

the RTK/Tie2 comprises Ang1. In some embodiments, the Ang1 comprises a full length Ang1. In some embodiments, the Ang1 comprises a polypeptide sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to **SEQ ID NO: 3**. In some embodiments, the Ang1 comprises a functional fragment of Ang1. In some embodiments, the functional fragment of the Ang1 comprises a fibronectin-like domain (FLD). In some embodiments, the FLD comprises a polypeptide sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to **SEQ ID NO: 5**. In some embodiments, the FLD is fused to a soluble polypeptide. In some embodiments, the soluble polypeptide comprises a polypeptide sequence that is at most 99%, at most 98%, at most 97%, at most 96%, at most 95%, at most 94%, or at most 93% identical to **SEQ ID NO: 1**. In some embodiments, the soluble polypeptide comprises a polypeptide sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or more identical to **SEQ ID NO: 2**. In some embodiments, the soluble polypeptide comprises a polypeptide sequence that is **SEQ ID NO: 2**. In some embodiments, the activator of the RTK/Tie2 is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to **SEQ ID NO: 6**. In some embodiments, the activator of the RTK/Tie2 comprises an antibody or a fragment thereof. In some embodiments, the activator of the RTK/Tie2 comprises a monovalent Fab', a divalent Fab2, a F(ab)'3 fragments, a single-chain variable fragment (scFv), a bis-scFv, (scFv)2, a diabody, a minibody, a nanobody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a single-domain antibody (sdAb), an Ig NAR, a camelid antibody, or a combination thereof, a binding fragment thereof, or a chemically modified derivative thereof. In some embodiments, the activator of the RTK/Tie2 binds to and inhibits Ang2. In some embodiments, the antibody or the fragment thereof binds to a polypeptide that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to **SEQ ID NO: 12**. In some embodiments, the antibody or the fragment thereof comprises a polypeptide sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of **SEQ ID NOs: 139-141**, a fragment thereof, or a combination thereof. In some embodiments, the activator of the RTK/Tie2 comprises an inhibitory RNA. In some embodiments, the inhibitory RNA comprises a shRNA, siRNA, miRNA, or a combination thereof. In some embodiments, the inhibitory RNA comprises shRNA. In some embodiments, the inhibitory RNA binds to an endogenous nucleic acid encoding an angiopoietin. In some embodiments, the angiopoietin comprises Ang2. In some embodiments, the Ang2 comprises a

some embodiments, the non-antibody VEGF inhibitor comprises a soluble VEGFR1, a soluble VEGFR2, a soluble VEGFR3, a soluble fragment thereof, or a combination thereof. In some embodiments, the non-antibody VEGF inhibitor comprises a VEGF-Trap or a modified version thereof. In some embodiments, the non-antibody VEGF inhibitor comprises an amino acid sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to **SEQ ID NO: 24**, **SEQ ID NO: 25**, **SEQ ID NO: 26**, or **SEQ ID NO: 31**, or a combination thereof, or a fragment thereof. In some embodiments, the Ang1 polypeptide is a full length Ang1. In some embodiments, the Ang1 polypeptide is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to **SEQ ID NO: 3**. In some embodiments, the Ang1 polypeptide comprises an Ang1 functional fragment comprising a fibronectin-like domain (FLD) of Ang1. In some embodiments, the Ang1 polypeptide is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or 100% identical to **SEQ ID NO: 5**. In some embodiments, the FLD is fused to a soluble polypeptide comprising a polypeptide sequence that is at most 99%, at most 98%, at most 96%, at most 95%, at most 94%, or at most 93% identical to **SEQ ID NO: 6**. In some embodiments, the Ang2 inhibitor comprises an antibody or a fragment thereof that binds to and inhibits Ang2. In some embodiments, the Ang2 inhibitor comprises a monovalent Fab', a divalent Fab2, a F(ab)'3 fragments, a single-chain variable fragment (scFv), a bis-scFv, (scFv)2, a diabody, a minibody, a nanobody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a single-domain antibody (sdAb), an Ig NAR, camelid antibody, or a combination thereof, a binding fragment thereof, or a chemically modified derivative thereof. In some embodiments, the antibody or the fragment thereof binds to a polypeptide that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to **SEQ ID NO: 12**. In some embodiments, the antibody or the fragment comprises a polypeptide sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of **SEQ ID NOs: 139-141**, or a fragment thereof, or a combination thereof. In some embodiments, the Ang2 inhibitor comprises a RNA interference (RNAi). In some embodiments, the RNAi comprises a shRNA, siRNA, miRNA, or a combination thereof. In some embodiments, the RNAi comprises shRNA that binds to endogenous nucleic acid encoding Ang2. In some embodiments, the RNAi binds to an Ang2 nucleic acid sequence that is at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to **SEQ ID NO: 13**. In some embodiments, the non-naturally occurring polynucleotide

[009] Described herein, in some aspects, is a cell comprising the non-naturally occurring polynucleotide described herein. In some embodiments, the cell comprises an embryonic stem cell, an embryonic stem cell-derived differentiated cell, a retinal pigment epithelium (RPE) cell, a neural progenitor cell, a photoreceptor precursor cell, a bone marrow-derived hematopoietic stem cell, or a bone marrow-derived hematopoietic stem progenitor cell.

[0010] Described herein, in some aspects, is a pharmaceutical composition comprising the non-naturally occurring polynucleotide the cell described herein. In some embodiments, the pharmaceutical composition is formulated for administering intrathecally, intraocularly, intravitreally, retinally, intravenously, intramuscularly, intraventricularly, intracerebrally, intracerebellarly, intracerebroventricularly, intraparenchymally, subcutaneously, intratumorally, pulmonarily, endotracheally, intraperitoneally, intravesically, intravaginally, intrarectally, orally, sublingually, transdermally, by inhalation, by inhaled nebulized form, by intraluminal-GI route, or a combination thereof to a subject in need thereof. In some embodiments, the pharmaceutical composition is for treating an ocular disease or condition. In some embodiments, the pharmaceutical composition decreases neovascularization, blood vessel leakage, inflammation, or a combination thereof in the subject.

[0010a] Described herein, in some aspects, is the non-naturally occurring polynucleotide as described herein for use in therapy.

[0011] Described herein, in some aspects, is a method for treating a disease or a condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the non-naturally occurring polynucleotide, the cell the pharmaceutical composition described herein. In some embodiments, the VEGF inhibitor and the activator of the RTK/Tie2 or the RTK/Tie2 decrease neovascularization signaling when expressed in a cell by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 500%, or more compared to neovascularization signaling in absence of the VEGF inhibitor and the activator of the RTK/Tie2 or the RTK/Tie2. In some embodiments, the VEGF inhibitor and the activator of the RTK/Tie2 or the RTK/Tie2 decrease neovascularization signaling in a cell by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 100%, at least 200%, at least 500%, or more compared to neovascularization signaling decreased by a comparable VEGF inhibitor and a comparable activator of a RTK/Tie2 or a comparable RTK/Tie2 encoded from two different non-naturally occurring polynucleotides. In some embodiments, the non-naturally occurring polynucleotide, the cell, or the pharmaceutical composition described herein

[0027] Fig. 8B illustrates a non-limiting exemplary pFB-AAV vector (AVMX110-Ang2-Antibody) encoding a non-antibody VEGF inhibitor (VEGF-Trap, **SEQ ID NO: 24**) and an ANG2 antibody (**SEQ ID NO: 141**).

[0028] Fig. 8C illustrates a non-limiting exemplary pFB-AAV vector encoding a scFv antibody VEGF inhibitor (**SEQ ID NO: 23**) linked (as denoted by “4xGGGS”) to an ANG2 antibody (**SEQ ID NO: 141**).

[0029] Fig. 8D illustrates a non-limiting exemplary pFB-AAV vector (AVMX110-anti-Ang2 shRNA) encoding a non-antibody VEGF inhibitor (VEGF-Trap, **SEQ ID NO: 24**) and an ANG2 silence sequence (e.g., nucleic acid sequence encoding inhibitory RNA).

[0030] Fig. 9A illustrates a non-limiting exemplary pFB-AAV vector (AVMX104: Anti-VEGF-ScFV-hCOMP-Ang1) encoding an antibody VEGF inhibitor (**SEQ ID NO: 34**) and either hCOMP-Ang1 (for treatment purpose, **SEQ ID NO: 6**) or FLAG-hCOMP-Ang1 (for pharmacokinetic purpose. **SEQ ID NO: 28**).

[0031] Fig. 9B illustrates a non-limiting exemplary pFB-AAV vector (AVMX105: Flt1-D2/KDR-D2) encoding a soluble VEGF inhibitor (**SEQ ID NO: 25**). The AAV vector can comprise at least more expression cassette for expressing any one of the VEGF inhibitor, activator of RTK/Tie2, or RTK/Tie2 described herein.

[0032] Fig. 9C illustrates a non-limiting exemplary pFB-AAV vector (AVMX106: Flt1-D2/KDR-D2-COMP-Ang1) encoding soluble VEGF inhibitor (**SEQ ID NO: 25**) and a hCOMP-Ang1.

[0033] Fig. 9D illustrates a non-limiting exemplary pFB-AAV vector (Flt1-D2/KDR-D2-hCOMP-Ang1) encoding a soluble VEGF inhibitor (**SEQ ID NO: 25**, top box, or **SEQ ID NO: 26**, lower box) and a hCOMP-Ang1.

[0034] Fig. 9E illustrates a non-limiting exemplary pFB-AAV vector (AVMX108: VEGF-scFv) encoding an scFv antibody VEGF inhibitor (**SEQ ID NO: 35**). The AAV vector can comprise at least one more expression cassette for expressing any one of the VEGF inhibitor, activator of RTK/Tie2, or RTK/Tie2 described herein.

[0035] Fig. 9F illustrates a non-limiting exemplary pFB-AAV vector (VEGF-ScFV-hCOMP-Ang1) encoding an scFv antibody VEGF inhibitor (**SEQ ID NO: 35**) and a hCOMP-Ang1.

[0036] Fig. 10A illustrates exemplary information FOR Ang1, COMP-Ang1, and disadvantages of full length Ang1.

[0037] Fig. 10B illustrates an exemplary dual expression AAV construct.

thereof comprising a peptide sequence that is least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or more identical to **SEQ ID NO: 12**, or a fragment thereof (**Table 15**). In some embodiments, the Ang2 antibody comprises a polypeptide sequence that is least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or more identical to **SEQ ID NO: 139**, **SEQ ID NO: 140**, **SEQ ID NO: 141**, or a fragment thereof, or a combination thereof. In some embodiments, the Ang2 antibody comprises a polypeptide sequence that is **SEQ ID NO: 139** and **SEQ ID NO: 140**. In some embodiments, the Ang2 antibody comprises a polypeptide sequence that is **SEQ ID NO: 141**.

Table 15. Ang2 and Ang2 antibody nucleic acid and polypeptide sequences

SEQ ID NO	Ang2 and Ang2 antibody nucleic acid and polypeptide sequence
	Ang2 nucleic acid sequence

SE Q ID NO	Ang2 and Ang2 antibody nucleic acid and polypeptide sequence
SE Q ID NO: 12	MWQIVFFTLS CDLVLAAYN NFRKSMDSIG KKQYQVQHGS CSYTFLLPEM DNCRSSSSPYVSNAVQRDAP LEYDDSVQRL QVLENIMENN TQWLMKLENY IQDNMKKEMVEIQQNAVQNNQ TAVMIEIGTN LLNQTAEQTR KLTDVEAQVL NQTTRLELQL LEHSLSTNKL EKQILDQTSE INKLQDKNSF LEKKVLAMED KHIIQLQSIK EEKDQLQVLV SKQNSIIEEL EKKIVTATVN NSVLQKQQHD LMETVNNLLT MMSTSNSKDP TVAKEEQISF RDCAEVFKSG HTTNGIYTLT FPNSTEEIKA YCDMEAGGGG WTIIQRREDG SVDFQRTWKE YKVGFGNPSG EYWLGNEFVS QLTNQQRYYL KIHLDKDWEGN EAYSLYEHFY LSSEELNYRI HLKGLTG TAG KISSISQPGN DFSTKDGDND KCICKCSQML TGGWWFDACG PSNLNGMYYP QRQNTNKFNG IKWYYWKGSG YSLKATTMMI RPA DF
	Ang2 antibody VH polypeptide sequence
SE Q ID NO: 139	QVQLVQSGAE VKKPGASVKVSCASGYTFTGYYMHWVRQA PGQGLEWMGW INPNSGGTNYAQKFQGRVTM TRDTSISTAY MELSRLRSDDTAVYYCARSPNPYYDSSGYYYPGAFDIWGQGTMTVSS
	Ang2 antibody VL polypeptide sequence
SE Q ID NO: 140	SYVLTQPPSV SVAPGQTARI TCGGNNIGSK SVHWYQQKPG QAPVLVVYDD SDRPSGIPERFSGSNSGNTA TLTISRVEAG DEADYYCQVW DSSSDHWVFG GGTKLTVLSS

	Ang2 scFv polypeptide sequence
S E Q I D N O : 1 4 1	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYDIHWVRQATGKGLEWVSAIGPAGDT YYPGSVKGRFTISRENAKNSLYLQMNSLRAGDTAVYYCARGLITFGGLIAPFDYWGQ GTLVTVSSGGGGSGGGGSGGGGSGGGGSEIVLTQSPGTLSPGERATLSCRASQSVSS TYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGT DFTLTISRLE PEDFAVYYCQ HYDNSQTFGQ GTKVEIKRTVAA

An ti- hu ma n An g2	Ne sva cu ma b scF v	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYDIHWVRQATGKGLEWVSAI GPAGDTYYPGSVKGRFTISRENAKNSLYLQMNSLRAGDTAVYYCARGLIT FGGLIAPFYWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSEIVLTQSPGTL SLSPGERATLSCRASQSVSSTYLAWYQQKPGQAPRLLIYGASSRATGIPDRF SGSGSGT DFTLTISRLE PEDFAVYYCQ HYDNSQTFGQ GTKVEIKRTVAA	S E Q I D N O : 1 4 1
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Table 2. Molecular cloning of plasmids encoding proteins and combinations via the use of exemplary AAV vector for VEGF inhibition and modulation of Ang1 or Ang2 expression

AMI071-pFB-scCMV-SV40intron-Vh-hCOMP-Ang1-FLAG was created by assembling the hCOMP-Ang1-FLAG fragment PCR-amplified from AMI063 with primers A095, A096, and A097 into the AflII and XhoI sites of AMI060
AMI077-pFB-scCMV-SV40intron-Vh-hCOMP-Ang1-FLAG-GC was created by assembling the codon-optimized hCOMP-Ang1-GC-FLAG fragment PCR-amplified from Twist synthesized DNA with primers A095 and A135 into the AflII and XhoI sites of AMI071
AMI136-pFB-CMV-SV40in-Aflibercept-GCRS(TCC)-CMV-SV40in-hCOMP-Ang1 was created by assembling the CMV-SV40in-Aflibercept-GCRS (TCC) fragment PCR-amplified from AMI120 with primers A426 and A427 into the KpnI sites of AMI092
AMI142-pFB-CMV-SV40in-Aflibercept-GCRS(TCC)-Furin-F2A-hCOMP-Ang1 was created by assembling the Furin-F2A-hCOMP-Ang1 fragment PCR-amplified with primers A522, A523, and A524, into the BstBI sites of AMI136
AMI143-pFB-CMV-SV40in-Aflibercept-GCRS(TCC)-QBI_SP163-hCOMP-Ang1 was created by assembling the joined PCR fragment (the QBI SP163 fragment PCR-amplified with primers A525 and A526, and AMI131 as template; the hCOMP-Ang1 fragment PCR-amplified with primers A527 and A524, and AMI063 as template, and these two fragments were joined together by PCR with primers A525 and A524) into the BstBI sites of AMI136
AMI144-pFB-CMV-SV40in-Aflibercept-GCRS(TCC)-4xGGGGS-hCOMP-Ang1 was created by assembling the 4xGGGGS-hCOMP-Ang1 fragment PCR-amplified with primers A528 and A529, and AMI063 as template into the BstBI sites of AMI136
AMI145-pFB-scCMV-SV40in-Aflibercept-GCRS(TCC)-hU6-shRNA1-Ang2 was created by assembling the hU6-shRNA1-Ang2 fragment PCR-amplified with primers A530 and A531 and V402 as template into SphI site of AMI120
AMI146-pFB-scCMV-SV40in-Vh-Ang2-10xHis was created by assembling the Vh-Ang2-10xHis fragment PCR-amplified with primers A532 and A533 and Ang2 purchased from Sinobiological HG10691-CH) as template into the AflII and XhoI sites of AMI071
AMI147-, AMI148-, AMI149-, AMI150-, AMI151-, and AMI152-pFB-scCMV-SV40in-Aflibercept-GCRS(TCC)-hU6-shRNA2-, 3-, scramble-, 4-, 5-, and 6-Ang2 were created by ligating the annealed oligo pairs A534-A535, A536-A537, A544-A545, A546-A547, A548-A549, A550-A551 respectively into the SphI and HindIII sites of AMI145