention that such diagnostic or therapeutic use employs amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments.

In particular, it is generally preferred according to the present invention that such diagnostic or therapeutic use employs amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments.

In particular, it is generally preferred according to the present invention that such diagnostic or therapeutic use employs amino acid numbers 247 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments.

A particularly preferred such diagnostic or therapeutic use according to the present invention, comprises for use in diagnosis or therapy of autoimmune disease associated with an immune reaction to a TSH receptor:

(i) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and

(ii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more further TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments;

wherein autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) with said polypeptide sequences, so as to enable said diagnosis or therapy.

More particularly, such diagnostic or therapeutic use may comprise:

(i) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and

(ii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more further TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments;

wherein autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies) with said polypeptide sequences, so as to enable said diagnosis or therapy.

Alternatively, such diagnostic or therapeutic use may comprise:

(i) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and

(ii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more further TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments;

wherein lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes) with said polypeptide sequences, so as to enable said diagnosis or therapy.

A particularly preferred diagnostic or therapeutic use according to the present invention, comprises for use in diagnosis or therapy of autoimmune disease associated with an immune reaction to a TSH receptor:

(i) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and

(ii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more filter TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments;

wherein autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) with said polypeptide sequences, so as to enable said diagnosis or therapy.

More particularly, such diagnostic or therapeutic use may comprise:

(i) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and

(ii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more flirter TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more

variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments;

wherein autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies) with said polypeptide sequences, so as to enable said diagnosis or therapy.

Alternatively, such diagnostic or therapeutic use may comprise:

(i) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and

(ii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more further TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments;

wherein lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes) with said polypeptide sequences, so as to enable said diagnosis or therapy.

It may also be further preferred that the above mentioned diagnostic or therapeutic use employing:

(i) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and

(ii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more further TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments;

further employs:

(iii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more further TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 381 to 385 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 381 to 385 of a TSH receptor, or variants, analogs or derivatives of such fragments.

More particularly, such preferred diagnostic or therapeutic use employs:

(i) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments;

(ii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more further TSH receptor epitopes with which autoantbodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments; and

(iii) a polypeptide sequence comprising, consisting of or consisting essentially of part or all of the primary structural conformation of one or more further TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said polypeptide sequence comprising, consisting of or consisting essentially of the primary structural conformation of amino acid numbers 381 to 385 of a TSH receptor

as depicted in any one of the amino acid sequences of FIG. **7**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 381 to 385 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **7**, or variants, analogs or derivatives of such fragments.

As will be appreciated from the accompanying Figures, the above mentioned amino acid sequences can be of human, porcine, bovine, canine, feline, mouse, rat or ovine origin, and the specific amino acid sequences in each of the above mentioned species are hereinafter described in greater detail with reference to FIGS. **1**, **3**, **5**, and **7**.

There also provided by the present invention one or more TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said one or more TSH receptor epitopes comprising, consisting of or consisting essentially of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

(in particular amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; or amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments).

More particularly, there is provided by the present invention one or more TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), said one or more TSH receptor epitopes comprising, consisting of or consisting essentially of of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

(in particular amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; or amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments).

Alternatively, there is provided by the present invention one or more TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), said one or more TSH receptor epitopes comprising, consisting of or consisting essentially of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

(in particular amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; or amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments).

The present invention further provides one or more TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), said one or more TSH receptor epitopes comprising, consisting of or consisting essentially of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; or amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments).

More particularly, the present invention further provides one or more TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), said one ore more TSH receptor epitopes comprising, consisting of or consisting essentially of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; or amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments).

The present invention further provides one or more TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), said TSH receptor epitopes comprising, consisting

of or consisting essentially of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; or amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments).

More preferably, it is generally preferred that one or more TSH receptor epitopes comprise one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 32 to 41 of a TSH receptor;
amino acid numbers 36 to 42 of a TSH receptor;
amino acid numbers 247 to 260 of a TSH receptor;
amino acid numbers 277 to 296 of a TSH receptor; and
amino acid numbers 381 to 385 of a TSH receptor;

(in particular amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; or amino acid numbers 247 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 247 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments).

A particularly preferred TSH receptor epitope according to the present invention comprises, consists of or consists essentially of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes).

A particularly preferred TSH receptor epitope according to the present invention comprises, consists of or consists essentially of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes).

A particularly preferred TSH receptor epitope according to the present invention comprises, consists of or consists essentially of amino acid numbers 247 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes).

There is also provided by the present invention a polypeptide with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) and which comprises, consists of or consists essentially of part or all of the primary structural conformation of one or more epitopes of a TSH receptor with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), which polypeptide comprises, consists of or consists essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

(in particular amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and/or amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments), with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), with the exception of a full length TSH receptor.

More particularly, there is provided by the present invention a polypeptide with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies) and which comprises, consists of or consists essentially of part or all of the primary structural conformation (that is a continuous sequence of amino acid residues) of one or more epitopes of a TSH receptor with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), which polypeptide comprises, consists of or consists essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

(in particular amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and/or amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments), with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), with the exception of a full length TSH receptor.

Alternatively, there is provided by the present invention a polypeptide with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes) and which comprises, consists of or consists essentially of part or all of the primary structural conformation (that is a

continuous sequence of amino acid residues) of one or more epitopes of a TSH receptor with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), which polypeptide comprises, consists of or consists essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

(in particular amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments; and/or amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments), with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), with the exception of a full length TSH receptor.

The present invention further provides a polypeptide with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) and which comprises, consists of or consists essentially of part or all of the primary structural conformation of one or more epitopes of a TSH receptor with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), which polypeptide comprises, consists of or consists essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and/or amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments), with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), with the exception of a full length TSH receptor.

More particularly, the present invention further provides a polypeptide with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies) and which comprises, consists of or consists essentially of part or all of the primary structural conformation of one or more epitopes of a TSH receptor with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), which polypeptide comprises, consists of or consists essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor;
amino acid numbers 246 to 260 of a TSH receptor;
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and/or amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments), with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), with the exception of a full length TSH receptor.

The present invention further provides a polypeptide with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes) and which comprises, consists of or consists essentially of part or all of the primary structural conformation of one or more epitopes of a TSH receptor with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), which polypeptide comprises, consists of or consists essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof or variants, analogs or derivatives of such fragments:

amino acid numbers 22 to 91 of a TSH receptor,
amino acid numbers 246 to 260 of a TSH receptor,
amino acid numbers 260 to 363 of a TSH receptor; and
amino acid numbers 380 to 418 of a TSH receptor;

as depicted in any one of the amino acid sequences of any of FIGS. **1**, **3**, **5** and **7**, (in particular amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments; and/or amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments), with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), with the exception of a full length TSH receptor.

More preferably, it is generally preferred that a polypeptide according to the present invention can comprise part or all of the primary structural conformation of one or more epitopes of a TSH receptor with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) and as such comprises, consists of or consists essentially of the primary structural conformation of one or more of the following, or one or more variants, analogs, derivatives or fragments thereof or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes):

amino acid numbers 32 to 41 of a TSH receptor,

amino acid numbers 36 to 42 of a TSH receptor,

amino acid numbers 247 to 260 of a TSH receptor,

amino acid numbers 277 to 296 of a TSH receptor; and

amino acid numbers 381 to 385 of a TSH receptor.

Preferably a polypeptide according to the present invention comprises, consists of or consists essentially of, amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments.

Preferably a polypeptide according to the present invention comprises, consists of or consists essentially of, amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments.

Preferably a polypeptide according to the present invention comprises, consists of or consists essentially of, amino acid numbers 247 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments.

It is also preferred according to the present invention that there is provided a polypeptide with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) and which comprises part or all of the primary structural conformation of TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), which polypeptide comprises, consists of or consists essentially of:

(i) the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes); and

(ii) the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes);

with the exception of a full length TSH receptor.

More particularly, there is provided by the present invention a polypeptide with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies) and which comprises part or all of the primary structural conformation of TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), which polypeptide comprises, consists of or consists essentially of:

(i) the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies); and

(ii) the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies);

with the exception of a full length TSH receptor.

Alternatively, there is provided by the present invention a polypeptide with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes) and which comprises part or all of the primary structural conformation of TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), which polypeptide comprises, consists of or consists essentially of:

(i) the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes); and

(ii) the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes);

with the exception of a full length TSH receptor.

The present invention further provides a polypeptide with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) and which comprises part or all of the primary structural conformation of epitopes of a TSH receptor with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), which polypeptide comprises, consists of or consists essentially of:

(i) the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one

of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes); and

(ii) the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes);

with the exception of a fill length TSH receptor.

More particularly, the present invention further provides a polypeptide with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies) and which comprises part or all of the primary structural conformation of TSH receptor epitopes with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies), which polypeptide comprises, consists of or consists essentially of:

(i) the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments, with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies); and

(ii) the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments, with which autoantibodies produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies);

with the exception of a full length TSH receptor.

The present invention further provides a polypeptide with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes) and which comprises part or all of the primary structural conformation of TSH receptor epitopes with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes), which polypeptide comprises, consists of or consists essentially of:

(i) the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments, with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes); and

(ii) the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments, with which lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such lymphocytes);

with the exception of a full length TSH receptor.

It is also preferred according to the present invention that there is provided a polypeptide with which autoantbodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) and which comprises part or all of the primary structural conformation of TSH receptor epitopes with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes), which polypeptide comprises, consists of or consists essentially of:

(i) the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can react (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes);

(ii) the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes); and

(iii) the primary structural conformation of amino acid numbers 381 to 385 of a TSH receptor, or one or more variants, analogs, derivatives or fragments of amino acid numbers 381 to 385 of a TSH receptor, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes);

with the exception of a full length TSH receptor.

More particularly, the present invention further provides a polypeptide with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes) and which comprises part or all of the primary structural conformation of epitopes of a TSH receptor with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH

receptor with such autoantibodies or lymphocytes), which polypeptide comprises, consists of or consists essentially of:

(i) the primary structural conformation of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 277 to 296 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **5**, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes);

(ii) the primary structural conformation of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 246 to 260 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **3**, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes);

(iii) the primary structural conformation of amino acid numbers 381 to 385 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **7**, or one or more variants, analogs, derivatives or fragments of amino acid numbers 381 to 385 of a TSH receptor as depicted in any one of the amino acid sequences of FIG. **7**, or variants, analogs or derivatives of such fragments, with which autoantibodies and/or lymphocytes produced in response to a TSH receptor can interact (suitably under conditions that allow interaction of a TSH receptor with such autoantibodies or lymphocytes);

with the exception of a full length TSH receptor.

As will be appreciated from the accompanying Figures, such amino acid sequences can be of human, porcine, bovine, canine, feline, mouse, rat or ovine origin, and the specific amino acid sequences in each of the above mentioned species are hereinafter described in greater detail with reference to FIGS. **1**, **3**, **5**, and **7**. Suitably, in the case where polypeptides according to the second aspect of the present invention comprise amino acid sequences corresponding to part or all of the primary structural conformation of more than one epitope of a TSH receptor, the respective amino acid sequences corresponding to part or all of the primary structural conformation of respective epitopes may be separated by linker amino acid sequences so as to preferably provide the respective amino acid sequences in a conformation, arrangement or sequence that resembles or substantially resembles a conformation, arrangement or sequence of amino acids as present in an active site of a TSH receptor, and/or can be effective in providing the above referred to respective amino acid sequences of a TSH receptor in a conformation, arrangement or sequence optimal for interaction with autoantibodies and/or lymphocytes as described herein.

Preferred polypeptide sequences and polypeptides according to the present invention comprise, consist of, or consist essentially of, the specifically referred to amino acid numbered sequences of a TSH receptor as respectively shown in any of accompanying FIGS. **1**, **3**, **5** or **7**. As indicated above, however, the present invention also covers "variants", "analogs", "derivatives" and "fragments" of specific amino acid sequences described herein and the terms "variants", "analogs", "derivatives" and "fragments" as used herein when referring to polypeptide sequences and polypeptides according to the present invention (such as polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures) can be characterised as polypeptide sequences and polypeptides which retain essentially the sameibiological function or activity (in terms of autoantibody and/or lymphocyte interaction as described herein) as polypeptide sequences and polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures. Suitably, variants, analogs, derivatives and fragments, or variants, analogs or derivatives of the fragments as described herein can have a primary structural conformation of amino acids as seen in the accompanying Figures in which several or a few (such as 5 to 10, 1 to 5 or 1 to 3) amino acid residues are substituted, deleted or added, in any combination. Especially preferred among these are silent substitutions, additions are deletions which do not alter or substantially alter the biological activity or function of polypeptides according to the present invention as specifically described above. Conservative substitutions can be preferred as hereinafter described in greater detail.

More particularly, variants, analogs or derivatives of polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures may be:

(i) ones in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue); or

(ii) ones in which one or more of the amino acid resides includes a substituent group; or

(iii) ones which further comprise additional amino acids that can be effective in providing the above referred to amino acid numbers of a TSH receptor that are present in a polypeptide of the present invention in a conformation, arrangement or sequence that resembles or substantially resembles a conformation, arrangement or sequence of amino acids as present in an active site of a TSH receptor, and/or can be effective in providing the above referred to amino acid numbers of a TSH receptor that are present in a polypeptide of the present invention in a conformation, arrangement or sequence optimal for interaction with autoantibodies and/or lymphocytes as described herein.

Such variants, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

Typically, variants, analogs or derivatives can be those that vary from a reference (such as polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures) by conservative amino acid substitutions. Such substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids A, V, L and I; among the hydroxyl residues S and T; among the acidic residues D and E; among the amide residues N and Q; among the basic residues K and R; and among the aromatic residues F and Y.

It may be preferred that variants, analogs or derivatives as provided by the present invention are ones which further comprise additional amino acids that can be effective in providing the above referred to amino acid numbers of a TSH receptor that are present in a polypeptide of the present invention in a conformation, arrangement or sequence that resembles or substantially resembles a conformation, arrangement or sequence of amino acids as present in an

active site of a TSH receptor, and/or can be effective in providing the above referred to amino acid numbers of a TSH receptor that are present in a polypeptide of the present invention in a conformation, arrangement or sequence optimal for interaction with autoantibodies and/or lymphocytes as described herein.

More particularly, the term "fragment" as used herein denotes a polypeptide having an amino acid sequence that entirely is the same as part but not all of the amino acid sequence of a polypeptide having a primary structural conformation of specified amino acids-as described herein with reference to the accompanying Figures, and variants or derivatives thereof and such fragments may be "free standing", i.e. not part of or fused to other amino acids or polypeptides, or they may be comprised within a larger polypeptide of which they form a part or region. As will be appreciated, fragments according to the present invention comprise or contain the primary structural conformation of amino acids present in one or more epitopes of a TSH receptor as described herein so as to be capable of interaction with autoantibodies and/or lymphocytes as described herein.

Polypeptides of the present invention, therefore, include polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures as well as polypeptides (namely variants, analogs and derivatives as referred to above) having at least 70% identity to polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures, preferably at least 80% identity to the polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures, and more preferably at least 90% identity to polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures and still more preferably at least 95% identity to polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures and also includes fragments of such polypeptides substantially as referred to above.

A polypeptide according to the present invention is suitably obtained by, or is obtainable by, expression of a polynucleotide according to the present invention substantially as hereinafter described. Alternatively, the polypeptides of the invention can be synthetically produced by conventional peptide synthesisers employing techniques which are well known in the art. A polypeptide according to the present invention so obtained can be advantageous in being free from association with other eukaryotic polypeptides or contaminants which might otherwise be associated therewith in its natural environment.

Polypeptides according to the present invention substantially as herein described can be expressed in various systems generating recombinant proteins. For example, for expression in *E coli*, cDNA coding for the appropriate polypeptides according to the present invention can be cloned into a vector, such as pET22, pMEX8, pGEX2T or pQE-81L His or an equivalent. In the case of expression in yeast (for example *Saccharomyces cerevisiae* or *Schizosaccharomyces pombe*), vectors such as pYES2, pESP2 or pYES2/CT or an equivalent, can be employed. AcMNPV (Bac-N-Blue) vector or an equivalent can be used for expression in insect cells and pRC/CMV, pcDNA3.1 vectors or an equivalent can be used for expression in mammalian cells, such as Chinese Hamster Ovary (CHO) cells. A polypeptide according to the present invention can be expressed as a discrete protein, or as a fusion protein linked to, for example, glutathione S transferase (GST) or poly histdine linker. For a discrete protein, affinity column chromatography purification using a mouse monoclonal antibody to the relevant part of a polypeptide according to the present invention coupled to a Sepharose particle can be used. If a polypeptide according to the present invention is fused to GST, glutathione Sepharose chromatography purification can be used to isolate the fusion protein. Specific proteases can be used to separate GST from a polypeptide according to the present invention and a second round of glutathione Sepharose chromatography can be used to separate GST from a polypeptide according to the present invention. In the case of peptides linked to poly histidine linker, the purification can be carried out using immobilised metal affinity chromatography.

The present invention further provides a process of preparing a polypeptide substantially as hereinbefore described, which process comprises:

(i) providing a host cell substantially as hereinbefore described;

(ii) growing the host cell; and

(iii) recovering a polypeptide according to the present invention therefrom.

Recovery of a polypeptide according to the present invention can typically employ conventional isolation and purification techniques, such as chromatographic separations or immunological separations, known to one of ordinary skill in the art.

In accordance with a further aspect of the present invention, there is provided a polynucleotide comprising:

(i) a nucleotide sequence encoding a polypeptide substantially as hereinbefore described;

(ii) a nucleotide sequence encoding a polypeptide substantially as hereinbefore described, which polypeptide comprises an amino acid sequence or sequences of specified amino acid numbers of a TSH receptor which is or arm defined by reference to any of FIGS. **1**, **3**, **5** and **7**;

(iii) a nucleotide sequence encoding a polypeptide of (ii), which nucleotide sequence comprises nucleotide bases encoding the above mentioned specified amino acid numbers of a TSH receptor which are defined by reference to any of FIGS. **1**, **3**, **5**, and **7**, and which nucleotide bases are defined by reference to any of FIGS. **2**, **4**, **6** and **8**;

(iv) a nucleotide sequence differing from the sequence of (iii) in codon sequence due to the degeneracy of the genetic code;

(v) a nucleotide sequence comprising an allelic variation of the sequence of (iii);

(vi) a nucleotide sequence comprising a fragment of any of the sequences of (i), (ii), (iii), (iv) or (v); or

(vii) a nucleotide sequence which hybridizes under stringent conditions to any of the sequences of (i), (ii), (iii), (iv), (v) or (vi).

The nucleotide bases of a polynucleotide according to the present invention, encoding the above mentioned epitope regions of a polypeptide according to the present invention, can be summarised as follows.

Amino Acid Numbers	Nucleotide Numbers
22-91	64-273
32-41	94-123
36-42	106-126
246-260	736-780

-continued

Amino Acid Numbers	Nucleotide Numbers
247-260	739-780
260-363	778-1089
277-296	829-888
380-418	1138-1254
381-385	1141-1155

Polynucleotides of the present invention may be in the form of DNA, including, for instance, cDNA, synthetic DNA and genomic DNA appropriately obtained by cloning or produced by chemical synthetic techniques or by a combination thereof A preferred embodiment of the present invention preferably comprises cDNA or synthetic DNA.

The coding sequence which encodes a polypeptide according to the present invention may be identical to the coding sequence of a polynucleotide as referred to above in (iii) and defined by reference to any of FIGS. **2**, **4**, **6** and **8**. It also may be a polynucleotide with a different sequence, which, as a result of the redundancy (degeneracy) of the genetic code, encodes a polypeptide according to the present invention.

The present invention further relates to variants of the herein above described polynucleotides which encode for polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures, variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of the fragments and substantially as hereinbefore described in greater detail. A variant of the polynucleotide may be a naturally occurring variant such as a naturally occurring allelic variant, or it may be a variant that is not known to occur naturally. Such non-naturally occurring variants of the polynucleotide may be made by mutagenesis techniques.

Among the variants in this regard are variants that differ from the aforementioned polynucleotides by nucleotide substitutions, deletions or additions. The substitutions, deletions or additions may involve one or more nucleotides. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions, again substantially as hereinbefore described.

Variant polynucleotides according to the present invention are suitably at least 70% identical over their entire length to a polynucleotide encoding polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures, and polynucleotides which are complementary to, or hybridise to, such polynucleotides. Alternatively, most highly preferred are polynucleotides that comprise a region that is at least 80% identical over its entire length to a polynucleotide encoding a polypeptides having a primary structural conformation of specified amino acids as described herein with reference to the accompanying Figures and polynucleotides which are complementary to, or hybridise to, such polynucleotides. In this regard, polynucleotides at least 90% identical over their entire length to the same are particularly preferred, and among these particularly preferred polynucleotides, those with at least 95% identity are especially preferred. Furthermore, those with at least 97% identity are highly preferred among those with at least 95% identity, and among these those with at least 98% identity and at least 99% identity are particularly highly preferred, with at least 99% identity being the more preferred.

Substantially as hereinbefore described the present invention further relates to polynucleotides that hybridise to the herein above-described sequences. In this regard, the present invention especially relates to polynucleotides which hybridise under stringent conditions to the herein above-described polynucleotides. As herein used, the term "stringent conditions" means hybridisation will occur only if there is at least 95% and preferably at least 97% complementary identity between the sequences.

The present invention also relates to vectors, which comprise a polynucleotide or polynucleotides of the present invention, host cells which are genetically engineered with vectors of the invention and the production of polypeptides of the invention by recombinant techniques.

The present invention, therefore, further provides a biologically functional vector system which carries a polynucleotide substantially as hereinbefore described and which is capable of introducing the polynucleotide into the genome of a host organism.

Host cells can be genetically engineered to incorporate polynucleotides and express polypeptides of the present invention and the present invention further provides a host cell which is transformed or transfected with a polynucleotide, or one or more polynucleotides, or a vector system, each substantially as herein described. The appropriate DNA sequence may be inserted into the vector by any of a variety of well-known and routine techniques.

According to a particularly preferred embodiment of the present invention, there is also provided a method of screening for autoantibodies or lymphocytes produced in response to a TSH receptor in a sample of body fluid obtained from a subject (in particular a human) suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) providing either (i) said sample of body fluid from said subject or (ii) lymphocytes isolated from said sample;

(b) contacting said sample or isolated lymphocytes with a polypeptide according to the present invention substantially as hereinbefore described (suitably under conditions that allow interaction of a TSH receptor with autoantibodies or lymphocytes produced in response to a TSH receptor) so as to permit said polypeptide to interact with autoantibodies, or lymphocytes, produced in response to a TSH receptor, and present in, or isolated from, said sample; and

(c) monitoring the degree, or effect, of interaction of said polypeptide with either said autoantibodies, or said lymphocytes, produced in response to a TSH receptor and present in, or isolated from, said sample, thereby providing an indication of the presence of said autoantibodies, or said lymphocytes, in said sample, or isolated from said sample.

Substantially as described above, a method according to the present invention is suitable for screening for autoantibodies or lymphocytes produced in response to a TSH receptor in a sample of body fluid obtained from a subject. A method according to the present invention can, however, be particularly adapted for use in screening for autoantibodies produced in response to a TSH receptor in a sample of body fluid obtained from a subject substantially as hereinafter described in greater detail.

There is in particular provided by the present invention, therefore, a method of screening for autoantibodies produced in response to a TSH receptor in a sample of body fluid obtained from a subject (in particular a human) suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) contacting said sample with a polypeptide according to the present invention substantially as hereinbefore described (suitably under conditions that allow interaction of a TSH receptor with autoantibodies produced in response to a TSH receptor) so as to permit said polypeptide to interact with autoantibodies produced in response to a TSH receptor and present in said sample; and

(c) monitoring the degree of interaction of said polypeptide with said autoantibodies produced in response to a TSH receptor and present in said sample, thereby providing an indication of the presence of said autoantibodies in said sample.

A method according to the present invention may typically employ a control, such as a sample of body fluid from a normal subject, in other words a subject known to be without autoimmune disease associated with an immune reaction to a TSH receptor.

A method of screening for autoantiodies to a -TSH receptor according to the present invention may comprise directly monitoring interaction of (i) autoantibodies to a TSH receptor present in the sample of body fluid from the subject and (ii) a polypeptide, as provided by the present invention substantially as hereinbefore described, typically by employing non-competitive sandwich type assay techniques known in the art.

Typically, in a method according to the present invention employing non-competitive techniques, monitoring of the degree of interaction of (i) autoantibodies to a TSH receptor present in the sample and (ii) a polypeptide according to the present invention substantially as hereinbefore described, can comprise providing labelling means either to a polypeptide according to the present invention substantially as hereinbefore described, or to a binding partner for autoantibodies to a TSH receptor, either of which technique would enable monitoring of the above described interaction. For example, a method according to the present invention may comprise directly or indirectly labelling a polypeptide according to the present invention substantially as hereinbefore described; contacting the thus labelled polypeptide with a sample of body fluid being screened for TSH receptor autoantibodies so as to provide a mixture thereof; and adding to the mixture a binding partner for autoantibodies to a TSH receptor (such as an anti -IgG reagent) present in the sample of body fluid, so as to cause precipitation of any complexes of labelled polypeptide and TSH receptor autoantibodies present in the mixture. Alternatively, it may be preferred that a method according to the present invention further comprises adding a labelled binding partner for TSH receptor autoantibodies (such as a labelled anti- IgG reagent, for example protein A or anti-human IgG, or labelled full length TSH receptor or an epitope thereof) to a mixture obtained by contacting (i) a polypeptide according to the present invention substantially as hereinbefore described immobilised to a support and (ii) a sample of body fluid being screened for autoantibodies to a TSH receptor.

It may alternatively be preferred that a method of screening for autoantibodies to a TSH receptor in the sample of body fluid according to the present invention, utilises the principles employed in known competitive assays. For example, a method according to the present invention may employ at least one competitor capable of competing with autoantibodies to a TSH receptor in the interaction thereof with a polypeptide according to the present invention substantially as hereinbefore described.

Typically, a competitor as employed in a competitive assay method according to the present invention may comprise one or more antibodies, which may be natural or partly or wholly synthetically produced. A competitor as employed in the present invention may alternatively comprise any other protein (for example TSH) having a binding domain or region which is capable of competing with autoantibodies to a TSH receptor in the interaction thereof with a polypeptide according to the present invention substantially as hereinbefore described. Preferably, however, a competitor as employed in the present invention comprises a monoclonal, recombinant or polyclonal antibody (especially a monoclonal antibody), capable of competing with TSH receptor autoantibodies in the interaction thereof with a polypeptide according to the present invention substantially as hereinbefore described.

Typically, therefore, a competitive assay method according to the present invention may further comprise providing at least one competitor, such as a monoclonal or polyclonal antibody, whereby in step (b) of a method as herein described a polypeptide according to the present invention substantially as hereinbefore described can interact with either a competitor, such as a monoclonal or polyclonal antibody, or autoantibodies to a TSH receptor present in said sample.

Typically monitoring in a competitive assay method according to the present invention comprises comparing:

(i) interaction of a polypeptide according to the present invention substantially as hereinbefore described and one or more competitors substantially as hereinbefore described (typically a monoclonal or polyclonal antibody), in the absence of said sample of body fluid being screened (that is a suspected disease sample), optionally in the presence of a sample of body fluid from a normal subject, typically a subject known to be without autoimmune disease associated with an immune reaction to a TSH receptor; with

(ii) interaction of a polypeptide according to the present invention substantially as hereinbefore described and one or more competitors substantially as hereinbefore described (typically a monoclonal or polyclonal antibody), in the presence of said sample of body fluid being screened.

Typically, the comparison involves observing a decrease in interaction of a polypeptide according to the present invention substantially as hereinbefore described and the competitor in (ii) compared to (i) so as to provide an indication of the presence of autoantibodies to a TSH receptor in said sample. Typically, the decrease in interaction can be observed by directly or indirectly labelling the competitor and monitoring any change in the interaction of the thus labelled competitor with a polypeptide according to the present invention substantially as hereinbefore described in the absence and in the presence of a sample of body fluid being screened for autoantibodies to a TSH receptor. Suitably a polypeptide according to the present invention substantially as hereinbefore described may be immobilised to facilitate the above mentioned monitoring.

Alternatively, there is also provided by the present invention a method of screening for autoantibodies to a TSH receptor in a sample of body fluid obtained from a subject (in particular a human) suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) contacting said sample with

(i) a full length TSH receptor (typically a recombinantly obtained full length TSH receptor), and

(ii) at least one competitor capable of competing with autoantibodies to a TSH receptor in the interaction

thereof with a polypeptide according to the present invention substantially as hereinbefore described,

(suitably under conditions that allow interaction of a TSH receptor with autoantibodies to a TSH receptor), so as to permit said fill length TSH receptor to interact with either autoantibodies to a TSH receptor present in said sample, or said competitor; and

(c) monitoring the interaction of said full length TSH receptor with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample.

The full length TSH receptor can typically be of human, porcine, bovine, canine, feline, mouse, rat or ovine origin and more preferably a recombinantly obtained full length TSH receptor. A competitor for use in such an assay typically comprises a monoclonal or polyclonal antibody (preferably monoclonal) substantially as hereinbefore described.

Suitably a detectable label that can be employed in a method according to the present invention can be selected from the group consisting of enzymic labels, isotopic labels, chemiluminescent labels, fluorescent labels, dyes and the like.

In the case where an isotopic label (such as ^{125}I, ^{14}C, ^{3}H or ^{35}S) is employed, monitoring may therefore comprise measuring radioactivity dependent on binding of a polypeptide according to the present invention substantially as hereinbefore described. Radioactivity is generally measured using a gamma counter, or liquid scintillation counter.

In the case of a method of screening for lymphocytes according to the present invention, it is generally preferred that lymphocytes are initially isolated from a sample of body fluid from a subject using techniques well known to one of ordinary skill in the art, followed by contact with a polypeptide according to the present invention so as to stimulate the proliferation of the isolated lymphocytes. Monitoring of the effect of interaction of a polypeptide according to the present invention and such proliferating lymphocytes, typically employs means known in the art for monitoring such proliferation of lymphocytes.

According to a further particularly preferred embodiment of the present invention, there is provided a kit for screening for autoantibodies or lymphocytes produced in response to a TSH receptor in a sample of body fluid obtained from a subject (in particular a human) suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said kit comprising:

(a) a polypeptide according to the present invention substantially as hereinbefore described;

(b) means for contacting either (i) a sample of body fluid obtained from said subject, or (ii) lymphocytes isolated from a sample of body fluid obtained from said subject, with said polypeptide according to the present invention substantially as hereinbefore described (suitably under conditions that allow interaction of a TSH receptor with autoantibodies or lymphocytes produced in response to a TSH receptor) so as to permit said polypeptide to interact with autoantibodies, or lymphocytes, produced in response to a TSH receptor, and present in, or isolated from, said sample; and

(c) means for monitoring the degree, or effect, of interaction of said polypeptide with either said autoantibodies, or said lymphocytes, produced in response to a TSH receptor and present in, or isolated from, said sample, thereby providing an indication of the presence of said autoantibodies, or lymphocytes, in said sample or isolated from said sample.

Substantially as described above, a kit according to the present invention is suitable for screening for autoantibodies or lymphocytes produced in response to a TSH receptor in a sample of body fluid obtained from a subject. A kit according to the present invention can, however, be particularly adapted for use in screening for autoantibodies produced in response to a TSH receptor in a sample of body fluid obtained from a subject substantially as hereinafter described in greater detail.

There is in particular provided by the present invention, therefore, a kit for screening for autoantibodies produced in response to a TSH receptor in a sample of body fluid obtained from a subject (in particular a human) suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said kit comprising:

(a) a polypeptide according to the present invention substantially as hereinbefore described;

(b) means for contacting a sample of body fluid obtained from said subject with said polypeptide according to the present invention substantially as hereinbefore described (suitably under conditions that allow interaction of a TSH receptor with autoantibodies produced in response to a TSH receptor) so as to permit said polypeptide to interact with autoantibodies produced in response to a TSH receptor and present in said sample; and

(c) means for monitoring the degree of interaction of said polypeptide with said autoantibodies produced in response to a TSH receptor and present in said sample, thereby providing an indication of the presence of said autoantibodies in said sample.

A kit according to the present invention may typically further comprise control means, such as means for providing a sample of body fluid from a normal subject, in other words a subject known to be without autoimmune disease associated with an immune reaction to a TSH receptor.

A kit for screening for autoantibodies to a TSH receptor according to the present invention may comprise means for directly monitoring interaction of (i) autoantibodies to a TSH receptor present in the sample of body fluid from the subject and (ii) a polypeptide, as provided by the present invention substantially as hereinbefore described, typically comprising non-competitive sandwich type assay means known in the art.

Typically, in a kit according to the present invention comprising non-competitive assay means, means are provided for monitoring the degree of interaction of (i) autoantibodies to a TSH receptor present in the sample and (ii) a polypeptide according to the present invention substantially as hereinbefore described, and can comprise labelling means provided either to a polypeptide according to the present invention substantially as hereinbefore described, or to a binding partner for autoantibodies to a TSH receptor, either of which would enable monitoring of the above described interaction. For example, a kit according to the present invention may comprise means for directly or indirectly labelling a polypeptide according to the present invention substantially as hereinbefore described; means for contacting the thus labelled polypeptide with a sample of body fluid being screened for a TSH receptor autoantibodies so as to provide a mixture thereof; a binding partner for autoantibodies to a TSH receptor (such as an anti -Ig reagent) present in the sample of body fluid; and means for adding the binding partner to the mixture so as to cause precipitation of any complexes of labelled polypeptide and TSH receptor autoantibodies present in the mixture. Alternatively, it may be preferred that a kit according to the present invention further comprises a labelled binding partner for TSH receptor autoantibodies (such as a labelled anti-IgG reagent, for example protein A or anti-human IgG, or

labelled full length a TSH receptor or an epitope thereof) and means for adding the labelled binding partner to a mixture obtained by contacting (i) a polypeptide according to the present invention substantially as hereinbefore described immobilised to a support and (ii) a sample of body fluid being screened for autoantibodies to a TSH receptor.

It may alternatively be preferred that a kit for screening for autoantibodies to a TSH receptor in the sample of body fluid according to the present invention, comprises known competitive assay means. For example, a kit according to the present invention may further comprise at least one competitor capable of competing with autoantibodies to a TSH receptor in the interaction thereof with a polypeptide according to the present invention substantially as hereinbefore described.

Typically, a competitor as employed in a competitive assay kit according to the present invention may comprise one or more antibodies, which may be natural or partly or wholly synthetically produced. A competitor as employed in the present invention may alternatively comprise any other protein having a binding domain or region which is capable of competing with autoantibodies to a TSH receptor in the interaction thereof with a polypeptide according to the present invention substantially as hereinbefore described. Preferably, however, a competitor as employed in the present invention comprises a monoclonal or polyclonal antibody (especially a monoclonal antibody), capable of competing with TSH receptor autoantibodies in the interaction thereof with a polypeptide according to the present invention substantially as hereinbefore described.

Typically, therefore, a competitive assay kit according to the present invention may further comprise at least one competitor, such as a monoclonal or polyclonal antibody, whereby a polypeptide according to the present invention substantially as hereinbefore described can interact with either a competitor, such as a monoclonal or polyclonal antibody, or autoantibodies to a TSH receptor present in a sample of body fluid being screened.

Typically monitoring means in a competitive assay kit according to the present invention comprise means for comparing:

(i) interaction of a polypeptide according to the present invention substantially as hereinbefore described and one or more competitors substantially as hereinbefore described (typically a monoclonal or polyclonal antibody), in the absence of said sample of body fluid being screened (that is a suspected disease sample), optionally in the presence of a sample of body fluid from a normal subject, typically a subject known to be without autoimmune disease associated with an immune reaction to a TSH receptor; with

(ii) interaction of a polypeptide according to the present invention substantially as hereinbefore described and one or more competitors substantially as hereinbefore described (typically a monoclonal or polyclonal antibody), in the presence of said sample of body fluid being screened.

Typically, the comparison involves observing a decrease in interaction of a polypeptide according to the present invention substantially as hereinbefore described and the competitor in (ii) compared to (i) so as to provide an indication of the presence of autoantibodies to a TSH receptor in said sample. Typically, the decrease in interaction can be observed by directly or indirectly labelling the competitor and monitoring any change in the interaction of the thus labelled competitor with a polypeptide according to the present invention substantially as hereinbefore described in the absence and in the presence of a sample of body fluid being screened for autoantibodies to a TSH receptor. Suitably a polypeptide according to the present invention substantially as hereinbefore described may be immobilised to facilitate the above mentioned monitoring.

Alternatively, there is also provided by the present invention a kit for screening for autoantibodies to a TSH receptor in a sample of body fluid obtained from a subject (in particular a human) suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said kit comprising:

(a) a fill length TSH receptor (typically a recombinantly obtained full length TSH receptor);

(b) at least one competitor capable of competing with autoantibodies to a TSH receptor in the interaction thereof with a polypeptide according to the present invention substantially as hereinbefore described,

(c) means for contacting said sample of body fluid from said subject, said fall length TSH receptor and said competitor (suitably under conditions that allow interaction of a TSH receptor with autoantibodies to a TSH receptor), so as to permit said full length TSH receptor to interact with either autoantibodies to a TSH receptor present in said sample, or said competitor; and

(d) means for monitoring the interaction of said full length TSH receptor with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample.

The full length TSH receptor can typically be of human, porcine, bovine, canine, feline, mouse, rat or ovine origin and more preferably a recombinantly obtained full length TSH receptor. A competitor for use in such an assay kit typically comprises a monoclonal or polyclonal antibody (preferably monoclonal) substantially as hereinbefore described.

Suitably a detectable label that can be employed in a kit according to the present invention can be selected from the group consisting of enzymic labels, isotopic labels, chemiluminescent labels, fluorescent labels, dyes and the like.

In the case where an isotopic label (such as ^{125}I, ^{14}C, ^{3}H or ^{35}S) is employed, monitoring means may therefore comprise means for measuring radioactivity dependent on binding of a polypeptide according to the present invention substantially as hereinbefore described. Radioactivity is generally measured using a gamma counter, or liquid scintillation counter.

In the case of a kit for screening for lymphocytes according to the present invention, it is generally preferred hat means are provided for initially isolating lymphocytes from a sample of body fluid from a subject, using techniques well known to one of ordinary skill in the art, and means are also provided for contacting a polypeptide according to the present invention with such isolated lymphocytes so as to stimulate proliferation of the latter by the former. Means (again known to one of ordinary skill in the art) for monitoring the effect of interaction of a polypeptide according to the present invention and such proliferating lymphocytes, are also provided in such a kit according to the present invention.

It will be appreciated from the foregoing description that the present invention provides assay methods and kits for detecting autoantibodies (in particular) or lymphocytes produced in response to a TSH receptor in a sample of body fluid substantially as hereinbefore described. The detection of such autoantibodies and/or lymphocytes produced in response to a TSH receptor in the sample of body fluid (or at least the level of such autoantibodies and/or lymphocytes in the sample) is indicative of the presence of autoimmune disease associated with an immune reaction to a TSH receptor in the subject from which the sample was obtained and can, therefore,

enable the diagnosis of the likely onset or presence of autoimmune disease associated with an immune reaction to a TSH receptor.

There is, therefore, further provided by the present invention a method of diagnosing the likely onset or presence of autoimmune disease associated with an immune reaction to a TSH receptor in a subject (in particular a human) suspected of suffering from, susceptible to, having or recovering from, autoimmune disease associated with an immune reaction to a TSH receptor, the method comprising detecting autoantibodies or lymphocytes produced in response to a TSH receptor in a sample of body fluid from the subject substantially as hereinbefore described, and whereby the detected autoantibodies and/or lymphocytes can provide a diagnosis of the likely onset or presence of autoimmune disease associated with an immune reaction to a TSH receptor in the subject.

There is still further provided by the present invention a method of delaying or preventing the onset of autoimmune disease associated with an immune reaction to a TSH receptor in an animal subject (in particular a human subject) suspected of suffering from, susceptible to or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, which method comprises initially detecting autoantibodies or lymphocytes indicative of the onset or presence of autoimmune disease associated with an immune reaction to a TSH receptor in a sample of body fluid obtained from the subject substantially as hereinbefore described, thereby providing a diagnosis of the likely onset of autoimmune disease associated with an immune reaction to a TSH receptor in the subject, and thereafter therapeutically treating the subject so as to delay the onset and/or prevent autoimmune disease associated with an immune reaction to a TSH receptor.

A polypeptide according to the present invention substantially as hereinbefore described is particularly suitable for use in the therapeutic treatment of autoimmune disease associated with an immune reaction to a TSH receptor. For example, tolerance can be achieved by administering a polypeptide according to the present invention substantially as hereinbefore described to a subject (in particular a human subject) suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor.

There is, therefore, further provided by the present invention a pharmaceutical composition comprising a polypeptide according to the present invention substantially as hereinbefore described, together with a pharmaceutically acceptable carrier, diluent or excipient therefor, wherein the polypeptide can interact with autoantibodies and/or lymphocytes produced in response to a TSH receptor.

The present invention further provides a polypeptide according to the present invention substantially as hereinbefore described for use in the manufacture of a medicament for the treatment of Graves' disease.

Compositions or medicaments according to the present invention should contain a therapeutic or prophylactic amount of at least one polypeptide according to the present invention in a pharmacoutically-acceptable carrier. The pharmaceuctical carrier can be any compatible, non-toxic substance suitable for delivery of the polypeptides to the patient. Sterile water, alcohol, fats, waxes, and inert solids may be used as the carrier. Pharmaceutically-acceptable adjuvants, buffering agents, dispersing agents and the like, may also be incorporated into the pharmaceutical compositions. Such compositions can contain a single polypeptide or may contain two or more polypeptides according to the present invention.

It may be desirable to couple a polypeptide according to the present invention to immunoglobulins, e.g. IgG, or to lymphoid cells from the patient being treated in order to promote tolerance. Such an approach is described in Bradley-Mullen, *Activation of Distinct Subsets of T Suppressor Cells with Type III Pneumococcal Polysaccharide Coupled to Syngeneic Spleen Cells*, in: IMMUNOLOGICAL TOLERANCE TO SELF AND NON-SELF, Buttisto et al., eds., Annals N.Y. Acad. Sci. Vol. 392, pp 156-166, 1982. Alternatively, the polypeptides may be modified to maintain or enhance binding to the MHC while reducing or eliminating binding to the associated T-cell receptor. In this way, the modified polypeptides may compete with natural a TSH receptor to inhibit helper T-cell activation and thus inhibit the immune response. In all cases, care should be taken that administration of the pharmaceutical compositions of the present invention ameliorate but do not potentiate the autoimmune response.

Pharmaceutical compositions according to the present invention are useful for parenteral administration. Preferably, the compositions will be administered parenterally, i.e. subcutaneously, intramuscularly, or intravenously. Thus, the invention provides compositions for parenteral administration to a patient, where the compositions comprise a solution or dispersion of the polypeptides in an acceptable carrier, as described above. The concentration of the polypeptides in the pharmaceutical composition can vary widely, i.e. from less than about 0.1% by weight, usually being at least about 1% by weight to as much as 20% by weight or more. Typical pharmaceutical compositions for intramuscular injection would be made up to contain, for example, 1 ml of sterile buffered water and 1 to 100 μg of a purified polypeptide of the present invention. A typical composition for intravenous infusion could be made up to contain 100 to 500 ml of sterile Ringer's solution and 100 to 500 mg of a purified polypeptide of the present invention. Actual methods for preparing parenterally administrable compositions are well known in the art and described in more detail in various sources, including, for example, *Remington's Pharmaceutical Science,* 15th Edition, Mack Publishing Company, Easton, Pa. (1980).

In addition to using a polypeptide according to the present invention directly in pharmaceutical compositions, it is also possible to use a polypeptide according to the present invention to enhance tolerance to a TSH receptor in a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, employing the following principles. More particularly, peripheral blood lymphocytes can be collected from the subject in a conventional manner and stimulated by exposure to a polypeptide according to the present invention, as defined above. Usually, other mitogens and growth enhancers will be present, e.g., phytohemagglutinin, interleukin 2, and the like. Proliferating T-helper cells may be isolated and cloned, also under the stimulation of a polypeptide according to the present invention. Clones which continue to proliferate may then be used to prepare therapeutic compositions for the subject. The cloned T-cells may be attenuated, e.g. by exposure to radiation, and administered to the subject in order to induce tolerance. Alternatively, the T-cell receptor or portions thereof may be isolated by conventional protein purification methods from the cloned T-cells and administered to the individual.

Such immunotherapy methods are described generally in Sinha et al. (1990) *Science* 248:1380-1388.

In some cases, after a T-helper cell has been cloned as described above, it may be possible to develop therapeutic peptides from the T-cell receptor, where the peptides would be beneficial for treating a patient population suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a

TSH receptor. In such cases, the T-cell receptor gene may be isolated and cloned by conventional techniques and peptides based on the receptor produced by recombinant techniques as described above. The recombinantly-produced peptides may then be incorporated in pharmaceutical compositions as described above.

There is also provided by the present invention a method of cloning lymphocytes produced in response to a TSH receptor, which method comprises:

providing a source of lymphocytes;

contacting the lymphocytes with a polypeptide according to the present invention substantially as hereinbefore described, so as to effect proliferation of said lymphocytes; and

isolating and cloning the proliferating lymphocytes.

The present invention also provides the use of cloned lymphocytes prepared as above, in the therapeutic treatment of autoimmune disease associated with an immune reaction to a TSH receptor. There is provided, therefore, a pharmaceutical composition comprising cloned lymphocytes prepared as above, together with a pharmaceutically acceptable carrier, diluent or excipient therefor and the use of such cloned lymphocytes in the manufacture of a medicament for the treatment of autoimmune disease associated with an immune reaction to a TSH receptor, in particular Graves' disease.

There is also provided by the present invention one or more therapeutic agents identified as providing a therapeutic effect by interaction with amino acids comprising part or all of the primary conformation of amino acids of one or more epitopes of a TSH receptor substantially as hereinbefore described, and the present invention further provides one or more therapeutic agents for use in therapeutically interacting with amino acids comprising part or all of the primary conformation of amino acids of one or more epitopes of a TSH receptor substantially as hereinbefore described and as such for use in the therapeutic treatment of an autoimmune disease associated with an immune reaction to a TSH receptor.

There is, therefore, still further provided by the present invention a method of treating autoimmune disease associated with an immune reaction to a TSH receptor in a subject, which method comprises initially detecting autoantibodies or lymphocytes produced in response to a TSH receptor in a sample of body fluid obtained from the subject substantially as hereinbefore described, thereby providing a diagnosis of autoimmune disease in the subject, and administering to the subject a therapeutically effective amount of at least one therapeutic agent effective in the treatment of such autoimmune disease, such as a polypeptide according to the present invention substantially as hereinbefore described.

The present invention also provides a method of treating autoimmune disease associated with an immune reaction to a TSH receptor in a subject (in particular a human subject), which method comprises administering to the subject a therapeutically effective amount of a therapeutic agent identified as providing a therapeutic effect by interaction with amino acids comprising part or all of the primary conformation of amino acids of one or more epitopes of a TSH receptor substantially as hereinbefore described

The amount of therapeutic agent administered will depend on the specific autoimmune disease state being treated, possibly the age of the patient and will ultimately be at the discretion of an attendant physician.

There is still further provided by the present invention, in combination, a kit substantially as hereinbefore described, together with a therapeutically effective amount of at least one therapeutic agent effective in the treatment of autoimmune disease associated with an immune reaction to a TSH receptor substantially as hereinbefore described.

Substantially as hereinbefore described, the sample of body fluid being screened by the present invention will typically comprise blood samples or other fluid blood fractions, such as in particular serum samples or plasma samples, but the sample may in principle be another biological fluid, such as saliva or urine or solubilised tissue extracts, or may be obtained by needle biopsy.

There is still further provided by the present invention a binding partner for a TSH receptor, such as an antibody to a TSH receptor, or a fragment of an antibody to a TSH receptor, which binding partner can interact with one or more epitopes to a TSH receptor substantially as hereinbefore described, in particular amino acid numbers 277 to 296 of a TSH receptor. Suitably, antibodies provided by the present invention can be monoclonal (preferred), recombinant or polyclonal. Typically an antibody, such as a monoclonal antibody, as provided by the present invention is in substantially purified form.

More specifically, a monoclonal antibody as provided by the present invention can comprise any of monoclonal antibodies 3C7, 2B4, 8E2, 18C5, 4D7, 16E5, 17D2, 3B3 and 14D3 or active fragments thereof, as described in the Examples and further illustrated by the accompanying Figures. Antibodies such as 2B4, 8E2, 1I8C5, 4D7, 16E5, 17D2, 3B3 and 14D3, or active fragments thereof, as described in the Examples preferably have a high affinity for a TSH receptor, such as at least about $10^8 molar^{-1}$. There is, therefore, further provided by the present invention a monoclonal antibody having an affinity of at least about $10^8 molar^{-1}$ for one or more epitopes of a TSH receptor and which epitope is provided by any one of the following amino acid sequences of a TSH receptor:

amino acids 22 to 91 of a TSH receptor; or

amino acids 246 to 260 of a TSH receptor;

or more particularly, consists essentially of any one of the following amino acid sequences of a TSH receptor:

amino acids 36 to 42 of a TSH receptor; or

amino acids 247 to 260 of a TSH receptor.

There is also provided by the present invention a monoclonal antibody having an affinity of at least about $10^8 molar^{-1}$ for one or more epitopes of a TSH receptor and which epitope is provided by any one of the following amino acid sequences of a TSH receptor:

amino acids 32 to 41 of a TSH receptor; or

amino acids 277 to 296 of a TSH receptor.

According to a particularly preferred embodiment of the present invention there is provided a binding partner for a TSH receptor, which binding partner is capable of binding to a TSH receptor so as to stimulate the TSH receptor, which binding partner does not comprise TSH or naturally produced autoantibodies to the TSH receptor.

Preferably the binding partner comprises an antibody, in particular a monoclonal or recombinant (preferably monoclonal) antibody, capable of binding to a TSH receptor so as to stimulate the TSH receptor. Examples of monoclonal antibodies disclosed herein which stimulate a TSH receptor in this way include 4D7, 16E5, 17D2 and 14D3.

In a preferred case the present invention provides a binding partner for a TSH receptor, which binding partner is capable of binding to the TSH receptor so as to stimulate the TSH receptor and which comprises:

an antibody V_H domain selected from the group consisting of:

V_H domains as shown in any one of FIGS. **10**, **14**, **18**, **22**, **42**, **46** or **50**, a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **10**, a V_H domain comprising

one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **14**, a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **18**, a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **22**, a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **42**, a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **46**, and a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **50**; and/or

an antibody V_L domain selected from the group consisting of: V_L domains as shown in any one of FIGS. **12**, **16**, **20**, **24**, **44**, **48** or **52**, a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **12**, a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **16**, a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **20**, a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **24**, a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **44**, a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **48**, and a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **52**.

It may be preferred according to the present invention that a binding partner substantially as hereinbefore described comprises an antibody V_H domain substantially as hereinbefore described paired with an antibody V_L domain substantially as hereinbefore described to provide an antibody binding site comprising both V_H and V_L domains for a TSH receptor, although as discussed further an antibody V_H domain, or an antibody V_L domain, may be independently used to bind a TSH receptor. It will be appreciated, therefore, that a binding partner substantially as hereinbefore described can comprise an antibody V_H domain substantially as hereinbefore described in the absence of an antibody V_L domain. It will also be appreciated, therefore, that a binding partner substantially as hereinbefore described can comprise an antibody V_L domain substantially as hereinbefore described in the absence of an antibody V_H domain Alternatively, a binding partner substantially as hereinbefore described can comprise an antibody V_H domain paired with an antibody V_L domain substantially as hereinbefore described to provide an antibody binding site comprising both V_H and V_L domains for a TSH receptor.

Preferred embodiments according to the present invention can thus include a binding partner substantially as hereinbefore described comprising an antibody V_H domain as shown in FIG. **10** paired with an antibody V_L domain as shown in FIG. **12** to provide an antibody binding site, comprising both these V_H and V_L domains for a TSH receptor; or a binding partner substantially as hereinbefore described comprising an antibody V_H domain as shown in FIG. **14** paired with an antibody V_L domain as shown in FIG. **16** to provide an antibody binding site, comprising both these V_H and V_L domains for a TSH receptor; or a binding partner substantially as hereinbefore described comprising an antibody V_H domain as shown in FIG. **18** paired with an antibody V_L domain as shown in FIG. **20** to provide an antibody binding site comprising both these V_H and V_L domains for a TSH receptor; or a binding partner substantially as hereinbefore described comprising an antibody V_H domain as shown in FIG. **22** paired with an antibody V_L domain as shown in FIG. **24** to provide an antibody binding site comprising both V_H and V_L domains for a TSH receptor; or a binding partner substantially as hereinbefore described comprising an antibody V_H domain as shown in FIG. **42** paired with an antibody V_L domain as shown in FIG. **44** to provide an antibody binding site comprising both V_H and V_L domains for a TSH receptor, or a binding partner substantially as hereinbefore described comprising an antibody V_H domain as shown in FIG. **46** paired with an antibody V_L domain as shown in FIG. **48** to provide an antibody binding site comprising both V_H and V_L domains for a TSH receptor, or a binding partner substantially as hereinbefore described comprising an antibody V_H domain as shown in FIG. **50** paired with an antibody V_L domain as shown in FIG. **52** to provide an antibody binding site comprising both V_H and V_L domains for a TSH receptor.

It is further envisaged according to the present invention that V_H domains substantially as hereinbefore described may be paired with V_L domains other than those specifically described herein. It is also further envisaged according to the present invention that V_L domains substantially as hereinbefore described may be paired with V_H domains other than those specifically described herein.

According to an alternative embodiment of the present invention there is provided a binding partner substantially as hereinbefore described for a TSH receptor, which binding partner is capable of binding to the TSH receptor so as to stimulate the TSH receptor and which can comprise:

an antibody V_H domain comprising:

a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **10**, or a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **14**, or a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **18**, or a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **22**, or a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **42**, or a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **46**, or a V_H domain comprising one or more V_H CDRs with an amino acid sequence corresponding to a V_H CDR as shown in FIG. **50**; and/or

an antibody V_L domain comprising:

a V_L domain comprising one or more V_L CDRS with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **12**, or a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **16**, or a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **20**, or a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **24**, or a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **44**, or a V_L domain comprising one or more V_L CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **48**, or a V_L domain comprising one or more V_L

CDRs with an amino acid sequence corresponding to a V_L CDR as shown in FIG. **52**.

One or more CDRs as referred to above may be taken from the hereinbefore described V_H and V_L domains and incorporated into a suitable framework. For example, the amino acid sequence of one or more CDRs substantially as hereinbefore described may be incorporated into framework regions of antibodies differing from those specifically disclosed herein, such antibodies thereby incorporating the one or more CDRs and being capable of binding to the TSH receptor, preferably to stimulate the TSH receptor substantially as hereinbefore described. Alternatively, a binding partner according to the present invention may comprise a polypeptide capable of binding to the TSH receptor so as to stimulate the TSH receptor substantially as hereinbefore described and comprising the primary structural conformation of amino acids as represented by one or more CDRs as specifically described herein, optionally together with further amino acids, which further amino acids may enhance the binding affinity of one or more CDRs as described herein for a TSH receptor or may have substantially no role in affecting the binding properties of the polypeptide for a TSH receptor.

Preferably a binding partner according to the present invention includes an antibody. The term "antibody" as used herein describes an immunoglobulin whether natural or partly or wholly synthetically produced. The term also covers any polypeptide having a binding domain which is, or is substantially homologous to, an antibody binding domain. Examples of antibodies are the immunoglobulin isotypes and their isotypic subclasses and fragments which comprise an antigen binding domain such as Fab, scFv or the like.

In particular, fragments of antibodies specifically as herein described form an important aspect of the present invention. In this way, where a binding partner according to the present invention comprises an antibody substantially as hereinbefore described, the antibody may comprise any of the following fragments: (i) the Fab fragment consisting of V_L, V_H, C_L and C_H1 domains; (ii) the Fd fragment consisting of the V_H and C_H1 domains; (iii) the Fv fragment consisting of the V_L and V_H domains; (iv) the dAb fragment which consists of a V_H domain; (v) isolated CDR regions; (vi) F(ab')2 fragments, a bivalent fragment comprising two linked Fab fragments; and (vii) single chain Fv molecules (scFv), wherein a V_H domain and a V_L domain are linked by a peptide linker which allows the two domains to associate to form an antigen binding site.

Alternatively, in the case where a binding partner according to the present invention comprises an antibody, the antibody may comprise a whole antibody, whereby the antibody includes variable and constant regions, which variable and constant regions can be further illustrated for the antibodies provided by the present invention by reference to any of FIGS. **9** to **24**, or **41** to **52**.

The present invention, also encompasses variants, analogs and derivatives of the specific binding partners, antibodies, V_H domains, V_L domains, CDRs and polypeptides disclosed herein, which variants, analogs and derivatives retain the ability to bind to the TSH receptor so as to stimulate the TSH receptor substantially as hereinbefore described. The terms variants, analogs and derivatives are substantially herein before further described in greater detail with respect to polypeptides according to the present invention and what is meant by these terms as hereinbefore described applies also to variants, analogs and derivatives of the specific binding partners according to the present invention.

The present invention also provides a further binding partner capable of binding to the TSH receptor so as to stimulate the TSH receptor substantially as hereinbefore described, and which further binding partner can compete for binding to the TSH receptor with any specific binding partner disclosed herein, which further binding partner does not comprise TSH or autoantibodies to a TSH receptor. In particular this further binding partner may comprise a further antibody having a binding site for an epitope region of a TSH receptor suitably as hereinbefore described, which further antibody is capable of binding to the TSH receptor so as to stimulate the TSH receptor substantially as hereinbefore described and can compete for binding to the TSH receptor with any specific binding partner disclosed herein.

There is also provided by the present invention a polynucleotide comprising:

(i) a nucleotide sequence as shown in any of FIGS. **25** to **40**, or **53** to **64**; or parts of such sequences as shown in FIGS. **26**, **28**, **30**, **32**, **34**, **36**, **38**, **40**, **54**, **56**, **58**, **60**, **62**, or **64**, encoding an amino acid sequence of an antibody V_H domain, an antibody V_L domain or CDR as shown in any of FIGS. **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **42**, **44**, **46**, **48**, **50** or **52**;

(ii) a nucleotide sequence encoding a binding partner substantially as hereinbefore described, or encoding an amino acid sequence of an antibody V_H domain, an antibody V_L domain or CDR of a binding partner substantially as hereinbefore described;

(iii) a nucleotide sequence encoding a binding partner having a primary structural conformation of amino acids as shown in any of FIGS. **9** to **24** or **41** to **52**, or encoding an amino acid sequence of an antibody V_H domain, an antibody V_L domain or CDR as shown in any of FIGS. **10**, **12**, **14**, **16**, **18**, **20**, **22**, **24**, **42**, **44**, **46**, **48**, **50** or **52**;

(iv) a nucleotide sequence differing from any sequence of (i) in codon sequence due to the degeneracy of the genetic code;

(v) a nucleotide sequence comprising an allelic variation of any sequence of (i);

(vi) a nucleotide sequence comprising a fragment of any of the sequences of (i), (ii), (iii), (iv) or (v), and in particular anucleotide sequence comprising a fragment of any of the sequences of (i), (ii), (iii), (iv) or (v) and encoding a Fab fragment, aFd fragment, a Fv fragment, a dAb fragment, an isolated CDR region, F(ab')2 fragments or a scFv fragment, of a binding partner substantially as hereinbefore described;

(vii) a nucleotide sequence differing from the any sequence of (i) due to mutation, deletion or substitution of a nucleotide base and encoding a binding partner substantially as hereinbefore described, or encoding an amino acid sequence of an antibody V_H domain, an antibody V_L domain or CDR of a binding partner substantially as hereinbefore described.

Variant polynucleotides according to the present invention are suitably at least 70% identical over their entire length to any polynucleotide sequence of (i), most highly preferred are polynucleotides that comprise a region that is at least 80% identical over its entire length to any polynucleotide sequence of (i), polynucleotides at least 90% identical over their entire length to any polynucleotide sequence of (i) are particularly preferred, and among these particularly preferred polynucleotides, those with at least 95% identity are especially preferred. What is meant by variants of specific polynucleotide sequences described herein is hereinbefore described in greater detail.

The present invention further provides a biologically functional vector system which carries a polynucleotide substan-

tially as hereinbefore described and which is capable of introducing the polynucleotide into the genome of a host organism.

The present invention also relates to host cells which are transformed with polynucleotides of the invention and the production of binding partners of the invention by recombinant techniques. Host cells can be genetically engineered to incorporate polynucleotides and express binding partners of the present invention.

A binding partner substantially as hereinbefore described may have diagnostic and therapeutic applications, and may advantageously interact or bind with one or more epitope regions of a TSH receptor substantially as hereinbefore described.

Accordingly, a binding partner substantially as hereinbefore described can be employed in screening methods for detecting autoantibodies substantially as hereinbefore described and also in diagnostic methods substantially as hereinbefore described. In this way, binding partners according to the present invention can be employed in place of competitors hitherto described for use in screening methods for detecting autoantibodies substantially as hereinbefore described and also in diagnostic methods substantially as hereinbefore described. Similarly, binding partners according to the present invention can be employed in place of competitors hitherto described for use in kits for use in detecting autoantibodies substantially as hereinbefore described.

The present invention also provides a method of screening for autoantibodies to a TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) contacting said sample with

(i) a full length TSH receptor, one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSH receptor, and

(ii) one or more binding partners substantially as hereinbefore described;

(suitably under conditions that allow interaction of a TSH receptor with autoantibodies produced in response to a TSH receptor) so as to permit said TSH receptor, said one or more epitopes thereof or said polypeptide, to interact with either autoantibodies to a TSH receptor present in said sample, or said one or more binding partners; and

(c) monitoring the interaction of said TSH receptor, said one or more epitopes thereof or said polypeptide, with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample.

Preferably, a method according to the present invention as referred to above, further comprises providing labelling means for the one or more binding partners, suitable labelling means being substantially as hereinbefore described.

The present invention also provides a method of screening for autoantibodies produced in response to a TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) contacting said sample with

(i) a full length TSH receptor, one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSH receptor, and

(ii) one or more binding members for a TSH receptor;

(suitably under conditions that allow interaction of a TSH receptor with autoantibodies produced in response to a TSH receptor) so as to permit said TSH receptor, said one or more epitopes thereof or said polypeptide, to interact with either autoantibodies to a TSH receptor present in said sample, or said one of more binding members; and

(c) monitoring the interaction of said TSH receptor, said one or more epitopes thereof or said polypeptide, with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample;

wherein said one or more binding members are directly or indirectly immobilised to a surface either prior to, or after step (b).

Typically the one or more binding members comprise one or more binding partners according to the present invention substantially as hereinbefore described. Suitably, labelling means are provided for the TSH receptor, the one or more epitopes thereof or the polypeptide.

The present invention also provides a kit for screening for autoantibodies to a TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said kit comprising:

(a) a full length TSH receptor, one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSH receptor;

(b) one or more binding partners substantially as hereinbefore described;

(c) means for contacting said sample of body fluid from said subject, said TSH receptor, said one or more epitopes thereof or said polypeptide, and said one or more binding partners, (suitably under conditions that allow interaction of a TSH receptor with autoantibodies produced in response to a TSH receptor) so as to permit said TSH receptor, said one or more epitopes thereof or said polypeptide, to interact with either autoantibodies to a TSH receptor present in said sample, or said one or more binding partners; and

(d) means for monitoring the interaction of said TSH receptor, said one or more epitopes thereof or said polypeptide, with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample.

Suitably, a kit as referred to above further comprises labelling means for the one or more binding partners, suitable labelling means being substantially as hereinbefore described.

The present invention also provides a kit for screening for autoantibodies to a TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said kit comprising:

(a) a full length TSH receptor, one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSH receptor;

(b) one or more binding members for a TSH receptor;

(c) means for contacting said sample of body fluid from said subject, said TSH receptor, said one or more epitopes thereof or said polypeptide, and said one or more binding members, (suitably under conditions that allow interaction of a TSH receptor with autoantibodies produced in response to a TSH receptor) so as to permit

said TSH receptor, said one or more epitopes thereof or said polypeptide, to interact with either autoantibodies to a TSH receptor present in said sample, or said one or more binding members;

(d) means for directly or indirectly immobilising said or one or more binding members to a surface, either before or after contacting said one or more binding members with said sample of body fluid from said subject and said TSH receptor, said one or more epitopes thereof or said polypeptide; and

(e) means for monitoring the interaction of said TSH receptor, said one or more epitopes thereof or said polypeptide, with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample.

Typically the one or more binding members comprise one or more binding partners according to the present invention substantially as hereinbefore described. Suitably, labelling means are provided for the TSH receptor, the one or more epitopes thereofor the polypeptide.

Suitably a method or kit as referred to above can employ a polypeptide or epitope according to the present invention substantially as hereinbefore described.

Substantially as hereinbefore described, in the presence of autoantibodies to the TSH receptor, binding of the TSH receptor to the immobilised binding member or binding partner will be decreased. Such a method and kit for screening for autoantibodies to a TSH receptor can be advantageous in alleviating problems that can be associated with TSH receptor when immobilised to a surface.

A binding partner substantially as hereinbefore described can also be usefully employed in therapy. There is, therefore, further provided by the present invention methods of treatment comprising administration of a specific binding partner substantially as hereinbefore described, pharmaceutical compositions comprising a specific binding partner substantially as hereinbefore described (together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor), and use of a specific binding partner substantially as hereinbefore described in the manufacture of a medicament or composition, in particular a medicament or composition for use in stimulating thyroid tissue, and/or tissue containing a TSH receptor. In particular, a specific binding partner according to the present invention can be employed in oncology, and in particular for use in the diagnosis, management and treatment of thyroid cancer.

Pharmaceutical compositions according to the present invention include those suitable for oral, parenteral and topical administration, although the most suitable route will generally depend upon the condition of a patient and the specific disease being treated. The precise amount of a binding partner substantially as hereinbefore described to be administered to a patient will be the responsibility of an attendant physician, although the dose employed will depend upon a number of factors, including the age and sex of the patient, the specific disease being treated and the route of administration substantially as described above.

There is further provided by the present invention a method of stimulating thyroid tissue, and/or tissue containing a TSH receptor, which method comprises administering to a patient in need of such stimulation a diagnostically or therapeutically effective amount of a binding partner substantially as hereinbefore described.

The present invention also provides in combination, a binding partner substantially as hereinbefore described, together with one or more further agents capable of stimulating thyroid tissue, and/or tissue containing a TSH receptor, for simultaneous, separate or sequential use in stimulating thyroid tissue, and/or tissue containing a TSH receptor. Preferably the one or more further agents comprise recombinant human TSH and/or one or more variants, analogs, derivatives or fragments thereof, or variants, analogs or derivatives of such fragments. Alternatively, the one or more further agents can act independently of binding to the TSH receptor.

The following illustrative explanations are provided to facilitate understanding of certain terms used herein. The explanations are provided as a convenience and are not limitative of the invention

BINDING PARTNER, or BINDING MEMBER, FOR A TSH RECEPTOR, describes a molecule having a binding specificity for a TSH receptor. A binding partner or binding member as described herein may be naturally derived or wholly or partially synthetically produced. Such a binding partner or binding member has a domain or region which specifically binds to and is therefore complementary to one or more epitope regions of a TSH receptor.

C DOMAIN denotes a region of relatively constant amino acid sequence in antibody molecules.

CDR denotes complementary determining regions which are present on both heavy and light chains of antibody molecules and represent regions of most sequence variability. CDRs represent approximately 15 to 20% of variable domains and represent antigen binding sites of an antibody.

FR denotes framework regions and represent the remainder of the variable light domains and variable heavy domains not present in CDRs.

HC denotes part of a heavy chain of an antibody molecule comprising the heavy chain variable domain and the first domain of an IgG constant region.

HOST CELL is a cell which has been transformed or transfected, or is capable of transformation or transfection by an exogenous polynucleotide sequence.

IDENTITY, as known in the art, is the relationship between two or more polypeptide sequences, or two or more polynucleotide sequences, as determined by comparing the sequences.

LC denotes a light chain of an antibody molecule.

STIMULATION OF A TSH RECEPTOR by a binding partner or binding member as described herein denotes the ability of the binding partner or binding member to bind to a TSH receptor and to thereby effect, for example, production of cyclic AMP as a result of such binding to the TSH receptor. Such stimulation is analogous to the responses seen on binding of TSHE or TSH receptor autoantbodies, to a TSH receptor and in this way a binding partner or binding member as described herein mimics the effect of TSH, or TSH receptor autoantibody, binding to a TSH receptor.

V DOMAIN denotes a region of highly variable amino acid sequence in antibody molecules.

V_HDOMAIN denotes variable regions or domains in heavy chains of antibody molecules.

V_LDOMAIN denotes variable regions or domains in light chains of antibody molecules.

The present invention will now be illustrated by the following Figures and Examples, which do not limit the scope of the invention in any way.

FIG. **1** lists amino acids 1 to 200 of (in the following order) human (HTSHR.PRO; SEQ ID NO:1), porcine (PTSHR.PRO; SEQ ID NO:2), bovine (BTSHR.PRO; SEQ ID NO:3), feline (CTSHR.PRO; SEQ ID NO:4), canine (DTSHR.PRO; SEQ ID NO:5), mouse (MTSHR.PRO; SEQ ID NO:6), rat (RTSHR.PRO; SEQ ID NO:7) and ovine (STSHRP.PRO;

SEQ ID NO:8) TSH receptors. Majority (SEQ ID NO: 93) represents the consensus sequence.

FIG. **2** lists nucleotide bases 1 to 300 coding for regions of (in the following order) feline (CAT.SEQ; SEQ ID NO:9), bovine (COW.SEQ; SEQ ID NO:10), canine (DOG.SEQ; SEQ ID NO:11), mouse (MOUSE.SEQ; SEQ ID NO:12), porcine (PTSHR.SEQ; SEQ ID NO:13), rat (RAT.SEQ; SEQ ID NO:14), ovine (SHEEP.SEQ; SEQ ID NO:15) and human (HTSHR.SEQ, SEQ ID NO:16) TSH receptors. Majority (SEQ ID NO: 94) represents the consensus sequence.

FIG. **3** lists amino acids 200 to 300 of (in the following order) human (HTSHR.PRO; SEQ ID NO:17), porcine (PTSHR.PRO; SEQ ID NO:18), bovine (BTSHR.PRO; SEQ ID NO:19), feline (CTSHR.PRO; SEQ ID NO:20), canine (DTSHR.PRO; SEQ ID NO:21), mouse (MTSHR.PRO; SEQ ID NO:22), rat (RTSHR.PRO; SEQ ID NO:23) and ovine (STSHRP.PRO; SEQ ID NO:24) TSH receptors. Majority (SEQ ID NO: 95) represents the consensus sequence.

FIG. **4** lists nucleotide bases 700 to 899 coding for regions of (in the following order) feline (CAT.SEQ; SEQ ID NO:25), bovine (COW.SEQ; SEQ ID NO:26), canine (DOG.SEQ; SEQ ID NO:27), mouse (MOUSE.SEQ; SEQ ID NO:28), porcine (PTSHR.SEQ; SEQ ID NO:29), rat (RAT.SEQ; SEQ ID NO:30), ovine (SHEEP.SEQ; SEQ ID NO:31) and human (HTSHR.SEQ; SEQ ID NO:32) TSH receptors. Majority (SEQ ID NO: 96) represents the consensus sequence.

FIG. **5** lists amino acids 250 to 449 of (in the following order) human (HTSHR.PRO; SEQ ID NO:33), porcine (PTSHR.PRO; SEQ ID NO:34), bovine (BTSHR.PRO; SEQ ID NO:35), feline (CTSHR.PRO; SEQ ID NO:36), canine (DTSHR.PRO; SEQ ID NO:37), mouse (MTSHR.PRO; SEQ ID NO:38), rat (RTSHR.PRO; SEQ ID NO:39) and ovine (STSHRP.PRO; SEQ ID NO:40) TSH receptors. Majority (SEQ ID NO: 97) represents the consensus sequence.

FIG. **6** lists nucleotide bases 750 to 1100 coding for regions of (in the following order) feline (CAT.SEQ; SEQ ID NO:41), bovine (COW.SEQ; SEQ ID NO:42), canine (DOG.SEQ; SEQ ID NO:43), mouse (MOUSE.SEQ; SEQ ID NO:44), porcine (PTSHR.SEQ; SEQ ID NO:45), rat (RAT.SEQ; SEQ ID NO:46), ovine (SHEEP.SEQ; SEQ ID NO:47) and human (HTSHR.SEQ; SEQ ID NO:48) TSH receptors. Majority (SEQ ID NO: 98) represents the consensus sequence.

FIG. **7** lists amino acids 350 to 500 of (in the following order) feline, bovine, canine, mouse, porcine, rat, ovine, and human TSH receptor.

FIG. **8** lists nucleotide bases 1100 to 1299 coding for regions of (in the following order) feline (CAT.SEQ; SEQ ID NO:57), bovine (COW.SEQ; SEQ ID NO:58), canine (DOG.SEQ; SEQ ID NO:59), mouse (MOUSE.SEQ; SEQ ID NO:60), porcine (PTSHR.SEQ; SEQ ID NO:61), rat (RAT.SEQ; SEQ ID NO:62), ovine (SHEEP.SEQ; SEQ ID NO:63) and human (HTSHR.SEQ; SEQ ID NO:64) TSH receptors. Majority (SEQ ID NO: 100) represents the consensus sequence.

FIG. **9** lists amino acids of the heavy chain (HC) of 4D7 (SEQ ID NO:65).

FIG. **10** lists amino acids of the heavy chain (HC) of 4D7 (SEQ ID NO:65), showing the variable region or domain (namely amino acid numbers 10 to 115), the CDRs (namely CDR1 amino acid numbers 31 to 35, CDRII amino acid numbers 50 to 66 and CDRIII amino acid numbers 99 to 104) and the constant region or domain (namely amino acid numbers 116 to 200).

FIG. **11** lists amino acids of the light chain (LC) of 4D7 (SEQ ID NO:66).

FIG. **12** lists amino acids of the light chain (LC) of 4D7 (SEQ ID NO:66), showing the variable region or domain (namely amino acid numbers 9 to 111), the CDRs (namely CDR1 amino acid numbers 24 to 38, CDRII amino acid numbers 54 to 60 and CDRIII amino acid numbers 93 to 101) and the constant region or domain (namely amino acids numbers 112 to 211).

FIG. **13** lists amino acids of the heavy chain (HC) of 16E5 (SEO ID NO:67).

FIG. **14** lists amino acids of the heavy chain (HC) of 16E5 (SEQ ID NO:67), showing the variable region or domain (namely amino acid numbers 9 to 120), the CDRs (namely CDR1 amino acid numbers 31 to 35, CDRII amino acid numbers 50 to 66 and CDRIII amino acid numbers 99 to 109) and the constant region or domain (namely amino acid numbers 121 to 205).

FIG. **15** lists amino acids of the light chain (LC) of 16E5 (SEQ ID NO:68).

FIG. **16** lists amino acids of the light chain (LC) of 16E5 (SEQ ID NO:68), showing the variable region or domain (namely amino acid numbers 9 to 107), the CDRs (namely CDR1 amino acid numbers 24 to 34, CDRII amino acid numbers 50 to 56 and CDRIII amino acid numbers 89 to 97) and the constant region or domain (namely amino acids numbers 108 to 207).

FIG. **17** lists amino acids of the heavy chain (HC) of 17D2 (SEQ ID NO:69).

FIG. **18** lists amino acids of the heavy chain (HC) of 17D2 (SEQ ID NO:69), showing the variable region or domain (namely amino acid numbers 9 to 120), the CDRs (namely CDR1 amino acid numbers 31 to 35, CDRII amino acid numbers 50 to 66 and CDRIII amino acid numbers 99 to 109) and the constant region or domain (namely amino acid numbers 121 to 205).

FIG. **19** lists amino acids of the light chain (LC) of 17D2 (SEQ ID NO:70).

FIG. **20** lists amino acids of the light chain (LC) of 17D2 (SEQ ID NO:70), showing the variable region or domain (namely amino acid numbers 9 to 107), the CDRs (namely CDR1 amino acid numbers 24 to 34, CDRII amino acid numbers 50 to 56 and CDRIII amino acid numbers 89 to 97) and the constant region or domain (namely amino acids numbers 108 to 207).

FIG. **21** lists amino acids of the heavy chain (HC) of 14D3 (SEQ ID NO:71).

FIG. **22** lists amino acids of the heavy chain (HC) of 14D3 (SEQ ID NO:71), showing the variable region or domain (namely amino acid numbers 9 to 120), the CDRs (namely CDR1 amino acid numbers 31 to 35, CDRII amino acid numbers 50 to 66 and CDRIII amino acid numbers 99 to 109) and the constant region or domain (namely amino acid numbers 121 to 205).

FIG. **23** lists amino acids of the light chain (LC) of 14D3 (SEQ ID NO:72).

FIG. **24** lists amino acids of the light chain (LC) of 14D3 (SEQ ID NO:72), showing the variable region or domain (namely amino acid numbers 9 to 107), the CDRs (namely CDR1 amino acid numbers 24 to 34, CDRII amino acid numbers 50 to 56 and CDRIII amino acid numbers 89 to 97) and the constant region or domain (namely amino acids numbers 108 to 207).

FIG. **25** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 4D7(SEQ ID NO:73) as shown in FIG. **9**.

FIG. **26** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 4D7 (SEQ ID NO:73) as shown in FIG. **9**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **10**.

FIG. **27** lists nucleotide bases encoding amino acids of the light chain (LC) of 4D7 (SEQ ID NO:74) as shown in FIG. **11**.

FIG. **28** lists nucleotide bases encoding amino acids of the light chain (LC) of 4D7 (SEQ ID NO:74) as shown in FIG. **11**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **12**.

FIG. **29** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 16E5 (SEQ ID NO:75) as shown in FIG. **13**.

FIG. **30** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 16E5 (SEQ ID NO:75) as shown in FIG. **13**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **14**.

FIG. **31** lists nucleotide bases encoding amino acids of the light chain (LC) of 16E5 (SEQ ID NO:76) as shown in FIG. **15**.

FIG. **32** lists nucleotide bases encoding amino acids of the light chain (LC) of 16E5 (SEQ ID NO:76) as shown in FIG. **15**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **16**.

FIG. **33** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 17D2 (SEQ ID NO:77) as shown in FIG. **17**.

FIG. **34** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 17D2 (SEQ ID NO:77) as shown in FIG. **17**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **18**.

FIG. **35** lists nucleotide bases encoding amino acids of the light chain (LC) of 17D2 (SEQ ID NO:78) as shown in FIG. **19**.

FIG. **36** lists nucleotide bases encoding amino acids of the light chain (LC) of 17D2 (SEQ ID NO:78) as shown in FIG. **19**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **20**.

FIG. **37** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 14D3 (SEQ ID NO:79) as shown in FIG. **21**.

FIG. **38** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 14D3 (SEQ ID NO:79) as shown in FIG. **21**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **22**.

FIG. **39** lists nucleotide bases encoding amino acids of the light chain (LC) of 14D3 (SEQ ID NO:80) as shown in FIG. **23**.

FIG. **40** lists nucleotide bases encoding amino acids of the light chain (LC) of 14D3 (SEQ ID NO:80) as shown in FIG. **23**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **24**.

FIG. **41** lists amino acids of the heavy chain (HC) of 3B3 (SEQ ID NO:81).

FIG. **42** lists amino acids of the heavy chain (HC) of 3B3 (SEQ ID NO:81), showing the variable region or domain (namely amino acid numbers 8 to 112), the CDRs (namely CDR1 amino acid numbers 31 to 35, CDRII amino acid numbers 50 to 66 and CDRIII amino acid numbers 99 to 101) and the constant region or domain (namely amino acid numbers 113 to 196).

FIG. **43** lists amino acids of the light chain (LC) of 3B3 (SEQ ID NO:82).

FIG. **44** lists amino acids of the light chain (LC) of 3B3 (SEQ ID NO:82), showing the variable region or domain (namely amino acid numbers 9 to 111), the CDRs (namely CDR1 amino acid numbers 24 to 38, CDRII amino acid numbers 54 to 60 and CDRIII amino acid numbers 93 to 101) and the constant region or domain (namely amino acids numbers 112 to 211).

FIG. **45** lists amino acids of the heavy chain (HC) of 3C7 (SEQ ID NO:83).

FIG. **46** lists amino acids of the heavy chain (HC) of 3C7 (SEQ ID NO:83), showing the variable region or domain (namely amino acid numbers 10 to 115), the CDRs (namely CDR1 amino acid numbers 31 to 35, CDRII amino acid numbers 50 to 66 and CDRIII amino acid numbers 99 to 104) and the constant region or domain (namely amino acid numbers 116 to 200).

FIG. **47** lists amino acids of the light chain (LC) of 3C7 (SEQ ID NO:84).

FIG. **48** lists amino acids of the light chain (LC) of 3C7 (SEQ ID NO:84), showing the variable region or domain (namely amino acid numbers 9 to 111), the CDRs (namely CDR1 amino acid numbers 24 to 38, CDRII amino acid numbers 54 to 60 and CDRIII amino acid numbers 93 to 101) and the constant region or domain (namely amino acids numbers 112 to 211).

FIG. **49** lists amino acids of the heavy chain (HC) of 2B4 (SEQ ID NO:85).

FIG. **50** lists amino acids of the heavy chain (HC) of 2B4 (SEQ ID NO:85), showing the variable region or domain (namely amino acid numbers 9 to 122), the CDRs (namely CDR1 amino acid numbers 31 to 35, CDRII amino acid numbers 50 to 66 and CDRIII amino acid numbers 99 to 111) and the constant region or domain (namely amino acid numbers 123 to 207).

FIG. **51** lists amino acids of the light chain (LC) of 2B4 (SEQ ID NO:86).

FIG. **52** lists amino acids of the light chain (LC) of 2B4 (SEQ ID NO:86), showing the variable region or domain (namely amino acid numbers 9 to 112), the CDRs (namely CDR1 amino acid numbers 24 to 39, CDRII amino acid numbers 78 to 82 and CDRIII amino acid numbers 94 to 102) and the constant region or domain (namely amino acids numbers 113 to 212).

FIG. **53** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 3B3 (SEQ ID NO:87) as shown in FIG. **41**.

FIG. **54** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 3B3 (SEQ ID NO:87) as shown in FIG. **41**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **42**.

FIG. **55** lists nucleotide bases encoding amino acids of the light chain (LC) of 3B3 (SEQ ID NO:88) as shown in FIG. **43**.

FIG. **56** lists nucleotide bases encoding amino acids of the light chain (LC) of 3B3 (SEQ ID NO:88) as shown in FIG. **43**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **44**.

FIG. **57** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 3C7 (SEQ ID NO:89) as shown in FIG. **45**.

FIG. **58** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 3C7 (SEQ ID NO:89) as shown in FIG. **45**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **46**.

FIG. **59** lists nucleotide bases encoding amino acids of the light chain (LC) of 3C7 (SEQ ID NO:90) as shown in FIG. **47**

FIG. **60** lists nucleotide bases encoding amino acids of the light chain (LC) of 3C7 (SEQ ID NO:90) as shown in FIG. **47**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **48**.

FIG. **61** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 2B4 (SEQ ID NO:91) as shown in FIG. **49**.

FIG. **62** lists nucleotide bases encoding amino acids of the heavy chain (HC) of 2B4 (SEQ ID NO:91) as shown in FIG. **49**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **50**.

FIG. **63** lists nucleotide bases encoding amino acids of the light chain (LC) of 2B4 (SEQ ID NO:92) as shown in FIG. **51**.

FIG. **64** lists nucleotide bases encoding amino acids of the light chain (LC) of 2B4 (SEQ ID NO:92) as shown in FIG. **51**, and shows the nucleotide bases encoding the variable region or domain, the CDRs and the constant region or domain as shown in FIG. **52**.

More specifically, the FIGS. **1** to **8** illustrate the following:

FIG. **1** lists amino acids 1 to 200 of TSH receptors in the above mentioned species, which include the following amino acid sequences employed in the present invention:

amino acids 22 to 91 of a TSH receptor,

amino acids 32 to 41 of a TSH receptor, and

amino acids 36 to 42 of a TSH receptor.

FIG. **2** lists nucleotide bases 1 to 300 in the above mentioned species, which include coding regions for the above mentioned amino acid sequences present in FIG. **1**.

FIG. **3** lists amino acids 200 to 300 of TSH receptors in the above mentioned species, which include the following amino acid sequences employed in the present invention:

amino acids 246 to 260 of a TSH receptor, and

amino acids 247 to 260 of a TSH receptor.

FIG. **4** lists nucleotide bases 700 to 899 in the above mentioned species, which include coding regions for the above mentioned amino acid sequences present in FIG. **3**.

FIG. **5** lists amino acids 250 to 449 of TSH receptors in the above mentioned species, which include the following amino acid sequences employed in the present invention:

amino acids 260 to 363 of a TSH receptor; and

amino acids 277 to 296 of a TSH receptor.

FIG. **6** lists nucleotide bases 750 to 1100 in the above mentioned species, which include coding regions for the above mentioned amino acid sequences present in FIG. **5**.

FIG. **7** lists amino acids 350 to 500 of TSH receptors in the above mentioned species, which include the following amino acid sequences employed in the present invention:

amino acids 380 to 418 of a TSH receptor; and

amino acids 381 to 385 of a TSH receptor.

FIG. **8** lists nucleotide bases 1100 to 1299 in the above mentioned species, which include coding regions for the above mentioned amino acid sequences present in FIG. **7**.

EXAMPLE 1

(1) Production of Mouse Monoclonal Antibodies to the TSH Receptor

BALB/c mice were immunised with a recombinant, highly purified mature form of the TSH receptor expressed in CHO cells. [Y Oda, J Sanders, M Evans, A Kiddie, A Munkley, C James, T Richards, J Wills, J Furmaniak, B Rees Smith "Epitope analysis of the human thyrotrophin (TSH) receptor using monoclonal antibodies." Thyroid 2000 10(12): 1051-1059.] Mouse antibodies were also raised by DNA immunization technique with full length human TSHR cDNA cloned in pcDNA3.1. MAbs were cloned using standard techniques and IgGs were purified from culture supernatants by affinity chromatography on Protein A Sepharose. The reactivity of MAbs with the TSH receptor was tested by (a) Western blotting with partially purified receptors, (b) inhibition of TSH binding to the TSH receptor, and (c) immunoprecipitation of ^{35}S-labelled TSH receptors produced in an in vitro transcription/translation system as described in Y Oda, J Sanders, S Roberts, M Maruyama, R Kato, M Perez, V B Peteresen, N Wedlock, J Furmaniak, B Rees Smith "Binding characteristics of antibodies to the TSH receptor." Journal of Molecular Endocrinology 1998 20: 233-244.

(2) Inhibition of ^{125}I-TSH Binding to the TSH Receptor

The inhibition of ^{125}I-TSH binding to the TSH receptor was analysed in an assay where, 50 μL of detergent solubilised TSH receptor was preincubated with 50 μL of MAb purified as described in step (1) for 15 minutes at room temperature before addition of 100 μL of ^{125}I-TSH (30,000cpm) followed by incubation at 37° C. for one hour. The complexes of ^{125}I-TSH/TSH receptor were precipitated by addition of 2 mL 16.5% polyethylene glycol and 25 μL healthy blood donor serum, centrifuged at 1500×g for 30 minutes at 4° C., aspirated and the radioactivity of the pellets counted using known techniques.

MAbs termed: 2B4 MAb (at IgG concentration of 5 μg/mL), 8E2 Mab (at IgG concentration of 1 μg/mL;) and 18C5 Mab (at IgG concentration 1 mg/mL) showed 76%, 38% and 91% inhibition of TSH binding, respectively. Fab fragments were produced from 2B4 Mab, 8E2 Mab and 18C5 Mab IgGs by digestion with L-cysteine/papain or pepsin, followed by the separation of Fc and Fab on Protein A column.

(3) Epitone Recognition by MAbs

Western blotting analysis [Y Oda, J Sanders, M Evans, A Kiddie, A Munildey, C Jaines, T Richards, J Wills, J FuOmniak, B Rees Smith "Epitope analysis of the human thyrotrophin (TSH) rector using monoclonal antibodies." Thyroid 2000 10(12): 1051-1059.] showed that 2B4 MAb bound to an epitope between amino acid (aa) 380 and 418, 8E2 MAb to an epitope between aa 22 and 91 and 18C5 MAb to an epitope between aa 246 and 260 of the TSH receptor sequence. Analysis with overlapping TSH receptor peptides covering these regions [Y Oda, J Sanders, M Evans, A Kiddie, A Munkley, C James, T Richards, J Wills, J Furmnaniak, B Rees Smith "Epitope analysis of the human thyrotrophin (TSH) receptor using monoclonal antibodies." Thyroid 2000 10(12): 1051-1059.] showed that 2B4 MAb reacted with the aa 381 to 385, 8E2 MAb with the aa 36 to 42 and 18C5 MAb with the aa 247 to 260.

(4) Preparation of ^{125}I-Labelled TSH Receptor

Solubilised preparations of TSH receptor were labelled with ^{125}I by way of ^{125}I-labelled MAB (4E31) reactive with the C-terminal end of the TSH receptor prepared as described in J Sanders, Y Oda, S Roberts, A Kiddie, T Richards, J Bolton, V McGrath, S Walters, D Jaskólski, J Furmaniak, B Rees Smith "The interaction of TSH receptor autoantibodies with ^{125}I-labelled TSH receptor." Journal of Clinical Endocrinology and Metabolism 1999 84(10):3797-3802. Aliquots of ^{125}I-labelled 4E31 F(ab)$_2$ were incubated for 15 minutes at room temperature with solubilised TSH receptor and then used an immunoprecipitation assay as described in step (5).

(5) Inhibition of TSH Receptor Autoantibody (TRAb) Binding to the TSH Receptor by MAbs

The inhibition of TRAb binding to the TSH receptor by MAbs was tested as follows:

10 μL of ^{125}I-labelled TSH receptor (30,000 cpm) prepared in step (4) was preincubated with 20 μL of 2B4 Fab (5 and 10 mg/mL) for 15 minutes at room temperature followed by incubation with 20 μL of TRAb positive patient serum for one hour at room temperature. 50 μL of solid phase Protein A (an anti-human IgG reagent) was then added and incubation continued for one hour at room temperature followed by washing step and centrifugation at 1500×g at 4° C. for 30 minutes; aspiration and counting of the radioactivity of the pellets. Similar experiments were carried out with 8E2 and 18C5 Fabs and the combination of two Fabs together.

Results of Example 1

Results of the inhibition of TRAb binding to the TSH receptor are shown in Table 1.

EXAMPLE 2

Methods

(1) Production of Mouse Monoclonal Antibodies to the TSH Receptor

BALB/C mice were immunised with a recombinant, highly purified mature form of the TSH receptor expressed in CHO cells (Y. Oda, J. Sanders, M. Evans, A. Kiddie, A. Munldey, C. James, T. Richards, J. Wills, J. Furmaniak, B. Rees Smith "Epitope analysis of the human thyrotropin (TSH) receptor using monoclonal antibodies" Thyroid 2000 10(12):1051-1059). Mouse antibodies were also raised by DNA immunisation techniques with full length human TSHR cDNA cloned in pRC/CM.1. MAbs were cloned using standard techniques and IgGs were purified from culture supernatants by affinity chromatography on Protein A Sepharose.

$(Fab)_2$ fragments were produced from the purified MAb IgGs by digestion with pepsin followed by chromatography on a protein A affinity column as described in Y. Oda, J. Sanders, S. Roberts, M. Maruyama, R P Kato, M. Perez, V B Petersen, N. Wedlock, J. Furmaniak, B. Rees Smith 1998 "Binding characteristics of antibodies to the TSH receptor". Journal of Molecular Endocrinology 20: 233-244.

Fab fragments were prepared by digestion of the purified MAbs with papain as described in E. Hendry, G. Taylor, F. Grennan-Jones, A. Sullivan, N. Liddy, J. Godfrey, N. Hayakawa, M. Powell J. Furmaniak, B Rees Smith 2001 "X-ray crystal structure of a monoclonal antibody that binds to a major autoantigenic epitope on thyroid peroxidase." Thyroid 11(12): 1091-1099.

The reactivity of MAbs with the TSH receptor was tested by (a) western blotting with partially purified receptors, (b) inhibition of the TSH binding to the TSH receptor and (c) immunoprecipitation of ^{35}S-labelled TSH receptors produced in an in vitro transcription/translation system as described in Y. Oda, J. Sanders, S. Roberts, M. Maruyama, R. Kato, M. Perez, V B. Petersen, N. Wedlock, J. Furmaniak, B. Rees Smith "Binding characteristics of antibodies to the TSH receptor" Journal of Molecular Endocrinology 1998 20: 233-244.

(2) Inhibition of ^{125}I TSH Binding to the TSH Receptor

(a) PEG Method for Use with Detergent Solubilised TSHR

The inhibition of ^{125}I TSH binding to detergent solubilised TSH receptor was analysed in an assay where 50 μl of MAb purified as described in Methods (1) above was preincubated with receptor for 15 minutes at room temperature before addition of 100 μl of ^{125}I TSH (30,000 cpm) followed by incubation at 37° C. for one hour. The complexes of ^{125}I TSH and TSH receptor were precipitated by addition of 2 mL 16.5% polyethylene glycol and 25 μL healthy blood donor serum, centrifuged at 1500×g for 30 minutes at 4° C., aspirated and the radioactivity of the pellets counted in a gamma counter.

(b) Method Using Tubes Coated with TSHR

In this procedure, plastic tubes are first coated with a MAb such as 4E31 which binds to a part of the TSHR unrelated to TSH or TRAb binding. Detergent solubilised TSHR preparations are then added, captured by the TSHR MAb and then become immobilised on the tube surface in such a way as to be able to bind TSH or TRAb. In particular the MAb 4E31 reactive with the TSHR C terminus (10 μg/mL $F(ab)_2$ preparation in 0.1 M Na_2CO_3 pH 9.2) was added to plastic tubes (Nunc Maxisorp, 200 μL per tube) and coating allowed to proceed overnight 4° C. After washing and post-coating (10 mg/mL bovine serum albumin) the tubes were washed again with assay buffer (10 mM Tris-HCl pH 7.8, 50 mM NaCl, 1 mg/mL bovine serum albumin, 0.1% Triton X-100). 200 μL of a detergent solubilised TSHR preparation was then added and incubated overnight at 4° C. followed by aspiration and washing steps. Thereafter, 20 μL of "start" buffer (10 mM Tris-HCl pH 7.8, 50 mM NaCl, bovine serum albumin 1 mg/mL, 6 mM NaN_3, 1% Triton X-100) was added to the TSHR coated tubes followed by 100 μL of purified MAb IgG or patient sera and incubated at room temperature for 2 hours with gentle shaking. After aspiration, the tubes were washed twice with 1 mL of assay buffer before addition of 100 μL of ^{125}I TSH (80,000 cpm) and incubation at room temperature for 20-60 min with shaking. The tubes were then washed twice with 1 mL of assay buffer, aspirated and counted in a gamma counter.

(3) Analysis of Thyroid Stimulating or Blocking Activities of MAbs.

The ability of MAbs to either stimulate the production of cyclic AMP in isolated porcine thyroid cells (thyroid stimulating activity) or to act as TSH antagonists by blocking TSH stimulation of cyclic AMP (blocking activity) was assessed using reagents from Yamasa Corporation, Tokyo, Japan.

In addition the ability of the MAbs to stimulate production of cyclic AMP in Chinese hamster ovary (CHO) cells expressing human TSHR was analysed as described by M. Kita, L. Ahma, P C. Marians, H. Viase, P. Unger, P. N. Graves, T. F. Davies 1999 "Regulation and transfer of a murine model of thyrotropin receptor antibody mediated Graves' disease." Endocrinology 140: 1392-1398.

(4) Binding of ^{125}I-labelled MAbs to the TSHR and Effect of TRAb

Purified IgG from two of the MAbs that showed thyroid simulating activity (16E5 and 14D3, table 2) were labelled with ^{125}I followed by separation of unincorporated ^{125}I by filtration on Sephadex G-50 as in (4) in Example 1.

Plastic tubes were coated with TSHR preparations as in 2b above. Thereafter, 100 μL of test serum (from healthy blood donors or from patients with Graves' disease) were added and tubes incubated for 2 hours at room temperature with shaking. After this incubation, the tubes were washed 2 times with assay buffer. Then, 100 μL of ^{125}I-labelled 16E5 or 14D3 IgG (30,000 cpm diluted in 20 mM Tris-HCl pH 7.3, 50 mM NaCl, 1 mg/mL bovine serum albumin, 0.1% Triton X-100) was added to the tubes and incubated for 1 hour at room temperature with shaking. The tubes were then washed twice with the same buffer that was used for diluting ^{125}I-labelled MAbs and counted in a gamma counter.

(5) Binding of TSHR to MAb Coated Tubes and Effect of TRAb

Detergent solubilised TSHR preparations (20 μL) were incubated for 1 hour at room temperature with 100 μL of test serum and 20 μL of start buffer (2b above). 100 μL of this

mixture was then added to plastic tubes coated with TSHR MAb (as in 2b above) and incubated for 1 hour with shaking at room temperature. Then the tubes were aspirated and washed twice (2b above) and 100 μL (30,000 cpm) of ^{125}I-labelled C-terminal TSHR MAb 4E31 F(ab)$_2$ preparation labelled with ^{125}I as in 4 above added. After further incubation for 1 hour at room temperature with shaking, the tubes were aspirated, washed twice and the radioactivity counted with a gamma counter.

Oligonucleotide primers were designed using the sequences as described previously (Kettleborough C. A. et al "Optimization of primers for cloning libraries of mouse immunoglobulin genes using the polymerase chain reaction." European Journal of Immunology 1993 23:206-211).

Both sense and antisense primers included additional 5' restriction endonuclease site sequences to facilitate cloning of PCR products. RT-PCR products were cloned into pUC18 DNA prepared by the Qiagen method (Qiagen) and sequenced by the Sanger-Coulson method.

Results of Example 2

(1) Thyroid stimulating activity of the TSHR MAbs is shown in tables 2 and 3. Four of the MAbs (16E5, 14D3, 17D2, and 4D7) were able to stimulate cyclic AMP production in isolated porcine thyroid cells. In addition when Fab fragments from three of these MAbs were tested, all three also stimulated cyclic AMP production (table 2). For comparison a TRAb positive patient serum showed similar levels of stimulation to the MAbs (table 2). Also, TSHR MAb 2B4 which has the ability to inhibit TSH binding to the TSHR strongly did not show thyroid stimulating activity (table 2). Another TSHR MAb and Fab (3B3) did not stimulate cyclic AMP production nor did the Tg MAb Fab 2G2 (table 2).

In a further series of experiments some of the MABS which were able to stimulate porcine thyroid cells (16E5 and 14D3) were tested for their ability to stimulate cyclic AMP production in CHO cells expressing human TSHR (table 3). Similar results were obtained to those observed with porcine thyroid cells.

(2) In the presence of sera from healthy blood donors, ^{125}I-labelled 16E5 bound to TSHR coated tubes is in the range from 23 to 35% of total counts added (table 4). In the presence of sera from patients with Graves' disease (all TRAb positive) the binding of ^{125}I-labelled 16E5 was markedly reduced and was in the range from 1.9 to 7.5% (table 4).

This indicated that Graves' disease patient sera with TRAb activity inhibit the binding of TSHR MAb 16E5 to the TSHR. Further experiments with labelled 16E5 are shown in table 5 where a comparison of the effects of Graves' disease patient sera on (a) ^{125}I-labelled 16E5 to TSHR coated tubes and (b) ^{125}I-labelled TSH binding to TSHR coated tubes. Similar experiments to those shown in table 5 were carried out with ^{125}I-labelled TSHR MAb 14D3 and the results are shown in table 6.

The effects of Graves' disease patient sera on TSHR coated tube binding by ^{125}I-labelled 16E5, 14D3 or TSH were similar with strong inhibition of binding being observed in most cases (tables 5 and 6). In contrast to Graves' disease patient sera, sera from healthy blood donors had little effect on labelled MAb or labelled TSH binding to TSHR coated tubes (tables 5 and 6). Table 7 shows the effect of sera containing autoantibodies other than the TSHR autoantibodies on TSHR coated tube binding by labelled TSH, 16E5 and 14D3. As can be seen from table 7, sera containing autoantibodies to glutamic acid decarboxylase (D1 and D2) or to 21 -hydroxylase (A1 and A2) had no effect on TSH or MAb binding. However, the serum G42 from a patient with Graves' disease showed a strong, dose-dependent inhibition of both TSH and MAb binding.

(3) As shown in table 8, plastic tubes coated with MAb 16E5 were able to bind TSHR and this binding was inhibited by Graves' sera containing TSHR autoantibodies. In particular, detection of TSHR binding by the ^{125}I-labelled TSHR MAb 4E31 showed that (a) in the presence of sera from healthy blood donors, labelled 4E31 binding ranged from 13.5-17.8% of total cpm added whereas (b) in the presence of Graves' sera, labelled MAb binding ranged from 1.8-4.8% of total cpm added. Similar results were obtained with plastic tubes coated with MAb 14D3 (table 9).

Conclusions

The results shown in tables 2-9 show:

(a) we have produced TSHR MAbs and MAb Fab fragments which can stimulate isolated thyroid cells in a similar way to TRAb in patient sera and in a similar way to TSH. Different MAbs show different degrees of stimulating activity.

(b) these MAbs can be used instead of labelled TSH in assays for TSHR autoantibodies (TRAb).

(c) when the MAbs are coated onto plastic surfaces, they can bind TSHR preparations. This binding is inhibited by TRAb in patient sera, thus providing a new type of TRAb assay.

(d) the ability of the MAbs to stimulate the thyroid means that they are potentially useful as alternatives to TSH in in vivo applications.

EXAMPLE 3

Inhibition of ^{125}I-16E5 Fab Binding to Solubilised TSH Receptor by TSH Receptor Mabs

Method

The inhibition of 11I-16E5 Fab binding to detergent solubilised TSH receptor was analysed in an assay where 50 μl of Mab IgG (100 μg/ml) purified as described above was incubated with receptor for 30 minutes at room temperature before addition of 100 μl of ^{125}I-16E5 Fab (30,000 cpm) followed by incubation at room temperature for 2 hours. The complexes of ^{125}I-16E5 Fab and TSH receptor were precipitated by addition of 2 ml 16.5% polyethylene glycol and 50 μl healthy blood donor serum, centrifuged at 1500×g for 30 minutes at 4° C., aspirated and the radioactivity of the pellets counted in a gamma counter.

The results are shown in Table 10. From Table 10 it can be seen that Mab 4D7 (which binds to epitope region 246 to 260 and stimulates isolated thyroid cells) quite strongly inhibits labelled 16E5 Fab binding to the TSH receptor (24.2% inhibition). Two other Mabs, 3C7 and 18C5 also quite strongly inhibit 16E5 Fab binding(17 and 15.7% inhibition respectively) and also bind to the epitope region 246 to 260. Weak or no inhibition is observed with the other Mabs. This suggests that epitope region 246 to 260 is involved in 16E5 binding to the TSH receptor. As the other stimulating Mabs 14D3 and 17D2 compete well with 16E5 binding to the TSH receptor as can be seen from Table 10, epitope region 246 to 260 is probably also important for TSH receptor binding by 14D3 and 17D2.

TABLE 1

Inhibition of binding of TRAb in patient serum (K3) to the TSH receptor by MAb Fabs.

	Serum K3 1/10	
	Labelled TSHR immunoprecipitated (%)	% inhibition
Buffer	17.5	—
2B4 (5 mg/ml)	10.1	42
2B4 (10 mg/ml)	3.9	77.7
18C5 (5 mg/ml)	13.7	21.7
18C5 (10 mg/ml)	9.7	44
8E2 (5 mg/ml)	15.0	14.3
8E2 (10 mg/ml)	13.0	25.7
2B4 + 18C5 (5 mg/ml)	5.7	67.4
18C5 + 8E2 (5 mg/ml)	12.4	29.1
2B4 + 8E2 (5 mg/ml)	8.1	53.7
Unlabelled TSH (2.94 mg/ml)	7.8	55.4
2B4 + 8E2 + 18C5 (3.3 mg/ml)	7.4	57.7

$$\% \text{ inhibition} = 100 - \left(\frac{A}{B} \times 100\right)$$

A=^{125}I-TSHR (cpm) immunoprecipitated in the presence of test sera and test Mab Fab as a percentage of total cpm of material added to the tube

B=^{125}I-TSHR (cpm) immunoprecipitated in the presence of test sera and assay buffer as a percentage of total cpm of material added to the tube

The above results show that:

(1) the sequences of the TSH receptor which are involved in the TSH binding are also involved in TRAb binding;

(2) mouse MAb reactive with these sequences can be used effectively to inhibit TRAb binding to the TSH receptor; and

(3) one or more of the MAbs reactive with one or more of the above TSH receptor sequences can be used to detect and measure TRAb.

TABLE 2

Thyroid stimulating activity of TSHR MAbs tested usin isolated prcineyth roid cells

Test sample	Stimulation (%)[1]	Inhibition of TSH binding (%)[2,3]
16E5 IgG 200 µg/ml	466	nt
20 µg/ml	332	83.3
2 µg/ml	269	73.6
0.2 µg/ml	157	nt
0.02 µg/ml	52	nt
14D3 IgG 200 µg/ml	557	nt
20 µg/ml	351	76.4
2 µg/ml	323	61.0
0.2 µg/ml	227	nt
0.02 µg/ml	78	nt
17D2 IgG 200 µg/ml	377	nt
20 µg/ml	207	81.3
2 µg/ml	134	73.7
4D7 IgG 200 µg/ml	259	33[4]
20 µg/ml	31	nt
3B3 IgG[a] 200 µg/ml	34	30.7
20 µg/ml	37	6.1
2B4 IgG[a] 20 µg/ml	100	nt
2 µg/ml	116	69.9
3C7 Fab 1 mg/ml	348	45.2
4D7 Fab 1 mg/ml	512	48.6

TABLE 2-continued

Thyroid stimulating activity of TSHR MAbs tested usin isolated prcineyth roid cells

Test sample	Stimulation (%)[1]	Inhibition of TSH binding (%)[2,3]
16E5 Fab 200 µg/ml	425	53[5]
14D3 Fab 200 µg/ml	648	64[5]
17D2 Fab 200 µg/ml	274	45[5]
3B3 Fab[a] 200 µg/ml	42	66.5[4]
2G2 Fab[6] 1 mg/ml	55	0
200 µg/ml	37	0
TRAb + ve patient dil 1:2	771	65[7]
dil 1:4	530	nt
Pool of healthy blood donor sera	29	0.6
TRAb negative serum	70	0

Table 2 footnotes:

[1]MAb IgG or Fab preparations were diluted in the pool of healthy blood donor sera. Stimulation (%) was calculated as 100x the ratio of: cyclic AMP produced in the presence of test sample to cyclic AMP produced in the presence of a pool of healthy blood donor sera. A stimulation level of >180% was assessed as positive i.e. this level of stimulation was always greater than that observed by sera from individual healthy blood donors.

[2]Inhibition of TSH binding level of >10% is positive.

[3]Method = coated tube.

[4]Inhibition tested at 250 µg/ml.

[5]Inhibition tested at 10 µg/ml.

[6]2G2 is a MAb reactive with thyroglobulin i.e. unreactive with the TSHR.

[7]Inhibition with undiluted serum.

[a]3B3 and 2B4 IgGs act as TSH antagonists i.e. block the ability of TSH to stimulate cyclic AMP production by isolated porcine thyroid cells.

nt = not tested at this concentration.

TABLE 3

Thyroid stimulating activity of TSHR MAbs tested usin CHO cells exp ressiyn human TSHR

Test Sample[1]	Stimulation (%)[2]	Inhibition of TSH binding (%)[3,4]
16E5 20 µg/ml	850	78.8[5]
14D3 20 µg/ml	908	71.8[5]
2B4 20 µg/ml	111	84.4
TRAb + ve patient	850	65.0[6]
Pool of healthy blood donor sera	100	0

Table 3 footnotes:

[1]All samples were diluted 1:10 prior to addition to cells.

[2]Stimulation (%) was calculated as 100x the ratio of: cyclic AMP produced in the presence of test sample to cyclic AMP produced in the presence of a pool of healthy blood donor sera.

[3]Inhibition of TSH binding level of >10% is positive.

[4]Method = coated tubes

[5]Inhibition tested at 10 µg/ml

[6]Tested for inhibition undiluted.

TABLE 4

Binding of ^{125}I-labelled MAb 16E5 to TSHR coated tubes and effect of TRAb in atient sera

Test material[1]	Inhibition of TSH binding (%)[2]	^{125}I-16E5 bound to TSHR coated tubes (% total counts added)
G1	21	5.6
G2	22.7	6.5
G3	24.7	3.5
G4	22.7	6.0
G5	28.1	3.6
G6	29.4	2.5
G7	29.3	5.8
G8	39	1.9
G9	31.9	6.8
G10	34.8	5.4
G11	34.5	3.4
G12	35.3	4.2
G13	35.6	6.2

TABLE 4-continued

Binding of ^{125}I-labelled MAb 16E5 to TSHR coated tubes and effect of TRAb in patient sera

Test material[1]	Inhibition of TSH binding (%)[2]	^{125}I-16E5 bound to TSHR coated tubes (% total counts added)
G14	36.9	2.8
G15	30.3	4.3
G16	35	2.2
G17	47.6	3.9
G18	44.3	3.4
G19	53.5	3.7
G20	59.2	7.5
G21	58.9	4.9
NPS	<14	27.5
NSF 1	<14	23.3
NSF 2	<14	30.2
NSF 3	<14	29.1
NSF 4	<14	22.8

TABLE 4-continued

Binding of ^{125}I-labelled MAb 16E5 to TSHR coated tubes and effect of TRAb in patient sera

Test material[1]	Inhibition of TSH binding (%)[2]	^{125}I-16E5 bound to TSHR coated tubes (% total counts added)
NSF 5	<14	28.9
NSF 6	<14	31.0
NSF 7	<14	29.2
NSF 8	<14	35.3
NSF 9	<14	26.3
NSF 10	<14	25.2

Table 4 Footnotes:

[1]sera G1-G22 are from patients with Graves' disease;

sera NSF 1-NSF 10 are from healthy blood donors;

NPS = pool of healthy blood donor sera

[2]Inhibition of TSH binding >14% is positive; PEG method used.

TABLE 5

Effect of Graves' disease patient sera on ^{125}I-16E5 binding and ^{125}I-TSH binding to TSHR coated tubes

Test material[1]	^{125}I-16E5 bound to TSHR coated tubes (% total counts added)[2]	Inhibition of ^{125}I-16E5 binding (%)[2,3]	^{125}I-TSH bound to TSHR coated tubes (% total counts added)[4]	Inhibition of ^{125}I TSH binding (%)[3,4]
G23	13.2	44.0	8.9	27.1
G28	5.8	75.4	3.8	68.5
G29	13.3	43.6	8.0	34.4
G30	9.2	61.0	5.3	56.9
G32	11.9	49.6	7.5	38.4
G36	15.5	34.3	10.1	17.5
G38	16.1	31.8	10.0	18.3
G41	17.8	24.6	10.8	11.4
G43	5.9	75.0	4.0	67.2
G44	18.6	21.2	12.4	−ve
G45	5.1	78.4	3.5	71.0
G46	3.8	83.9	2.7	77.9
G47	7.2	69.5	4.3	64.8
G48	6.9	70.8	4.8	60.8
G49	9.1	61.4	6.1	49.6
G50	8.7	63.1	6.3	48.4
G51	11.9	49.6	7.9	35.2
G52	12.3	47.9	7.4	39.0
NSF 4	23.0	2.6	12.5	−ve
NSF 5	25.3	−ve	12.3	−ve
NSF 10	22.4	5.1	12.5	−ve
NSF 16	23.3	1.3	12.0	1.8
NSF 17	24.2	−ve	11.5	5.3
NSF 18	19.9	15.7	11.2	8.0
NSF 20	21.5	8.9	12.3	−ve
NSF 21	23.3	1.3	12.3	−ve
NSF 22	24.5	−ve	12.4	−ve
NSF 26	26.5	−ve	12.8	−ve

Table 5 footnotes:

[1]Sera G23-G52 are from patients with Graves' disease;

sera NSF are from healthy blood donors

[2]mean binding in the presence of healthy blood donor sera was 23.6% for ^{125}I-16E5.

[3]inhibition of binding was calculated using the formula % inhibition = 100 − (A/B × 100)

where A = binding in the presence of test serum;

B = mean binding in the presence of healthy blood donor sera

[4]mean binding in the presence of healthy blood donor sera was 12.2% for ^{125}I-TSH.

TABLE 6

Binding of ^{125}I-labelled MAb 14D3 to TSHR coated tubes and effect of TRAb in patient sera

Test material[1]	^{125}I-14D3 bound to TSHR coated tubes (% total counts added)[2]	Inhibition of ^{125}I-14D3 binding (%)[2,3]	^{125}I-TSH bound to TSHR coated tubes (% total counts added)[4]	Inhibition of ^{125}I TSH binding (%)[3,4]
G23	13.9	20	8.9	26.6
G24	11.3	35	6.9	43.4
G25	14.1	19	7.2	40.5
G26	7.3	58	2.6	78.3
G27	12.3	29.7	7.3	40.1
G28	8.0	54.4	3.8	68.3
G29	13.2	24.4	8.0	34.0
G30	12.5	28.4	5.3	56.6
G31	9.8	44	4.3	64.3
G32	11.4	34.8	7.5	38.0
G33	12.7	27.2	6.1	49.9
G34	10.9	37.5	7.5	37.8
G35	9.8	43.6	4.3	64.6
G36	13.5	22.8	10.1	16.9
G37	11.9	31.6	9.3	23.4
G38	11.3	35.4	10.0	17.6
G39	12.3	29.5	7.9	34.8
G40	9.8	44.0	7.2	40.9
G41	14.0	19.8	10.8	10.7
NSF 4	17.4	0.3	12.5	−ve
NSF 5	16.5	9.1	12.3	−ve
NSF 10	17.6	−ve	12.5	−ve
NSF 16	17.7	−ve	12.0	1.1
NSF 17	17.0	2.7	11.5	4.6
NSF 18	16.6	8.6	11.2	7.3
NSF 20	18.3	−ve	12.3	−ve
NSF 21	16.8	3.6	12.3	−ve
NSF 22	16.3	6.7	12.4	−ve
NSF 26	18.4	−ve	12.8	−ve

Table 6 footnotes:

[1]Sera G23-G41 are from patients with Graves' disease;

sera NSF are from healthy blood donors

[2]mean binding in the presence of healthy blood donor sera was 17.4% for ^{125}I-14D3.

[3]inhibition of binding was calculated using the formula % inhibition = 100 − (A/B × 100)

where A = binding in the presence of test serum;

B = mean binding in the presence of healthy blood donor sera

[4]mean binding in the presence of healthy blood donor sera was 12.1% for ^{125}I-TSH.

TABLE 7

Effect of sera from various patients on TSHR coated tube bindin b labelled TSH 16E5 and 14D3

Test sample[1]	% inhibition of binding to TSHR coated tubes [2] using: ^{125}I-TSH	^{125}I-16E5	^{125}I-14D3
G42/5	87	71	77
G42/10	82	56	51
G42/20	70	34	24
D1/10	2	3	2
D1/100	−2	3	0
D2/10	1	1	−7
D2/100	−2	0	0
A1/10	−1	3	2
A1/100	−1	3	−1
A2/10	5	3	5
A2/100	1	3	1

Table 7 Footnotes:

[1]Serum G42 is from a patient with Graves' disease;

sera D1 and D2 are from patients with type 1 diabetes mellitus (positive for autoantibodies to glutamic acid decarboxylase)

sera A1 and A2 are from patients with Addison's disease (positive for steroid 21-hydroxylase autoantibodies)

All test samples were diluted in a pool of serum from healthy blood donors and dilution factor shown as /5, /10, /20 or /100

[2] inhibition of binding was calculated using the formula % inhibition = 100 − (A/B × 100)

where A = binding in the presence of test serum;

B = mean binding in the presence of a pool of healthy blood donor sera

TABLE 8

Effect of patient sera on binding of TSHR to 16E5 F(ab)$_2$ coated tubes

Test material[1]	^{125}I-4E31 labelled TSHR bound to 16E5 F(ab)$_2$ coated tubes (% total counts added)	Inhibition of TSHR binding[2]	Inhibition of TSH binding (%)[3]
G43	1.8	91.4	72.3
G44	4.8	77.2	45.1
G45	3.0	85.6	71.8
G46	2.0	90.2	83.8
G47	1.8	91.4	75.3
NSF 10	17.8	−15	<14
NSF 17	14.8	4	<14
NSF 21	13.5	12	<14

Table 8 footnotes:

[1]Sera G43-G47 are from patients with Graves' disease;

sera NSF are from healthy blood donors

[2]inhibition of binding was calculated using the formula % inhibition = 100 − (A/B × 100)

where A = binding 4E31 binding in the presence of test serum;

B = mean labelled 4E31 binding for healthy blood donor sera (15.4%)

[3]inhibition of TSH binding >14% is positive; PEG method used.

TABLE 9

Effect of patient sera on binding of the TSHR to 14D3 F(ab)$_2$ coated tubes

Test material[1]	^{125}I-4E31 labelled TSHR bound to 14D3 F(ab)$_2$ coated tubes (% total counts added)	Inhibition of TSHR binding[2]	Inhibition of TSH binding (%)[3]
Serum A	4.0	70	72
Serum B	6.9	49	40
Serum C	3.0	78	85
Serum D	2.6	81	80
NSF 5	15.1	−12	<14
NSF 17	14.6	−9	<14
NSF 21	12.0	10	<14
NSF 23	11.8	12	<14

Table 9 footnotes:
[1]Sera A-D are from patients with Graves' disease;
sera NSF are from healthy blood donors
[2]inhibition of binding was calculated using the formula % inhibition = 100 − (A/B × 100)
where A = labelled 4E31 binding in the presence of test serum;
B = mean labelled 4E31 binding for healthy blood donor sera (13.4%)
[3]inhibition of TSH binding >14% is positive; PEG method used.

TABLE 10

Inhibition of ^{125}I-16E5 Fab binding to TSHR by TSHR MAbs

IgG (100 μg/ml)	% inhibition	Epitope region (aa)
16E5	70.4	—
14D3	67.6	—
17D2	69.2	—
2G2	−ve	Thyroglobulin specific
5D6	−ve	22-41
8E2	−ve	22-41
4B5	7.1	22-41

TABLE 10-continued

Inhibition of ^{125}I-16E5 Fab binding to TSHR by TSHR MAbs

IgG (100 μg/ml)	% inhibition	Epitope region (aa)
10C4	−ve	37-56
10D5	−ve	37-71
4D2	−ve	37-71
2E2	−ve	52-71
1D6	−ve	202-221
7B5	−ve	202-221
16B6	−ve	202-221
3C3	11.2	202-236
4B4	−ve	217-236
4E4	−ve	217-236
8D3	−ve	217-236
6D7	−ve	217-236
18C5	15.7	246-260
3C7	17	246-260
4D7	24.2	246-260
3B3	8.8	277-296
5B5	−ve	307-326
4E6	−ve	307-326
6E2	−ve	322-341
9C2	−ve	322-341
6B4	−ve	337-356
3E4	−ve	337-371
3F3	−ve	352-371
3B2	−ve	352-371
7C2	−ve	367-386
2B4	−ve	381-385
3E6	5.4	381-385
8E3	4.8	381-385
7C4	−ve	381-385
1D5	4.2	381-385
4E2	−ve	381-385
3D3	−ve	382-401
2C4	−ve	382-401
10C2	−ve	382-401
7E5	−ve	382-401

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            20                  25                  30

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        35                  40                  45

Ser Leu Pro Pro Ser Thr Gln Thr Leu Lys Leu Ile Glu Thr His Leu
    50                  55                  60

Arg Thr Ile Pro Ser His Ala Phe Ser Asn Leu Pro Asn Ile Ser Arg
65                  70                  75                  80

Ile Tyr Val Ser Ile Asp Val Thr Leu Gln Gln Leu Glu Ser His Ser
                85                  90                  95

Phe Tyr Asn Leu Ser Lys Val Thr His Ile Glu Ile Arg Asn Thr Arg
            100                 105                 110
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Asn Leu Thr Tyr Ile Asp Pro Asp Ala Leu Lys Glu Leu Pro Leu Leu
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Lys Phe Leu Gly Ile Phe Asn Thr Gly Leu Lys Met Phe Pro Asp Leu
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Thr Lys Val Tyr Ser Thr Asp Ile Phe Phe Ile Leu Glu Ile Thr Asp
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Asn Pro Tyr Met Thr Ser Ile Pro Val Asn Ala Phe Gln Gly Leu Cys
                165                 170                 175

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        35                  40                  45

Pro Leu Pro Pro Asn Thr Gln Thr Leu Lys Phe Ile Glu Thr His Leu
    50                  55                  60

Lys Thr Ile Pro Ser Arg Ala Phe Ser Asn Leu Pro Asn Ile Ser Arg
65                  70                  75                  80

Ile Tyr Leu Ser Ile Asp Ala Thr Leu Gln Gln Leu Glu Ser Gln Ser
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Phe Tyr Asn Leu Ser Lys Met Thr His Ile Glu Ile Arg Asn Thr Arg
            100                 105                 110

Ser Leu Thr Tyr Ile Asn Pro Gly Ala Leu Lys Asp Leu Pro Leu Leu
        115                 120                 125

Lys Phe Leu Gly Ile Phe Asn Thr Gly Leu Arg Ile Phe Pro Asp Leu
    130                 135                 140

Thr Lys Val Tyr Ser Thr Asp Val Phe Phe Ile Leu Glu Ile Thr Asp
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Asn Pro Tyr Met Thr Ser Ile Pro Ala Asn Ala Phe Gln Gly Leu Cys
                165                 170                 175

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Gln Gly His Ala Phe Asn Gly Thr
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            20                  25                  30

Gln Glu Asp Asp Phe Arg Val Thr Cys Lys Asp Ile Gln Ser Ile Pro
        35                  40                  45

Ser Leu Pro Pro Ser Thr Gln Thr Leu Lys Phe Ile Glu Thr His Leu
    50                  55                  60

Lys Thr Ile Pro Ser Arg Ala Phe Ser Asn Leu Pro Asn Ile Ser Arg
65                  70                  75                  80

Ile Tyr Leu Ser Ile Asp Ala Thr Leu Gln Gln Leu Glu Ser His Ser
                85                  90                  95

Phe Tyr Asn Leu Ser Lys Val Thr His Ile Glu Ile Arg Asn Thr Arg
            100                 105                 110

Ser Leu Thr Tyr Ile Asp Ser Gly Ala Leu Lys Glu Leu Pro Leu Leu
        115                 120                 125

Lys Phe Leu Gly Ile Phe Asn Thr Gly Leu Arg Val Phe Pro Asp Leu
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Thr Lys Ile Tyr Ser Thr Asp Val Phe Phe Ile Leu Glu Ile Thr Asp
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Asn Pro Tyr Met Thr Ser Ile Pro Ala Asn Ala Phe Gln Gly Leu Cys
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            20                  25                  30

Gln Glu Asp Asp Phe Arg Val Thr Cys Lys Asp Ile His Arg Ile Pro
        35                  40                  45

Ser Leu Pro Pro Ser Thr Gln Thr Leu Lys Phe Ile Glu Thr His Leu
    50                  55                  60

Lys Thr Ile Pro Ser Arg Ala Phe Ser Asn Leu Pro Asn Ile Ser Arg
65                  70                  75                  80

Ile Tyr Leu Ser Ile Asp Ala Thr Leu Gln Arg Leu Glu Ser His Ser
                85                  90                  95

Phe Tyr Asn Leu Ser Lys Met Thr His Ile Glu Ile Arg Asn Thr Arg
            100                 105                 110

Ser Leu Thr Tyr Ile Asp Pro Gly Ala Leu Lys Glu Leu Pro Leu Leu
        115                 120                 125

Lys Phe Leu Gly Ile Phe Asn Thr Gly Leu Gly Val Phe Pro Asp Leu
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Thr Lys Val Tyr Ser Thr Asp Val Phe Phe Ile Leu Glu Ile Thr Asp
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Asn Pro Tyr Met Thr Ser Ile Pro Ala Asn Ala Phe Gln Gly Leu Cys
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            20                  25                  30

Gln Glu Asp Asp Phe Arg Val Thr Cys Lys Asp Ile His Arg Ile Pro
        35                  40                  45

Thr Leu Pro Pro Ser Thr Gln Thr Leu Lys Phe Ile Glu Thr Gln Leu
    50                  55                  60

Lys Thr Ile Pro Ser Arg Ala Phe Ser Asn Leu Pro Asn Ile Ser Arg
65                  70                  75                  80

Ile Tyr Leu Ser Ile Asp Ala Thr Leu Gln Arg Leu Glu Ser His Ser
                85                  90                  95

Phe Tyr Asn Leu Ser Lys Met Thr His Ile Glu Ile Arg Asn Thr Arg
            100                 105                 110

Ser Leu Thr Ser Ile Asp Pro Asp Ala Leu Lys Glu Leu Pro Leu Leu
        115                 120                 125

Lys Phe Leu Gly Ile Phe Asn Thr Gly Leu Gly Val Phe Pro Asp Val
    130                 135                 140

Thr Lys Val Tyr Ser Thr Asp Val Phe Phe Ile Leu Glu Ile Thr Asp
145                 150                 155                 160

Asn Pro Tyr Met Ala Ser Ile Pro Ala Asn Ala Phe Gln Gly Leu Cys
                165                 170                 175

Asn Glu Thr Leu Thr Leu Lys Leu Tyr Asn Asn Gly Phe Thr Ser Ile
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Gln Gly His Ala Phe Asn Gly Thr
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            20                  25                  30

Gln Glu Asp Asp Phe Arg Val Thr Cys Lys Glu Leu His Arg Ile Pro
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Ser Leu Pro Pro Ser Thr Gln Thr Leu Lys Leu Ile Glu Thr His Leu
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    50                  55                  60

Lys Thr Ile Pro Ser Leu Ala Phe Ser Ser Leu Pro Asn Ile Ser Arg
65                  70                  75                  80

Ile Tyr Leu Ser Ile Asp Ala Thr Leu Gln Arg Leu Glu Pro His Ser
                85                  90                  95

Phe Tyr Asn Leu Ser Lys Met Thr His Ile Glu Ile Arg Asn Thr Arg
            100                 105                 110

Ser Leu Thr Tyr Ile Asp Pro Asp Ala Leu Thr Glu Leu Pro Leu Leu
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Lys Phe Leu Gly Ile Phe Asn Thr Gly Leu Arg Ile Phe Pro Asp Leu
    130                 135                 140

Thr Lys Ile Tyr Ser Thr Asp Ile Phe Phe Ile Leu Glu Ile Thr Asp
145                 150                 155                 160

Asn Pro Tyr Met Thr Ser Val Pro Glu Asn Ala Phe Gln Gly Leu Cys
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<213> ORGANISM: rat
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 1

<400> SEQUENCE: 7

Met Arg Pro Gly Ser Leu Leu Gln Leu Thr Leu Leu Leu Ala Leu Pro
1               5                   10                  15

Arg Ser Leu Trp Gly Arg Gly Cys Thr Ser Pro Pro Cys Glu Cys His
            20                  25                  30

Gln Glu Asp Asp Phe Arg Val Thr Cys Lys Glu Leu His Gln Ile Pro
        35                  40                  45

Ser Leu Pro Pro Ser Thr Gln Thr Leu Lys Leu Ile Glu Thr His Leu
    50                  55                  60

Lys Thr Ile Pro Ser Leu Ala Phe Ser Ser Leu Pro Asn Ile Ser Arg
65                  70                  75                  80

Ile Tyr Leu Ser Ile Asp Ala Thr Leu Gln Arg Leu Glu Pro His Ser
                85                  90                  95

Phe Tyr Asn Leu Ser Lys Met Thr His Ile Glu Ile Arg Asn Thr Arg
            100                 105                 110

Ser Leu Thr Tyr Ile Asp Pro Asp Ala Leu Thr Glu Leu Pro Leu Leu
        115                 120                 125

Lys Phe Leu Gly Ile Phe Asn Thr Gly Leu Arg Ile Phe Pro Asp Leu
    130                 135                 140

Thr Lys Ile Tyr Ser Thr Asp Val Phe Phe Ile Leu Glu Ile Thr Asp
145                 150                 155                 160

Asn Pro Tyr Met Thr Ser Val Pro Glu Asn Ala Phe Gln Gly Leu Cys
                165                 170                 175

Asn Glu Thr Leu Thr Leu Lys Leu Tyr Asn Asn Gly Phe Thr Ser Ile
            180                 185                 190

Gln Gly His Ala Phe Asn Gly Thr
        195                 200
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<210> SEQ ID NO 8
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: ovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 1

<400> SEQUENCE: 8

Met Arg Pro Thr Pro Leu Leu Arg Leu Ala Leu Leu Leu Val Leu Pro
1 5 10 15

Ser Ser Leu Trp Gly Glu Arg Cys Pro Ser Pro Pro Cys Glu Cys Arg
20 25 30

Gln Glu Asp Asp Phe Arg Val Thr Cys Lys Asp Ile Gln Arg Ile Pro
35 40 45

Ser Leu Pro Pro Ser Thr Gln Thr Leu Lys Phe Ile Glu Thr His Leu
50 55 60

Lys Thr Ile Pro Ser Arg Ala Phe Ser Asn Leu Pro Asn Ile Ser Arg
65 70 75 80

Ile Tyr Leu Ser Ile Asp Ala Thr Leu Gln Gln Leu Glu Ser His Ser
85 90 95

Phe Tyr Asn Leu Ser Lys Val Thr His Ile Glu Ile Arg Asn Thr Arg
100 105 110

Ser Leu Thr Tyr Ile Asp Ser Gly Ala Leu Lys Glu Leu Pro Leu Leu
115 120 125

Lys Phe Leu Gly Ile Phe Asn Thr Gly Leu Arg Val Phe Pro Asp Leu
130 135 140

Thr Lys Ile Tyr Ser Thr Asp Val Phe Phe Ile Leu Glu Ile Thr Asp
145 150 155 160

Asn Pro Tyr Met Thr Ser Val Pro Ala Asn Ala Phe Gln Gly Leu Ser
165 170 175

Asn Glu Thr Leu Thr Leu Lys Leu Tyr Asn Asn Gly Phe Thr Ser Ile
180 185 190

Gln Gly His Ala Phe Asn Gly Thr
195 200

<210> SEQ ID NO 9
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: feline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 2

<400> SEQUENCE: 9

atgaggcaga cgcccctgct gcagctggcg ttacttctct ccctgcccag gagcctgggg 60

gggaaagggt gtccgtctcc gccctgcgag tgtcaccagg aagatgactt cagagtcacc 120

tgcaaggata ttcaccgtat ccccagccta ccgcccagca cgcagactct gaaatttata 180

gagactcatc tgaaaaccat tcccagtcgt gcattttcaa atctgcccaa tatttccagg 240

atctacttgt caatagatgc aactctgcag cgactggaat cacattcctt ctacaatttg 300

<210> SEQ ID NO 10
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: bovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 2

<400> SEQUENCE: 10

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atgcggccga cgcccctcct gcggctggcg ctgtttctgg tcctgcccag cagcctcggt 60

ggggagaggt gtccgtctcc gccctgcgaa tgccgccagg aggacgactt cagagtcacc 120

tgcaaggaca tccagagcat ccctagctta ccccccagca cgcagaccct gaagtttata 180

gagactcatc tgaaaaccat tcccagtcgt gcgttctcaa atctgcccaa tatttccagg 240

atctacttgt caatagatgc aactctgcag cagctggaat cacattcctt ctacaattta 300

<210> SEQ ID NO 11
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: canine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 2

<400> SEQUENCE: 11

atgaggccgc cgcccctgct gcacctggcg ctgcttctcg ccctgcccag gagcctgggg 60

gggaaggggt gtccttctcc cccctgtgag tgccaccagg aggatgactt cagagtcacc 120

tgcaaggata tccaccgcat ccccacccta ccacccagca cgcagactct gaagtttata 180

gagactcagc tgaaaaccat tcccagtcgt gcattttcaa atctgcccaa tatttccagg 240

atctacttgt caatagatgc aactctgcag cggctggaat cacattcctt ctacaattta 300

<210> SEQ ID NO 12
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 2

<400> SEQUENCE: 12

atgaggccag ggtccctgct gctgcttgtt ctgctgctcg ccctgtccag gagcctgcgg 60

ggcaaagagt gtgcgtctcc accctgtgag tgtcaccagg aggacgactt cagagtcacc 120

tgcaaggagc tccaccgaat ccccagcctg ccgcccagca cccagactct gaagctcatc 180

gagactcatc tgaagaccat acccagtctt gcattttcga gtctgcccaa tatttccagg 240

atctatttat ctatagatgc aactctgcag cggctggaac cacattcttt ctacaatttg 300

<210> SEQ ID NO 13
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: porcine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 2

<400> SEQUENCE: 13

atgagtctga cgcccctgtt gcagctggcg ctcgttctcg ccctgcccag gagcctcagg 60

gggaaagggt gtccgtctcc gccctgcgaa tgccaccagg aggacgactt cagagtcacc 120

tgcaaggata tccacagcat ccccccctta ccacccaata ctcagacact aaagtttata 180

gagactcatc tgaaaaccat ccccagtcgt gcattttcaa atctgcccaa tatttccagg 240

atctacctgt caatagatgc aactctacag cagctggaat cacagtcctt ctacaatttg 300

<210> SEQ ID NO 14
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: rat
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 2

<400> SEQUENCE: 14

atgaggccag ggtccctgct ccagctcact ctgctgctcg ccctgcccag gagcctctgg 60

ggcagagggt gtacttctcc accctgcgaa tgccaccagg aggacgactt cagagtcacc 120

tgcaaggaac tccaccaaat ccccagccta ccgcccagca cccagactct gaagctcatc 180

gagactcacc tgaagaccat tcccagtctt gccttttcga gcctgcccaa tatttccagg 240

atctatctat ccatagatgc cactctgcag cgactggagc cacattcttt ctacaatttg 300

<210> SEQ ID NO 15
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: ovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 2

<400> SEQUENCE: 15

atgcggccga cgcccctcct gcggttggcg ctgcttctgg tcctgcccag cagcctctgg 60

ggggagaggt gtccgtctcc gccctgcgaa tgccgccagg aggacgactt cagagtcacc 120

tgcaaggaca tccagcgcat ccctagctta ccccccagca cgcagaccct gaagtttata 180

gagactcatc tgaaaaccat tcccagtcgt gcgttctcaa atttgcccaa tatttccagg 240

atctacttgt caatagatgc gactttgcag caactggaat cacattcctt ctacaattta 300

<210> SEQ ID NO 16
<211> LENGTH: 300
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 2

<400> SEQUENCE: 16

atgaggccgg cggacttgct gcagctggtg ctgctgctcg acctgcccag ggacctgggc 60

ggaatggggt gttcgtctcc accctgcgag tgccatcagg aggaggactt cagagtcacc 120

tgcaaggata ttcaacgcat ccccagctta ccgcccagta cgcagactct gaagcttatt 180

gagactcacc tgagaactat tccaagtcat gcattttcta atctgcccaa tatttccaga 240

atctacgtat ctatagatgt gactctgcag cagctggaat cacactcctt ctacaatttg 300

<210> SEQ ID NO 17
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 3

<400> SEQUENCE: 17

Thr Lys Leu Asp Ala Val Tyr Leu Asn Lys Asn Lys Tyr Leu Thr Val
1 5 10 15

Ile Asp Lys Asp Ala Phe Gly Gly Val Tyr Ser Gly Pro Ser Leu Leu
20 25 30

Asp Val Ser Gln Thr Ser Val Thr Ala Leu Pro Ser Lys Gly Leu Glu
35 40 45

His Leu Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu
50 55 60

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Pro Leu Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr
65                  70                  75                  80

Pro Ser His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile
                85                  90                  95

Leu Glu Ser Leu Met
            100


<210> SEQ ID NO 18
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: porcine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 3

<400> SEQUENCE: 18

Thr Lys Leu Asp Ala Val Tyr Leu Asn Lys Asn Lys Tyr Leu Thr Val
1               5                   10                  15

Ile Asp Lys Asp Ala Phe Gly Gly Val Phe Ser Gly Pro Thr Leu Leu
            20                  25                  30

Asp Val Ser Tyr Thr Ser Val Thr Ala Leu Pro Pro Lys Gly Leu Glu
        35                  40                  45

His Leu Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu
    50                  55                  60

Pro Leu Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr
65                  70                  75                  80

Pro Ser His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile
                85                  90                  95

Leu Glu Ser Leu Met
            100


<210> SEQ ID NO 19
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: bovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 3

<400> SEQUENCE: 19

Thr Lys Leu Asp Ala Val Tyr Leu Asn Lys Asn Lys Tyr Leu Thr Val
1               5                   10                  15

Ile Gly Gln Asp Ala Phe Ala Gly Val Tyr Ser Gly Pro Thr Leu Leu
            20                  25                  30

Asp Ile Ser Tyr Thr Ser Val Thr Ala Leu Pro Ser Lys Gly Leu Glu
        35                  40                  45

His Leu Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Arg Lys Leu
    50                  55                  60

Pro Leu Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr
65                  70                  75                  80

Pro Ser His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile
                85                  90                  95

Leu Gln Ser Leu Met
            100


<210> SEQ ID NO 20
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: feline
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Figure 3

<400> SEQUENCE: 20

Thr Lys Leu Asp Ala Val Tyr Leu Asn Lys Asn Lys Tyr Leu Thr Ala
1 5 10 15

Ile Asp Gln Asp Ala Phe Gly Gly Val Tyr Ser Gly Pro Thr Leu Leu
20 25 30

Asp Val Ser Tyr Thr Ser Val Thr Ala Leu Pro Ser Lys Gly Leu Glu
35 40 45

His Leu Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu
50 55 60

Pro Leu Thr Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr
65 70 75 80

Pro Ser His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile
85 90 95

Leu Glu Ser Phe Met
100

<210> SEQ ID NO 21
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: canine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 3

<400> SEQUENCE: 21

Thr Lys Leu Asp Ala Val Tyr Leu Asn Lys Asn Lys Tyr Leu Ser Ala
1 5 10 15

Ile Asp Lys Asp Ala Phe Gly Gly Val Tyr Ser Gly Pro Thr Leu Leu
20 25 30

Asp Val Ser Tyr Thr Ser Val Thr Ala Leu Pro Ser Lys Gly Leu Glu
35 40 45

His Leu Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu
50 55 60

Pro Leu Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr
65 70 75 80

Pro Ser His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile
85 90 95

Leu Glu Ser Leu Met
100

<210> SEQ ID NO 22
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 3

<400> SEQUENCE: 22

Thr Lys Leu Asp Ala Val Tyr Leu Asn Lys Asn Lys Tyr Leu Thr Ala
1 5 10 15

Ile Asp Asn Asp Ala Phe Gly Gly Val Tyr Ser Gly Pro Thr Leu Leu
20 25 30

Asp Val Ser Ser Thr Ser Val Thr Ala Leu Pro Ser Lys Gly Leu Glu
35 40 45

His Leu Lys Glu Leu Ile Ala Lys Asp Thr Trp Thr Leu Lys Lys Leu
50 55 60

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Pro Leu Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr
65                  70                  75                  80

Pro Ser His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile
                85                  90                  95

Leu Glu Ser Leu Met
            100


<210> SEQ ID NO 23
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: rat
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 3

<400> SEQUENCE: 23

Thr Lys Leu Asp Ala Val Tyr Leu Asn Lys Asn Lys Tyr Leu Thr Ala
1               5                   10                  15

Ile Asp Lys Asp Ala Phe Gly Gly Val Tyr Ser Gly Pro Thr Leu Leu
            20                  25                  30

Asp Val Ser Ser Thr Ser Val Thr Ala Leu Pro Ser Lys Gly Leu Glu
        35                  40                  45

His Leu Lys Glu Leu Ile Ala Lys Asn Thr Trp Thr Leu Lys Lys Leu
    50                  55                  60

Pro Leu Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr
65                  70                  75                  80

Pro Ser His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile
                85                  90                  95

Leu Glu Ser Leu Met
            100


<210> SEQ ID NO 24
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: ovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 3

<400> SEQUENCE: 24

Thr Lys Leu Asp Ala Val Tyr Leu Asn Lys Asn Lys Tyr Leu Thr Val
1               5                   10                  15

Ile Asp Gln Asp Ala Phe Ala Gly Val Tyr Ser Gly Pro Thr Leu Leu
            20                  25                  30

Asp Ile Ser Tyr Thr Ser Val Thr Ala Leu Pro Ser Lys Gly Leu Glu
        35                  40                  45

His Leu Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu
    50                  55                  60

Pro Leu Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr
65                  70                  75                  80

Pro Ser His Cys Cys Ala Phe Lys Asn Gln Lys Asn Ile Arg Gly Ile
                85                  90                  95

Leu Gln Ser Leu Met
            100


<210> SEQ ID NO 25
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: feline
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Figure 4

<400> SEQUENCE: 25

tcttacacca gtgtcactgc cctgccatcc aaaggcctgg agcacctgaa ggaattgata 60

gcaagaaaca cttggactct aaagaaactt ccacttacct tgagtttcct tcacctcaca 120

cgggctgacc tttcttatcc aagccactgc tgtgctttta agaatcagaa gaaaatcaga 180

ggaatccttg agtccttcat 200

<210> SEQ ID NO 26
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: bovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 4

<400> SEQUENCE: 26

tcttatacca gtgtcacagc cctaccatcc aaaggcctgg aacacctgaa ggaattgata 60

gcaagaaaca cttggactct aaggaaactt cctctttcct tgagtttcct tcacctcaca 120

cgggctgacc tttcttatcc gagccactgc tgcgctttta agaatcagaa gaaaatcaga 180

ggaatccttc agtctttaat 200

<210> SEQ ID NO 27
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: canine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 4

<400> SEQUENCE: 27

tcttacacca gtgttactgc cctgccatcc aaaggcctgg agcatctaaa ggagctgata 60

gcaagaaaca cttggactct aaagaaactc ccactttcct tgagtttcct tcaccttaca 120

cgggctgacc tttcttatcc aagccactgc tgtgctttta agaatcagaa gaaaatcaga 180

ggaatccttg agtccttaat 200

<210> SEQ ID NO 28
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 4

<400> SEQUENCE: 28

tcttccacca gcgtcactgc ccttccttcc aaaggcctgg agcacctcaa agaactgatc 60

gcaaaagaca cctggactct caaaaagctc ccgctgtcgt tgagtttcct ccacctcact 120

cgggctgacc tctcttaccc gagccactgc tgcgctttta agaaccagaa gaaaatcagg 180

ggaatcctgg agtctttgat 200

<210> SEQ ID NO 29
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: porcine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 4

<400> SEQUENCE: 29

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tcttatacca gtgttactgc cctgccaccc aaaggcctgg aacacctgaa ggaactgata 60

gcaagaaata cttggactct aaagaaactt ccactgtcct tgagtttcct tcacctcaca 120

cgagctgacc tttcttatcc aagccactgc tgtgctttta agaatcagaa gaagatcaga 180

ggaatccttg agtctttaat 200

<210> SEQ ID NO 30
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: rat
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 4

<400> SEQUENCE: 30

tcttccacca gcgttactgc tcttccttcc aaaggcctgg agcacctcaa agagctgatc 60

gcgaagaaca cctggactct caaaaagctc cccctgtcct tgagcttcct ccacctcact 120

cgggctgacc tctcttaccc aagtcactgc tgtgctttta agaaccagaa gaaaatcagg 180

ggaatcctag agtctttgat 200

<210> SEQ ID NO 31
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: ovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 4

<400> SEQUENCE: 31

tcttatacca gtgtcactgc cctaccatcc aaaggcctgg aacacctgaa ggaattgata 60

gcaagaaaca cttggactct aaagaaactt cctctttcct tgagtttcct tcacctcaca 120

cgggctgacc tttcttatcc gagccactgc tgtgctttta agaatcagaa gaatatcaga 180

ggaatccttc agtctttaat 200

<210> SEQ ID NO 32
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 4

<400> SEQUENCE: 32

tctcaaacca gtgtcactgc ccttccatcc aaaggcctgg agcacctgaa ggaactgata 60

gcaagaaaca cctggactct taagaaactt ccactttcct tgagtttcct tcacctcaca 120

cgggctgacc tttcttaccc aagccactgc tgtgccttta agaatcagaa gaaaatcaga 180

ggaatccttg agtccttgat 200

<210> SEQ ID NO 33
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 5

<400> SEQUENCE: 33

Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu Pro Leu
1 5 10 15

Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr Pro Ser

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            20                  25                  30

His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile Leu Glu
        35                  40                  45

Ser Leu Met Cys Asn Glu Ser Ser Met Gln Ser Leu Arg Gln Arg Lys
    50                  55                  60

Ser Val Asn Ala Leu Asn Ser Pro Leu His Gln Glu Tyr Glu Glu Asn
65                  70                  75                  80

Leu Gly Asp Ser Ile Val Gly Tyr Lys Glu Lys Ser Lys Phe Gln Asp
                85                  90                  95

Thr His Asn Asn Ala His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp
            100                 105                 110

Glu Ile Ile Gly Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr
        115                 120                 125

Leu Gln Ala Phe Asp Ser His Tyr Asp Tyr Thr Ile Cys Gly Asp Ser
    130                 135                 140

Glu Asp Met Val Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu
145                 150                 155                 160

Asp Ile Met Gly Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser
                165                 170                 175

Leu Leu Ala Leu Leu Gly Asn Val Phe Val Leu Leu Ile Leu Leu Thr
            180                 185                 190

Ser His Tyr Lys Leu Asn Val Pro
        195                 200


<210> SEQ ID NO 34
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: porcine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 5

<400> SEQUENCE: 34

Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu Pro Leu
1               5                   10                  15

Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr Pro Ser
            20                  25                  30

His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile Leu Glu
        35                  40                  45

Ser Leu Met Cys Asn Glu Ser Ser Ile Arg Ser Leu Arg Gln Arg Lys
    50                  55                  60

Ser Val Asn Ala Val Asn Gly Pro Phe Tyr Gln Glu Tyr Glu Glu Asp
65                  70                  75                  80

Leu Gly Asp Thr Ser Val Gly Asn Lys Glu Asn Ser Lys Phe Gln Asp
                85                  90                  95

Thr His Ser Asn Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp
            100                 105                 110

Glu Ile Ile Gly Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr
        115                 120                 125

Leu Gln Ala Phe Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Gly Ser
    130                 135                 140

Glu Asp Met Val Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu
145                 150                 155                 160

Asp Ile Met Gly Tyr Arg Phe Leu Arg Ile Val Val Trp Phe Val Ser
                165                 170                 175

Leu Leu Ala Leu Leu Gly Asn Val Phe Val Leu Val Ile Leu Leu Thr
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            180                 185                 190

Ser His Tyr Lys Leu Thr Val Pro
        195                 200


<210> SEQ ID NO 35
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: bovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 5
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (80)..(80)
<223> OTHER INFORMATION: spacer for sequence alignment of figure 5

<400> SEQUENCE: 35

Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Arg Lys Leu Pro Leu
1               5                   10                  15

Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr Pro Ser
            20                  25                  30

His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile Leu Gln
        35                  40                  45

Ser Leu Met Cys Asn Glu Ser Ser Ile Arg Gly Leu Arg Gln Arg Lys
    50                  55                  60

Ser Ala Ser Ala Leu Asn Gly Pro Phe Tyr Gln Glu Tyr Glu Asp Xaa
65                  70                  75                  80

Leu Gly Asp Gly Ser Ala Gly Tyr Lys Glu Asn Ser Lys Phe Gln Asp
                85                  90                  95

Thr Gln Ser Asn Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp
            100                 105                 110

Glu Ile Ile Gly Phe Gly Gln Gln Leu Lys Asn Pro Gln Glu Glu Thr
        115                 120                 125

Leu Gln Ala Phe Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Gly Ser
    130                 135                 140

Glu Asp Met Val Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu
145                 150                 155                 160

Asp Ile Met Gly Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser
                165                 170                 175

Leu Leu Ala Leu Leu Gly Asn Val Phe Val Leu Val Ile Leu Leu Thr
            180                 185                 190

Ser His Tyr Lys Leu Thr Val Pro
        195                 200


<210> SEQ ID NO 36
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: feline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 5
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (111)..(111)
<223> OTHER INFORMATION: spacer for sequence alignment of Figure 5

<400> SEQUENCE: 36

Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu Pro Leu
1               5                   10                  15

Thr Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr Pro Ser
            20                  25                  30
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His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile Leu Glu
        35                  40                  45

Ser Phe Met Cys Asn Asp Ser Ser Ile Arg Ser Leu Arg Gln Arg Lys
    50                  55                  60

Ser Val Asn Ala Leu Asn Gly Pro Phe Asp Gln Glu Tyr Glu Glu Tyr
65                  70                  75                  80

Leu Gly Asp Ser His Ala Gly Tyr Lys Asp Asn Ser Lys Phe Gln Asp
                85                  90                  95

Thr Arg Ser Asn Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Xaa Asp
            100                 105                 110

Glu Ile Leu Gly Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr
        115                 120                 125

Leu Gln Ala Phe Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Gly Asn
    130                 135                 140

Glu Asp Met Val Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu
145                 150                 155                 160

Asp Ile Met Gly Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser
                165                 170                 175

Leu Leu Ala Leu Leu Gly Asn Val Phe Val Leu Ile Ile Leu Leu Thr
            180                 185                 190

Ser His Tyr Lys Leu Thr Val Pro
        195                 200


<210> SEQ ID NO 37
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: canine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 5

<400> SEQUENCE: 37

Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu Pro Leu
1               5                   10                  15

Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr Pro Ser
            20                  25                  30

His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile Leu Glu
        35                  40                  45

Ser Leu Met Cys Asn Glu Ser Ser Ile Arg Ser Leu Arg Gln Arg Lys
    50                  55                  60

Ser Val Asn Thr Leu Asn Gly Pro Phe Asp Gln Glu Tyr Glu Glu Tyr
65                  70                  75                  80

Leu Gly Asp Ser His Ala Gly Tyr Lys Asp Asn Ser Gln Phe Gln Asp
                85                  90                  95

Thr Asp Ser Asn Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp
            100                 105                 110

Glu Ile Leu Gly Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr
        115                 120                 125

Leu Gln Ala Phe Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Gly Asn
    130                 135                 140

Glu Asp Met Val Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu
145                 150                 155                 160

Asp Ile Met Gly Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser
                165                 170                 175

Leu Leu Ala Leu Leu Gly Asn Val Phe Val Leu Ile Val Leu Leu Thr
            180                 185                 190
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Ser His Tyr Lys Leu Thr Val Pro
195 200

<210> SEQ ID NO 38
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 5

<400> SEQUENCE: 38

Lys Glu Leu Ile Ala Lys Asp Thr Trp Thr Leu Lys Lys Leu Pro Leu
1 5 10 15

Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr Pro Ser
20 25 30

His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile Leu Glu
35 40 45

Ser Leu Met Cys Asn Glu Ser Ser Ile Arg Asn Leu Arg Gln Arg Lys
50 55 60

Ser Val Asn Ile Leu Arg Gly Pro Ile Tyr Gln Glu Tyr Glu Glu Asp
65 70 75 80

Pro Gly Asp Asn Ser Val Gly Tyr Lys Gln Asn Ser Lys Phe Gln Glu
85 90 95

Ser Pro Ser Asn Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp
100 105 110

Glu Val Val Gly Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr
115 120 125

Leu Gln Ala Phe Glu Ser His Tyr Asp Tyr Thr Val Cys Gly Asp Asn
130 135 140

Glu Asp Met Val Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu
145 150 155 160

Asp Ile Met Gly Tyr Arg Phe Leu Arg Ile Val Val Trp Phe Val Ser
165 170 175

Leu Leu Ala Leu Leu Gly Asn Ile Phe Val Leu Leu Ile Leu Leu Thr
180 185 190

Ser His Tyr Lys Leu Thr Val Pro
195 200

<210> SEQ ID NO 39
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: rat
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 5

<400> SEQUENCE: 39

Lys Glu Leu Ile Ala Lys Asn Thr Trp Thr Leu Lys Lys Leu Pro Leu
1 5 10 15

Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr Pro Ser
20 25 30

His Cys Cys Ala Phe Lys Asn Gln Lys Lys Ile Arg Gly Ile Leu Glu
35 40 45

Ser Leu Met Cys Asn Glu Ser Ser Ile Arg Asn Leu Arg Gln Arg Lys
50 55 60

Ser Val Asn Val Met Arg Gly Pro Val Tyr Gln Glu Tyr Glu Glu Gly
65 70 75 80

Leu Gly Asp Asn His Val Gly Tyr Lys Gln Asn Ser Lys Phe Gln Glu

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                85                  90                  95

Gly Pro Ser Asn Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp
            100                 105                 110

Glu Ile Ile Gly Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr
        115                 120                 125

Leu Gln Ala Phe Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Asp Asn
    130                 135                 140

Glu Asp Met Val Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu
145                 150                 155                 160

Asp Ile Met Gly Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser
                165                 170                 175

Pro Met Ala Leu Leu Gly Asn Val Phe Val Leu Phe Val Leu Leu Thr
            180                 185                 190

Ser His Tyr Lys Leu Thr Val Pro
        195                 200


<210> SEQ ID NO 40
<211> LENGTH: 200
<212> TYPE: PRT
<213> ORGANISM: ovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 5

<400> SEQUENCE: 40

Lys Glu Leu Ile Ala Arg Asn Thr Trp Thr Leu Lys Lys Leu Pro Leu
1               5                   10                  15

Ser Leu Ser Phe Leu His Leu Thr Arg Ala Asp Leu Ser Tyr Pro Ser
            20                  25                  30

His Cys Cys Ala Phe Lys Asn Gln Lys Asn Ile Arg Gly Ile Leu Gln
        35                  40                  45

Ser Leu Met Cys Asn Glu Ser Ser Ile Trp Gly Leu Arg Gln Arg Lys
    50                  55                  60

Ser Ala Ser Ala Leu Asn Gly Pro Phe Tyr Gln Glu Tyr Glu Glu Asp
65                  70                  75                  80

Leu Gly Asp Gly Ser Ala Gly Tyr Lys Glu Asn Ser Lys Phe Gln Asp
                85                  90                  95

Thr His Ser Asn Ser His Tyr Tyr Val Phe Phe Glu Asp Gln Glu Asp
            100                 105                 110

Glu Ile Ile Gly Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr
        115                 120                 125

Leu Gln Ala Phe Asp Asn His Tyr Asp Tyr Thr Val Cys Gly Gly Ser
    130                 135                 140

Glu Glu Met Val Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu
145                 150                 155                 160

Asp Ile Met Gly Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser
                165                 170                 175

Leu Leu Ala Leu Leu Gly Asn Val Phe Val Leu Val Ile Leu Leu Thr
            180                 185                 190

Ser His Tyr Lys Leu Thr Val Pro
        195                 200


<210> SEQ ID NO 41
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: feline
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<223> OTHER INFORMATION: Figure 6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (329)..(331)
<223> OTHER INFORMATION: spacers for sequence alignment of figure 6

<400> SEQUENCE: 41

ggaattgata gcaagaaaca cttggactct aaagaaactt ccacttacct tgagtttcct 60

tcacctcaca cgggctgacc tttcttatcc aagccactgc tgtgctttta agaatcagaa 120

gaaaatcaga ggaatccttg agtccttcat gtgtaatgac agcagtattc ggagcctgcg 180

tcagagaaaa tctgtgaatg ctttgaatgg tcccttcgac caggaatatg aagagtatct 240

aggtgacagc catgctggat ataaggacaa ctctaagttc caggatactc gcagcaactc 300

tcattattat gtcttctttg aagaacaann ngacgagatc cttggttttg g 351

<210> SEQ ID NO 42
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: bovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (236)..(238)
<223> OTHER INFORMATION: spacers for sequence alignment of figure 6

<400> SEQUENCE: 42

ggaattgata gcaagaaaca cttggactct aaggaaactt cctctttcct tgagtttcct 60

tcacctcaca cgggctgacc tttcttatcc gagccactgc tgcgctttta agaatcagaa 120

gaaaatcaga ggaatccttc agtctttaat gtgtaacgag agcagtattc ggggcctgcg 180

tcagagaaaa tccgcaagtg ctttgaatgg tcccttctac caggaatatg aggatnnnct 240

gggtgatggc agtgctgggt acaaggagaa ctccaagttc caagataccc aaagcaactc 300

tcattactat gtcttctttg aggagcaaga agatgagatc atcggttttg g 351

<210> SEQ ID NO 43
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: canine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 6

<400> SEQUENCE: 43

ggagctgata gcaagaaaca cttggactct aaagaaactc ccactttcct tgagtttcct 60

tcaccttaca cgggctgacc tttcttatcc aagccactgc tgtgctttta agaatcagaa 120

gaaaatcaga ggaatccttg agtccttaat gtgtaatgaa agcagtattc ggagcctgcg 180

ccagagaaaa tctgtgaata ctttgaatgg ccccttgac caggaatatg aagagtatct 240

gggtgacagc catgctgggt acaaggacaa ctctcagttc caggataccg atagcaattc 300

tcattattat gtcttcttcg aagaacaaga agatgagatc ctcggttttg g 351

<210> SEQ ID NO 44
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 6

<400> SEQUENCE: 44

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agaactgatc gcaaaagaca cctggactct caaaaagctc ccgctgtcgt tgagtttcct 60

ccacctcact cgggctgacc tctcttaccc gagccactgc tgcgctttta agaaccagaa 120

gaaaatcagg ggaatcctgg agtctttgat gtgtaatgag agcagtatcc ggaaccttcg 180

tcaaaggaaa tcagtgaaca tcttgagggg tcccatctac caggaatatg aagaagatcc 240

gggtgacaac agtgttgggt acaaacaaaa ctccaagttc caggagagcc caagcaactc 300

tcactattac gtcttctttg aagaacaaga ggatgaggtc gttggtttcg g 351

<210> SEQ ID NO 45
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: porcine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 6

<400> SEQUENCE: 45

ggaactgata gcaagaaata cttggactct aaagaaactt ccactgtcct tgagtttcct 60

tcacctcaca cgagctgacc tttcttatcc aagccactgc tgtgctttta agaatcagaa 120

gaagatcaga ggaatccttg agtctttaat gtgtaatgag agcagtattc ggagcctgcg 180

tcagagaaaa tctgtgaatg ctgtaaatgg tccctttac caagaatatg aagaggatct 240

gggcgacacg agtgttggga ataaggaaaa ctccaagttc caggataccc atagcaactc 300

ccattactac gtcttctttg aagaacaaga ggatgagatc attggttttg g 351

<210> SEQ ID NO 46
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: rat
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 6

<400> SEQUENCE: 46

agagctgatc gcgaagaaca cctggactct caaaaagctc cccctgtcct tgagcttcct 60

ccacctcact cgggctgacc tctcttaccc aagtcactgc tgtgctttta agaaccagaa 120

gaaaatcagg ggaatcctag agtctttgat gtgtaatgag agtagtatcc ggaacctgcg 180

tcaaagaaag tcagtgaacg tcatgagggg tcccgtctac caggaatatg aagaaggtct 240

gggtgacaac catgttgggt acaaacaaaa ctccaagttc caggagggcc caagcaactc 300

tcactattac gtcttctttg aagaacaaga ggacgagatc atcggtttcg g 351

<210> SEQ ID NO 47
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: ovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 6

<400> SEQUENCE: 47

ggaattgata gcaagaaaca cttggactct aaagaaactt cctctttcct tgagtttcct 60

tcacctcaca cgggctgacc tttcttatcc gagccactgc tgtgctttta agaatcagaa 120

gaatatcaga ggaatccttc agtctttaat gtgtaacgag agcagtattt ggggcctgcg 180

tcagagaaaa tccgcgagtg ctttgaatgg tcccttctac caggaatatg aagaggatct 240

gggtgatggc agtgctgggt acaaggagaa ctccaagttc caagataccc acagcaactc 300

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tcattactat gtcttctttg aggatcaaga agatgagatc atcggttttg g 351

<210> SEQ ID NO 48
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 6

<400> SEQUENCE: 48

ggaactgata gcaagaaaca cctggactct taagaaactt ccactttcct tgagtttcct 60

tcacctcaca cgggctgacc tttcttaccc aagccactgc tgtgccttta agaatcagaa 120

gaaaatcaga ggaatccttg agtccttgat gtgtaatgag agcagtatgc agagcttgcg 180

ccagagaaaa tctgtgaatg ccttgaatag ccccctccac caggaatatg aagagaatct 240

gggtgacagc attgttgggt acaaggaaaa gtccaagttc caggatactc ataacaacgc 300

tcattattac gtcttctttg aagaacaaga ggatgagatc attggttttg g 351

<210> SEQ ID NO 49
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 7

<400> SEQUENCE: 49

Ala His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp Glu Ile Ile Gly
1 5 10 15

Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr Leu Gln Ala Phe
20 25 30

Asp Ser His Tyr Asp Tyr Thr Ile Cys Gly Asp Ser Glu Asp Met Val
35 40 45

Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu Asp Ile Met Gly
50 55 60

Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu
65 70 75 80

Leu Gly Asn Val Phe Val Leu Leu Ile Leu Leu Thr Ser His Tyr Lys
85 90 95

Leu Asn Val Pro Arg Phe Leu Met Cys Asn Leu Ala Phe Ala Asp Phe
100 105 110

Cys Met Gly Met Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr
115 120 125

His Ser Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly
130 135 140

Cys Asn Thr Ala Gly Phe Phe
145 150

<210> SEQ ID NO 50
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: porcine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 7

<400> SEQUENCE: 50

Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp Glu Ile Ile Gly
1 5 10 15

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Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr Leu Gln Ala Phe
            20                  25                  30

Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Gly Ser Glu Asp Met Val
        35                  40                  45

Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu Asp Ile Met Gly
    50                  55                  60

Tyr Arg Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu
65                  70                  75                  80

Leu Gly Asn Val Phe Val Leu Val Ile Leu Leu Thr Ser His Tyr Lys
                85                  90                  95

Leu Thr Val Pro Arg Phe Leu Met Cys Asn Leu Ala Phe Ala Asp Phe
            100                 105                 110

Cys Met Gly Met Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr
        115                 120                 125

Gln Ser Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly
    130                 135                 140

Cys Asn Thr Ala Gly Phe Phe
145                 150


<210> SEQ ID NO 51
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: bovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 7

<400> SEQUENCE: 51

Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp Glu Ile Ile Gly
1               5                   10                  15

Phe Gly Gln Gln Leu Lys Asn Pro Gln Glu Glu Thr Leu Gln Ala Phe
            20                  25                  30

Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Gly Ser Glu Asp Met Val
        35                  40                  45

Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu Asp Ile Met Gly
    50                  55                  60

Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu
65                  70                  75                  80

Leu Gly Asn Val Phe Val Leu Val Ile Leu Leu Thr Ser His Tyr Lys
                85                  90                  95

Leu Thr Val Pro Arg Phe Leu Met Cys Asn Leu Ala Phe Ala Asp Phe
            100                 105                 110

Cys Met Gly Leu Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr
        115                 120                 125

Gln Ser Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly
    130                 135                 140

Cys Asn Thr Ala Gly Phe Phe
145                 150


<210> SEQ ID NO 52
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: feline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: spacer for sequence alignment of figure 7
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<400> SEQUENCE: 52

Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Xaa Asp Glu Ile Leu Gly
1 5 10 15

Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr Leu Gln Ala Phe
20 25 30

Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Gly Asn Glu Asp Met Val
35 40 45

Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu Asp Ile Met Gly
50 55 60

Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu
65 70 75 80

Leu Gly Asn Val Phe Val Leu Ile Ile Leu Leu Thr Ser His Tyr Lys
85 90 95

Leu Thr Val Pro Arg Phe Leu Met Cys Asn Leu Ala Phe Ala Asp Phe
100 105 110

Cys Met Gly Met Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr
115 120 125

His Ser Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly
130 135 140

Cys Asn Ala Ala Gly Phe Phe
145 150

<210> SEQ ID NO 53
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: canine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 7

<400> SEQUENCE: 53

Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp Glu Ile Leu Gly
1 5 10 15

Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr Leu Gln Ala Phe
20 25 30

Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Gly Asn Glu Asp Met Val
35 40 45

Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu Asp Ile Met Gly
50 55 60

Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu
65 70 75 80

Leu Gly Asn Val Phe Val Leu Ile Val Leu Leu Thr Ser His Tyr Lys
85 90 95

Leu Thr Val Pro Arg Phe Leu Met Cys Asn Leu Ala Phe Ala Asp Phe
100 105 110

Cys Met Gly Met Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr
115 120 125

His Ser Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly
130 135 140

Cys Asn Thr Ala Gly Phe Phe
145 150

<210> SEQ ID NO 54
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 7

<400> SEQUENCE: 54

Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp Glu Val Val Gly
1 5 10 15

Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr Leu Gln Ala Phe
20 25 30

Glu Ser His Tyr Asp Tyr Thr Val Cys Gly Asp Asn Glu Asp Met Val
35 40 45

Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu Asp Ile Met Gly
50 55 60

Tyr Arg Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu
65 70 75 80

Leu Gly Asn Ile Phe Val Leu Leu Ile Leu Leu Thr Ser His Tyr Lys
85 90 95

Leu Thr Val Pro Arg Phe Leu Met Cys Asn Leu Ala Phe Ala Asp Phe
100 105 110

Cys Met Gly Val Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr
115 120 125

His Ser Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly
130 135 140

Cys Asn Thr Ala Gly Phe Phe
145 150

<210> SEQ ID NO 55
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: rat
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 7

<400> SEQUENCE: 55

Ser His Tyr Tyr Val Phe Phe Glu Glu Gln Glu Asp Glu Ile Ile Gly
1 5 10 15

Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr Leu Gln Ala Phe
20 25 30

Asp Ser His Tyr Asp Tyr Thr Val Cys Gly Asp Asn Glu Asp Met Val
35 40 45

Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu Asp Ile Met Gly
50 55 60

Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser Pro Met Ala Leu
65 70 75 80

Leu Gly Asn Val Phe Val Leu Phe Val Leu Leu Thr Ser His Tyr Lys
85 90 95

Leu Thr Val Pro Arg Phe Leu Met Cys Asn Leu Ala Phe Ala Asp Phe
100 105 110

Cys Met Gly Val Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr
115 120 125

His Thr Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly
130 135 140

Cys Asn Thr Ala Gly Phe Phe
145 150

<210> SEQ ID NO 56
<211> LENGTH: 151
<212> TYPE: PRT

<213> ORGANISM: ovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 7

<400> SEQUENCE: 56

Ser His Tyr Tyr Val Phe Phe Glu Asp Gln Glu Asp Glu Ile Ile Gly
1 5 10 15

Phe Gly Gln Glu Leu Lys Asn Pro Gln Glu Glu Thr Leu Gln Ala Phe
20 25 30

Asp Asn His Tyr Asp Tyr Thr Val Cys Gly Gly Ser Glu Glu Met Val
35 40 45

Cys Thr Pro Lys Ser Asp Glu Phe Asn Pro Cys Glu Asp Ile Met Gly
50 55 60

Tyr Lys Phe Leu Arg Ile Val Val Trp Phe Val Ser Leu Leu Ala Leu
65 70 75 80

Leu Gly Asn Val Phe Val Leu Val Ile Leu Leu Thr Ser His Tyr Lys
85 90 95

Leu Thr Val Pro Arg Phe Leu Met Cys Asn Leu Ala Phe Ala Asp Phe
100 105 110

Cys Met Gly Leu Tyr Leu Leu Leu Ile Ala Ser Val Asp Leu Tyr Thr
115 120 125

Gln Ser Glu Tyr Tyr Asn His Ala Ile Asp Trp Gln Thr Gly Pro Gly
130 135 140

Cys Asn Thr Ala Gly Phe Phe
145 150

<210> SEQ ID NO 57
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: feline
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 8

<400> SEQUENCE: 57

gccaggagct taaaaaccca caagaagaga ccctacaggc cttcgatagc cattatgact 60

acactgtgtg tggaggcaat gaagacatgg tgtgtactcc caagtcagat gagttcaacc 120

cctgtgaaga cataatgggc tacaagttcc tgagaattgt ggtgtggttt gttagtctgc 180

tggctctcct gggcaatgtc 200

<210> SEQ ID NO 58
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: bovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 8

<400> SEQUENCE: 58

gccaacagct caaaaacccc caggaggaga ccctgcaggc ctttgacagc cattacgact 60

ataccgtgtg tgggggcagt gaggacatgg tgtgtacccc caagtcggat gagttcaacc 120

cctgtgagga catcatgggc tacaagttcc tgagaatcgt ggtgtggttt gtgagtctgc 180

tggctctcct gggcaacgtc 200

<210> SEQ ID NO 59
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: canine

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 8

<400> SEQUENCE: 59

ggcaggagct taaaaaccca caggaagaga ccctccaggc ctttgatagc cattatgact 60

acactgtgtg tggtggcaat gaagacatgg tgtgtactcc taagtcagat gagttcaacc 120

cctgtgaaga cataatgggc tacaagttcc tgaggattgt ggtgtggttt gttagtctgc 180

tggctctcct gggcaatgtc 200

<210> SEQ ID NO 60
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 8

<400> SEQUENCE: 60

gccaagagct caaaaatcct caggaagaga ctctccaagc cttcgagagc cactatgact 60

acacggtgtg tggggacaac gaggacatgg tgtgtacccc caagtcggac gagtttaacc 120

cctgtgaaga tatcatgggc tacaggttcc tgagaatcgt ggtgtggttt gtcagtctgc 180

tggctctcct gggcaatatc 200

<210> SEQ ID NO 61
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: porcine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 8

<400> SEQUENCE: 61

gccaagagct caaaaacccc caggaagaga ccctccaggc ctttgacagc cattacgact 60

acaccgtgtg tgggggcagt gaagacatgg tgtgcacccc caagtcagat gagttcaacc 120

cctgtgaaga cataatgggc tacaggttcc tgagaatcgt ggtgtggttc gttagcctgc 180

tggctctcct gggcaatgtc 200

<210> SEQ ID NO 62
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: rat
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 8

<400> SEQUENCE: 62

gccaagagct caaaaatcct caggaagaga ctctccaagc cttcgacagc cactatgact 60

acactgtgtg tggggacaac gaggacatgg tgtgtacccc caagtcagac gagtttaacc 120

cctgtgaaga tatcatgggc tacaagttcc tgagaatcgt ggtatggttt gtcagtccga 180

tggctctcct gggcaacgtc 200

<210> SEQ ID NO 63
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: ovine
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 8

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<400> SEQUENCE: 63

gccaagagct taaaaacccc caggaggaga ccctgcaggc ctttgacaac cattacgact 60

ataccgtgtg cgggggggagt gaggagatgg tgtgtacccc caagtcggat gagttcaacc 120

cctgtgagga catcatgggc tacaagttcc tgagaattgt ggtgtggttt gtgagtctgc 180

tggctctcct gggcaacgtc 200

<210> SEQ ID NO 64
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: human
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figure 8

<400> SEQUENCE: 64

gccaggagct caaaaacccc caggaagaga ctctacaagc ttttgacagc cattatgact 60

acaccatatg tggggacagt gaagacatgg tgtgtacccc caagtccgat gagttcaacc 120

cgtgtgaaga cataatgggc tacaagttcc tgagaattgt ggtgtggttc gttagtctgc 180

tggctctcct gggcaatgtc 200

<210> SEQ ID NO 65
<211> LENGTH: 209
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 9 & 10

<400> SEQUENCE: 65

Asp Val Gln Leu Lys His Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile
35 40 45

Gly Leu Ile Asn Pro Tyr Thr Gly Gly Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Phe
65 70 75 80

Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Asn Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro
115 120 125

Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val
130 135 140

Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser
145 150 155 160

Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu
165 170 175

Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser
180 185 190

Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Lys Thr Lys Val
195 200 205

Asp

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<210> SEQ ID NO 66
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 11 & 12

<400> SEQUENCE: 66

Ser Ile Val Met Ser Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Thr Val Asp Asn Tyr
20 25 30

Gly Phe Ser Phe Met His Trp Phe Gln Gln Ile Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ser Leu Asn Ile His
65 70 75 80

Pro Met Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys Gln Gln Ser Lys
85 90 95

Glu Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
115 120 125

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
130 135 140

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145 150 155 160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
180 185 190

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
195 200 205

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
210 215

<210> SEQ ID NO 67
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 13 & 14

<400> SEQUENCE: 67

Asp Val Gln Leu Val Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Asn Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asp Pro Tyr Asn Gly Ala Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Glu Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Trp Asp Trp Asp Pro Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val
        115                 120                 125

Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Ser Gly Ser Ser Val Thr
    130                 135                 140

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr
145                 150                 155                 160

Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Ser Pro Ala Val
                165                 170                 175

Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser
            180                 185                 190

Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala
        195                 200                 205

Ser Lys Thr Lys Val Asp
    210


<210> SEQ ID NO 68
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 15 & 16

<400> SEQUENCE: 68

Asp Ile Leu Leu Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Ser
            20                  25                  30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
        35                  40                  45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Phe Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Val Glu Ser
65                  70                  75                  80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Asn Arg Trp Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
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<210> SEQ ID NO 69
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 17 & 18

<400> SEQUENCE: 69

Asp Val Gln Ile Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ala Tyr
20 25 30

Asn Met His Trp Val Lys Gln Thr His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Asp Pro Tyr Ser Gly Ala Thr Ser Tyr His Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Arg Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Trp Asp Trp Asp Pro Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val
115 120 125

Tyr Pro Leu Ala Pro Gly Cys Gly Asp Thr Thr Gly Ser Ser Val Thr
130 135 140

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Ser Val Thr Val Thr
145 150 155 160

Trp Asn Ser Gly Ser Leu Ser Ser Ser Val His Thr Phe Pro Ala Leu
165 170 175

Leu Gln Ser Gly Leu Tyr Thr Met Ser Ser Ser Val Thr Val Pro Ser
180 185 190

Ser Ala Trp Pro Ser Gln Thr Val Thr Cys Ser Val Ala His Pro Ala
195 200 205

Ser Asn Thr Thr Val Asp
210

<210> SEQ ID NO 70
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 19 & 20

<400> SEQUENCE: 70

Ser Val Glu Met Ser Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ile Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Ser
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Ala Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Ser Asn Ser Trp Pro Leu

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                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210


<210> SEQ ID NO 71
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 21 & 22

<400> SEQUENCE: 71

Asp Val Gln Met Gln Gln Pro Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15

Ser Leu Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
            20                  25                  30

Asn Met His Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Asp Pro Tyr Ser Gly Ala Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60

Glu Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Arg Trp Asp Trp Asp Pro Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Ala Pro Ser Val
        115                 120                 125

Tyr Pro Leu Ala Pro Val Cys Gly Asp Thr Ser Gly Ser Ser Val Thr
    130                 135                 140

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Leu Thr
145                 150                 155                 160

Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Thr Ser
            180                 185                 190

Ser Thr Trp Pro Ser Gln Ser Ile Thr Cys Asn Val Ala His Pro Ala
        195                 200                 205

Ser Asn Thr Lys Val Asp
    210
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<210> SEQ ID NO 72
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 23 & 24

<400> SEQUENCE: 72

Asn Ile Leu Met Thr Gln Ser Pro Ala Ile Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Val Ser Phe Ala Cys Arg Ala Ser Gln Ser Ile Gly Thr Ser
20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Thr Asn Arg Trp Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
100 105 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
115 120 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
130 135 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145 150 155 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
165 170 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
180 185 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
195 200 205

Phe Asn Arg Asn Glu Cys
210

<210> SEQ ID NO 73
<211> LENGTH: 627
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 25 & 26

<400> SEQUENCE: 73

gacgtccagc tgaagcactc aggacctgag ctggtgaagc ctggagcttc aatgaagata 60

tcctgtaagg cttctggtta ctcattcact ggctacacca tgaactgggt gaagcagagc 120

catggaaaga accttgagtg gattggactt attaatcctt acactggtgg tactaactac 180

aaccagaagt tcaagggcaa ggccaaatta actgtagaca agtcatccag cacagccttc 240

atggagctcc tcagtctgac atctgaggac tctgcagtct attactgtgc aagagatggt 300

aaccttgact actggggcca aggcaccact ctcacagtct cctcagccaa aacgacaccc 360

ccatctgtct atccactggc ccctggatct gctgcccaaa ctaactccat ggtgaccctg 420

ggatgcctgg tcaagggcta tttccctgag ccagtgacag tgacctggaa ctctggatcc 480

ctgtccagcg gtgtgcacac cttcccagct gtcctgcagt ctgacctcta cactctgagc 540

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agctcagtga ctgtcccctc cagcacctgg cccagcgaga ccgtcacctg caacgttgcc 600

cacccagcca gcaagaccaa ggtcgac 627

<210> SEQ ID NO 74
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 27 & 28

<400> SEQUENCE: 74

agcattgtga tgtcacagtc gccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca gagccagcga aactgttgat aattatggct ttagttttat gcactggttc 120

caacagatac cgggacagcc acccaaactc ctcatctatg ctgcatccaa ccaaggatcc 180

ggggtccctg ccaggtttag tggcagtggg tctgggacag acttcagcct caacatccat 240

cctatggagg aggatgatac tgcaatgtat ttctgtcagc aaagtaagga ggttccgtac 300

acgttcggag gggggaccaa gctggaaata aaacgggctg atgctgcacc aactgtatcc 360

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 480

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 540

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600

actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgt 654

<210> SEQ ID NO 75
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 29 & 30

<400> SEQUENCE: 75

gacgtccagt tggtgcaatc tggacctgag ctggtgaagc ctggagcttc agtgaagatg 60

tcctgcaagg cttctggtta ctcattcact ggctacaaca tgcactgggt gaagcagagc 120

catggaaaga gccttgagtg gattgggtat attgatcctt acaatggtgc tactagctac 180

aaccagaaat tcgaggacaa ggccacattg actgtagaca aatcttccag cacagcctac 240

atgcagctca acagcctgac atctgaggac tctgcagtct attactgtgc aagaagatgg 300

gactgggacc cttatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 360

gccaaaacaa cagccccatc ggtctatcca ctggcccctg tgtgtggaga tacaagtggc 420

tcctcggtga ctctaggatg cctggtcaag ggttatttcc ctgagccagt gaccttgacc 480

tggaactctg gatccctgtc cagtggtgtg cacacctccc cagctgtcct gcagtctgac 540

ctctacaccc tcagcagctc agtgactgta acctcgagca cctggcccag ccagtccatc 600

acctgcaatg tggcccaccc ggccagcaag accaaggtcg ac 642

<210> SEQ ID NO 76
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 31 & 32

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<400> SEQUENCE: 76

gacatcttgc tgactcagtc tccagccatc ctgtctgtga gtccaggaga aagagtcagt 60

ttctcctgca gggccagtca gagcattggc acaagcatac actggtatca gcaaagaaca 120

aatggttctc caaggcttct cataaagtat gcttctgagt ccatctctgg gatattttct 180

aggtttagtg gcagtggatc agggacagat tttactctta ccatcaacag tgtggagtct 240

gaagatattg cagattatta ctgtcaacaa agtaataggt ggccgctcac gttcggagct 300

gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> SEQ ID NO 77
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 33 & 34

<400> SEQUENCE: 77

gacgtccaga tccagcagtc tgggcctgag ctggtgaagc ctggagcttc agtgaagatg 60

tcctgcaagg cttctggtta ctcattcact gcctacaaca tgcactgggt gaagcagacc 120

catggaaaga gccttgagtg gattggttat attgatcctt acagtggtgc tactagctac 180

caccagaaat tcaagggcaa ggccacattg actgttgaca aatcttccag cacagcctac 240

atgcgcctca acagcctgac atctgaggac tctgcagtct attactgtgc aagaagatgg 300

gactgggacc cttatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 360

gccaaaacaa cacccccatc agtctatcca ctggcccctg ggtgtggaga tacaactggt 420

tcctccgtga ctctgggatg cctggtcaag ggctacttcc ctgagtcagt gactgtgact 480

tggaactctg gatccctgtc cagcagtgtg cacaccttcc cagctctcct gcagtctgga 540

ctctacacta tgagcagctc agtgactgtc ccctccagcg cctggccaag tcagaccgtc 600

acctgcagcg ttgctcaccc ggccagcaac accacggtcg ac 642

<210> SEQ ID NO 78
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 35 & 36

<400> SEQUENCE: 78

agcgttgaga tgtcacagtc gccagccatc ctgtctgtga gtccaggaga aagaatcagt 60

ttctcctgca gggccagtca gagcattggc acaagcatac actggtatca gcaaagaaca 120

aatggttctc caaggcttct cattaagtat gcttctgcgt ctatctctgg gatcccttcc 180

aggtttagtg gcagtggatc agggacagat tttactctta gcatcaacag tgtggagtct 240

gaagatattg cagattatta ctgtcaacaa agtaatagct ggccgctcac gttcggtgct 300

gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

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tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> SEQ ID NO 79
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 37 & 38

<400> SEQUENCE: 79

gacgtccaga tgcagcagcc tgggcctgag ctggtgaagc ctggagcttc actaaagatg 60

tcctgcaagg cttctggtta ctcattcact ggctacaaca tgcactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggatat attgatcctt acagtggtgc tactagctac 180

aaccagaaat tcgagggcaa ggccacattg actgtagaca aatcttccag cacagcctac 240

atgcagctca acagcctgac atctgaggac tctgcagtct attactgtgc aagaagatgg 300

gactgggacc cttatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca 360

gccaaaacaa cagccccatc ggtctatcca ctggcccctg tgtgtggaga tacaagtggc 420

tcctcggtga ctctaggatg cctggtcaag ggttatttcc ctgagccagt gaccttgacc 480

tggaactctg gatccctgtc cagtggtgtg cacaccttcc cagctgtcct gcagtctgac 540

ctctacaccc tcagcagctc agtgactgta acctcgagca cctggcccag ccagtccatc 600

acctgcaatg tggcccaccc agccagcaac accaaggtcg ac 642

<210> SEQ ID NO 80
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 39 & 40

<400> SEQUENCE: 80

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aatggttctc caaggcttct cataaagtat gcttctgagt ctatctctgg gatcccttcc 180

aggtttagtg gcagtggatc agggacagat tttactctta gcatcaacag tgtggagtct 240

gaagatattg cagattatta ctgtcaacaa actaataggt ggccgctcac gttcggtgct 300

gggaccaagc tggagctgaa acgggctgat gctgcaccaa ctgtatccat cttcccacca 360

tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac 420

cccaaagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg 480

aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcacg 540

ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca 600

tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gt 642

<210> SEQ ID NO 81
<211> LENGTH: 206
<212> TYPE: PRT

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<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 41 & 42

<400> SEQUENCE: 81

Asp Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Thr Ser Gly Val Asn Ile Lys Asp Thr
20 25 30

Tyr Met His Trp Met Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro Lys Phe
50 55 60

Arg Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Val Tyr
65 70 75 80

Val Gln Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Tyr Asp Gly Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
100 105 110

Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
115 120 125

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
130 135 140

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
145 150 155 160

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
165 170 175

Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
180 185 190

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp
195 200 205

<210> SEQ ID NO 82
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 43 & 44

<400> SEQUENCE: 82

Asn Ile Val Met Thr Gln Thr Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Ser Tyr
20 25 30

Gly Asn Asn Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro
35 40 45

Arg Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Thr Asn
65 70 75 80

Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln Gln Ser His
85 90 95

Lys Asp Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
100 105 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
115 120 125

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Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145                 150                 155                 160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
            180                 185                 190

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
        195                 200                 205

Ile Val Lys Ser Phe Lys Ala Asn Glu Cys
    210                 215


<210> SEQ ID NO 83
<211> LENGTH: 209
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 45 & 46

<400> SEQUENCE: 83

Asp Val Gln Leu Lys His Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15

Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
            20                  25                  30

Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Asp Trp Ile
        35                  40                  45

Gly Leu Ile Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asp Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Gly Leu Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
            100                 105                 110

Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro
        115                 120                 125

Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val
    130                 135                 140

Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser
145                 150                 155                 160

Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu
                165                 170                 175

Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser
            180                 185                 190

Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Lys Thr Lys Val
        195                 200                 205

Asp


<210> SEQ ID NO 84
<211> LENGTH: 218
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 47 & 48
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<400> SEQUENCE: 84

Asp Ile Val Met Thr Gln Thr Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Phe Cys Arg Ala Ser Gln Ser Val Asp Tyr Asn
20 25 30

Gly Ile Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Phe
85 90 95

Glu Asp Pro His Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
115 120 125

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
130 135 140

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145 150 155 160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
180 185 190

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
195 200 205

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
210 215

<210> SEQ ID NO 85
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 49 & 50

<400> SEQUENCE: 85

Asp Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Arg Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Arg Tyr
20 25 30

Trp Ile His Trp Leu Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Phe Pro Gly Asn Arg Asp Thr Ser Tyr Asn Gln Arg Phe
50 55 60

Lys Gly Lys Ala Glu Val Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Asp Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Trp Pro Tyr Tyr Gly Ser Ile Tyr Val Asn Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro
115 120 125

Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met

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    130                 135                 140

Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
            180                 185                 190

Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
        195                 200                 205

Pro Ala Ser Ser Thr Lys Val Asp
    210                 215


<210> SEQ ID NO 86
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 51 & 52

<400> SEQUENCE: 86

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Ser Leu Gly
1               5                   10                  15

Asp Gln Ala Ser Ile Ser Cys Arg Thr Ser Gln Asn Leu Val His Arg
            20                  25                  30

Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Gly
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
        115                 120                 125

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
145                 150                 155                 160

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
            180                 185                 190

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
        195                 200                 205

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
    210                 215


<210> SEQ ID NO 87
<211> LENGTH: 618
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 53 & 54

<400> SEQUENCE: 87
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tcctgcacca cttctggcgt caacattaaa gacacctata tgcactggat gaagcagagg 120

cctgaacagg gcctggagtg gattggaagg attgatcctg cgaatggtaa tactaaatat 180

gacccgaaat tccggggcaa ggccactata acagcagaca catcctccaa cacggtctac 240

gtgcaactca gaagcctgac atctgaggac actgccgtct attactgtgc ctatgatggt 300

tactggggcc aagggactct ggtcactgtc tctgcagcca aaacgacacc cccatctgtc 360

tatccactgg cccctggatc tgctgcccaa actaactcca tggtgaccct gggatgcctg 420

gtcaagggct atttccctga gccagtgaca gtgacctgga actctggatc cctgtccagc 480

ggtgtgcaca ccttcccagc tgtcctgcag tctgacctct acactctgag cagctcagtg 540

actgtccct ccagcacctg gcccagcgag accgtcacct gcaacgttgc ccacccggcc 600

agcagcacca aggtcgac 618

<210> SEQ ID NO 88
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 55 & 56

<400> SEQUENCE: 88

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atatcctgca gagccagtga aagtgttgat agttatggca ataattttat gcactggtac 120

cagcagaaac caggacagtc acccagactc ctcatctatc gtgcatccaa cctagaatct 180

gggatccctg ccaggttcag tggcagtggg tctaggacag acttcaccct caccactaat 240

cctgtggagg ctgatgatgt tgcaacctat tactgtcagc aaagtcataa ggatccgctc 300

acgttcggtg ctgggaccaa gctggagctg aaacgggctg atgctgcacc aactgtatcc 360

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 480

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 540

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600

actcacaaga catcaacttc acccattgtc aagagcttca aggaacatga gtgt 654

<210> SEQ ID NO 89
<211> LENGTH: 626
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 57 & 58

<400> SEQUENCE: 89

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cctgcaaggc ttctggttac tcattcactg gctacaccat gaactgggtg aagcagagcc 120

atggaaagaa ccttgagtgg attggactta ttaatcctta caatggtggt actagctacg 180

accagaagtt caagggcaag gccacattaa ctgtagacaa gtcatccagc acagcctaca 240

tggagctcct cagtctgaca tctgaggact ctgcagtcta ttactgtgca agagatggcc 300

tgatggacta ctggggtcaa ggaacctcag tcaccgtctc ctcagccaaa acgacacccc 360

catctgtcta tccactggcc cctggatctg ctgcccaaac taactccatg gtgaccctgg 420

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gatgcctggt caagggctat ttccctgagc cagtgacagt gacctggaac tctggatccc 480

tgtccagcgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac actctgagca 540

gctcagtgac tgtcccctcc agcacctggc ccagcgagac cgtcacctgc aacgttgccc 600

acccggccag caagaccaag gtcgac 626

<210> SEQ ID NO 90
<211> LENGTH: 654
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 59 & 60

<400> SEQUENCE: 90

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atcttctgca gagccagcca gagtgtcgat tataatggaa ttagttatat gcactggttc 120

caacagaaac caggacagcc acccaaactc ctcatctatg ctgcatccaa cctagaatct 180

gggatccctg ccaggttcag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggagg aggaagatgc tgcaacctat tactgtcagc aaagttttga ggatccgcac 300

acgttcggag gggggaccaa gctggaaata aaacgggctg atgctgcacc aactgtatcc 360

atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg 420

aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa 480

aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc 540

agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc 600

actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgt 654

<210> SEQ ID NO 91
<211> LENGTH: 648
<212> TYPE: DNA
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 61 & 62

<400> SEQUENCE: 91

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cctggacagg gtctagaatg gattggtgct atttttcctg gaaatcgtga taccagttac 180

aaccagaggt tcaagggcaa ggccgaagtg actgcagtca catccgccag cactgcctac 240

ttggacctca gtagcctgac aaatgaggac tctgcggtct attactgtac aagatggcct 300

tactatggtt ccatctacgt taactttgac tactggggcc aaggcaccac tctcacagtc 360

tcctcagcca aaacgacacc cccatctgtc tatccactgg cccctggatc tgctgcccaa 420

actaactcca tggtgaccct gggatgcctg gtcaagggct atttccctga gccagtgaca 480

gtgacctgga actctggatc cctgtccagc ggtgtgcaca ccttcccagc tgtcctgcag 540

tctgacctct acactctgag cagctcagtg actgtcccct ccagcacctg gcccagcgag 600

accgtcacct gcaacgttgc ccacccagcc agcagcacca aggtcgac 648

<210> SEQ ID NO 92
<211> LENGTH: 657
<212> TYPE: DNA
<213> ORGANISM: mouse

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<223> OTHER INFORMATION: Figures 63 & 64

<400> SEQUENCE: 92

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atctcttgca gaactagtca gaaccttgta cacaggaatg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgattt acaaaatttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaggtac acatgttcct 300

ccgacgttcg gtggaggcac caagctggaa atcaaacggg ctgatgctgc accaactgta 360

tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 420

ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 480

caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 540

agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 600

gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgt 657

The invention claimed is:

1. A method of screening a sample of body fluid for TSH receptor autoantibodies wherein said sample is from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) contacting said sample with a polypeptide comprising a full length TSH receptor, so as to permit said polypeptide to bind with TSH receptor autoantibodies present in said sample;

(b) contacting said sample with one or more monoclonal antibodies that binds TSH receptor and competes with said autoantibodies for binding to said polypeptide, wherein said one or more monoclonal antibodies is positive for thyroid stimulating activity at a concentration of 20 μg/ml in a cyclic AMP thyroid cell assay and positive for inhibition of TSH binding to TSH receptor at a concentration of 20 μg/ml, said one or more monoclonal antibodies being classified as positive for thyroid stimulating activity if the thyroid stimulating activity is greater than 180 percent in the cyclic AMP thyroid cell assay wherein said percent thyroid stimulation activity comprises 100×(ratio of cyclic AMP produced in the thyroid cell assay in the presence of said monoclonal antibody to cyclic AMP produced in the thyroid cell assay in the presence of sera pooled from healthy blood donors) and said one or more monoclonal antibodies being classified as positive for inhibition of TSH binding to TSH receptor if the inhibition of TSH binding to TSH receptor is greater than 10%; and

(c) detecting binding of said polypeptide with said autoantibodies thereby providing an indication of the presence of said autoantibodies in said sample.

2. A method of screening a sample of body fluid for TSH receptor autoantibodies wherein said sample is from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) providing said sample of body fluid from said subject;

(b) contacting said sample with

(i) a full length TSH receptor, and

(ii) at least one monoclonal antibody that binds the TSH receptor in (i) and is positive for thyroid stimulating activity at a concentration of 20 μg/ml in a cyclic AMP thyroid cell assay and positive for inhibition of TSH binding to TSH receptor at a concentration of 20 μg/ml, said one or more monoclonal antibodies being classified as positive for thyroid stimulating activity if the thyroid stimulating activity of said one or more monoclonal antibodies is greater than 180 percent in the cyclic AMP thyroid cell assay wherein said percent thyroid stimulation activity comprises 100×(ratio of cyclic AMP produced in the thyroid cell assay in the presence of said monoclonal antibody to cyclic AMP produced in the thyroid cell assay in the presence of sera pooled from healthy blood donors) and said one or more monoclonal antibodies being classified as positive for inhibition of TSH binding to TSH receptor if the inhibition of TSH binding to TSH receptor is greater than 10%,

so as to permit said TSH receptor to bind with either autoantibodies to a TSH receptor present in said sample, or said monoclonal antibody; and

(c) detecting the binding of said TSH receptor with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample.

3. A method of screening a sample of body fluid for autoantibodies to a TSH receptor wherein said sample is from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) contacting said sample with

(i) a full length TSH receptor; and

(ii) one or more monoclonal antibodies for a TSH receptor that are capable of binding to the TSH receptor so as to stimulate the TSH receptor wherein said monoclonal antibodies:

(1) are positive for TSH stimulating activity at a concentration of 20 μg/ml in a cyclic AMP thyroid cell assay, said one or more monoclonal antibodies being classified as positive if the thyroid stimulat-

ing activity of said one or more monoclonal antibodies is greater than 180 percent in the cyclic AMP thyroid cell assay wherein said percent thyroid stimulation activity comprises 100×(ratio of cyclic AMP produced in the thyroid cell assay in the presence of said monoclonal antibody to cyclic AMP produced in the thyroid cell assay in the presence of sera pooled from healthy blood donors); and

(2) are positive for inhibition of TSH binding to TSH receptor at a concentration of 20 μg/ml, said one or more monoclonal antibodies being classified as positive for inhibition of TSH binding to TSH receptor if the inhibition of TSH binding to TSH receptor is greater than 10%;

so as to permit said TSH receptor to bind with either autoantibodies to a TSH receptor present in said sample, or said one or more monoclonal antibodies for the TSH receptor; and

(b) detecting binding of said TSH receptor with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample.

4. A method according to claim **3**, which comprises providing labeling means for said one or more antibodies for a TSH receptor, which antibody is capable of binding to a TSH receptor so as to stimulate the TSH receptor, which antibody does not comprise TSH or naturally produced autoantibodies to the TSH receptor.

5. A method according to claim **3**, wherein said one or more monoclonal antibodies includes a monoclonal antibody comprising:

(a) a V_H domain comprising amino acid residues 9 to 120 of SEQ ID NO:67 and a V_L domain comprising amino acid residues 9 to 107 of SEQ ID NO:68;

(b) a V_H domain comprising amino acid residues 9 to 120 of SEQ ID NO:69 and a V_L domain comprising amino acid residues 9 to 107 of SEQ ID NO:70; or

(c) a V_H domain comprising amino acid residues 9 to 120 of SEQ ID NO:71 and a V_L domain comprising amino acid residues 9 to 107 of SEQ ID NO:72.

6. A method according to claim **3**, wherein said one or more monoclonal antibodies for a TSH receptor have a binding affinity for TSH receptor of at least about 10^8 molar^{-1}.

7. A method according to claim **3**, wherein said one or more monoclonal antibodies includes a monoclonal antibody comprising a V_H domain comprising amino acid residues 9 to 120 of SEQ ID NO:67 and a V_L domain comprising amino acid residues 9 to 107 of SEQ ID NO:68.

8. A method according to claim **3**, wherein said one or more monoclonal antibodies includes a monoclonal antibody comprising:

i) a V_H domain wherein CDR1 comprises amino acid residues 31 to 35 of SEQ ID NO: 67, CDR2 comprises amino acid residues 50 to 66 of SEQ ID NO:67, and CDR3 comprises amino acid residues 99 to 109 of SEQ ID NO:67; and

a V_L domain wherein CDR1 comprises amino acid residues 24 to 34 of SEQ ID NO:68, CDR2 comprises amino acid residues 50 to 56 of SEQ ID NO:68, and CDR3 comprises amino acid residues 89 to 97 of SEQ ID NO: 68;

ii) a V_H domain wherein CDR 1 comprises amino acid residues 31 to 35 of SEQ ID NO:69, CDR 2 comprises amino acid residues 50 to 66 of SEQ ID NO:69, and CDR 3 comprises amino acid residues 99 to 109 of SEQ ID NO:69, and

a V_L domain wherein CDR1 comprises amino acid residues 24 to 34 of SEQ ID NO:70, CDR2 comprises amino acid residues 50 to 56 of SEQ ID NO:70, and CDR3 comprises amino acid residues 89 to 97 of SEQ ID NO: 70; or

iii) a V_H domain wherein CDR1 comprises amino acid residues 31 to 35 of SEQ ID NO: 71, CDR2 comprises amino acid residues 50 to 66 of SEQ ID NO:71, and CDR 3 comprises amino acid residues 99 to 109 of SEQ ID NO:71, and

a V_L domain wherein CDR1 comprises amino acid residues 24 to 34 of SEQ ID NO:72, CDR2 comprises amino acid residues 50 to 56 of SEQ ID NO:72, and CDR3 comprises amino acid residues 89 to 97 of SEQ ID NO: 72.

9. A method of screening a sample of body fluid for TSH receptor autoantibodies wherein said sample is from a subject suspected of suffering from, susceptible to, having or recovering from autoimmune disease associated with an immune reaction to a TSH receptor, said method comprising:

(a) contacting said sample with

(i) a full length TSH receptor, and

(ii) one or more monoclonal antibodies to a TSH receptor that are capable of binding to the TSH receptor so as to stimulate the TSH receptor, wherein said monoclonal antibodies:

(1) are positive for TSH stimulating activity at a concentration of 20 μg/ml in a cyclic AMP thyroid cell assay, said one or more monoclonal antibodies being classified as positive if the thyroid stimulating activity of said one or more monoclonal antibodies is greater than 180 percent in the cyclic AMP thyroid cell assay wherein said percent thyroid stimulation activity comprises 100×(ratio of cyclic AMP produced in the thyroid cell assay in the presence of said monoclonal antibody to cyclic AMP produced in the thyroid cell assay in the presence of sera pooled from healthy blood donors); and

(2) are positive for inhibition of TSH binding to TSH receptor at a concentration of 20 μg/ml, said one or more monoclonal antibodies being classified as positive for inhibition of TSH binding to TSH receptor if the inhibition of TSH binding to TSH receptor is greater than 10%;

so as to permit said TSH receptor to bind with either autoantibodies to a TSH receptor present in said sample, or said one or more monoclonal antibodies; and

(b) detecting binding of said TSH receptor with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to a TSH receptor in said sample;

wherein said one or more monoclonal antibodies are directly or indirectly immobilised to a surface either prior to, or after step (a).

10. A method according to claim **9**, wherein said-antibody is capable of binding to a TSH receptor so as to stimulate the TSH receptor, which antibody does not comprise TSH or naturally produced autoantibodies to the TSH receptor.

11. A method according to claim **9**, which comprises providing labeling means for said TSH receptor, said one or more epitopes thereof or said polypeptide.

12. A method according to claim **9**, wherein said one or more monoclonal antibodies includes a monoclonal antibody comprising:

(a) a V_H domain comprising amino acid residues 9 to 120 of SEQ ID NO:67 and a V_L domain comprising amino acid residues 9 to 107 of SEQ ID NO:68;

(b) a V_H domain comprising amino acid residues 9 to 120 of SEQ ID NO:69 and a V_L domain comprising amino acid residues 9 to 107 of SEQ ID NO:70; or

(c) a V_H domain comprising amino acid residues 9 to 120 of SEQ ID NO:71 and a V_L domain comprising amino acid residues 9 to 107 of SEQ ID NO:72.

13. A method according to claim **9**, wherein said one or more monoclonal antibodies for a TSH receptor have a binding affinity for TSH receptor of at least about 10^8 $molar^{-1}$.

14. A method according to claim **9**, wherein said one or more monoclonal antibodies includes a monoclonal antibody comprising a V_H domain comprising amino acid residues 9 to 120 of SEQ ID NO:67 and a V_L domain comprising amino acid residues 9 to 107 of SEQ ID NO:68.

15. A method according to claim **9**, wherein said one or more monoclonal antibodies includes a monoclonal antibody comprising:

i) a V_H domain wherein CDR1 comprises amino acid residues 31 to 35 of SEQ ID NO: 67, CDR2 comprises amino acid residues 50 to 66 of SEQ ID NO:67, and CDR3 comprises amino acid residues 99 to 109 of SEQ ID NO:67; and

a V_L domain wherein CDR1 comprises amino acid residues 24 to 34 of SEQ ID NO:68, CDR2 comprises amino acid residues 50 to 56 of SEQ ID NO:68, and CDR3 comprises amino acid residues 89 to 97 of SEQ ID NO: 68;

ii) a V_H domain wherein CDR 1 comprises amino acid residues 31 to 35 of SEQ ID NO:69, CDR 2 comprises amino acid residues 50 to 66 of SEQ ID NO:69, and CDR 3 comprises amino acid residues 99 to 109 of SEQ ID NO:69, and

a V_L domain wherein CDR1 comprises amino acid residues 24 to 34 of SEQ ID NO:70, CDR2 comprises amino acid residues 50 to 56 of SEQ ID NO:70, and CDR3 comprises amino acid residues 89 to 97 of SEQ ID NO:70; or iii) a V_H domain wherein CDR1 comprises amino acid residues 31 to 35 of SEQ ID NO:71, CDR2 comprises amino acid residues 50 to 66 of SEQ ID NO:71, and CDR 3 comprises amino acid residues 99 to 109 of SEQ ID NO:71, and

a V_L domain wherein CDR1 comprises amino acid residues 24 to 34 of SEQ ID NO:72, CDR2 comprises amino acid residues 50 to 56 of SEQ ID NO:72, and CDR3 comprises amino acid residues 89 to 97 of SEQ ID NO:72.

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专利名称(译)	促甲状腺激素（TSH）受体的表位区，其用途和抗体		
公开(公告)号	US8298769	公开(公告)日	2012-10-30
申请号	US10/488074	申请日	2002-08-21
[标]申请(专利权)人(译)	R S R有限公司		
申请(专利权)人(译)	RSR有限公司		
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IPC分类号	G01N33/53 G01N33/50 A61K38/17 A61K39/395 A61P35/00 A61P37/06 A61P43/00 C07K14/72 C07K16/28 C12N15/09 C12N15/12 C12P21/08 G01N33/15 G01N33/564 G01N33/76		
CPC分类号	C07K14/723 C07K16/2869 G01N33/564 C07K16/26 G01N33/68 G01N33/76 A61K2039/505 C07K2317/34 A61K38/00		
代理机构(译)	商户德律P.C.		
优先权	2001020649 2001-08-23 GB 2002015212 2002-07-01 GB		
其他公开文献	US20050118638A1		
外部链接	Espacenet USPTO		

摘要(译)

本发明涉及促甲状腺激素（TSH）受体的表位区域，其用途和抗体。

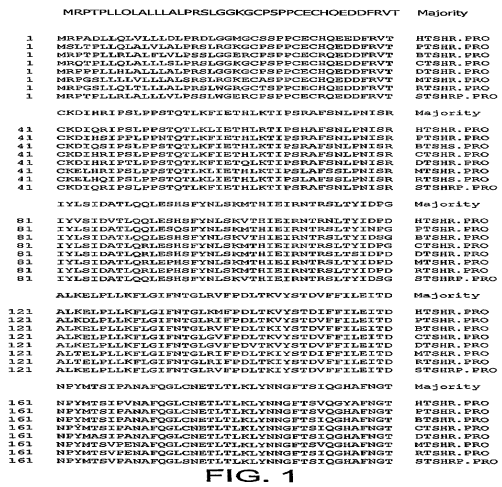

FIG. 1