COMPOSITIONS AND METHODS FOR OCULAR TRANSGENE EXPRESSION

CROSS-REFERENCE

[0001] This application claims the benefit of US Provisional Application Serial Number 63/173,280 filed on April 9, 2021, the entirety of which is hereby incorporated by reference herein.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 8, 2022, is named 59561-703_601_SL.txt and is 159,002 bytes in size.

BACKGROUND

[0003] Aflibercept (VEGF-Trap) is a recombinant fusion protein that acts as a decoy receptor for vascular endothelial growth factor subtypes A (VEGF-A), VEGF-B, and placental growth factor (PIGF). By binding to these ligands, aflibercept is able to prevent these ligands from binding to vascular endothelial growth factor receptors (VEGFR), VEGFR-1 and VEGFR-2, to suppress neovascularization and decrease vascular permeability. Aflibercept consists of domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused with the Fc fragment of IgG1. Aflibercept is commercially marketed under the trade name EYLEA® (aflibercept), which is an ophthalmic intravitreal aflibercept fusion protein injection.

SUMMARY

[0004] Current treatments employing aflibercept suffer from short durability and repeated monthly injections in order to suppress the neovascularization. Several gene therapy studies using AAV vectors carrying the coding sequence for VEGF-Trap has been investigated for long term treatment of the neovascularization. However, these studies suffer from low expression levels of the agent and therefore reduced treatment efficacy. Accordingly, it has become increasingly clear that the full potential of this technology will only be realized after modifications are made for improved delivery and expression of VEGF-Trap and other anti-angiogenic agents.

[0004a] Described herein, in one aspect, is a non-naturally occurring nucleic acid comprising a sequence encoding a biologic comprising an anti-angiogenic agent, said sequence comprising a modification in a coding region of the sequence as compared to an otherwise comparable sequence lacking the modification in the coding region, said modification comprising a replacement of at least four non-AGG arginine codons with AGG.

[0004b] Described herein, in another aspect, is a biologic encoded by the non-naturally occurring nucleic acid as described herein.

[0004c] Described herein, in another aspect, is an engineered cell comprising the non-naturally occurring nucleic acid as described herein.

[0004d] Described herein, in another aspect, is a plurality of adeno-associated viral (AAV) particles comprising the non-naturally occurring nucleic acid as described herein.

[0004e] Described herein, in another aspect, is a composition comprising the plurality of AAV particles as described herein in unit dosage form.

[0004f] Described herein, in another aspect, is a container comprising: (a) the non-naturally occurring nucleic acid as described herein; (b) the biologic as described herein; (c) the engineered cell as described herein, or (d) the plurality of AAV particles as described herein.

[0004g] Described herein, in another aspect, is a method of modifying cells, the method comprising contacting (a) a plurality of cells with the non-naturally occurring nucleic acid as described herein; (b) a plurality of cells with the plurality of adeno-associated viral (AAV) particles as described herein; or both (a) and (b)

[0004h] Described herein, in another aspect, is a pharmaceutical composition comprising: (a) the non-naturally occurring nucleic acid as described herein; (b) the biologic as described herein; or (c) the plurality of AAV particles as described herein.

[0004i] Described herein, in another aspect, is the (a) non-naturally occurring nucleic acid as described herein; (b) biologic as described herein; (c) plurality of AAV particles as described herein; or (d) pharmaceutical composition as described herein, for use as a medicament.

[0005] Described herein, in some aspects, is an isolated, non-naturally occurring nucleic acid comprising a sequence encoding a biologic comprising an anti-angiogenic agent, said sequence comprising a modification in a coding region of the sequence as compared to an otherwise comparable sequence lacking the modification in the coding region, said modification comprising a replacement of at least four non-AGG arginine codons with AGG. In some embodiments, the sequence that encodes the anti-angiogenic agent further comprises a second modification. In