(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 ~~invention~~ 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 aspect, there is ~~the invention~~ 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 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

comprises (a) HVR-L1 comprising the amino acid sequence RASQGISSYLA (SEQ ID NO: 29) or $RASQX_1X_2X_3X_4YLA$, 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 $DASX_1X_2ES$, 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 $QQYYX_1YPFT$, wherein $X_1$ is L or S (SEQ ID NO: 33). In some embodiments, the antibody comprises one or more heavy chain variable domain framework sequences selected from the group consisting of SEQ ID NO: 34-37. In some embodiments, the antibody comprises (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). In some embodiments, the antibody comprises a VH sequence of one of SEQ ID NOs: 1 to 11. In some embodiments, the antibody comprises a VL sequence of one of SEQ ID NOs: 12 to 22. In some embodiments, the antibody comprises 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. In some embodiments, the antibody comprises the VH and VL sequences of an antibody show in Figures 4 and 5. In some embodiments, the antibody is a full length IgG1 antibody.

In one aspect, there is provided 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.

In another aspect, there is ~~the invention~~ provided isolated nucleic acid encoding an antibody as described herein ~~of the invention~~. In another aspect, there is ~~some embodiments, the invention~~ provided a host cell comprising a nucleic acid as described herein ~~of the invention~~. In another aspect, there is ~~some embodiments, the invention~~ provided a method of producing an antibody comprising culturing a host cell as described herein ~~of the invention~~ so that the antibody is produced. In some embodiments, the method further comprises recovering the antibody from the host cell.

In another aspect, there is ~~some embodiments, the invention~~ provided an immunoconjugate comprising an antibody as described herein ~~of the invention~~ and a cytotoxic agent. In another aspect, there is ~~some embodiments, the invention~~ provided a pharmaceutical formulation comprising an antibody as described herein ~~of the invention~~ and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical formulation further comprises 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 TSPAN12 agonist, plasmin, plasminogen, tissue plasminogen activator, a TNF-α inhibitor, and/or a steroid, e.g. triamcinolone or dexamethasone.

In another aspect, there is ~~some embodiments, the invention~~ provided an antibody as described herein ~~of the invention~~ for use as a medicament. In another aspect, there is ~~some embodiments, the invention~~ provided an antibody as described herein ~~of the invention~~ 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 (Osteporosis-Pseudoglioma Syndrome), subconjunctival hemorrhage, or hypertensive retinopathy. In another aspect, there is ~~some embodiments, the invention~~ provided an antibody as described herein ~~of the invention~~ for use in potentiating Norrin activity and/or Norrin/Fzd4 signaling. In some embodiments, the disclosure ~~invention~~ provides an antibody of the disclosure ~~invention~~ 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 ~~invention~~ 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 ~~invention~~. 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 ~~invention~~ 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 ~~invention~~ to potentiate Norrin activity and/or Norrin/Fzd4 signaling. In some embodiments, the disclosure ~~invention~~ provides a method of rescuing a signaling defect in an individual caused by mutation in Norrin and/or Fzd4 comprising administering an ~~the~~ antibody of the disclosure ~~claim 1~~.

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 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 rescuing a signaling defect in an individual caused by mutation in Norrin and/or Fzd4.

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. ~~A method of~~ 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 ~~comprising administering to the individual an effective amount of the antibody of claim 1~~.

27. ~~A method of~~ 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 ~~comprising administering to the individual an effective amount of the antibody of claim 1 to potentiate Norrin activity and/or Norrin/Fzd4 signaling~~.

28. ~~A method of~~ 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 ~~comprising administering the antibody of claim 1~~.