Applications of Sustained Release Delivery Systems in Ocular Disease

Formulation and Delivery Systems For Peptide and Protein 2012
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Content

• Market Overview
• Unmet Needs in Glaucoma and Retinal Disease
• Emerging Treatments
Know Your Technology Options, Technical and Market Constraints

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Delivery System</th>
<th>Device</th>
</tr>
</thead>
</table>
| - Efficacy / side effects  
- Continuous or pulsatile  
- Cost per gram  
- Physicochemical properties | - Process complexity  
- Bioavailability  
- Cost per unit  
- Compatibility with molecule | - Device complexity  
- Ease of use / acceptance  
- Cost per unit  
- Formulation compatibility |

Biology & Chemistry  
PK & Formulation  
Device & Handling
Ocular Delivery Techniques and Challenges

- **Intraocular implants**
  - Increased risk of retinal detachment and intravitreal hemorrhage.
  - Invasive.

- **Intravitreal injections**
  - Increased risk of retinal detachment, hemorrhage, endophthalmitis and cataracts.
  - Rapidly diluted.
  - Repeat procedures necessary.

- **Systemic administration**
  - Limited/variable penetration.
  - Potential for systemic toxicity.

- **Topical application**
  - Limited penetration (<5%).
  - Rapid tear washout.
  - Poor patient compliance.
Market Overview – All Ocular Indications

Global sales in billions of USD, market share

- Glaucoma: 5.3, 37%
- Allergy/inflammation/infection: 4.1, 28%
- Retinal disorders: 1.9, 13%
- Dry eye: 1.7, 12%
- Others: 1.4, 10%

90% of Ocular Products are Topical

IMS Health 2009
## Top Ocular Pharmaceutical Products

<table>
<thead>
<tr>
<th>Company</th>
<th>Indication</th>
<th>World sales (millions of USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucentis</td>
<td>Wet AMD</td>
<td>1,785</td>
</tr>
<tr>
<td>Xalatan</td>
<td>Glaucoma</td>
<td>1,524</td>
</tr>
<tr>
<td>Travatan</td>
<td>Glaucoma</td>
<td>565</td>
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<tr>
<td>Patanol/Pataday</td>
<td>Allergy</td>
<td>511</td>
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<tr>
<td>Restasis</td>
<td>Dry Eye</td>
<td>480</td>
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<tr>
<td>Cosopt</td>
<td>Glaucoma</td>
<td>462</td>
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<tr>
<td>Lumigan</td>
<td>Glaucoma</td>
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<td>Alphagan</td>
<td>Glaucoma</td>
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<tr>
<td>Azopt</td>
<td>Glaucoma</td>
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<tr>
<td>Vigamox</td>
<td>Infection</td>
<td>252</td>
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<tr>
<td>Tobradex</td>
<td>Inflammation</td>
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<tr>
<td>Hyalein</td>
<td>Dry Eye</td>
<td>209</td>
</tr>
</tbody>
</table>

IMS Health 2009
The Eye and Its Many Chambers

Aqueous Humor

Anterior (Front of Eye)  Posterior (Back of Eye)
Glaucoma Treatments (Front of the Eye)

• Majority are topical drops
• Treat symptomatic increase in intraocular pressure (aqueous humor)
• Delivery Systems
  • Primary focus on moving multiple daily drops to once per day
  • Inserts in development for once per week administration
• Unmet Need for Delivery Systems
  • Once every three months injection
  • Subconjunctival injection depot
  • Patients see the doctor once every three months
Glaucoma Delivery System Opportunities

• Sustained Release Depot System
  • PLGA or other polymer implant or microparticle
  • Primarily small molecules
  • Polymer inserts

• Physician administered therapy
  • Glaucoma physicians not yet comfortable with injection
  • Must be a simple injection

• Delivery Constraints
  • Injection site is conjunctiva
  • Safety first – must not cause inflammation or tolerability issues
  • Volume of injection is preferably 50 microliters
    • 100 to 200 microliters may be tolerated
  • 27 gauge needle or better
Back of the Eye Diseases

Diseases of the Retina, Vitreous, and Macula
Back of the Eye Drug Delivery Approaches

- I-vation™ TA
- Durasert™ technology
  - Retisert®
  - Vitrasert®
- IBI-20089 RETAAC
- NOVA63035
- NT-501
- Iluvien®
- Ozurdex®
Back of the Eye Diseases

• Diseases of the Retina, Vitreous, and Macula
  • Age related macular degeneration
  • Retinitis pigmentosa
  • Diabetic retinopathies
  • Neural changes induced by glaucoma

• Age-Related Macular Degeneration (AMD)
  • Leading cause of severe vision loss in people over 50
    • 20/200 or worse visual acuity
  • Most people have dry form – no treatment available
  • Wet form is less common but treatment exists
    • Laser photocoagulation therapy
    • Pharmacotherapies
Back of the Eye Diseases

Dry AMD
• Cells of macula breakdown
• Drusen deposits
• Death of RPE and photoreceptor cells
• Blurry or spotty loss of clear, straight ahead vision
• 90% of cases

Wet AMD
• Abnormal blood vessels grow - neovascularization
• Leak fluid and blood scarring macula
• Straight ahead vision can be distorted or lost in a short period of time
• 10% of cases
• 90% of legal blindness
Imaging Techniques for Early Detection

Normal

Dry AMD

Wet AMD

Wet AMD Symptoms

05DEC2012 DDS Form CRhodes
AMD Treatment Options Growing Rapidly (Preclinical, Clinical, Approved)

BA Zarbin and PJ Rosenfeld, RETINA 30:1350–1367, 2010
Targets for Drug Development

• Steps in AMD Pathogenesis
  • Oxidative damage
  • Lipofuscin accumulation
  • Chronic inflammation
  • Mutations in the complement pathway
  • Noncomplement mutations that influence chronic inflammation and/or oxidative damage

• Steps in Neovascularization
  • Angiogenic factor production
  • Factor release
  • Binding of factors to extracellular receptors
  • Endothelial cell activation and basement membrane degradation
  • Endothelial cell proliferation
  • Directed endothelial cell migration
  • Extracellular matrix remodeling
  • Tube formation
  • Vascular stabilization

BA Zarbin and PJ Rosenfeld, RETINA 30:1350–1367, 2010
Properties of Biologics in Systemic Disease

- **Peptides**
- **Proteins**
- **Antibodies**

<table>
<thead>
<tr>
<th>SC or IV Dose (mg)</th>
<th>Plasma Half-life (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Molecular Weight (kDa)
Pharmacokinetics in the Eye

Fig. 1. Schematic presentation of the ocular structure with the routes of drug kinetics illustrated. The numbers refer to following processes:
1) transcorneal permeation from the lacrimal fluid into the anterior chamber,
2) non-corneal drug permeation across the conjunctiva and sclera into the anterior uvea,
3) drug distribution from the blood stream via blood-aqueous barrier into the anterior chamber,
4) elimination of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and Slemm's canal,
5) drug elimination from the aqueous humor into the systemic circulation across the blood-aqueous barrier,
6) drug distribution from the blood into the posterior eye across the blood-retina barrier,
7) intravitreal drug administration,
8) drug elimination from the vitreous via posterior route across the blood-retina barrier, and
9) drug elimination from the vitreous via anterior route to the posterior chamber.

Local Intravitreal Injection
Reduces Dose by 10 – 100 Fold
Increases Half-life in the Vitreous by 3 – 5 Fold

- Peptides
- Proteins
- Antibodies

Ocular Dose (mg)
Molecular Weight (kDa)
Intravitreal Half-life (hrs)
Pharmacokinetics in the Eye

• Vitreous
  • Large hydrophilic and charged molecules active transport mechanisms
  • Often slower elimination than systemic circulation

• Peculiarities for Development
  • Cannot sample ocular tissues in humans, only plasma
  • Exposure response relationships and tissue distribution in animals critical
  • Plasma levels guide human studies based on models from animals
Ranibizumab Pharmacokinetics in the Eye
[Lucentis approved for AMD, DME, RVO]

Intravitreal half-life 3.5 days

Intravenous half-life 15 hours

Gaudreault et al., IOVS 2005 46(2)726-733
### Current and Future Drugs for Choroidal Neovascularization

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Brand name</th>
<th>Mode of action</th>
<th>Dosage form</th>
<th>Release-controlling excipient</th>
<th>Developmental stage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bevacizumab</strong></td>
<td>Avastin®</td>
<td>Anti-VEGF mAb</td>
<td>IVT, injection</td>
<td></td>
<td>Off-label use</td>
</tr>
<tr>
<td><strong>Ranibizumab</strong></td>
<td>Lucentis®</td>
<td>Anti-VEGF mAb, fragment</td>
<td>IVT, injection</td>
<td></td>
<td>Launched</td>
</tr>
<tr>
<td><strong>Pegaptanib</strong></td>
<td>Macugen®</td>
<td>Anti-VEGF aptamer</td>
<td>IVT, injection</td>
<td></td>
<td>Launched</td>
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<tr>
<td><strong>Verteporfin</strong></td>
<td>Visudyne®</td>
<td>Photosensitizer</td>
<td>IV</td>
<td>Liposome</td>
<td>Launched</td>
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<tr>
<td><strong>Afiblercept</strong></td>
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<td><strong>Bevasiranib</strong></td>
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<td><strong>AGN-211745</strong></td>
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<td><strong>Mecamylamine</strong></td>
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<td><strong>Sirolimus</strong></td>
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<td><strong>PF-4523655</strong></td>
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<tr>
<td><strong>Everolimus</strong></td>
<td>Certican®</td>
<td>mTOR inhibitor</td>
<td>SCJ, injection</td>
<td>PEG</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Combretastatin A4 phosphate (fosbretabulin)</strong></td>
<td>Zybrestat™</td>
<td>Tubulin polymerization inhibitor</td>
<td>IVT, injection</td>
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<td>Phase II</td>
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<tr>
<td><strong>CGC11047</strong></td>
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<td>Polymine analogue</td>
<td>SCJ, injection</td>
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<td>Phase I</td>
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<tr>
<td><strong>JSM6427</strong></td>
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<td>Integrin α5β1 receptor antagonist</td>
<td>IVT, injection</td>
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<td>Phase I</td>
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<tr>
<td><strong>AdGVPEDF0.11D</strong></td>
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<td>PEDF production</td>
<td>IVT, injection</td>
<td>Viral vector</td>
<td>Phase I</td>
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<tr>
<td><strong>POT-4</strong></td>
<td></td>
<td>C3 inhibitor</td>
<td>IVT, injection</td>
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<td>Phase I</td>
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<tr>
<td><strong>ARC1905</strong></td>
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<td>Anti-C5 aptamer</td>
<td>IVT, injection</td>
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<td>Phase I</td>
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<tr>
<td><strong>Sonepczumab</strong></td>
<td>iSONEP™</td>
<td>Anti-sphingosine-1-phosphate mAb</td>
<td>IVT, injection</td>
<td></td>
<td>Phase I</td>
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<tr>
<td><strong>Infliximab</strong></td>
<td>Remicade®</td>
<td>Anti-TNFα mAb</td>
<td>IVT, injection</td>
<td></td>
<td>Phase I</td>
</tr>
</tbody>
</table>

C3 = complement component 3; C5 = complement component 5; IV = intravenous; IVT = intravitreal; mAb = monoclonal antibody; mTOR = mammalian target of rapamycin; nAChR = nicotinic acetylcholine receptor; PEDF = pigment epithelium-derived factor; PEG = polyethylene glycol; SCJ = subconjunctival; siRNA = small interfering RNA; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.
### Current and Future Drugs for Macular Edema

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Brand name</th>
<th>Mode of action</th>
<th>Dosage form</th>
<th>Release-controlling excipient</th>
<th>Developmental stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamcinolone acetonide</td>
<td>Kenalog®</td>
<td>Anti-inflammation, cytokine production inhibition</td>
<td>IVT, injection</td>
<td></td>
<td>Off-label use</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Triesence™</td>
<td>Anti-inflammation, cytokine production inhibition</td>
<td>IVT, injection</td>
<td></td>
<td>Launched</td>
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<tr>
<td>Triamcinolone acetonide</td>
<td>Triveris™</td>
<td>Anti-inflammation, cytokine production inhibition</td>
<td>IVT, injection</td>
<td></td>
<td>Launched</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Ozurdex™</td>
<td>Anti-inflammation, cytokine production inhibition</td>
<td>IVT, implant</td>
<td>PLGA</td>
<td>Approved</td>
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<tr>
<td>Candesartan cilexetil®</td>
<td>Blopress®</td>
<td>Angiotensin II type 1 receptor antagonist</td>
<td>Oral</td>
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<td>Phase III</td>
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<tr>
<td>Fluocinolone acetonide</td>
<td>Iluvien™</td>
<td>Anti-inflammation, cytokine production inhibition</td>
<td>IVT, implant</td>
<td>Polymide/PVA</td>
<td>Phase III</td>
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<tr>
<td>Pegaptanib</td>
<td>Macugen®</td>
<td>Anti-VEGF aptamer</td>
<td>IVT, injection</td>
<td></td>
<td>Phase III</td>
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<tr>
<td>Ranibizumab</td>
<td>Lucentis®</td>
<td>Anti-VEGF mAb, fragment</td>
<td>IVT, injection</td>
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<td>Phase III</td>
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<tr>
<td>Ruboxisaurin</td>
<td>Arxan®</td>
<td>PKC-β inhibitor</td>
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<td>Aflibercept</td>
<td>VEGF Trap-Eye</td>
<td>Decoy VEGFR</td>
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<td>Bevasiranib</td>
<td>Macamylamine hydrochloride</td>
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<td>IVT, injection</td>
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<td>Sirolimus</td>
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<td>Triamcinolone acetonide (IDi-20089)</td>
<td>Anti-C-raf antisense</td>
<td>IVT, injection</td>
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<td>Dexamethasone prodrug (NOVA-63035)</td>
<td>Cortiject®</td>
<td>Anti-inflammation, cytokine production inhibition</td>
<td>IVT, injection</td>
<td>Eyeject®</td>
<td>Phase I</td>
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<tr>
<td>Infliximab</td>
<td>Remicade®</td>
<td>Anti-TNFα mAb</td>
<td>IVT, injection</td>
<td></td>
<td>Phase I</td>
</tr>
</tbody>
</table>

*EVA = ethylene-vinyl acetate copolymer; IVT = intravitreal; mAb = monoclonal antibody; mTOR = mammalian target of rapamycin; nAChR = nicotinic acetylcholine receptor; PEG = polyethylene glycol; PKC = protein kinase C; PLGA = poly(lactide-co-glycolide); PMMA = poly(methyl methacrylate); PVA = poly(vinyl alcohol); SCJ = subconjunctival; siRNA = small interfering RNA; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.*

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Kuno and Fujii, Drugs Aging 2010 27(2)117-134

USDEC 2012 DDS Form CRhodes
# Current and Future Drugs for AMD

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Brand name</th>
<th>Mode of action</th>
<th>Dosage form</th>
<th>Release-controlling excipient</th>
<th>Developmental stage</th>
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<tr>
<td>AL-8309B</td>
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<td>Serotonin 5-HT\textsubscript{1A} receptor agonist</td>
<td>Eye drop</td>
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<td>Phase III</td>
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<tr>
<td></td>
<td>Glatiramer acetate</td>
<td>Copaxone\textsuperscript{®}</td>
<td>SC, injection</td>
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<td>Phase II/III</td>
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<td>NT-501</td>
<td>Immunomodulator</td>
<td>IVT, implant</td>
<td>Semi-permeable membrane</td>
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<tr>
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<td></td>
<td>Visual cycle modulator</td>
<td>Oral</td>
<td></td>
<td>Phase II</td>
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<tr>
<td>OT-551</td>
<td></td>
<td>Antioxidant, NF-\textgamma B inhibitor</td>
<td>Eye drop</td>
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<td>Phase II</td>
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<td>Brimonidine</td>
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<td>(\alpha\textsubscript{2})-Adrenoceptor agonist</td>
<td>IVT, implant</td>
<td>PLGA</td>
<td>Phase II</td>
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<tr>
<td>Fluocinolone acetonide</td>
<td>Iluvien\textsuperscript{™}</td>
<td>Anti-inflammation, immunomodulator</td>
<td>IVT, implant</td>
<td>Polyimide/PVA</td>
<td>Phase II</td>
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<tr>
<td>Zinc cysteine complex</td>
<td>Zinthionein\textsuperscript{™}</td>
<td>Antioxidant</td>
<td>Oral</td>
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<tr>
<td>Sirolimus</td>
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<td>mTOR inhibitor</td>
<td>SCJ, injection</td>
<td>PEG</td>
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<td>ACU-4429</td>
<td></td>
<td>Visual cycle modulator</td>
<td>Oral</td>
<td></td>
<td>Phase I</td>
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</tbody>
</table>

\textsuperscript{C}NTF = ciliary neurotrophic factor; IVT = intravitreal; mTOR = mammalian target of rapamycin; NF-\(\kappa\)B = nuclear factor \(\kappa\)-light-chain-enhancer of activated B cells; PEG = polyethylene glycol; PLGA = poly(lactide-co-glycolide); PVA = poly(vinyl alcohol); SC = subcutaneous; SCJ = subconjunctival.
Antibodies

Aflibercept (Eylea)

Ranibizumab (Lucentis)

Mouse Anti-VEGF-A mAb (~150 kDa)

Humanization

Affinity maturation (140×)

(rhu Fab v1)

Construction of full length antibody

Avastin (bevacizumab) 149 kDa

VEGF receptor-1 (a) and VEGF receptor-2 (b) are related receptors that have 7 extracellular Ig domains, and an intracellular tyrosine kinase domain.

VEGF Trap (c) contains the Ig domain 2 of VEGF receptor-1 fused to the Ig domain 3 of VEGF receptor-2, which is in turn fused to the IgG1 Fc.

05DEC2012 DDS Form CRhodes
Oligonucleotides, Aptamers, siRNA

Pegaptanib (Macugen)

Where R is

and n is approximately 450.

Peptides

POT-4 analogue of Compstatin
Back of The Eye Treatments

• Majority today are implants of small molecules
• Emerging therapies are once per month intravitreal injections of proteins
• Delivery Systems for Peptides and Proteins
  • Reduce monthly injection frequency
  • Reduce doctors visits and improve therapy
• Unmet Need for Delivery Systems
  • Intravitreal injection depot for once every 4 to 6 months
Back of the Eye Delivery System Opportunities

• Sustained Release Depot System
  • PLGA or other polymer implant or microparticle
  • Systems designed for Proteins and Peptides
  • Maintaining stability is key

• Physician administered therapy
  • Retinal physicians very comfortable with injection
  • Must be a simple injection

• Delivery Constraints
  • Injection site is vitreous cavity
  • Safety first – must not cause inflammation or tolerability issues
  • Volume of injection is preferably 50 microliters
    • 100 microliters may be tolerated
  • 27 gauge needle or better
Primary Routes of Ocular Administration

**Anterior chamber**
- Topical drops
- Implants with drug that diffuses to front of eye

**Posterior chamber**
- Direct injection into vitreous
- Implants with drug that diffuses to vitreous, choroid

B Short, Toxicol Pathol 2008, 36 (1) 49-62