SUSTAINED DRUG DELIVERY SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/106,136 filed on October 16th, 2008.

FIELD OF THE INVENTION

[0002] This invention relates generally to therapeutics and specifically to drug delivery methodologies for prolonging *in vivo* efficacy of the drug, and more particularly to drug delivery to the back of the eye.

DESCRIPTION OF THE RELATED ART

[0003] Diseases of the back of the eye, such as age-related macular degeneration (AMD) and diabetic retinopathy, are affecting increasing numbers of people as our population ages. For efficacious therapy of these degenerative ocular diseases, therapeutic agents need to be delivered at sufficient concentration to the back of the eye, particularly the retina.

[0004] Topical delivery of drops is the most common means to administer therapeutic agents to the eye but only a very small percentage of the applied dose reaches the intraocular tissue. Because of the blood-retina-barrier, systemic administration requires large doses to reach therapeutic levels in the eye and therefore may cause unacceptable side effects. Direct injection into the vitreous humor within the globe of the eye is attractive because the barrier to the retina from this site is minimal. However, penetration of the globe can be associated with serious sight-threatening adverse events including infection and retinal detachments. Injections outside of the globe (e.g., subconjunctival) are inefficient in reaching the target tissue due to clearance of the

therapeutic agent to the bloodstream in the choroid and the tight barrier of the retinal pigment epithelium to hydrophilic compounds. Some therapeutics in the form of nanoparticles and liposomes can be introduced via intravitreal injections. However, they tend to obscure vision by scattering light entering the eye.

[0005] Another method of delivering therapeutic compounds to the eye is the use of implants. For example, two non-biodegradable ophthalmic implants are currently on the market, delivering ganciclovir and fluocinolone acetonide to treat cytomegalovirus retinitis and uveitis, respectively. These can achieve steady delivery of small molecules to the vitreous for years. However, this method involves the risks associated with invasive surgery to implant and remove these devices. As an improvement over non-biodegradable implants, biodegradable implants are in clinical studies that require less invasive procedures, possibly even suture-less office implantation.

[0006] It will be desirable to provide drug delivery systems that prolong the availability of the drug to the target tissue, but do not have the limitations associated with frequent dosing or interfering with vision.

[0007] Recently, treatment of eye diseases such as AMD has been revolutionized by two developments: (1) the realization that vascular endothelial growth factor (VEGF) is a causative factor in the disease, and (2) approval of an anti-VEGF antibody fragment for treatment of AMD administered via intravitreal injection, Genentech's Ranibizumab (LUCENTIS®). In addition, a full length antibody directed against VEGF such as Genentech's Bevacizumab (AVASTIN®, hereinafter also referred to as Avastin), is frequently injected into the vitreous off-label to treat back of the eye diseases. These new treatment options have had a huge impact because they are the first treatments for AMD that improve vision in many patients, where previous treatments simply delayed vision loss. Ranibizumab and Bevacizumab act by binding to and inactivating

VEGF. The duration of effect is determined by drug half-life; in general, a longer half-life provides longer duration and, therefore, less frequent dosing.

[0008] Clinical pharmocokinetic data are generally limited to serum due to difficulty in sampling ocular tissue. Elimination of Ranibizumab from the eye has been studied more extensively in monkeys (Gaudreault *et al.*, *Invest. Ophthalmol. Vis. Sci.* **46**:726-733, 2005). Ranibizumab was cleared uniformly from all ocular compartments, including the vitreous and retina, with a terminal half-life of approximately 3 days. The serum half-life after intravitreal injection was similar, (approximately 3.5 days) whereas the half-life was approximately 0.5 day after intravenous injection. This suggests the serum concentrations after intravitreal injection are controlled by the elimination rate from the eye. The package insert of Lucentis states that "… monthly 500 microgram intravitreal injections of Ranibizumab achieve results superior to less frequent dosing". However, given the attendant risks of intravitreal injections noted above, it is widely recognized that physicians would prefer, and patients would benefit from, less frequent dosing.

[0009] Further, though methods of sustained drug delivery using cationic complexes are promising, (e.g., see Singh *et al.*, *J. Cont. Rel.*, **32**: 17-25, 1994; Singh *et al.*, *J. Cont. Rel.*, **35**: 165-179, 1995), they have yet to be applied to treatment of the localized areas of the body such as the eye. For example, U.S. Patent No. 7,244,438 by Lingnau *et al.* discloses a drug formulation where cationic amino acids are physically combined with a therapeutic agent for systemic delivery. A physical combination of this sort will not be as suitable for sustained drug delivery as a chemically combined drug composition. Further, the charge density of the cationic moiety that is disclosed by Lingnau *et al.* would exhibit both undesirably high antigenicity, as well as an undesirably high toxicity.

[0010] Further, polycations such as polyethylenimine and polylysine are traditionally often utilized in nonviral gene delivery systems to protect nucleic acid therapeutics (e.g., DNA and

within the internal sequence of the protein. In this scenario, the peptide is co-linear with the therapeutic protein and can be present in individual copies or in tandem repeats.

[0043] The cationic tail is configured to bind to components of the desired tissue target site without specificity. However, the length and sequence of the peptide may be configured for optimal binding affinity to specific components such as hyaluronic acid. The peptide may be 2-30 amino acid residues in length, and may contain an abundance of basic residues (Arg, Lys, His). Amino acid residues not involved in hyaluronan binding (e.g., glycine, serine) can be added to the sequence, if needed, to provide proper spacing for the charges on the retaining peptide.

[0044] Various cationic building blocks may be used in formulating the therapeutic compound with a multivalent cationic retaining moiety. Such building blocks include amino acids that are positively charged at physiologic conditions, including those naturally occurring amino acids such as lysine, histidine, and arginine. The cationic moiety may be configured to mimic hyaluronan-binding proteins (such as CD44) in terms of composition and spatial arrangement of amino acids. Various other chemical species can be used for the retaining cationic moiety. These include polycations containing the building blocks of polymers used to form polyplexes and lipoplexes in gene delivery, such as polyethylenimine, polyamidoamine, spermine, DOTAP, and polymers derivatized with imidazole-containing pendant groups. That is, polycations that have been used in nonviral gene therapy systems are also applicable to this invention. As previously mentioned in the background section, polycations such as polyethylenimine and polylysine are utilized in nonviral gene delivery systems to protect nucleic acid therapeutics (e.g., DNA and siRNA) from degradation and facilitate uptake into cells. With respect to the preferred embodiment of the present invention, the process is intended to encourage the cationic moiety to form an *in situ* depot of molecularly dispersed, soluble protein that has reduced elimination rates due to reversible, non-specific binding with biological tissue. Various anionic building blocks may be used to create an anionic retaining moiety. Examples

WHAT IS CLAIMED IS:

1) A drug composition comprising:

a charged moiety coupled to a therapeutic compound, wherein the charged moiety is configured to interact with at least one type of component of opposite charge in a biological tissue to create an *in situ* depot for prolonged drug delivery, wherein the biological tissue is eye tissue.

2) The drug composition of claim 1, wherein the charged moiety is cationic and the component of opposite charge is anionic.

3) The drug composition of claim 2, wherein the anionic component is hyaluronic acid.

4) The drug composition of claim 2, wherein the cationic moiety is configured to interact with glycosaminoglycans.

5) The drug composition of claim 2, wherein the cationic moiety comprises cationic amino acids.

6) The drug composition of claim 1, wherein the charged moiety is anionic and the component of opposite charge is cationic.

7) The drug composition of claim 6, wherein the anionic moiety comprises anionic amino acids.

8) The drug composition of claim 1, wherein the charged moiety has one or more charges.

9) The drug composition of claim 8, wherein the charged moiety has at least three charges.

10) The drug composition of claim 9, wherein the charged moiety contains at least one spacer.

11) The drug composition of claim 10, wherein the spacer is located at a coupling site between the therapeutic compound and the charged moiety.

12) The drug composition of claim 11, wherein the spacer is located between the charges of the charged moiety.

13) The drug composition of claim 1, wherein at least two charged moieties are coupled to a therapeutic compound.

14) The drug composition of claim 1, wherein the biological tissue comprises glycosaminoglycans.

15) The drug composition of claim 1, wherein the therapeutic compound is an anti-VEGF compound.

16) The drug composition of claim 15, wherein the anti-VEGF compound is one of Ranibizumab, Bevacizumab, or VEGF Trap.

17) The composition of claim 1, wherein the therapeutic compound has a molecular weight of at least 2,000 Daltons.

18) The composition of claim 1, wherein the coupling is achieved using a stable covalent bond.

19) The composition of claim 18, wherein the coupling is achieved using reactivity of maleimide activated peptide with free thiols.

20) The composition of claim 1, wherein the coupling is achieved using a chemically labile covalent bond.

21) The composition of claim 20, wherein the labile bond is an ester linkage.

22) A method for manufacturing a drug composition comprising:

coupling a charged moiety to a therapeutic compound, wherein the charged moiety is configured to interact with at least one type of component of opposite charge in a human body to create an *in situ* depot for prolonged drug delivery, wherein the therapeutic compound is an anti-VEGF compound.

23) The method of claim 22, wherein the charged moiety is cationic and the component of opposite charge is anionic.

24) The method of claim 22, wherein the charged moiety is anionic and the component of opposite charge is cationic.

25) The method of claim 22, wherein the charged moiety comprises amino acid residues.

26) The method of claim 25, wherein the anti-VEGF compound is one of Ranibizumab, Bevacizumab or VEGF Trap.

27) The method of claim 22, wherein the coupling is achieved through a chemical process.

28) The method of claim 22, wherein the coupling is achieved through a recombinant DNA technique.

29) The method of claim 22, wherein the coupling is achieved using a stable covalent bond.

30) The method of claim 29, wherein the coupling is achieved using reactivity of maleimide activated peptide with free thiols.

31) The method of claim 22, wherein the coupling is achieved using a chemically labile covalent bond.

32) The method of claim 31, wherein the labile bond is an ester bond.