

CLAIMS

1. A multi-specific binding molecule comprising 1) an anti-betacellulin (BTC) binding moiety and 2) an anti-vascular endothelial growth factor (VEGF) binding moiety, wherein the anti-BTC binding moiety comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 as set forth in:

- a. SEQ ID NOs: 1, 2, 3, 14, 15, and 16, respectively; SEQ ID NOs: 4, 2, 3, 14, 15, and 16, respectively; SEQ ID NOs: 5, 6, 3, 17, 18, and 19, respectively; or SEQ ID NOs: 7, 8, 9, 20, 18, and 16, respectively;
- b. SEQ ID NOs: 25, 26, 27, 38, 39, and 40, respectively; SEQ ID NOs: 28, 26, 27, 38, 39, and 40, respectively; SEQ ID NOs: 29, 30, 27, 41, 42, and 43, respectively; or SEQ ID NOs: 31, 32, 33, 44, 42, and 40, respectively;
- c. SEQ ID NOs: 25, 49, 50, 58, 59, and 60, respectively; SEQ ID NOs: 28, 49, 50, 58, 59, and 60, respectively; SEQ ID NOs: 29, 51, 50, 61, 62, and 63, respectively; or SEQ ID NOs: 31, 52, 53, 64, 62, and 60, respectively; or
- d. SEQ ID NOs: 69, 70, 71, 82, 83, and 84, respectively; SEQ ID NOs: 72, 70, 71, 82, 83, and 84, respectively; SEQ ID NOs: 73, 74, 71, 85, 18, and 86, respectively; or SEQ ID NOs: 75, 76, 77, 87, 18, and 84, respectively,

wherein the anti-BTC binding moiety and the anti-VEGF binding moiety are an antibody or antigen binding fragment thereof.

2. The multi-specific binding molecule of claim 1, wherein the anti-VEGF binding moiety and/or the anti-BTC binding moiety is in a format selected from the group consisting of an isolated antibody, Fab arm exchange, crossmab, a Fab, a Fab', a F(ab')₂, a Fv, and a scFv.

3. The multi-specific binding molecule of claim 2, wherein the anti-BTC binding moiety is an anti-BTC Fab and the anti-VEGF binding moiety is an anti-VEGF Fab, wherein the anti-BTC Fab comprises a heavy chain (HA) and a light chain (LA), and wherein the anti-VEGF Fab comprises a heavy chain (HB) and a light chain (LB).

4. The multi-specific binding molecule of claim 3, wherein the HA and the HB are linked in the format from the N-terminus to the C-terminus: N-HA-linker 1-HB-C, and wherein the LA and the LB are linked in the format from the N-terminus to the C-terminus: N-LA-linker 2-LB-C.

5. The multi-specific binding molecule of claim 1, wherein the anti-BTC binding moiety comprises a VH and a VL comprising an amino acid sequence with at least 90% sequence identity to:

- a. SEQ ID NOs: 10 and 21, respectively;
- b. SEQ ID NOs: 34 and 45, respectively;
- c. SEQ ID NOs: 54 and 65, respectively; or
- d. SEQ ID NOs: 78 and 88, respectively.

6. The multi-specific binding molecule of claim 5, wherein the anti-BTC binding moiety comprises a heavy chain and a light chain with an amino acid sequence as set forth in:

- e. SEQ ID NOs: 12 and 23, respectively;
- f. SEQ ID NOs: 36 and 47, respectively;
- g. SEQ ID NOs: 56 and 67, respectively; or
- h. SEQ ID NOs: 80 and 90, respectively.

7. The multi-specific binding molecule of claim 1, wherein the anti-VEGF binding moiety comprises a VH and VL comprising an amino acid sequence with at least 90% sequence identity to SEQ ID NOs: 101 and 112, respectively.

8. The multi-specific binding molecule of claim 7, wherein the anti-VEGF binding moiety comprises a heavy chain and a light chain with the amino acid sequence as set forth in SEQ ID NOs: 103 and 114, respectively, or wherein the heavy chain and light chain are encoded by a nucleic acid sequence with 100% sequence identity to SEQ ID NOs: 104 and 115, respectively.

9. The multi-specific binding molecule of claim 1, wherein the anti-BTC binding moiety comprises a variable heavy chain domain (VHA) and a variable light chain domain (VLA) that bind to BTC, and wherein the anti-VEGF binding moiety comprises a variable heavy chain domain (VHB) and a variable light chain domain (VLB) that bind to VEGF, wherein the multi-specific binding molecule is in the format from the N-terminus to C-terminus as: N-VHA-heavy chain constant domain (CH1A)-linker 1-VHB-heavy chain constant domain (CH1B)-C and N-VLA-light chain constant domain (CKA)-linker 2-VLB-light chain constant domain (CKB)-C, which comprises a heavy chain comprising the VHA, CH1A, linker 1, VHB, and CH1B, and which comprises a light chain comprising the VLA, CKA, linker 2, VLB, and CKB, wherein the heavy chain and the light chain is as set forth in:

- i. SEQ ID NOs: 120 and 125, respectively;

- j. SEQ ID NOs: 130 and 135, respectively;
 - k. SEQ ID NOs: 140 and 145, respectively; or
 - l. SEQ ID NOs: 149 and 154, respectively.
10. A polynucleotide comprising a nucleotide sequence encoding the anti-BTC binding moiety of the multi-specific binding molecule of claim 1.
 11. An expression cassette or a vector comprising the polynucleotide of claim 10.
 12. A pharmaceutical composition comprising an effective amount of the multi-specific binding molecule of claim 1.
 13. The pharmaceutical composition of claim 12 for use in treating a subject having an ophthalmic disorder in need thereof, wherein an effective amount of the composition is to be administered to the subject, and wherein the ophthalmic disorder is selected from the group consisting of diabetic macular edema (DME), age-related macular degeneration (AMD), neovascular AMD, neovascular glaucoma, diabetic retinopathy, macular edema, pathologic myopia, retinal vein occlusions, retinopathy of prematurity, and abnormal vascular proliferation associated with phakomatoses.
 14. Use of the pharmaceutical composition of claim 12 in the manufacture of a medicament for the treatment of a subject having an ophthalmic disorder in need thereof, wherein an effective amount of the composition is to be administered to the subject, and wherein the ophthalmic disorder is selected from the group consisting of diabetic macular edema (DME), age-related macular degeneration (AMD), neovascular AMD, neovascular glaucoma, diabetic retinopathy, macular edema, pathologic myopia, retinal vein occlusions, retinopathy of prematurity, and abnormal vascular proliferation associated with phakomatoses.
 15. The pharmaceutical composition of claim 14, wherein the ophthalmic disorder is DME.
 16. The pharmaceutical composition of claim 14, wherein the ophthalmic disorder is neovascular AMD.