(2012); Yang *et al.* Molecular Vision 17:1128-1135 (2011); Poulter *et al.* The American Journal of Human Genetics 86, 248–253 (2010)). Models for these genetic diseases are available in mice knocked out for the corresponding homologous genes.

Despite the many advances in the field of ocular angiogenesis, there remains a need to identify targets and develop means that can supplement or enhance the efficacy of existing therapies.

SUMMARY

The disclosure provides anti-LRP5 antibodies and methods of making and using the same, particularly in the treatment of conditions and diseases associated with angiogenesis.

In one embodiment ~~aspect~~, there is provided an isolated antibody that binds to Low-density lipoprotein receptor-related protein 5 (LRP5), wherein the antibody potentiates Norrin activity and/or Norrin/Fzd4 signaling. In some embodiments, the antibody is a monoclonal antibody. In some embodiments the antibody is a human, humanized, or chimeric antibody. In some embodiments, the antibody is an antibody fragment that binds LRP5.

In one aspect, there is provided an isolated antibody that binds bivalently to Low-density lipoprotein receptor-related protein 5 (LRP5), wherein the antibody potentiates Norrin activity and/or Norrin/Fzd4 (Frizzled4) signaling, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMX$_1$, wherein X$_1$ is H or S (SEQ ID NO: 28), (b) HVR-H2 comprising the amino acid sequence GX$_1$ISX$_2$X$_3$GX$_4$STYYADSVKG, wherein X$_1$ is A or G, X$_2$ is A or S, X$_3$ is P or S, X$_4$ is S or W (SEQ ID NO: 26), or SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23) or WIPQSYPFX$_1$SYKSGFDY, wherein X$_1$ is A or R (SEQ ID NO: 24), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29) or RASQX$_1$X$_2$X$_3$X$_4$YLA, wherein X$_1$ is A, G, S or V, X$_2$ is I or M, X$_3$ is F, G, S or Y, and X$_4$ is G, S or Y (SEQ ID NO: 30); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31) or DASX$_1$X$_2$ES, wherein X$_1$ is S or T and X$_2$ is L or R (SEQ ID NO: 32); and (f) HVR-L3 comprising the amino acid sequence QQYYX$_1$YPFT, wherein X$_1$ is L or S (SEQ ID NO: 33).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQVMGYYLA (SEQ ID NO: 45); (e) HVR-

L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMS (SEQ ID NO: 48), (b) HVR-H2 comprising the amino acid sequence GAISSSGSSTYYADSVKG (SEQ ID NO: 49), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMS (SEQ ID NO: 48), (b) HVR-H2 comprising the amino acid sequence GAISAPGSSTYYADSVKG (SEQ ID NO: 50), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMS (SEQ ID NO: 48), (b) HVR-H2 comprising the amino acid sequence GAISSPGWSTYYADSVKG (SEQ ID NO: 51), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMS (SEQ ID NO: 48), (b) HVR-H2 comprising the amino acid sequence GGISSPGSSTYYADSVKG (SEQ ID NO: 52), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31); and (f) HVR-L3 comprising the amino acid sequence QQYYLYPFT (SEQ ID NO: 53).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFRSYKSGFDY (SEQ ID NO: 54), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQSIYYYLA (SEQ ID NO: 55); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQVIYGYLA (SEQ ID NO: 56); (e) HVR-L2 comprising the amino acid sequence DASTRES (SEQ ID NO: 57); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQGIFYYLA (SEQ ID NO: 58); (e) HVR-L2 comprising the amino acid sequence DASTLES (SEQ ID NO: 59); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In one aspect, there is provided an isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQAIYSYLA (SEQ ID NO: 60); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

In some embodiments, the antibody comprises (a) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23) or WIPQSYPFX$_1$SYKSGFDY, wherein X$_1$ is A or R (SEQ ID NO: 24), (b) HVR-L3 comprising the amino acid sequence QQYYX$_1$YPFT, wherein X$_1$ is L or S (SEQ ID NO: 25), and (c) HVR-H2 comprising the amino acid sequence GX$_1$ISX$_2$X$_3$GX$_4$STYYADSVKG, wherein X$_1$ is A or G, X$_2$ is A or S, X$_3$ is P or S, X$_4$ is S or W (SEQ ID NO: 26), or SRISSNGGSTYYADSVKG (SEQ ID NO: 27). In some embodiments, the antibody comprises (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMX$_1$, wherein X$_1$ is H or S (SEQ ID NO: 28), (b) HVR-H2 comprising the amino acid sequence GX$_1$ISX$_2$X$_3$GX$_4$STYYADSVKG, wherein X$_1$ is A or G, X$_2$ is A or S, X$_3$ is P or S, X$_4$ is S or W (SEQ ID NO: 26), or SRISSNGGSTYYADSVKG (SEQ ID NO: 27) and (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23) or WIPQSYPFX$_1$SYKSGFDY, wherein X$_1$ is A or R (SEQ ID NO: 24). In some embodiments, the antibody further comprises (a) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29) or RASQX$_1$X$_2$X$_3$X$_4$YLA, wherein X$_1$ is A, G, S or V, X$_2$ is I or M, X$_3$ is F, G, S or Y, and X$_4$ is G, S or Y (SEQ ID NO: 30); (b) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31) or DASX$_1$X$_2$ES, wherein X$_1$ is S or T and X$_2$ is L or R (SEQ ID NO: 32); and (c) HVR-L3 comprising the amino acid sequence QQYYX$_1$YPFT, wherein X$_1$ is L or S (SEQ ID NO: 33). In some embodiments, the antibody

and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy. In another aspect, there is provided an antibody as described herein for use in potentiating Norrin activity and/or Norrin/Fzd4 signaling. In some embodiments, the disclosure provides an antibody of the disclosure for use in the manufacture of a medicament. In one aspect, there is provided use of the antibody as described herein in the manufacture of a medicament. In some embodiments, the medicament is for treatment of a retinopathy including proliferative diabetic retinopathy, CNV, AMD, diabetic and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy. In some embodiments, the medicament is for potentiating Norrin activity and/or Norrin/Fzd4 signaling.

In some embodiments, the disclosure provides a method of treating an individual having a retinopathy including proliferative diabetic retinopathy, CNV, AMD, diabetic and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy comprising administering to the individual an effective amount of an antibody of the disclosure. In some embodiments, the method further comprises administering to the individual an effective amount of an additional therapeutic agent, e.g. a VEGF antagonist (including, e.g., an anti-VEGF antibody or antibody fragment, e.g. ranibizumab, a soluble VEGF receptor, e.g. aflibercept, or an aptamer, e.g. pegaptanib), a recombinant NORRIN protein, a TSPAN12 agonist, plasmin, plasminogen, tissue plasminogen activator, a TNF-α inhibitor, and/or a steroid, e.g. triamcinolone or dexamethasone. In some embodiments, the disclosure provides a method of potentiating Norrin activity and/or Norrin/Fzd4 signaling in an individual comprising administering to the individual an effective amount of an antibody of the disclosure to potentiate Norrin activity and/or Norrin/Fzd4 signaling. In some embodiments, the disclosure provides a method of rescuing a signaling defect in an individual caused by mutation in Norrin and/or Fzd4 comprising administering an antibody of the disclosure.

In one aspect, there is provided the use of an effective amount of the antibody as described herein in the manufacture of a medicament for treating an individual having a retinopathy including proliferative diabetic retinopathy, CNV, AMD, diabetic and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy.

In one embodiment ~~aspect~~, there is provided the use of an effective amount of the antibody as described herein in the manufacture of a medicament for potentiating Norrin activity and/or Norrin/Fzd4 signaling in an individual.

In one aspect, there is provided ~~the use of~~ the antibody as described herein ~~in the manufacture of a medicament~~ for use in rescuing a signaling defect in an individual caused by mutation in Norrin and/or Fzd4.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to Low-density lipoprotein receptor-related protein 5 (LRP5), wherein the antibody potentiates Norrin activity and/or Norrin/Fzd4 signaling.

2. The antibody of claim 1, which is a monoclonal antibody.

3. The antibody of claim 1, which is a human, humanized, or chimeric antibody.

4. The antibody of claim 1, which is an antibody fragment that binds LRP5.

5. The antibody of claim 1, wherein the antibody comprises (a) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23) or WIPQSYPFX$_1$SYKSGFDY, wherein X$_1$ is A or R (SEQ ID NO: 24), (b) HVR-L3 comprising the amino acid sequence QQYYX$_1$YPFT, wherein X$_1$ is L or S (SEQ ID NO: 25), and (c) HVR-H2 comprising the amino acid sequence GX$_1$ISX$_2$X$_3$GX$_4$STYYADSVKG, wherein X$_1$ is A or G, X$_2$ is A or S, X$_3$ is P or S, X$_4$ is S or W (SEQ ID NO: 26), or SRISSNGGSTYYADSVKG (SEQ ID NO: 27).

6. The antibody of claim 1, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMX$_1$, wherein X$_1$ is H or S (SEQ ID NO: 28), (b) HVR-H2 comprising the amino acid sequence GX$_1$ISX$_2$X$_3$GX$_4$STYYADSVKG, wherein X$_1$ is A or G, X$_2$ is A or S, X$_3$ is P or S, X$_4$ is S or W (SEQ ID NO: 26), or SRISSNGGSTYYADSVKG (SEQ ID NO: 27) and (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23) or WIPQSYPFX$_1$SYKSGFDY, wherein X$_1$ is A or R (SEQ ID NO: 24).

7. The antibody of claim 6, further comprising (a) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29) or RASQX$_1$X$_2$X$_3$X$_4$YLA, wherein X$_1$ is A, G, S or V, X$_2$ is I or M, X$_3$ is F, G, S or Y, and X$_4$ is G, S or Y (SEQ ID NO: 30); (b) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31) or DASX$_1$X$_2$ES, wherein X$_1$ is S or T and X$_2$ is L or R (SEQ ID NO: 32); and (c) HVR-L3 comprising the amino acid sequence QQYYX$_1$YPFT, wherein X$_1$ is L or S (SEQ ID NO: 33).

8. The antibody of claim 1, comprising (a) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29) or RASQX$_1$X$_2$X$_3$X$_4$YLA, wherein X$_1$ is A, G, S or V, X$_2$ is I or M, X$_3$ is G, F, Y or S, and X$_4$ is G, Y or S (SEQ ID NO: 30); (b) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31) or DASX$_1$X$_2$ES, wherein X$_1$ is S or T and X$_2$ is L or R (SEQ ID NO: 32); and (c) HVR-L3 comprising the amino acid sequence QQYYX$_1$YPFT, wherein X$_1$ is L or S (SEQ ID NO: 33).

9. The antibody of claim 6, further comprising one or more heavy chain variable domain framework sequences selected from the group consisting of SEQ ID NO: 34-37.

10. The antibody of claim 1, comprising (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of one of SEQ ID NOs: 1 to 11; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of one of SEQ ID NOs: 12 to 22; or (c) a VH sequence as in (a) and a VL sequence as in (b).

11. The antibody of claim 10, comprising a VH sequence of one of SEQ ID NOs: 1 to 11.

12. The antibody of claim 10, comprising a VL sequence of one of SEQ ID NOs: 12 to 22.

13. An antibody comprising a VH sequence of one of SEQ ID NOs: 1 to 11 and a VL sequence of one of SEQ ID NOs: 12 to 22.

14. The antibody of claim 1, which is a full length IgG1 antibody.

15. Isolated nucleic acid encoding the antibody of claim 1.

16. A host cell comprising the nucleic acid of claim 15.

17. A method of producing an antibody, comprising culturing the host cell of claim 16 so that the antibody is produced.

18. An immunoconjugate comprising the antibody of claim 1 and a cytotoxic agent.

19. A pharmaceutical formulation comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.

20. The antibody of claim 1 for use as a medicament.

21. The antibody of claim 1 for use in treating a retinopathy including proliferative diabetic retinopathy, CNV, AMD, diabetic and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteoporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy.

22. The antibody of claim 1 for use in potentiating Norrin activity and/or Norrin/Fzd4 signaling.

23. Use of the antibody of claim 1 in the manufacture of a medicament.

24. The use of claim 23, wherein the medicament is for treatment of a retinopathy including proliferative diabetic retinopathy, CNV, AMD, diabetic and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the

eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy.

25. The use of claim 23, wherein the medicament is for potentiating Norrin activity and/or Norrin/Fzd4 signaling.

26. The use of an effective amount of the antibody of claim 1 in the manufacture of a medicament for treating an individual having a retinopathy including proliferative diabetic retinopathy, CNV, AMD, diabetic and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy.

27. The use of an effective amount of the antibody of claim 1 in the manufacture of a medicament for potentiating Norrin activity and/or Norrin/Fzd4 signaling in an individual.

28. The use of the antibody of claim 1 in the manufacture of a medicament for rescuing a signaling defect in an individual caused by mutation in Norrin and/or Fzd4.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds bivalently to Low-density lipoprotein receptor-related protein 5 (LRP5), wherein the antibody potentiates Norrin activity and/or Norrin/Fzd4 (Frizzled4) signaling, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMX$_1$, wherein X$_1$ is H or S (SEQ ID NO: 28), (b) HVR-H2 comprising the amino acid sequence GX$_1$ISX$_2$X$_3$GX$_4$STYYADSVKG, wherein X$_1$ is A or G, X$_2$ is A or S, X$_3$ is P or S, X$_4$ is S or W (SEQ ID NO: 26), or SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23) or WIPQSYPFX$_1$SYKSGFDY, wherein X$_1$ is A or R (SEQ ID NO: 24), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29) or RASQX$_1$X$_2$X$_3$X$_4$YLA, wherein X$_1$ is A, G, S or V, X$_2$ is I or M, X$_3$ is F, G, S or Y, and X$_4$ is G, S or Y (SEQ ID NO: 30); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31) or DASX$_1$X$_2$ES, wherein X$_1$ is S or T and X$_2$ is L or R (SEQ ID NO: 32); and (f) HVR-L3 comprising the amino acid sequence QQYYX$_1$YPFT, wherein X$_1$ is L or S (SEQ ID NO: 33).

2. The antibody of claim 1, which is a monoclonal antibody.

3. The antibody of claim 1, which is a human, humanized, or chimeric antibody.

4. The antibody of claim 1, which is an antibody fragment that binds LRP5.

5. The antibody of claim 1 , further comprising one or more heavy chain variable domain framework sequences selected from the group consisting of SEQ ID NO: 34-37.

6. An antibody comprising a VH sequence of one of SEQ ID NOs: 1 to 11 and a VL sequence of one of SEQ ID NOs: 12 to 22.

7. The antibody of claim 1, which is a full length IgG1 antibody.

8. Isolated nucleic acid encoding the antibody of claim 1.

9. A host cell comprising the nucleic acid of claim 8 .

10. A method of producing an antibody comprising culturing the host cell of claim 9 so that the antibody is produced.

11. An immunoconjugate comprising the antibody of claim 1 and a cytotoxic agent.

12. A pharmaceutical formulation comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.

13. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino

acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQVMGYYLA (SEQ ID NO: 45); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

14. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMS (SEQ ID NO: 48), (b) HVR-H2 comprising the amino acid sequence GAISSSGSSTYYADSVKG (SEQ ID NO: 49), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

15. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 7 and the VL sequence of SEQ ID NO: 18.

16. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 1 and the VL sequence of SEQ ID NO: 12.

17. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMS (SEQ ID NO: 48), (b) HVR-H2 comprising the amino acid sequence GAISAPGSSTYYADSVKG (SEQ ID NO: 50), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

18. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMS (SEQ ID NO: 48), (b) HVR-H2 comprising the amino acid sequence GAISSPGWSTYYADSVKG (SEQ ID NO: 51), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

19. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMS (SEQ ID NO: 48), (b) HVR-H2 comprising the amino acid sequence GGISSPGSSTYYADSVKG (SEQ ID NO: 52), (c) HVR-H3 comprising the amino acid sequence YYRYAPYRSLGMDV (SEQ ID NO: 23), (d) HVR-L1 comprising the amino

acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence AASSLQS (SEQ ID NO: 31); and (f) HVR-L3 comprising the amino acid sequence QQYYLYPFT (SEQ ID NO: 53).

20. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

21. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFRSYKSGFDY (SEQ ID NO: 54), (d) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

22. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQSIYYYLA (SEQ ID NO: 55); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

23. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQVIYGYLA (SEQ ID NO: 56); (e) HVR-L2 comprising the amino acid sequence DASTRES (SEQ ID NO: 57); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

24. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQGIFYYLA (SEQ ID NO: 58); (e) HVR-L2 comprising the amino acid sequence DASTLES (SEQ ID NO: 59); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

25. An isolated antibody that binds to LRP5 comprising (a) HVR-H1 comprising the amino acid sequence GFTFSSYAMH (SEQ ID NO: 43), (b) HVR-H2 comprising the amino acid sequence SRISSNGGSTYYADSVKG (SEQ ID NO: 27), (c) HVR-H3 comprising the amino acid sequence WIPQSYPFASYKSGFDY (SEQ ID NO: 44), (d) HVR-L1 comprising the amino acid sequence RASQAIYSYLA (SEQ ID NO: 60); (e) HVR-L2 comprising the amino acid sequence DASSLES (SEQ ID NO: 46); and (f) HVR-L3 comprising the amino acid sequence QQYYSYPFT (SEQ ID NO: 47).

26. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 2 and the VL sequence of SEQ ID NO: 13.

27. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 3 and the VL sequence of SEQ ID NO: 14.

28. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 4 and the VL sequence of SEQ ID NO: 15.

29. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 5 and the VL sequence of SEQ ID NO: 16.

30. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 6 and the VL sequence of SEQ ID NO: 17.

31. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 8 and the VL sequence of SEQ ID NO: 19.

32. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 9 and the VL sequence of SEQ ID NO: 20.

33. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 10 and the VL sequence of SEQ ID NO: 21.

34. The antibody of claim 6, wherein the antibody comprises the VH sequence of SEQ ID NO: 11 and the VL sequence of SEQ ID NO: 22.

35. An immunoconjugate comprising the antibody of any one of claims 13, 14, or 17-25 and a cytotoxic agent.

36. A pharmaceutical formulation comprising the antibody of any one of claims 13, 14, or 17-25 and a pharmaceutically acceptable carrier.

37. An immunoconjugate comprising the antibody of any one of claims 15, 16, or 26-34 and a cytotoxic agent.

38. A pharmaceutical formulation comprising the antibody of any one of claims 15, 16, or 26-34 and a pharmaceutically acceptable carrier.

39. The antibody of claim 1 for use as a medicament.

40. The antibody of claim 1 for use in treating a retinopathy including proliferative diabetic retinopathy, CNV, AMD, diabetic and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteoporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy.

41. The antibody of claim 1 for use in potentiating Norrin activity and/or Norrin/Fzd4 signaling.

42. Use of the antibody of claim 1 in the manufacture of a medicament.

43. The use of an effective amount of the antibody of claim 1 in the manufacture of a medicament for treating an individual having a retinopathy including proliferative diabetic retinopathy, CNV, AMD, diabetic and other ischemia-related retinopathies, DME, pathological myopia, von Hippel-Lindau disease, histoplasmosis of the eye, CRVO, BRVO, corneal neovascularization, retinal neovascularization, ROP, FEVR, Coats' disease, Norrie Disease, OPPG (Osteoporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy.

44. The antibody of claim 1 for use in rescuing a signaling defect in an individual caused by mutation in Norrin and/or Fzd4.

SEQUENCE LISTING

<110> GENENTECH, INC. ET AL.

<120> ANTI-LRP5 ANTIBODIES AND METHODS OF USE

<130> P4855R1-WO

<140>
<141>

<150> 61/588,100
<151> 2012-01-18

<160> 42

<170> PatentIn version 3.5

<210> 1
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 1

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Ala Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
            100                 105                 110

Trp Gly Gln
        115
```

<210> 2
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 2

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Ala Ile Ser Ala Pro Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
            100                 105                 110

Trp Gly Gln
        115
```

<210> 3
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 3

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Ala Ile Ser Ser Pro Gly Trp Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
```

85 90 95

Ala Arg Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
100 105 110

Trp Gly Gln
115

<210> 4
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 4
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Gly Ile Ser Ser Pro Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
100 105 110

Trp Gly Gln
115

<210> 5
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 5
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
            100                 105                 110

Phe Asp Tyr Trp Gly Gln
        115
```

<210> 6
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 6

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Arg Ser Tyr Lys Ser Gly
            100                 105                 110
```

Phe Asp Tyr Trp Gly Gln
115

<210> 7
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 7
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 8
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 8
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 9
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 9
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 10
<211> 118
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 10
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 11
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 11
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 12
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 12
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 13
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 13
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 14
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 14
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 15
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 15
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Leu Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 16
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 16
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 17
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 17
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 18
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 18
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Met Gly Tyr Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 19
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 19
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Tyr Tyr Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 20
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 20
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Tyr Gly Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Arg Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 21
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 21
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Phe Tyr Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 22
<211> 108
<212> PRT

<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 22
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Ile Tyr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 23
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 23
Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
1 5 10

<210> 24
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> VARIANT
<222> (9)..(9)
<223> /replace="Arg"

<220>

<221> misc_feature
<222> (9)..(9)
<223> /note="Residue given in the sequence has no preference
with respect to the annotation for said position"

<400> 24
Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly Phe Asp
1 5 10 15

Tyr

<210> 25
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Ser"

<220>
<221> misc_feature
<222> (5)..(5)
<223> /note="Residue given in the sequence has no preference
with respect to the annotation for said position"

<400> 25
Gln Gln Tyr Tyr Leu Tyr Pro Phe Thr
1 5

<210> 26
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> VARIANT
<222> (2)..(2)
<223> /replace="Gly"

<220>
<221> misc_feature
<222> (2)..(2)
<223> /note="Residue given in the sequence has no preference
with respect to the annotation for said position"

<220>
<221> VARIANT
<222> (5)..(6)
<223> /replace="Ser"

<220>
<221> misc_feature
<222> (5)..(6)
<223> /note="Residues given in the sequence have no preference
with respect to those in the annotations for said positions"

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Trp"

<220>
<221> misc_feature
<222> (8)..(8)
<223> /note="Residue given in the sequence has no preference
with respect to the annotation for said position"

<400> 26
Gly Ala Ile Ser Ala Pro Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 27
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<400> 27
Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 28
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic
peptide"

<220>
<221> VARIANT
<222> (10)..(10)
<223> /replace="Ser"

<220>
<221> misc_feature
<222> (10)..(10)
<223> /note="Residue given in the sequence has no preference
with respect to the annotation for said position"

<400> 28

Gly Phe Thr Phe Ser Ser Tyr Ala Met His
1 5 10

<210> 29
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 29
Arg Ala Ser Gln Gly Ile Ser Ser Tyr Leu Ala
1 5 10

<210> 30
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Gly" or "Ser" or "Val"

<220>
<221> VARIANT
<222> (6)..(6)
<223> /replace="Met"

<220>
<221> VARIANT
<222> (7)..(7)
<223> /replace="Gly" or "Ser" or "Tyr"

<220>
<221> VARIANT
<222> (8)..(8)
<223> /replace="Ser" or "Tyr"

<220>
<221> misc_feature
<222> (5)..(8)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 30
Arg Ala Ser Gln Ala Ile Phe Gly Tyr Leu Ala
1 5 10

<210> 31
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source

<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 31
Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 32
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> VARIANT
<222> (4)..(4)
<223> /replace="Thr"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Arg"

<220>
<221> misc_feature
<222> (4)..(5)
<223> /note="Residues given in the sequence have no preference with respect to those in the annotations for said positions"

<400> 32
Asp Ala Ser Ser Leu Glu Ser
1 5

<210> 33
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<220>
<221> VARIANT
<222> (5)..(5)
<223> /replace="Ser"

<220>
<221> misc_feature
<222> (5)..(5)
<223> /note="Residue given in the sequence has no preference with respect to the annotation for said position"

<400> 33
Gln Gln Tyr Tyr Leu Tyr Pro Phe Thr
1 5

<210> 34

<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 34
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser
20 25

<210> 35
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 35
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
1 5 10

<210> 36
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 36
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 37
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 37
Trp Gly Gln
1

<210> 38

<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 38
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys
20

<210> 39
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 39
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> 40
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> 40
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> 41
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<221> source
<223> /note="Description of Artificial Sequence: Synthetic peptide"

<400> 41
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 42

<211> 1615
<212> PRT
<213> Homo sapiens

<400> 42

```
Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu
1               5                  10                  15

Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser
            20                  25                  30

Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala
        35                  40                  45

Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp
    50                  55                  60

Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr
65                  70                  75                  80

Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly
                85                  90                  95

Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly
            100                 105                 110

Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu
        115                 120                 125

Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val
    130                 135                 140

Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro
145                 150                 155                 160

Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile
                165                 170                 175

Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser
            180                 185                 190

Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys
        195                 200                 205

Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu
    210                 215                 220

Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro
225                 230                 235                 240

Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln
                245                 250                 255
```

```
Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys
            260                 265                 270

Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser
        275                 280                 285

Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly
    290                 295                 300

Gly Cys Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr
305                 310                 315                 320

Cys Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Arg Thr Cys
                325                 330                 335

Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu
            340                 345                 350

Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln
        355                 360                 365

Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu
    370                 375                 380

Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala
385                 390                 395                 400

Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn
                405                 410                 415

Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp
            420                 425                 430

Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr
        435                 440                 445

Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile
    450                 455                 460

Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu
465                 470                 475                 480

Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val
                485                 490                 495

Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu
            500                 505                 510

Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu
        515                 520                 525
```

```
Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys
    530                 535                 540

Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp
545                 550                 555                 560

Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala
                565                 570                 575

Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys
            580                 585                 590

Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg
        595                 600                 605

Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg
    610                 615                 620

Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys
625                 630                 635                 640

Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His
                645                 650                 655

Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr
            660                 665                 670

Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His
        675                 680                 685

Ile Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met
    690                 695                 700

Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro
705                 710                 715                 720

Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp
                725                 730                 735

Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg
            740                 745                 750

Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu
        755                 760                 765

Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro
    770                 775                 780

Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val
785                 790                 795                 800
```

```
Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln
                805                 810                 815

Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn
            820                 825                 830

Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro
        835                 840                 845

Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn
    850                 855                 860

Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr
865                 870                 875                 880

Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His
                885                 890                 895

Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln
            900                 905                 910

Cys Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys
        915                 920                 925

Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro
    930                 935                 940

Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile
945                 950                 955                 960

Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu
                965                 970                 975

Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr
            980                 985                 990

Trp Val Asp Gly Arg Gln Asn Ile  Lys Arg Ala Lys Asp  Asp Gly Thr
        995                 1000                1005

Gln Pro  Phe Val Leu Thr Ser  Leu Ser Gln Gly Gln  Asn Pro Asp
    1010                1015                1020

Arg Gln  Pro His Asp Leu Ser  Ile Asp Ile Tyr Ser  Arg Thr Leu
    1025                1030                1035

Phe Trp  Thr Cys Glu Ala Thr  Asn Thr Ile Asn Val  His Arg Leu
    1040                1045                1050

Ser Gly  Glu Ala Met Gly Val  Val Leu Arg Gly Asp  Arg Asp Lys
    1055                1060                1065
```

```
Pro Arg  Ala Ile Val Val Asn  Ala Glu Arg Gly Tyr  Leu Tyr Phe
    1070                 1075                 1080

Thr Asn  Met Gln Asp Arg Ala  Ala Lys Ile Glu Arg  Ala Ala Leu
    1085                 1090                 1095

Asp Gly  Thr Glu Arg Glu Val  Leu Phe Thr Thr Gly  Leu Ile Arg
    1100                 1105                 1110

Pro Val  Ala Leu Val Val Asp  Asn Thr Leu Gly Lys  Leu Phe Trp
    1115                 1120                 1125

Val Asp  Ala Asp Leu Lys Arg  Ile Glu Ser Cys Asp  Leu Ser Gly
    1130                 1135                 1140

Ala Asn  Arg Leu Thr Leu Glu  Asp Ala Asn Ile Val  Gln Pro Leu
    1145                 1150                 1155

Gly Leu  Thr Ile Leu Gly Lys  His Leu Tyr Trp Ile  Asp Arg Gln
    1160                 1165                 1170

Gln Gln  Met Ile Glu Arg Val  Glu Lys Thr Thr Gly  Asp Lys Arg
    1175                 1180                 1185

Thr Arg  Ile Gln Gly Arg Val  Ala His Leu Thr Gly  Ile His Ala
    1190                 1195                 1200

Val Glu  Glu Val Ser Leu Glu  Glu Phe Ser Ala His  Pro Cys Ala
    1205                 1210                 1215

Arg Asp  Asn Gly Gly Cys Ser  His Ile Cys Ile Ala  Lys Gly Asp
    1220                 1225                 1230

Gly Thr  Pro Arg Cys Ser Cys  Pro Val His Leu Val  Leu Leu Gln
    1235                 1240                 1245

Asn Leu  Leu Thr Cys Gly Glu  Pro Pro Thr Cys Ser  Pro Asp Gln
    1250                 1255                 1260

Phe Ala  Cys Ala Thr Gly Glu  Ile Asp Cys Ile Pro  Gly Ala Trp
    1265                 1270                 1275

Arg Cys  Asp Gly Phe Pro Glu  Cys Asp Asp Gln Ser  Asp Glu Glu
    1280                 1285                 1290

Gly Cys  Pro Val Cys Ser Ala  Ala Gln Phe Pro Cys  Ala Arg Gly
    1295                 1300                 1305

Gln Cys  Val Asp Leu Arg Leu  Arg Cys Asp Gly Glu  Ala Asp Cys
    1310                 1315                 1320
```

```
Gln Asp  Arg Ser Asp Glu Ala  Asp Cys Asp Ala Ile  Cys Leu Pro
     1325                1330                1335

Asn Gln  Phe Arg Cys Ala Ser  Gly Gln Cys Val Leu  Ile Lys Gln
     1340                1345                1350

Gln Cys  Asp Ser Phe Pro Asp  Cys Ile Asp Gly Ser  Asp Glu Leu
     1355                1360                1365

Met Cys  Glu Ile Thr Lys Pro  Pro Ser Asp Asp Ser  Pro Ala His
     1370                1375                1380

Ser Ser  Ala Ile Gly Pro Val  Ile Gly Ile Ile Leu  Ser Leu Phe
     1385                1390                1395

Val Met  Gly Gly Val Tyr Phe  Val Cys Gln Arg Val  Val Cys Gln
     1400                1405                1410

Arg Tyr  Ala Gly Ala Asn Gly  Pro Phe Pro His Glu  Tyr Val Ser
     1415                1420                1425

Gly Thr  Pro His Val Pro Leu  Asn Phe Ile Ala Pro  Gly Gly Ser
     1430                1435                1440

Gln His  Gly Pro Phe Thr Gly  Ile Ala Cys Gly Lys  Ser Met Met
     1445                1450                1455

Ser Ser  Val Ser Leu Met Gly  Gly Arg Gly Gly Val  Pro Leu Tyr
     1460                1465                1470

Asp Arg  Asn His Val Thr Gly  Ala Ser Ser Ser Ser  Ser Ser Ser
     1475                1480                1485

Thr Lys  Ala Thr Leu Tyr Pro  Pro Ile Leu Asn Pro  Pro Pro Ser
     1490                1495                1500

Pro Ala  Thr Asp Pro Ser Leu  Tyr Asn Met Asp Met  Phe Tyr Ser
     1505                1510                1515

Ser Asn  Ile Pro Ala Thr Ala  Arg Pro Tyr Arg Pro  Tyr Ile Ile
     1520                1525                1530

Arg Gly  Met Ala Pro Pro Thr  Thr Pro Cys Ser Thr  Asp Val Cys
     1535                1540                1545

Asp Ser  Asp Tyr Ser Ala Ser  Arg Trp Lys Ala Ser  Lys Tyr Tyr
     1550                1555                1560

Leu Asp  Leu Asn Ser Asp Ser  Asp Pro Tyr Pro Pro  Pro Pro Thr
     1565                1570                1575
```

```
Pro His  Ser Gln Tyr Leu Ser  Ala Glu Asp Ser Cys  Pro Pro Ser
    1580                 1585                 1590

Pro Ala  Thr Glu Arg Ser Tyr  Phe His Leu Phe Pro  Pro Pro Pro
    1595                 1600                 1605

Ser Pro  Cys Thr Asp Ser Ser
    1610                 1615
```

SEQUENCE LISTING

<110> WU, YAN
YE, WEILAN
BURTON, JEREMY BRYANT
CHIU, CECILIA

<120> ANTI-LRP5 ANTIBODIES AND METHODS OF USE

<130> P4855R1-US
<140> US 13/744,766
<141> 2013-01-18

<150> 61/588,100
<151> 2012-01-18

<160> 60

<170> PatentIn version 3.5

<210> 1
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 1

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1					5				10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
			20					25					30		
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Gly	Ala	Ile	Ser	Ser	Ser	Gly	Ser	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75					80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90					95
Ala	Arg	Tyr	Tyr	Arg	Tyr	Ala	Pro	Tyr	Arg	Ser	Leu	Gly	Met	Asp	Val
			100					105					110		
Trp	Gly	Gln													
		115													

<210> 2
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 2
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ala Ile Ser Ala Pro Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
100 105 110

Trp Gly Gln
115

<210> 3
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 3
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Ala Ile Ser Ser Pro Gly Trp Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

85 90 95

Ala Arg Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
100 105 110

Trp Gly Gln
115

<210> 4
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 4
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Gly Ile Ser Ser Pro Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
100 105 110

Trp Gly Gln
115

<210> 5
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 5
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 6
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 6
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Arg Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 7
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 7
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 8
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 8
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 9
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 9
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 10
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 10
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly
100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 11
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 11
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly

100 105 110

Phe Asp Tyr Trp Gly Gln
115

<210> 12
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 12
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 13
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 13
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 14
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 14
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 15
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 15
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Leu Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 16
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 16
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 17
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 17
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 18
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 18
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Met Gly Tyr Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 19
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 19
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Tyr Tyr Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 20
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 20
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Tyr Gly Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Arg Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 21
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 21
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Phe Tyr Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Thr Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 22
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 22
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Ile Tyr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Ser Tyr Pro Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 23
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 23
Tyr Tyr Arg Tyr Ala Pro Tyr Arg Ser Leu Gly Met Asp Val
1 5 10

<210> 24
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> MOD_RES
<222> (9)..(9)
<223> Ala or Arg

<400> 24
Trp Ile Pro Gln Ser Tyr Pro Phe Xaa Ser Tyr Lys Ser Gly Phe Asp
1 5 10 15

Tyr

<210> 25
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> MOD_RES
<222> (5)..(5)

<223> Leu or Ser

<400> 25
Gln Gln Tyr Tyr Xaa Tyr Pro Phe Thr
1 5

<210> 26
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> MOD_RES
<222> (2)..(2)
<223> Ala or Gly

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Ala or Ser

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Pro or Ser

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Ser or Trp

<400> 26
Gly Xaa Ile Ser Xaa Xaa Gly Xaa Ser Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 27
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 27
Ser Arg Ile Ser Ser Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 28
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> MOD_RES
<222> (10)..(10)
<223> His or Ser

<400> 28
Gly Phe Thr Phe Ser Ser Tyr Ala Met Xaa
1 5 10

<210> 29
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 29
Arg Ala Ser Gln Gly Ile Ser Ser Tyr Leu Ala
1 5 10

<210> 30
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Ala, Gly, Ser or Val

<220>
<221> MOD_RES
<222> (6)..(6)
<223> Ile or Met

<220>
<221> MOD_RES
<222> (7)..(7)
<223> Phe, Gly, Ser or Tyr

<220>
<221> MOD_RES
<222> (8)..(8)
<223> Gly, Ser or Tyr

<400> 30
Arg Ala Ser Gln Xaa Xaa Xaa Xaa Tyr Leu Ala
1 5 10

<210> 31
<211> 7
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 31
Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 32
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> MOD_RES
<222> (4)..(4)
<223> Ser or Thr

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Leu or Arg

<400> 32
Asp Ala Ser Xaa Xaa Glu Ser
1 5

<210> 33
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<220>
<221> MOD_RES
<222> (5)..(5)
<223> Leu or Ser

<400> 33
Gln Gln Tyr Tyr Xaa Tyr Pro Phe Thr
1 5

<210> 34
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 34
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser
20 25

<210> 35
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 35
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
1 5 10

<210> 36
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 36
Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 37
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 37
Trp Gly Gln
1

<210> 38
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 38
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys
20

<210> 39
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 39
Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> 40
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 40
Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
20 25 30

<210> 41
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 41
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
1 5 10

<210> 42
<211> 1615
<212> PRT
<213> Homo sapiens

<400> 42
Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu
1 5 10 15

Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser
20 25 30

Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala
35 40 45

Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp
50 55 60

```
Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr
65                  70                  75                  80

Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly
                85                  90                  95

Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly
            100                 105                 110

Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu
        115                 120                 125

Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val
    130                 135                 140

Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro
145                 150                 155                 160

Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile
                165                 170                 175

Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser
            180                 185                 190

Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys
        195                 200                 205

Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu
    210                 215                 220

Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro
225                 230                 235                 240

Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln
                245                 250                 255

Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys
            260                 265                 270

Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser
        275                 280                 285

Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly
    290                 295                 300

Gly Cys Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr
305                 310                 315                 320

Cys Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Arg Thr Cys
                325                 330                 335
```

Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu
340 345 350

Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln
355 360 365

Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu
370 375 380

Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala
385 390 395 400

Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn
405 410 415

Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp
420 425 430

Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr
435 440 445

Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile
450 455 460

Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu
465 470 475 480

Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val
485 490 495

Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu
500 505 510

Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu
515 520 525

Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys
530 535 540

Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp
545 550 555 560

Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala
565 570 575

Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys
580 585 590

Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg
595 600 605

Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg
610 615 620

Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys
625 630 635 640

Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His
645 650 655

Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr
660 665 670

Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His
675 680 685

Ile Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met
690 695 700

Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro
705 710 715 720

Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp
725 730 735

Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg
740 745 750

Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu
755 760 765

Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro
770 775 780

Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val
785 790 795 800

Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln
805 810 815

Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn
820 825 830

Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro
835 840 845

Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn
850 855 860

Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr
865 870 875 880

```
Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His
                885                 890                 895

Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln
            900                 905                 910

Cys Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys
        915                 920                 925

Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro
    930                 935                 940

Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile
945                 950                 955                 960

Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu
                965                 970                 975

Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr
            980                 985                 990

Trp Val Asp Gly Arg Gln Asn Ile  Lys Arg Ala Lys Asp  Asp Gly Thr
        995                 1000                1005

Gln Pro  Phe Val Leu Thr Ser  Leu Ser Gln Gly Gln  Asn Pro Asp
    1010                1015                1020

Arg Gln  Pro His Asp Leu Ser  Ile Asp Ile Tyr Ser  Arg Thr Leu
    1025                1030                1035

Phe Trp  Thr Cys Glu Ala Thr  Asn Thr Ile Asn Val  His Arg Leu
    1040                1045                1050

Ser Gly  Glu Ala Met Gly Val  Val Leu Arg Gly Asp  Arg Asp Lys
    1055                1060                1065

Pro Arg  Ala Ile Val Val Asn  Ala Glu Arg Gly Tyr  Leu Tyr Phe
    1070                1075                1080

Thr Asn  Met Gln Asp Arg Ala  Ala Lys Ile Glu Arg  Ala Ala Leu
    1085                1090                1095

Asp Gly  Thr Glu Arg Glu Val  Leu Phe Thr Thr Gly  Leu Ile Arg
    1100                1105                1110

Pro Val  Ala Leu Val Val Asp  Asn Thr Leu Gly Lys  Leu Phe Trp
    1115                1120                1125

Val Asp  Ala Asp Leu Lys Arg  Ile Glu Ser Cys Asp  Leu Ser Gly
    1130                1135                1140
```

```
Ala Asn  Arg Leu Thr Leu Glu  Asp Ala Asn Ile Val  Gln Pro Leu
    1145                1150                1155

Gly Leu  Thr Ile Leu Gly Lys  His Leu Tyr Trp Ile  Asp Arg Gln
    1160                1165                1170

Gln Gln  Met Ile Glu Arg Val  Glu Lys Thr Thr Gly  Asp Lys Arg
    1175                1180                1185

Thr Arg  Ile Gln Gly Arg Val  Ala His Leu Thr Gly  Ile His Ala
    1190                1195                1200

Val Glu  Glu Val Ser Leu Glu  Glu Phe Ser Ala His  Pro Cys Ala
    1205                1210                1215

Arg Asp  Asn Gly Gly Cys Ser  His Ile Cys Ile Ala  Lys Gly Asp
    1220                1225                1230

Gly Thr  Pro Arg Cys Ser Cys  Pro Val His Leu Val  Leu Leu Gln
    1235                1240                1245

Asn Leu  Leu Thr Cys Gly Glu  Pro Pro Thr Cys Ser  Pro Asp Gln
    1250                1255                1260

Phe Ala  Cys Ala Thr Gly Glu  Ile Asp Cys Ile Pro  Gly Ala Trp
    1265                1270                1275

Arg Cys  Asp Gly Phe Pro Glu  Cys Asp Asp Gln Ser  Asp Glu Glu
    1280                1285                1290

Gly Cys  Pro Val Cys Ser Ala  Ala Gln Phe Pro Cys  Ala Arg Gly
    1295                1300                1305

Gln Cys  Val Asp Leu Arg Leu  Arg Cys Asp Gly Glu  Ala Asp Cys
    1310                1315                1320

Gln Asp  Arg Ser Asp Glu Ala  Asp Cys Asp Ala Ile  Cys Leu Pro
    1325                1330                1335

Asn Gln  Phe Arg Cys Ala Ser  Gly Gln Cys Val Leu  Ile Lys Gln
    1340                1345                1350

Gln Cys  Asp Ser Phe Pro Asp  Cys Ile Asp Gly Ser  Asp Glu Leu
    1355                1360                1365

Met Cys  Glu Ile Thr Lys Pro  Pro Ser Asp Asp Ser  Pro Ala His
    1370                1375                1380

Ser Ser  Ala Ile Gly Pro Val  Ile Gly Ile Ile Leu  Ser Leu Phe
    1385                1390                1395
```

Val Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Val Cys Gln
1400 1405 1410

Arg Tyr Ala Gly Ala Asn Gly Pro Phe Pro His Glu Tyr Val Ser
1415 1420 1425

Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser
1430 1435 1440

Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser Met Met
1445 1450 1455

Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu Tyr
1460 1465 1470

Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser
1475 1480 1485

Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser
1490 1495 1500

Pro Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser
1505 1510 1515

Ser Asn Ile Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Ile Ile
1520 1525 1530

Arg Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys
1535 1540 1545

Asp Ser Asp Tyr Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr
1550 1555 1560

Leu Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr
1565 1570 1575

Pro His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser
1580 1585 1590

Pro Ala Thr Glu Arg Ser Tyr Phe His Leu Phe Pro Pro Pro Pro
1595 1600 1605

Ser Pro Cys Thr Asp Ser Ser
1610 1615

<210> 43
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 43
Gly Phe Thr Phe Ser Ser Tyr Ala Met His
1 5 10

<210> 44
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 44
Trp Ile Pro Gln Ser Tyr Pro Phe Ala Ser Tyr Lys Ser Gly Phe Asp
1 5 10 15

Tyr

<210> 45
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 45
Arg Ala Ser Gln Val Met Gly Tyr Tyr Leu Ala
1 5 10

<210> 46
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 46
Asp Ala Ser Ser Leu Glu Ser
1 5

<210> 47
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 47
Gln Gln Tyr Tyr Ser Tyr Pro Phe Thr
1 5

<210> 48
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 48
Gly Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5 10

<210> 49
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 49
Gly Ala Ile Ser Ser Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 50
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 50
Gly Ala Ile Ser Ala Pro Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 51
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 51
Gly Ala Ile Ser Ser Pro Gly Trp Ser Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 52
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 52
Gly Gly Ile Ser Ser Pro Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
1 5 10 15

Lys Gly

<210> 53
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 53
Gln Gln Tyr Tyr Leu Tyr Pro Phe Thr
1 5

<210> 54
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 54
Trp Ile Pro Gln Ser Tyr Pro Phe Arg Ser Tyr Lys Ser Gly Phe Asp
1 5 10 15

Tyr

<210> 55
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 55
Arg Ala Ser Gln Ser Ile Tyr Tyr Tyr Leu Ala
1 5 10

<210> 56
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 56
Arg Ala Ser Gln Val Ile Tyr Gly Tyr Leu Ala
1 5 10

<210> 57
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 57
Asp Ala Ser Thr Arg Glu Ser
1 5

<210> 58
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 58
Arg Ala Ser Gln Gly Ile Phe Tyr Tyr Leu Ala
1 5 10

<210> 59
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 59
Asp Ala Ser Thr Leu Glu Ser
1 5

<210> 60
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 60
Arg Ala Ser Gln Ala Ile Tyr Ser Tyr Leu Ala
1 5 10