

CLAIMS

WHAT IS CLAIMED IS:

1. A non-naturally occurring polynucleotide comprising one or more expression cassettes for expressing:
 - a) a VEGF inhibitor; and
 - b) a receptor tyrosine kinase (RTK)/Tie2 or an activator of RTK/Tie2.
2. The non-naturally occurring polynucleotide of claim 1, wherein a) and b) are expressed as separate polypeptides or as a contiguous polypeptide cleavable into separate polypeptides comprising the VEGF inhibitor, and the RTK/Tie2 or the activator of RTK/Tie2.
3. The non-naturally occurring polynucleotide of claim 2, wherein the contiguous polypeptide comprises a protease cleavable sequence, a Furin cleavable sequence, or a self-cleaving polypeptide sequence.
4. The non-naturally occurring polynucleotide of claim 1, wherein the VEGF inhibitor comprises an anti-VEGF antibody or VEGF-TRAP.
5. The non-naturally occurring polynucleotide of claim 1, wherein the activator of the RTK/Tie2 comprises a angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), angiopoietin-3 (Ang-3), angiopoietin-4 (Ang-4), or a functional fragment of any one thereof.
6. The non-naturally occurring polynucleotide of claim 5, wherein the Ang-1 comprises or consists of 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**.
7. The non-naturally occurring polynucleotide of claim 5, wherein the functional fragment of the Ang-1 comprises or consists of a fibronectin-like domain (FLD).
8. The non-naturally occurring polynucleotide of claim 7, wherein the FLD comprises or consists of 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**.
9. The non-naturally occurring polynucleotide of claim 7, wherein the FLD is fused to a soluble polypeptide.
10. The non-naturally occurring polynucleotide of claim 9, wherein the soluble polypeptide comprises or consists of 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** or **SEQ ID NO: 1**.

11. The non-naturally occurring polynucleotide of claim 1, wherein 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**.
12. The non-naturally occurring polynucleotide of claim 1, wherein the activator of the RTK/Tie2 comprises an antibody or a fragment thereof.
13. The non-naturally occurring polynucleotide of claim 1, wherein the activator of the RTK/Tie2 binds to and inhibits Ang-2.
14. The non-naturally occurring polynucleotide of claim 1, wherein the antibody or the fragment thereof comprises or consists of 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.
15. The non-naturally occurring polynucleotide of claim 1, wherein the activator of the RTK/Tie2 comprises an inhibitory RNA.
16. The non-naturally occurring polynucleotide of claim 15, wherein the inhibitory RNA comprises a shRNA, siRNA, miRNA, or a combination thereof.
17. A viral vector comprising the non-naturally occurring polynucleotide of claim 1.
18. The viral vector of claim 17, wherein the viral vector is an adeno-associated viral (AAV) vector.
19. The non-naturally occurring polynucleotide of claim 1 for use in therapy.