We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Clinical Application of Drug Delivery Systems for Treating AMD

Noriyuki Kuno and Shinobu Fujii
Santen Pharmaceutical Co., Ltd.
Japan

1. Introduction

Due to transparent ocular media, it is relatively easy to observe intraocular tissues such as the vitreous and retina without invasion, and various administration approaches including intravitreal and subretinal injection, or implantation can be applicable. Since the eye-ball is a closed organ, novel therapeutic molecules such as an antisense oligonucleotide for cytomegalovirus retinitis (Fomivirsen; Vitraven®, Isis Pharmaceuticals, Inc., Carlsbad, CA U.S. and Novartis, Basel, Switzerland), an aptamer (e.g. Pegaptanib sodium; Macugen®, Pfizer, Inc., New York, NY, U.S.) or a small interfering RNA for neovascular (wet) age-related macular degeneration (AMD), have been investigated in human eyes before their applications for systemic diseases. In addition, many injectable or implantable drug delivery systems for chronic vitreoretinal diseases including AMD, diabetic macular edema, retinal vein occlusion, uveitis, and retinitis pigmentosa (RP), using polymer technology and/or mechanical engineering, have been developing (Figure 1).

This chapter focuses on drug delivery systems under clinical applications and in late experimental stage for the treatment of both wet and atrophic (dry) AMD (Table 1).

2. Significance of drug delivery systems for AMD

For the treatment of wet AMD, a standard therapy is monthly intravitreal injections of ranibizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody fragment (Lucentis®, Genentech, Inc., South San Francisco, CA, U.S.) (Genentech Inc.) and photodynamic therapy (PDT) by systemic administration of verteporfin (Visudyne®, QLT Ophthalmics, Inc., Menlo Park, CA, U.S.). The monthly cost of Lucentis® is about $2,000 and that means effective treatment by Lucentis® faces a serious social problem (Martin et al., 2010, Gower et al., 2010, Patel et al., 2010). Also frequent intravitreal injections might cause several complications, it has been reported that prevalence of lens damage, endophthalmitis and rhegmatogenous retinal detachment were 0.006% (2 of 32,318 injections) (Meyer, Rodrigues et al., 2010), 0.029% (3 of 10,254 cases) (Pilli et al., 2008) and 0.013% (5 of 35,942 injections) (Meyer, Michels et al., 2010), respectively. In addition, recently sustained elevation of intraocular pressure (IOP) after intravitreal injections of anti-VEGF agents has been reported (Good et al., 2011). Although the mechanism of IOP elevation is unclear, aggregation of proteins and/or leaching of silicone from the syringe barrel and rubber stopper might cause to clog the trabecular meshwork. It has also been demonstrated that

aggregated proteins induce a more significant immunological response than non-aggregated proteins (Rosenberg, 2006). Furthermore, a lack of selective targeting of verteporfin to neovascular endothelial cells causes to damage the normal retinal tissues such as the retinal pigment epithelium (RPE) and photoreceptors. Therefore, it is necessary to develop drug delivery systems which can be easily and non-invasively administered, have long-term controlled-release by a single administration, and/or selective-targeting potency to the pathologic tissues for the treatment of AMD to overcome the disadvantages in the current wet AMD therapy.
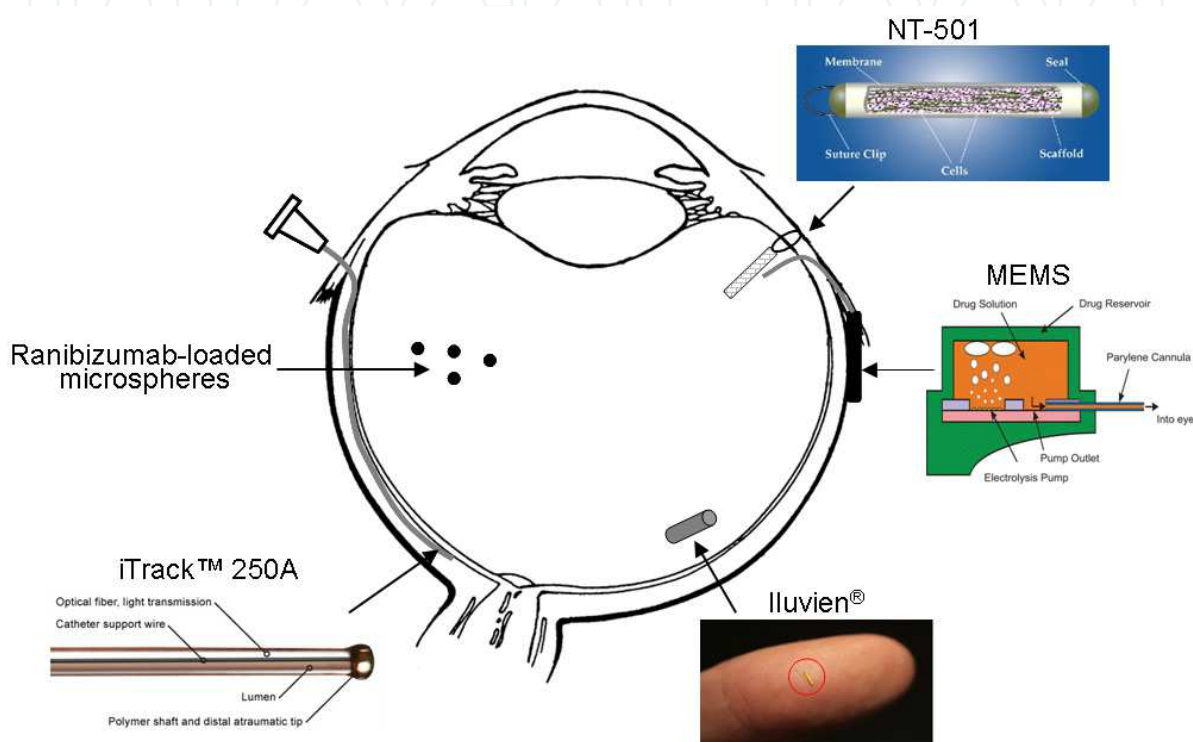

Fig. 1. Example of drug delivery systems for the treatment of AMD

On the other hand, tachyphylaxis is a diminished therapeutic response to a drug after repeated administrations over time. It has been reported that 8.5% (5 of 59 patients) of wet AMD patients who received repeated intravitreal injections of bevacizumab developed tachyphylaxis (Forooghian et al., 2009). The median time to develop tachyphylaxis after the first bevacizumab injection was 100 weeks with a median of 8 injections before tachyphylaxis development. Other groups have also reported that tachyphylaxis with ranibizumab and bevacizumab for wet AMD (Schaal et al., 2008, Keane et al., 2008, Eghoj & Sorensen, 2011) was found. It is thought that the generation of neutralizing antibodies to bevacizumab did not significantly contribute to the development of tachyphylaxis (Forooghian et al., 2011). A combination of bevacizumab and triamcinolone acetonide (TA) improved the reduction of bevacizumab efficacy caused by anti-VEGF tachyphylaxis. Therefore, there is an urgent need to develop drugs and their drug delivery systems targeting other pathways not involving VEGF for patients who develop anti-VEGF tachyphylaxis or non-responders.

In addition to wet AMD, dry AMD is a chronic, progressive retinal degenerative disease, therefore, drug delivery systems are absolutely needed.

Active ingredient	Brand name	Development stage	Mode of action	Administration Route	Excipients/ Carriers
PEGylation					
Pegaptanib	Macugen®	Launched	Anti-VEGF aptamer	IVT injection	PEG
ARC1905	-	P1 (dAMD) P1 (wAMD)	Anti-C5 aptamer	IVT injection	PEG
E10030	-	P2 (wAMD)	Anti-PDGF aptamer	IVT injection	PEG
Sustained release					
Fluocinolone acetonide	Iluvien®	P2 (dAMD) P2 (wAMD)	Inhibition of microglial activation	IVT implant	Polyimide/PVA
NT-501	-	P2 (dAMD)	Neurotrophin (CNTF)	IVT implant	Semi-permeable membrane
Brimonidine	-	P2 (dAMD)	α2 adrenergic agonist	IVT implant	PLGA
Targeting					
Verteporfin	Visudyne®	Launched	PDT	IV injection	Negatively-charged liposome
WST-11	Stakel®	P2 (wAMD)	PDT	IV injection	-
I-con1	-	P1/2a (wAMD)	NK cell-mediated apoptosis	IVT injection	-
VEGFR epitope peptide	-	P1 (wAMD)	CTLs-mediated apoptosis	SC injection	-
Gene induction					
PEDF	-	P1 (wAMD)	Antiangiogenesis by PEDF	IVT injection	Ad
sFLT01	-	P1 (wAMD)	VEGF decoy	IVT injection	AAV2
Endstatin Angiostatin	RetinoStat®	P1 (wAMD)	Antiangiogenesis by endostatin, angiostatin	SRT injection	EIAV

Ad, adenovirus; AAV2, adeno-associated virus serotype 2; AMD, age-related macular degeneration; C5, complement factor 5; CNTF, ciliary neurotrophic factor; CTLs, cytotoxic T lymphocytes; EIAV, equine infectious anaemia virus; IV, intravenous; IVT, intravitreal; NK, natural killer; PDGF, platelet-derived growth factor; PDT, photodynamic therapy; PEDF, pigment epithelium-derived factor; PEG, poly(ethylene gycol); PLGA, poly(lactide-co-glycolide); PVA, poly(vinyl alcohol); SC, subcutaneous; SRT, subretinal; VEGF, vascular endothelial growth factor

Table 1. Promising drug candidates for wet/dry AMD in clinical trials

3. Traditional formulation

An eye-drop, irrespective of the instilled volume, often eliminates rapidly within 5 to 6 minutes after an administration, and only a small amount (1–3%) of an eye-drop actually reaches the intraocular tissue. Therefore, it is difficult to provide and maintain an adequate concentration of drug in the precorneal area. More than 75% of applied ophthalmic solution is lost via nasolachrymal drainage and absorbed systemically via conjunctiva, then ocular drug availability is very low (Kuno & Fujii, 2011b). Generally topical applied drugs do not reach the posterior segment of the eye, thus, some additives or carriers to enhance the retention time and intraocular absorption are needed. Several eye-drops formulations are challenged to treat for AMD under clinical trials.

3.1 Pazopanib

Some studies have suggested that inhibition of VEGF signalling alone is sufficient to suppress choroidal neovascularization (CNV), however, others have demonstrated a more potent suppression of angiogenesis by inhibiting multiple tyrosine kinase receptors (Bergers et al., 2003, Erber et al., 2004, Kwak et al., 2000). It may be a more desirable therapeutic approach that drugs inhibit multiple angiogenic pathways. Pazopanib is a multi-tyrosine kinase inhibitor of VEGF receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR) -1 and -3, cytokine receptor (Kit), interleukin-2 receptor inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). *In vitro*, pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, Kit and PDGFR-β receptors. *In vivo*, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice (GlaxoSmithKline plc.). Pazopanib is currently prescribed for advanced renal cell carcinoma.

Yafai et al. have demonstrated that eye-drop formulation of pazopanib complexed with cyclodextrin significantly inhibited CNV in laser-induced CNV rat model (Yafai et al., 2011). Since this effect was obtained by overdose of eye-drops (30 μL/eye), it is doubtful whether this effective inhibition of CNV resulted from a topical absorption of pazopanib. A phase II clinical study of pazopanib eye-drops for the treatment of wet AMD is currently underway (ClinicalTrials.gov. NCT01134055). Unfortunately, actual formulation of pazopanib eye-drops used in clinical study is not disclosed.

3.2 Tandospirone

Serotonin (5-hydroxytryptamine; 5-HT) and its multiple receptors regulate various physiological functions. 5-HT$_{1A}$ receptor plays an important role for the control of sleep, feeding and anxiety. 5-HT$_{1A}$ receptor agonists have also neuroprotective effects in animal models including central nervous system ischemia (Saruhashi et al., 2002, Mauler & Horvath, 2005, Ramos et al., 2004, Kukley et al., 2001, Torup et al., 2000, Piera et al., 1995), acute subdermal hematoma (Fournier et al., 1993), traumatic brain injury (Alessandri et al., 1999, Kline et al., 2002), excitotoxicity (Oosterink et al., 2003, Cosi et al., 2005), a Parkinson's disease model animal induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (Bibbiani et al., 2001, Bezard et al., 2006), and sciatic nerve crush (Fournier et al., 1993). Additionally, it

was reported that the 5-HT$_{1A}$ agonists delayed the progression of motor neuron degeneration in pmn mice (Duong et al., 1998) and reduced lipid peroxidation in a rat epilepsy model (de Freitas et al., 2010). Such neuroprotective effects are considered to be caused by neuronal membrane hyperpolarization via G protein-coupled K$^+$ channels, decreasing glutamate release, blocking Ca^{2+} channels or Na$^+$ channels, activation of MAPK (mitogen-actiated protein kinase)/ERK (extracellular signal-regulated kinase) signalling pathway resulting expression of anti-apoptotic proteins and inhibition of caspase, and an expression of brain derived neurotrophic factor (BDNF) mRNA, S100β and nerve growth factor. Also 5-HT$_{1A}$ was expressed in rats and rabbits retina (Kusol & Brunken, 2000).

Recently, it has been reported that tandospirone, 5-HT$_{1A}$ agonist, which is widely used for the treatment of anxiety disorders, has a neuroprotective effect for retinal lesions due to light-damage (Collier et al., 2009, Rhoades et al., 2009, Wang et al., 2009, Collier et al., 2010). The studies have also suggested tandospirone increases of MEK (mitogen-activated extracellular signal regulated kinase) 1/2 and ERK 1/2 phosphorylation, leading to the subsequent upregulation of anti-oxidant and anti-apoptotic proteins, including superoxide dismutase (SOD)-1, SOD-2, B-cell lymphoma (Bcl)-2 and Bcl-$_{XL}$ (Rhoades et al., 2009), or a decrease complement factors (C3, CFB, CFH) and membrane attack complex (MAC) deposition in the outer retina (Wang et al., 2009) (Figure 2). Currently, an eye-drops formulation of tandospirone (AL-8309B, Alcon Laboratories, Inc., Fort Worth, TX, U.S.) is under a Phase III study for the treatment of dry AMD (ClinicalTrials.gov. NCT00890097). Actual eye-drop formulation of tandospirone currently conducted in clinical study is not also disclosed.
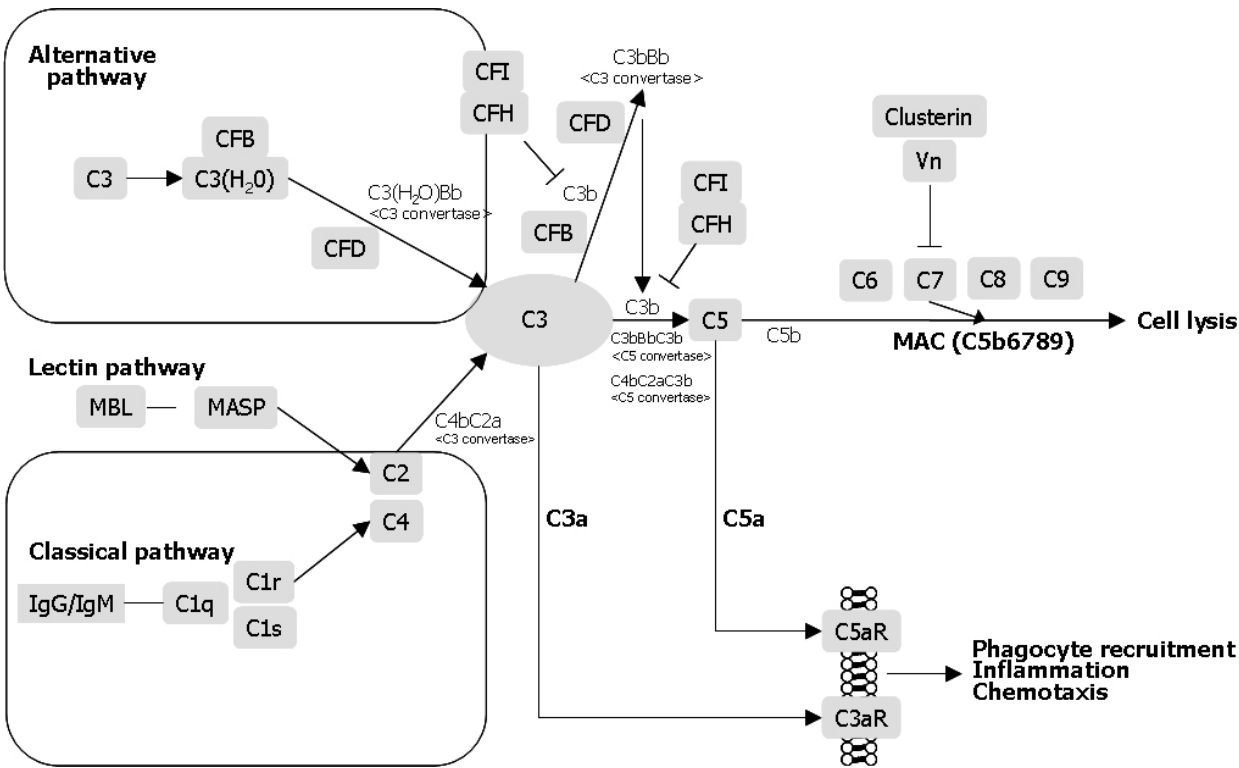

Fig. 2. Complement cascade

In the classical pathway, the cascade is initiated by the binding of C1q to antibody-antigen complex. The lectin pathway is initiated by the binding of carbohydrates associated with microbes to lectin proteins such as mannose-binding lectin (MBL). C1q and MBL form complexes with mannose-binding lectin-associated serine protease (MASP), which cleave C4 into C4a and C4b,C2 into C2a and C2b. C4b binds to C2a (C4bC2a), work as a C3 convertase resulting degradation of C3 into C3a and C3b. C3b binds with C4bC2a to form C4bC2aC3b work as a C5 convertases.

In the alternative pathway, C3 convertase is formed via a spontaneous hydrolysis of an internal C3 thioester into C3(H2O). C3(H2O) binds to factor B and D and forms soluble C3 convertase; C3(H2O)Bb and subsequently formed membrane-bound C3 convertase; C3bBb resulting cleavage of C3 into C3a and C3b. C3b binds C3bBb to form C3bBbC3b (C5 convertase).

In all pathways, C5 convertases cleaves C5 to C5a and C5b. C5b initiates the formation of the membrane attack complex (MAC) consisting of C5b, C6, C7, C8, and C9. The MAC creates a pore in the cell membrane of its targets (microbes, damaged cells) leading to cell lysis and death. The anaphylatoxins C3a and C5a work to increase vascular permeability, initiate degranulation of mast cells and neutrophils, induce cytokine release from macrophages, and mediate leukocyte chemotaxis.

Complement factor H (CFH) inhibits C3b through complement factor I (CFI) binding. Clusterin and vitronection (Vn) inhibits MAC formation by binding with a complex of C5b-7.

4. PEGylation

Covalent bonding of drug molecules to poly(ethylene glycol) (PEG), referred to as PEGylation, is a popular approach to modify and enhance the water solubility and pharmacokinetic and pharmacodynamic properties of biological and small-molecule drugs. In general, PEGs are inert water-soluble polymers, but recently it has been reported that a subretinal injection of PEG induced CNV with dose-dependency via complement activation in mice (Lyzogubov et al., 2011). PEGs can be attached to proteins and other therapeutic molecules, leading to increase the hydrodynamic volume of the therapeutic molecules. In addition, PEGs can shield drugs from interactions with enzymes and from inactivation by the immune system. As a result, PEGylated drugs can exhibit prolonged half-life, higher stability, increased water solubility, and reduced immunogenicity. It is thought that conjugates bearing branched chain PEG show increased thermal stability and higher resistance to enzymatic degradation compared to bearing linear PEG (Hamidi et al., 2008).

4.1 Macugen®

Pegaptanib sodium is a chemically-modified oligonucleotide of 28 nucleotides which linked with 40 kDa branched PEG (two arms of 20 kDa linear PEG units), which binds to $VEGF_{165}$. Pegaptanib was approved by FDA in 2004, and was both the first approved aptamer-based drug and the first approved pharmacotherapy for wet AMD. In rabbit eyes at 24 hours after an intravitreal injection, radiolabeled pegaptanib could be penetrated and distributed in the retina (Eyetech Inc.). In a monkey pharmacokinetics study, pegaptanib was eliminated from the vitreous with a half-life of 94 hours (Drolet et al., 2000), which has been increased by 3.91

times compared to the parent drug (non-PEGylated aptamer) (Simone Fishburn, 2008). After an intravitreal injection, pegaptanib is absorbed intact into the systemic circulation, but the concentration in plasma was 800-several thousand-fold lower than that in the vitreous. In addition, the elimination half-life was 9.3 hours after a single intravenous injection in rhesus monkeys (1 mg/kg). This "flip-flop" kinetics might cause to estimate the vitreous humor half-life in the vitreous from the plasma half-life in human. In clinical situation, pegaptanib is used as intravitreal injections of 0.3 mg once every 6 weeks.

4.2 ARC1905

ARC1905 (Ophthotech Corp., Princeton, NJ, U.S.) is a chemically-modified oligonucleotide of 39 nucleotides bound to branched PEG (two arms of 20 kDa linear PEG units), and binds to complement factor C5, leading to prevent the formation of key terminal fragments C5a and MAC (C5b-9). C5a is an important inflammatory activator inducing vascular permeability, recruitment and activation of phagocytes. MAC is involved to initiate cell lysis. Therefore, by inhibiting these C5-mediated inflammation and RPE death leading to geographic atrophy (GA), ARC1905 might be promising for both wet and dry AMD (Kuno & Fujii, 2011a). A phase I study to evaluate the safety, tolerability, and pharmacokinetic profile of multiple doses of intravitreal ARC1905 in combination with multiple doses of Lucentis® is currently in progress. In addition, it has been demonstrated by histopathological examination human dry AMD lesions strongly stained for C5a and MAC at key pathology sites (Anderson et al., 2002). A Phase I clinical trial to evaluate of an intravitreal ARC1905 in patients with GA is undergoing (ClinicalTrials.gov. NCT00950638).

4.3 E10030

E10030 (Ophthotech Corp.) is a chemically-modified oligonucleotide of 29 nucleotides linked with branched PEG (two arms of 20 kDa linear PEG units), and binds to PDGF-B, which is known to play a role of in the recruitment and maturation of pericytes that can increase resistance to the anti-VEGF treatment for wet AMD. PDGF and its receptor (PDGFR) do not act on vascular endothelial cells, but on pericytes. Therefore, inhibition of PDGF signalling might cause to achieve regression of neovascular vessels. Jo et al. have demonstrated that a combination therapy with anti-VEGF aptamer (Pegaptanib sodium) and anti-PDGFR-β antibody is more effective for CNV prevention and regression compared to monotherapy in the laser-induced CNV model (Jo et al., 2006). In an open-label Phase I clinical study conducted by Ophthotech, 59% of patients treated with E10030 and Lucentis® gained significant vision (3-line gain or better) at 12 weeks after the start of therapy. Interestingly, there was a mean decrease of 86% in the area of CNV at 12 weeks (Ophthotech Corporation). A randomized, controlled, Phase II study of E10030 in combination with Lucentis® for the treatment of wet AMD is currently underway (ClinicalTrials.gov. NCT01089517).

5. Sustained-release systems

To reduce the frequency of administration, many controlled drug delivery systems have been investigated by using biodegradable or non-biodegradable polymeric devices for the treatment of various retinal diseases as well as AMD (Kuno & Fujii, 2010). In general, drug release from biodegradable matrices consisting of poly(lactide-co-glycolide) (PLGA) is

degradation-controlled, in contrast, diffusion-controlled drug release is obtained from non-biodegradable matrices such as silicone and ethylene-vinyl acetate copolymers (EVA). Some sustained-release formulations with constant drug release properties are currently under late clinical stage, but stimuli-responsive formulations with drug release triggered by pathophysiological condition do not exist in developmental stage yet.

5.1 Iluvien®

It has been reported that activated microglia was accumulated in the degenerative retinas including light-damage mouse (Zhang et al., 2005), rd mouse (Zeiss & Johnson, 2004), Royal College of Surgeons (RCS) rat (Thanos, 1992, Roque et al., 1996), and human eyes of RP and AMD (Gupta et al., 2003). Activated microglia is mainly accumulated within outer nuclear layer and adjacent to the RPE. In contrast, resting microglia shows a downregulated phenotype and a low level of membrane receptors expression; however, it quickly transforms into phagocyte when stimulated by infectious agents, cellular debris, and membrane fragments, such as lipopolysaccharides (Kreutzberg, 1996, Gehrmann, 1996, Pawate et al., 2004, Whitton, 2007). Within 24 hours of activation, microglial cells enlarge, acquire an ameboid macrophage-like shape, leading to increased microglial IgG reactivity and upregulation of complement receptors, and intercellular adhesion molecules (Orr et al., 2002). Activated microglia releases cytotoxic molecules, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-10, interferon (IFN)-γ, hydrogen peroxide, and superoxide anion (Orr et al., 2002, Boje & Arora, 1992, Banati et al., 1993, Kreutzberg, 1995, Kim & de Vellis, 2005), which may induce apoptosis in otherwise healthy cells such as photoreceptors, RPE, and vascular endothelial cells. Once the activating stimulus is eliminated, microglia quickly returns to their resting state. While the stimulus continues, however, microglial cells express major histocompatibility complex (MHC) class I and II (Kreutzberg, 1995, Nakanishi, 2003) and inflammatory glycoproteins (Aloisi, 2001), which are self-stimulating and stimulate/recruit other immune cells. Microglia then clusters around neurons, adheres to their surfaces, continually produces cytotoxins that leads to neuronal death, and consequently recruit and activate additional microglia (Kreutzberg, 1996, Banati et al., 1993, Klegeris & McGeer, 2000) via chemokines such as CCL-5 (RANTES), macrophage inflammation protein (MIP)-1α and MIP-1β, monocyte chemoattractant protein (MCP)-1 and MCP-3 (Boje & Arora, 1992, Banati et al., 1993, McGeer et al., 1993, Min et al., 2004).

Recently, a retinal neuroprotective effect of sustained-release of a corticosteroid, fluocinolone acetonide (FA) for progressive retinal degeneration has been demonstrated in RCS rat (Glybina et al., 2009) and S334ter mutant rhodopsin transgenic rats (Glybina et al., 2010). In both animal models, FA treatment was associated with significant decrease in the number of microglial cells in both the outer and inner nuclear layer. In addition, corticosteroids have a genomic neuroprotective effect via Trk activation, leading to a trophic effect (Jeanneteau et al., 2008). An injectable, rod-shaped intravitreal implant with FA (Iluvien®; length: 3.5 mm, diameter: 0.37 mm, formerly Medidur™) has been developed by Alimera Sciences (Alpharetta, GA, U.S.) for the treatment of dry AMD under Phase II study (ClinicalTrials.gov. NCT00695318). Furthermore, the feasibility study of Medidur™ as a maintenance therapy for wet AMD patients who have been treated with Lucentis® for at least 6 months and have reached a plateau is currently in a pilot Phase II (ClinicalTrials.gov. NCT00605423).

5.2 Ranibizumab-loaded microspheres

Despite the remarkable effectiveness for treating wet AMD and other retinal diseases by Lucentis®, patients and physicians have been hoping for an alternative to the frequent intravitreal injections. SurModics, Inc. (Eden Prairie, MN, U.S.) and Genentech, Inc. have been developing a biodegradable microparticles incorporated ranibizumab currently under preclinical stage (SurModics Inc). It is hoped that ranibizumab-loaded microparticles can deliver ranibizumab over a period of approximately 4 to 6 months (Helzner, 2010).

5.3 NT-501

Neuroprotective effect of ciliary neurotrophic factor (CNTF) has been confirmed in various animal models of retinal degeneration including light-damaged rats, mutant rhodopsin transgenic mice, and a dog model. In addition, the long-term effect of CNTF has been shown by repeated intravitreal injections of CNTF in an autosomal dominant feline model of rod-cone dystrophy or an intravitreal injection of adeno-associated viral (AAV) vectors incorporated CNTF-cDNA in mutant rhodopsin transgenic rats. Neurotech Pharmaceuticals, Inc. (Lincoln, RI, U.S.) has been developing "Encapsulated Cell Technology", which provides an extracellular delivery of CNTF through long-term and stable intraocular release at constant doses through a device implanted in the vitreous. It contains human RPE cell line (ARPE-19) genetically modified to secrete recombinant human CNTF. The device (NT-501) consists of a sealed semi-permeable membrane capsule surrounding a scaffold of 6 strands of polyethylene terephthalate yarn, which can be loaded with cells (length; 6 mm, diameter; 1 mm). The device is surgically implanted in the vitreous through a tiny scleral incision and is anchored by a single suture through a titanium loop at one end of the device. The semi-permeable membrane allows the outward diffusion of CNTF and other cellular metabolites and the inward diffusion of nutrients necessary to support the cell survival in the vitreous cavity while protecting the contents from host cellular immunologic attack.

A Phase I clinical trial for RP has been completed and demonstrated well tolerated for 6 months implantation (Sieving et al., 2006). Eighteen-month results in a Phase II study for patients with GA with dry AMD were reported (Jaffe et al., 2010) (Zhang et al., 2011); participants were randomized in a 2:1:1 ratio to receive a high (20 ng/day) or low dose (5 ng/day) NT-501, or to sham surgery, respectively. Among eyes with baseline best corrected visual acuity (BCVA) 20/63, the mean BCVA in the high dose group was 10.5 and 10.0 letters greater than the low dose/sham group at 12 months (p=0.03) and 18 months, respectively. Stabilized visual acuity was accompanied by the corresponding structural changes; NT-501 treatment resulted in a dose-dependent increase of retinal thickness as early as 4 months after implantation and this increase was maintained through 6, 12 and 18 months (p<0.001). The growth rate of GA area was reduced in treated eyes compared to fellow eyes at 12 and 18 months. In addition, NT-501 also prevented secondary cone degeneration in RP patients (Talcott et al., 2011).

5.4 Brimonidine-loaded intravitreal implant

Brimonidine is an α2 adrenergic agonist, which can release various neurotrophins including BDNF, CNTF (Lonngren et al., 2006, Kim et al., 2007), and b-FGF (Lai et al., 2002). These neurotrophins have potential to prevent apoptosis of photoreceptors and/or RPE (Azadi et

al., 2007, Zhang et al., 2009). A biodegradable, rod-shaped PLGA intravitreal implant containing brimonidine tartrate is now in a Phase II clinical study for dry AMD (ClinicalTrials.gov. NCT00658619) by Allergan Inc. (Irvine, CA, U.S.).

6. Targeting systems

Selective targeting to the neovascular lesions is desired for the improvement of therapeutic efficacy and the reduction of normal tissue damage. Active targeting to neovascular endothelial cells using highly-expressed specific molecules on endothelial cells has been widely investigated for the treatment of CNV. In addition, immunotherapy in conjunction with active targeting is also developing for regression of CNV.

6.1 Visudyne®

Visudyne® (QLT Ophthalmics, Inc., Menlo Park, CA, U.S.) is an intravenous liposomal formulation containing a photosensitizer, verteporfin in PDT for predominantly classic subfoveal CNV due to wet AMD, pathologic myopia or presumed ocular histoplasmosis (QLT Ophthalmics). Plasma lipoproteins, such as low-density lipoprotein (LDL), have been proposed to enhance the delivery of hydrophobic verteporfin to malignant tissue since tumor cells have increased the number of LDL receptors (Allison et al., 1994). In addition, liposomes composed of negatively charged phospholipids such as phosphatidylglycerol are taken up into tumor cells by LDL receptor-mediated endocytosis (Amin et al., 2002). It is thought that verteporfin released into the blood stream from liposomes is associated with LDL and is taken up into neovascular tissue, on the other hand, un-dissociated verteporfin, which is still encapsulated in the liposomes, is selectively accumulated in neovascular endothelial cells via LDL receptor-mediated endocytosis, since phosphatidylglycerol is the major constituent of Visudyne®.

Since LDL receptors are also expressed in RPE as well as endothelial cells (Hayes et al., 1989), verteporfin PDT causes damage to RPE associated with photoreceptor lesions. Indeed, adverse effects by verteporfin PDT have been reported (Tzekov et al., 2006, Ozdemir et al., 2006, Oner et al., 2005a, 2005b) in clinical situation. To enhance PDT effects and minimize damage of normal tissues, highly selective targeting might be necessary.

6.2 WST-11 (Stakel®)

Serum albumin has the unique ability to reversibly or covalently bind various endogenous or exogenous ligands with high affinity, resulting in working as a transporter and depot protein for various compounds (Kragh-Hansen, 1990). The cellular uptake of serum albumin via receptor (albondin)-mediated endocytosis (Schnitzer & Oh, 1994, John et al., 2001) might cause highly efficient intracellular trafficking. WST-11 (Stakel®, Steba Biotech S.A., Toussus-Le-Noble, France) is a negatively charged, water-soluble bacteriochlorophyll derivative with maximum absorption wavelength in the near infrared (753 nm) and rapid clearance from the body (Mazor et al., 2005, Brandis et al., 2005). WST-11 binds to serum albumin and has potent anti-neovascularization via the generation of hydroxyl radicals when stimulated by the proper light wavelength. Berdugo et al. have demonstrated that WST-11 PDT, which selectively occludes CNV, could be achieved in laser-induced CNV model of rats without the damages to the retinal tissues such as RPE and photoreceptors unlike verteporfin PDT.

Steba Biotech S.A. currently conducts a Phase II study for WST-11 PDT in wet AMD patients (ClinicalTrials.gov. NCT01021956).

6.3 I-con1

Tissue factor (TF) acts as a primary cellular initiator of blood coagulation, and has following additional biological functions involving neovascularization. TF can induce angiogenesis by upregulating VEGF and also promote angiogenesis via TF-initiated coagulation pathways. Thrombin stimulation of platelets, which is a major VEGF transporter, releases VEGF (Mohle et al., 1997), leading to stimulate endothelial cells to induce and expose more TF, following further thrombin formation. In addition, TF expressed in surgically excited CNV membrane and AMD eyes was related to active inflammation site accompanied by an accumulation of macrophages and fibrin deposition (Grossniklaus et al., 2002). It has been reported that TF mRNA expression in AMD was 32-fold higher than in the non-AMD (Cho et al., 2011) and TF was expressed only on neovascular endothelial cells not normal vascular endothelial cells (Contrino et al., 1996). Therefore, TF might be a specific target for neovascular tissues.

hI-con1 (Iconic Therapeutics, Inc., Atlanta, GA, U.S.) is a chimeric IgG-like homodimeric protein composed of a targeting-domain (mutated, inactivated factor VIIa, which is a ligand for TF) fused to an effector-domain (human IgG Fc) with an intact hinge region (Iconic Therapeutics). Once hI-con1 binds to TF on the surface of neovascular endothelial cells, the effector-domain mobilizes natural killer (NK) cells mediated via the Fc receptor, leading to activating the complement cascade (Wang et al., 1999, Hu & Li, 2010) and inducing the selective apoptosis of TF-expressing cells. Consequently, NK cells do not induce apoptosis of other cells including normal vascular tissue and RPE and neural retina. Bora et al. have demonstrated that intravitreal mouse factor VII-human IgG1 Fc chimeric conjugate inhibited CNV in a laser-induced CNV model in mice (Bora et al., 2003). In addition, Tezel et al. reported that this immunoprotein could selectively regress already-established CNV in laser-induced pig model (Tezel et al., 2007). A Phase I/IIa study of intravitreal hI-con1 for wet AMD is currently underway (Iconic Therapeutics).

6.4 Anti-VEGFR vaccine

VEGFR2 (Flk-1) plays a pivotal role in endothelial cell proliferation and migration (Millauer et al., 1993, Risau, 1997), and is upregulated during CNV formation (Wada et al., 1999). VEGFR2 vaccination therapy has been progressed in the cancer field (Niethammer et al., 2002, Wada et al., 2005, Pan et al., 2008). The strategy of VEGFR vaccination therapy for wet AMD is to induce apoptosis of neovascular endothelial cells, and inhibition and regression of CNV by cytotoxic T lymphocytes (CTLs). Takahashi et al. have demonstrated that vaccination with human VEGFR2-derived epitope peptide (VEGFR2-773) significantly inhibited CNV in laser-induced A2/Kb transgenic mice, which express chimeric human-mouse MHC class I molecule, and this chimeric molecule shows 71% concordance with the human CTL repertoire (Vitiello et al., 1991). VEGFR2 peptide induces CTLs in the histocompatibility leukocyte antigen (HLA) class I-restricted manner (Wada et al., 2005).

It is thought that the advantage of VEGFR2 vaccination is long-lasting therapeutic effect on the vascular endothelial cells since endothelial cells are genetically stable and do not show

the downregulation of HLA class I molecules (Niethammer et al., 2002). It has been reported that, 60.8% and 19.9% in Japanese population share a common HLA-A*2402 allele and HLA-A*0201 allele, respectively (Date et al., 1996). HLA-A*2402 restricted VEGFR1- and VEGFR2-derived peptide vaccination therapy for wet AMD is conducted under a Phase I study in Japan (ClinicalTrials.gov. NCT00791570).

7. Gene therapy

Adenoviral (Ad) and AAV vectors are non-integrating and transduce both dividing and non-dividing cells. However, Ad and AAV elicit CTLs-mediated immune responses resulting in limitation of duration of transgene expression (McConnell & Imperiale, 2004). Helper-dependent Ad can extend the duration of ocular expression from less than 3 months to up to 1 year (Lamartina et al., 2007). Lentiviral vectors can induce stable, long-term transgene expression in the retinal (Balaggan et al., 2006). Lentivirus, which are integrating vectors, have the risk of insertional oncogenesis. Highly deleted (Molina et al., 2004), self-inactivating (Berkowitz et al., 2001) and non-integrating (Yanez-Munoz et al., 2006) lentiviral vectors have been developed as safer vectors. In general, subretinal injections are conducted in the operating room and are more invasive than intravitreal injections. If a single subretinal injection of a vector to provide prolonged suppression of CNV, it might be reasonable and feasible to substitute for repeated intravitreal injections of Lucentis®.

7.1 Pigment epithelium-derived factor

AdPEDF.11D is E1-, partial E3-, and E4-deleted Ad vector, which is replication-deficient, expressing pigment epithelium-derived factor (PEDF). A Phase I study of intravitreal AdPEDF.11D conducted by GenVec, Inc. (Gaithersburg, MD, U.S.) has completed. The results have shown that several complications such as mild inflammation, corneal edema, and elevated IOP were observed in some patients, but systemic hematogenous vector spread and systemic immune responses were not observed. Although hyperpermeability appeared to resolve in some patients received high-dose AdPEDF.11D, unfortunately, patients received high-dose (10^8-$10^{9.5}$ particle units) had no change in visual acuity compared to low-dose (10^6-$10^{7.5}$ particle units) patients whose visual acuity appeared to worsen over the course of study (Campochiaro et al., 2006). Further clinical trials have not progressed after the completion of a Phase I study in 2006.

7.2 sFLT01

sFLT01 is an antiangiogenic fusion protein consisting of the VEGF/placental growth factor (PIGF) binding domain of human Flt-1 (hVEGFR1) fused to the Fc portion of human IgG1 through a polyglycine linker (Bagley et al., 2011). Therefore, sFLT01 acts as a VEGF decoy. It has been reported that an intravitreal injection of AAV serotype 2 (AAV2) vector coding for sFLT01 (AAV2-sFLT01) significantly inhibited CNV in laser-induced CNV model of mice and monkeys (Lukason et al., 2011) and retinal neovascularization in mouse oxygen-induced retinopathy model (Pechan et al., 2009). Interestingly, sFLT01 expression in the retina continued for up to 12 months after an intravitreal injection (Pechan et al., 2009). A Phase I clinical trial of AAV2-sFLT01 is currently conducted by Genzyme (Cambridge, MA, U.S.) (ClinicalTrials.gov. NCT01024998).

7.3 RetinoStat®

RetinoStat® (Oxford Biomedica, Oxford, UK) is an equine infectious anaemia virus (EIAV)-based lentiviral vector expressing human endostatin and angiostatin, which are endogenous angiostatic factors. EIAV can transduce both dividing and non-dividing cells. Endostatin is an internal fragment of collagen XVIII, and downregulates the expression of the antiapoptotic proteins such as Bcl-2 and Bcl-$_{XL}$ (Dhanabal et al., 1999), and may interact with endothelial cell surface receptors and integrins leading to apoptosis of endothelial cells in active neovascularization, but not mature vasculature. In addition, endostatin blocks VEGF signalling via a direct interaction with VEGFR2 (Kim et al., 2002). Angiostatin is a cleavage product of plasminogen, which has the kringle domains, and promotes apoptosis of proliferating vascular endothelial cells similar to endostatin (Claesson-Welsh et al., 1998, Hari et al., 2000). Also, angiostatin downregulates VEGF expression (Hajitou et al., 2002, Sima et al., 2004). RetinoStat® incorporates RPE-specific vitelliform macular dystrophy gene (VMD2) promoter, leading to limited transgene expression to RPE after a subretinal injection (Kan et al., 2009). Kachi et al. have demonstrated that a subretinal injection of RetinoStat® significantly inhibited CNV in laser-induced CNV model of mice (Kachi et al., 2009). A Phase I study of subretinal RetinoStat® in wet AMD patients is currently ongoing (ClinicalTrials.gov. NCT01301443).

8. Devices

Mechanical devices have been developing for the purpose of more selective drug targeting, chronic infusion, or stimuli-responsive drug release.

8.1 Microcatheter

A microcatheter, iTrack™ 250A (iScience Interventional™, Menlo Park, CA, U.S.) is originally designed for canaloplasty (iScience Interventional™), which is a new treatment for glaucoma (Lewis et al., 2009, 2011). The iTrack™ 250A consists of an optical fiber to allow transmission of light to the microcannula tip for surgical illumination and guidance. Recently, this microcatheter is challenged to use for suprachoroidal drug delivery (Olsen, 2007, Rizzo et al., 2010). The pharmacokinetic study of suprachoroidal delivery of TA in pigs has shown that TA remained in the ocular tissues for at least 120 days, and the systemic exposure was very low (Olsen et al., 2006). In contrast, the study to compare the pharmacokinetics of bevacizumab between intravitreal and suprachoroidal injections to pigs (Olsen et al., 2011) reported that the profile of intravitreal injections of bevacizumab was more sustained than that of suprachoroidal injections at the same dosage level. Intravitreal injected bevacizumab distributed more to the inner retina, whereas suprachoroidal injected bevacizumab distributed primarily to the choroid, RPE, and photoreceptor outer segments. Scharioth et al. have tried to conduct suprachoroidal injections of bevacizumab in the wet AMD patients who were non-responder of intravitreal anti-VEGF therapy and/or initial BCVA < 0.05 (Scharioth et al., 2011). In the case of the patient who had a history of 21 intravitreal anti-VEGF injections with poor response to this therapy, and BCVA was 0.1, a significant reduction of pigment epithelial detachment was observed at 4 weeks after a suprachoroidal injection of bevacizumab, BCVA slightly improved to 0.16 and the subfoveal

membrane totally disappeared at 8 weeks. During 6 months of follow-up, no signs of recurrence were observed.

8.2 Micropump™ system

A microelectromechanical systems (MEMS) drug delivery device is investigated for the treatment of chronic and refractory ocular diseases (Lo et al., 2009, Saati et al., 2010). MEMS device can be re-filled with the drug solution, giving long-term drug therapy which avoids repeated surgeries. The first generation of MEMS is a manually-controlled system limited by variations in the drug-release duration and force applied for depressing of the reservoir. To resolve this problem, the next generation device consists of an electrolysis chamber with electrolysis actuation to precisely delivery the desired dosage volume, a drug reservoir with refill port, battery and electronics. Biocompatible and flexible parylene is used to construct the MEMS. Battery and wireless inductive power transfer can be used to drive electrolysis. Electrolysis is a low power process in which the electrochemically-induced phase change of water to hydrogen and oxygen gas generates pressure in the reservoir forcing the drug through the cannula (Saati et al., 2010). The reservoir is implanted in the subconjunctival space and flexible cannula is inserted through incision into the anterior or posterior segment. Gonzalez-Soto et al. have demonstrated that a slower prolonged infusion of the same volume and concentration of intravitreal ranibizumab is equivalent to a bolus intravitreal injection of ranibizumab to human VEGF-induced retinal hyperpermeability model of rabbits (Gonzalez-Soto et al., 2011).

Replenish, Inc. (Pasadena, CA, U.S.) plans to enter clinical trials for a refillable and programmable pump that would be implanted in the eye to feed medicine for glaucoma or AMD. The Replenish device can last more than 5 years before needing replacement, much longer than current treatments (Flanigan, 2009).

8.3 ODTx

On Demand Therapeutics, Inc. (Menlo Park, CA, U.S.) has been developing a multi-reservoir implantable device for laser-activated drug delivery to the posterior segment of the eye (RetinaToday, 2010) (On Demand Therapeutics Inc). The injectable, biocompatible, non-resorbable device (ODTx) contains reservoirs designed for drug release in optimized doses. The reservoirs are capable of storing small- or large-molecule drugs that can be released via a standard, non-invasive laser activation procedure. The multiple reservoir system allows for ophthalmologists to control drug delivery by activating specific reservoirs, while unactivated reservoirs remain intact. Unfortunately, clinical trials of ODTx have not progressed yet.

9. Conclusion

Recent advances in drug delivery systems under clinical situation and in the late experimental stages are described in this chapter. AMD is chronic, progressive and refractory retinal degenerative disease, and induced by complex pathophysiological conditions. It is necessary to consider further the most efficacious combinations of optimal drugs, doses, routes, and drug release patterns (sustained-release, pulsatile-release, or

controlled-release by responding to a trigger) based on the pathophysiology and progressive courses of the targeted disease.

10. References

Alessandri, B., Tsuchida, E. & Bullock, R. M. (1999). The neuroprotective effect of a new serotonin receptor agonist, BAY X3702, upon focal ischemic brain damage caused by acute subdural hematoma in the rat. *Brain Res*, Vol.845, No.2, 232-235

Allison, B. A., Pritchard, P. H. & Levy, J. G. (1994). Evidence for low-density lipoprotein receptor-mediated uptake of benzoporphyrin derivative. *Br J Cancer*, Vol.69, No.5, 833-839

Aloisi, F. (2001). Immune function of microglia. *GLIA*, Vol.36, No.2, 165-179

Amin, K., Wasan, K. M., Albrecht, R. M. & Heath, T. D. (2002). Cell association of liposomes with high fluid anionic phospholipid content is mediated specifically by LDL and its receptor, LDLr. *J Pharm Sci*, Vol.91, No.5, 1233-1244

Anderson, D. H., Mullins, R. F., Hageman, G. S. & Johnson, L. V. (2002). A role for local inflammation in the formation of drusen in the aging eye. *Am J Ophthalmol*, Vol.134, No.3, 411-431

Azadi, S., Johnson, L. E., Paquet-Durand, F., Perez, M. T., Zhang, Y., Ekstrom, P. A. & van Veen, T. (2007). CNTF+BDNF treatment and neuroprotective pathways in the rd1 mouse retina. *Brain Res*, Vol.1129, No.1, 116-129

Bagley, R. G., Kurtzberg, L., Weber, W., Nguyen, T. H., Roth, S., Krumbholz, R., Yao, M., Richards, B., Zhang, M., Pechan, P., Schmid, S., Scaria, A., Kaplan, J. & Teicher, B. A. (2011). sFLT01: A novel fusion protein with antiangiogenic activity. *Molecular Cancer Therapeutics*, Vol.10, No.3, 404-415

Balaggan, K. S., Binley, K., Esapa, M., Iqball, S., Askham, Z., Kan, O., Tschernutter, M., Bainbridge, J. W. B., Naylor, S. & Ali, R. R. (2006). Stable and efficient intraocular gene transfer using pseudotyped EIAV lentiviral vectors. *Journal of Gene Medicine*, Vol.8, No.3, 275-285

Banati, R. B., Gehrmann, J., Schubert, P. & Kreutzberg, G. W. (1993). Cytotoxicity of microglia. *GLIA*, Vol.7, No.1, 111-118

Bergers, G., Song, S., Meyer-Morse, N., Bergsland, E. & Hanahan, D. (2003). Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. *Journal of Clinical Investigation*, Vol.111, No.9, 1287-1295

Berkowitz, R., Ilves, H., Wei Yu, L., Eckert, K., Coward, A., Tamaki, S., Veres, G. & Plavec, I. (2001). Construction and molecular analysis of gene transfer systems derived from bovine immunodeficiency virus. *Journal of Virology*, Vol.75, No.7, 3371-3382

Bezard, E., Gerlach, I., Moratalla, R., Gross, C. E. & Jork, R. (2006). 5-HT1A receptor agonist-mediated protection from MPTP toxicity in mouse and macaque models of Parkinson's disease. *Neurobiol Dis*, Vol.23, No.1, 77-86

Bibbiani, F., Oh, J. D. & Chase, T. N. (2001). Serotonin 5-HT1A agonist improves motor complications in rodent and primate parkinsonian models. *Neurology*, Vol.57, No.10, 1829-1834

Boje, K. M. & Arora, P. K. (1992). Microglial-produced nitric oxide and reactive nitrogen oxides mediate neuronal cell death. *Brain Res*, Vol.587, No.2, 250-256

Bora, P. S., Hu, Z., Tezel, T. H., Sohn, J. H., Kang, S. G., Cruz, J. M. C., Bora, N. S., Garen, A. & Kaplan, H. J. (2003). Immunotherapy for choroidal neovascularization in a laser-induced mouse model simulating exudative (wet) macular degeneration. *Proc Natl Acad Sci U S A*, Vol.100, No.5, 2679-2684

Brandis, A., Mazor, O., Neumark, E., Rosenbach-Belkin, V., Salomon, Y. & Scherz, A. (2005). Novel water-soluble bacteriochlorophyll derivatives for vascular-targeted photodynamic therapy: Synthesis, solubility, phototoxicity and the effect of serum proteins. *Photochemistry and Photobiology*, Vol.81, No.4, 983-993

Campochiaro, P. A., Nguyen, Q. D., Shah, S. M., Klein, M. L., Holz, E., Frank, R. N., Saperstein, D. A., Gupta, A., Stout, J. T., Macko, J., DiBartolomeo, R. & Wei, L. L. (2006). Adenoviral vector-delivered pigment epithelium-derived factor for neovascular age-related macular degeneration: Results of a phase I clinical trial. *Human Gene Therapy*, Vol.17, No.2, 167-176

Cho, Y., Cao, X., Shen, D., Tuo, J., Parver, L. M., Rickles, F. R. & Chan, C. C. (2011). Evidence for enhanced tissue factor expression in age-related macular degeneration. *Laboratory Investigation*, Vol.91, No.4, 519-526

Claesson-Welsh, L., Welsh, M., Ito, N., Anand-Aptei, B., Soker, S., Zetter, B., O'Reilly, M. & Folkman, J. (1998). Angiostatin induces endothelial cell apoptosis and activation of focal adhesion kinase independently of the integrin-binding motif RGD. *Proc Natl Acad Sci U S A*, Vol.95, No.10, 5579-5583

ClinicalTrials.gov. NCT00950638, A study of ARC1905 (Anti-C5 aptamer) in subjects with dry age-related macular degeneration, Available from:
    <http://clinicaltrials.gov/ct2/show/NCT00950638?term=ARC1905&rank=1>

ClinicalTrials.gov. NCT00605423, The MAP Study: Fluocinolone acetonide (FA)/Medidur™ for age related macular degeneration (AMD) Pilot, Available from:
    <http://clinicaltrials.gov/ct2/show/NCT00605423?term=Iluvien&rank=12>

ClinicalTrials.gov. NCT00890097, Geographic atrophy treatment evaluation (GATE), Accessed January 26, 2011, Available from:
    <http://clinicaltrials.gov/ct2/show/NCT00890097?term=AL-8309B&rank=1>

ClinicalTrials.gov. NCT01301443, Phase I dose escalation safety study of RetinoStat in advanced age-related macular degeneration (AMD) (GEM), Available from:
    <http://clinicaltrials.gov/ct2/show/NCT01301443?term=RetinoStat&rank=1>

ClinicalTrials.gov. NCT01024998, Safety and tolerability study of AAV2-sFLT01 in patients with neovascular age-related macular degeneration, Available from:
    <http://clinicaltrials.gov/ct2/show/NCT01024998?term=sFLT01&rank=1>

ClinicalTrials.gov. NCT00695318, Fluocinolone acetonide intravitreal inserts in geographic atrophy, Available from:
    <http://clinicaltrials.gov/ct2/show/NCT00695318?term=Iluvien&rank=15>

ClinicalTrials.gov. NCT01134055, Dose ranging study of pazopanib to treat neovascular age-related macular degeneration, Available from:
    <http://clinicaltrials.gov/ct2/show/NCT01134055?term=pazopanib+and+eye+drop&rank=3>

ClinicalTrials.gov. NCT01021956, Safety and preliminary efficacy study of WST11 (Stakel®)-mediated VTP therapy in subjects with CNV associated with AMD, Available from:
    <http://clinicaltrials.gov/ct2/show/NCT01021956?term=WST11&rank=6>

ClinicalTrials.gov. NCT00791570, Anti-VEGFR vaccine therapy in treating patients with neovascular maculopathy, Available from:
      <http://clinicaltrials.gov/ct2/show/NCT00791570?term=Osaka+University&rank=5>

ClinicalTrials.gov. NCT00658619, Safety and efficacy of brimonidine intravitreal implant in patients with geographic atrophy due to age-related macular degeneration (AMD), 26.01.2011, Available from: <http://clinicaltrials.gov/ct2/show/NCT00658619>

ClinicalTrials.gov. NCT01089517, A safety and efficacy study of E10030 (Anti-PDGF pegylated aptamer) plus Lucentis for neovascular age-related macular degeneration, Available from:
      <http://clinicaltrials.gov/ct2/show/NCT01089517?term=E10030&rank=2>

Collier, R. J., Martin, E. A., Cully-Adams, C., Dembinska, O., Hoang, H., Hellberg, M., Krueger, S., Kapin, M. & Romano, C. (2009). Serotonin 5-HT_{1A} agonists protect against blue light-induced phototoxicity. *ARVO Meeting Abstracts*, 675

Collier, R. J., Patel, Y., Martin, E. A., Dembinska, O., Hellberg, M., Krueger, D. S., Kapin, M. A. & Romano, C. (2010). Agonists at the serotonin receptor (5HT_{1A}) protect the retina from severe photo-oxidative stress. *Invest Ophthalmol Vis Sci*, doi:10.1167/iovs.1110-6304

Contrino, J., Hair, G., Kreutzer, D. L. & Rickles, F. R. (1996). In situ detection of tissue factor in vascular endothelial cells: Correlation with the malignant phenotype of human breast disease. *Nature Medicine*, Vol.2, No.2, 209-215

Cosi, C., Waget, A., Rollet, K., Tesori, V. & Newman-Tancredi, A. (2005). Clozapine, ziprasidone and aripiprazole but not haloperidol protect against kainic acid-induced lesion of the striatum in mice, in vivo: role of 5-HT_{1A} receptor activation. *Brain Res*, Vol.1043, No.1-2, 32-41

Date, Y., Kimura, A., Kato, H. & Sasazuki, T. (1996). DNA typing of the HLA-A gene: Population study and identification of four new alleles in Japanese. *Tissue Antigens*, Vol.47, No.2, 93-101

de Freitas, R. L., Santos, I. M., de Souza, G. F., Tome Ada, R., Saldanha, G. B. & de Freitas, R. M. (2010). Oxidative stress in rat hippocampus caused by pilocarpine-induced seizures is reversed by buspirone. *Brain Res Bull*, Vol.81, No.4-5, 505-509

Dhanabal, M., Ramchandran, R., Waterman, M. J. F., Lu, H., Knebelmann, B., Segal, M. & Sukhatme, V. P. (1999). Endostatin induces endothelial cell apoptosis. *Journal of Biological Chemistry*, Vol.274, No.17, 11721-11726

Drolet, D. W., Nelson, J., Tucker, C. E., Zack, P. M., Nixon, K., Bolin, R., Judkins, M. B., Farmer, J. A., Wolf, J. L., Gill, S. C. & Bendele, R. A. (2000). Pharmacokinetics and safety of an anti-vascular endothelial growth factor aptamer (NX1838) following injection into the vitreous humor of rhesus monkeys. *Pharmaceutical Research*, Vol.17, No.12, 1503-1510

Duong, F., Fournier, J., Keane, P. E., Guenet, J. L., Soubrie, P., Warter, J. M., Borg, J. & Poindron, P. (1998). The effect of the nonpeptide neurotrophic compound SR 57746A on the progression of the disease state of the pmn mouse. *Br J Pharmacol*, Vol.124, No.4, 811-817

Eghoj, M. S. & Sorensen, T. L. (2011). Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. *British Journal of Ophthalmology*, doi:10.1136/bjo.2011.203893

Erber, R., Thurnher, A., Katsen, A. D., Groth, G., Kerger, H., Hammes, H. P., Menger, M. D., Ullrich, A. & Vajkoczy, P. (2004). Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. *The FASEB journal*, Vol.18, No.2, 338-340

Eyetech Inc. Macugen® (pegapranib sodium injection), Available from:
    <http://www.macugen.com/macugenUSPI.pdf>

Flanigan, J. (2009). Biotech tries to shrug off setbacks, The New York Times.

Forooghian, F., Chew, E. Y., Meyerle, C. B., Cukras, C. & Wong, W. T. (2011). Investigation of the role of neutralizing antibodies against bevacizumab as mediators of tachyphylaxis. *Acta Ophthalmologica*, Vol.89, No.2, e206-e207

Forooghian, F., Cukras, C., Meyerle, C. B., Chew, E. Y. & Wong, W. T. (2009). Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. *Retina*, Vol.29, No.6, 723-731

Fournier, J., Steinberg, R., Gauthier, T., Keane, P. E., Guzzi, U., Coude, F. X., Bougault, I., Maffrand, J. P., Soubrie, P. & Le Fur, G. (1993). Protective effects of SR 57746A in central and peripheral models of neurodegenerative disorders in rodents and primates. *Neuroscience*, Vol.55, No.3, 629-641

Gehrmann, J. (1996). Microglia: a sensor to threats in the nervous system? *Res Virol*, Vol.147, No.2-3, 79-88

Genentech Inc. Lucentis®, Available from:
    <http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf>

GlaxoSmithKline plc. Votrient (pazopanib) tablets, Available from:
    <http://us.gsk.com/products/assets/us_votrient.pdf>

Glybina, I. V., Kennedy, A., Ashton, P., Abrams, G. W. & Iezzi, R. (2009). Photoreceptor neuroprotection in RCS rats via low-dose intravitreal sustained-delivery of fluocinolone acetonide. *Invest Ophthalmol Vis Sci*, Vol.50, No.10, 4847-4857

Glybina, I. V., Kennedy, A., Ashton, P., Abrams, G. W. & Iezzi, R. (2010). Intravitreous delivery of the corticosteroid fluocinolone acetonide attenuates retinal degeneration in S334ter-4 rats. *Invest Ophthalmol Vis Sci*, Vol.51, No.8, 4243-4252

Gonzalez-Soto, R., Brant-Fernandes, R. A., Humayun, M. S., Varma, R., Journey, M. & Caffey, S. (2011). Intravitreal infusion of ranibizumab with an infusion pump in rabbits. *ARVO Meeting Abstracts*, 3246

Good, T. J., Kimura, A. E., Mandava, N. & Kahook, M. Y. (2011). Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. *British Journal of Ophthalmology*, Vol.95, No.8, 1111-1114

Gower, E. W., Cassard, S. D., Bass, E. B., Schein, O. D. & Bressler, N. M. (2010). A cost-effectiveness analysis of three treatments for age-related macular degeneration. *Retina*, Vol.30, No.2, 212-221

Grossniklaus, H. E., Ling, J. X., Wallace, T. M., Dithmar, S., Lawson, D. H., Cohen, C., Elner, V. M., Elner, S. G. & Sternberg Jr, P. (2002). Macrophage and retinal pigment

epithelium expression of angiogenic cytokines in choroidal neovascularization. *Molecular Vision*, Vol.8, 119-126

Gupta, N., Brown, K. E. & Milam, A. H. (2003). Activated microglia in human retinitis pigmentosa, late-onset retinal degeneration, and age-related macular degeneration. *Exp Eye Res*, Vol.76, No.4, 463-471

Hajitou, A., Grignet, C., Devy, L., Berndt, S., Blacher, S., Deroanne, C. F., Bajou, K., Fong, T., Chiang, Y., Foidart, J. M. & Noel, A. (2002). The antitumoral effect of endostatin and angiostatin is associated with a down-regulation of vascular endothelial growth factor expression in tumor cells. *The FASEB journal*, Vol.16, No.13, 1802-1804

Hamidi, M., Rafiei, P. & Azadi, A. (2008). Designing PEGylated therapeutic molecules: Advantages in ADMET properties. *Expert Opinion on Drug Discovery*, Vol.3, No.11, 1293-1307

Hari, D., Beckett, M. A., Sukhatme, V. P., Dhanabal, M., Nodzenski, E., Lu, H., Mauceri, H. J., Kufe, D. W. & Weichselbaum, R. R. (2000). Angiostatin induces mitotic cell death of proliferating endothelial cells. *Molecular Cell Biology Research Communications*, Vol.3, No.5, 277-282

Hayes, K. C., Lindsey, S., Stephan, Z. F. & Brecker, D. (1989). Retinal pigment epithelium possesses both LDL and scavenger receptor activity. *Invest Ophthalmol Vis Sci*, Vol.30, No.2, 225-232

Helzner, J. (2010). Progress on sustained-delivery Lucentis, Retinal Physicians.

Hu, Z. & Li, J. (2010). Natural killer cells are crucial for the efficacy of Icon (factor VII/human IgG1 Fc) immunotherapy in human tongue cancer. *BMC immunology*, Vol.11, 49

Iconic Therapeutics Plans for clinical studies, Available from:
        <http://www.iconictherapeutics.com/rdprograms.html>

Iconic Therapeutics hI-con1™, Available from:
        <http://www.iconictherapeutics.com/icon1.html>

iScience Interventional™ Interventional Ophthalmology, Available from:
        <http://www.iscienceinterventional.com/US/interventional.htm>

Jaffe, G. J., Tao, W. & Group, C. S. (2010). A Phase 2 study of encapsulated CNTF-secreting cell implant (NT-501) in patients with geographic atrophy associated with dry AMD-18 month results. *ARVO Meeting Abstracts*, 6415

Jeanneteau, F., Garabedian, M. J. & Chao, M. V. (2008). Activation of Trk neurotrophin receptors by glucocorticoids provides a neuroprotective effect. *Proc Natl Acad Sci U S A*, Vol.105, No.12, 4862-4867

Jo, N., Mailhos, C., Ju, M., Cheung, E., Bradley, J., Nishijima, K., Robinson, G. S., Adamis, A. P. & Shima, D. T. (2006). Inhibition of platelet-derived growth factor B signaling enhances the efficacy of anti-vascular endothelial growth factor therapy in multiple models of ocular neovascularization. *American Journal of Pathology*, Vol.168, No.6, 2036-2053

John, T. A., Vogel, S. M., Minshall, R. D., Ridge, K., Tiruppathi, C. & Malik, A. B. (2001). Evidence for the role of alveolar epithelial gp60 in active transalveolar albumin transport in the rat lung. *Journal of Physiology*, Vol.533, No.2, 547-559

Kachi, S., Binley, K., Yokoi, K., Umeda, N., Akiyama, H., Muramatu, D., Iqball, S., Kan, O., Naylor, S. & Campochiaro, P. A. (2009). Equine infectious anemia viral vector-mediated codelivery of endostatin and angiostatin driven by retinal pigmented epithelium-specific VMD2 promoter inhibits choroidal neovascularization. *Human Gene Therapy*, Vol.20, No.1, 31-39

Kan, O., Widdowson, P., Hamirally, S., Binley, K., Nork, M., Miller, P., Bantseev, V., Christian, B., Iqball, S., Mitrophanous, K. A. & Naylor, S. (2009). Ocular tolerance of a lentiviral vector-based angiostatic gene therapy product (RetinoStat®) in rodent, rabbit, and nonhuman primate models. *Human Gene Therapy*, Vol.20, No.4, 403

Keane, P. A., Liakopoulos, S., Ongchin, S. C., Heussen, F. M., Msutta, S., Chang, K. T., Walsh, A. C. & Sadda, S. R. (2008). Quantitative subanalysis of optical coherence tomography after treatment with ranibizumab for neovascular age-related macular degeneration. *Invest Ophthalmol Vis Sci*, Vol.49, No.7, 3115-3120

Kim, H. S., Chang, Y. I., Kim, J. H. & Park, C. K. (2007). Alteration of retinal intrinsic survival signal and effect of alpha2-adrenergic receptor agonist in the retina of the chronic ocular hypertension rat. *Vis Neurosci*, Vol.24, No.2, 127-139

Kim, S. U. & de Vellis, J. (2005). Microglia in health and disease. *J Neurosci Res*, Vol.81, No.3, 302-313

Kim, Y. M., Hwang, S., Pyun, B. J., Kim, T. Y., Lee, S. T., Gho, Y. S. & Kwon, Y. G. (2002). Endostatin blocks vascular endothelial growth factor-mediated signaling via direct interaction with KDR/Flk-1. *Journal of Biological Chemistry*, Vol.277, No.31, 27872-27879

Klegeris, A. & McGeer, P. L. (2000). Interaction of various intracellular signaling mechanisms involved in mononuclear phagocyte toxicity toward neuronal cells. *J Leukoc Biol*, Vol.67, No.1, 127-133

Kline, A. E., Yu, J., Massucci, J. L., Zafonte, R. D. & Dixon, C. E. (2002). Protective effects of the 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin against traumatic brain injury-induced cognitive deficits and neuropathology in adult male rats. *Neurosci Lett*, Vol.333, No.3, 179-182

Kragh-Hansen, U. (1990). Structure and ligand binding properties of human serum albumin. *Danish medical bulletin*, Vol.37, No.1, 57-84

Kreutzberg, G. W. (1995). Microglia, the first line of defence in brain pathologies. *Arzneimittel-Forschung*, Vol.45, No.3 A, 357-360

Kreutzberg, G. W. (1996). Microglia: A sensor for pathological events in the CNS. *Trends in Neurosciences*, Vol.19, No.8, 312-318

Kukley, M., Schaper, C., Becker, A., Rose, K. & Krieglstein, J. (2001). Effect of 5-hydroxytryptamine 1A receptor agonist BAY X 3702 on BCL-2 and BAX proteins level in the ipsilateral cerebral cortex of rats after transient focal ischaemia. *Neuroscience*, Vol.107, No.3, 405-413

Kuno, N. & Fujii, S. (2010). Biodegradable intraocular therapies for retinal disorders: Progress to date. *Drugs and Aging*, Vol.27, No.2, 117-134

Kuno, N. & Fujii, S. (2011a). Dry age-related macular degeneration: Recent progress of therapeutic approaches. *Curr Mol Pharmacol*, in press

Kuno, N. & Fujii, S. (2011b). Recent advances in ocular drug delivery systems. *Polymers*, Vol.3, No.1, 193-221

Kusol, K. & Brunken, W. J. (2000). 5-HT(1A) and 5-HT7 receptor expression in the mammalian retina. *Brain Res*, Vol.875, No.1-2, 152-156

Kwak, N., Okamoto, N., Wood, J. M. & Campochiaro, P. A. (2000). VEGF is major stimulator in model of choroidal neovascularization. *Invest Ophthalmol Vis Sci*, Vol.41, No.10, 3158-3164

Lai, R. K., Chun, T., Hasson, D., Lee, S., Mehrbod, F. & Wheeler, L. (2002). Alpha-2 adrenoceptor agonist protects retinal function after acute retinal ischemic injury in the rat. *Vis Neurosci*, Vol.19, No.2, 175-185

Lamartina, S., Cimino, M., Roscilli, G., Dammassa, E., Lazzaro, D., Rota, R., Ciliberto, G. & Toniatti, C. (2007). Helper-dependent adenovirus for the gene therapy of proliferative retinopathies: Stable gene transfer, regulated gene expression and therapeutic efficacy. *Journal of Gene Medicine*, Vol.9, No.10, 862-874

Lewis, R. A., von Wolff, K., Tetz, M., Koerber, N., Kearney, J. R., Shingleton, B. J. & Samuelson, T. W. (2009). Canaloplasty: Circumferential viscodilation and tensioning of Schlemm canal using a flexible microcatheter for the treatment of open-angle glaucoma in adults. Two-year interim clinical study results. *Journal of Cataract and Refractive Surgery*, Vol.35, No.5, 814-824

Lewis, R. A., Von Wolff, K., Tetz, M., Koerber, N., Kearney, J. R., Shingleton, B. J. & Samuelson, T. W. (2011). Canaloplasty: Three-year results of circumferential viscodilation and tensioning of Schlemm canal using a microcatheter to treat open-angle glaucoma. *Journal of Cataract and Refractive Surgery*, Vol.37, No.4, 682-690

Lo, R., Li, P. Y., Saati, S., Agrawal, R. N., Humayun, M. S. & Meng, E. (2009). A passive MEMS drug delivery pump for treatment of ocular diseases. *Biomed Microdevices*, 959-970

Lonngren, U., Napankangas, U., Lafuente, M., Mayor, S., Lindqvist, N., Vidal-Sanz, M. & Hallbook, F. (2006). The growth factor response in ischemic rat retina and superior colliculus after brimonidine pre-treatment. *Brain Res Bull*, Vol.71, No.1-3, 208-218

Lukason, M., Dufresne, E., Rubin, H., Pechan, P., Li, Q., Kim, I., Kiss, S., Flaxel, C., Collins, M., Miller, J., Hauswirth, W., MacLachlan, T., Wadsworth, S. & Scaria, A. (2011). Inhibition of choroidal neovascularization in a nonhuman primate model by intravitreal administration of an AAV2 vector expressing a novel anti-VEGF molecule. *Molecular Therapy*, Vol.19, No.2, 260-265

Lyzogubov, V. V., Tytarenko, R. G., Liu, J., Bora, N. S. & Bora, P. S. (2011). Polyethylene glycol (PEG)-induced mouse model of choroidal neovascularization. *Journal of Biological Chemistry*, Vol.286, No.18, 16229-16237

Martin, D. F., Maguire, M. G. & Fine, S. L. (2010). Identifying and eliminating the roadblocks to comparative-effectiveness research. *New England Journal of Medicine*, Vol.363, No.2, 105-107

Mauler, F. & Horvath, E. (2005). Neuroprotective efficacy of repinotan HCl, a 5-HT1A receptor agonist, in animal models of stroke and traumatic brain injury. *J Cereb Blood Flow Metab*, Vol.25, No.4, 451-459

Mazor, O., Brandis, A., Plaks, V., Neumark, E., Rosenbach-Belkin, V., Salomon, Y. & Scherz, A. (2005). WST11, A novel water-soluble bacteriochlorophyll derivative; cellular uptake, pharmacokinetics, biodistribution and vascular-targeted photodynamic

activity using melanoma tumors as a model. *Photochemistry and Photobiology*, Vol.81, No.2, 342-351

McConnell, M. J. & Imperiale, M. J. (2004). Biology of adenovirus and its use as a vector for gene therapy. *Human Gene Therapy*, Vol.15, No.11, 1022-1033

McGeer, P. L., Kawamata, T., Walker, D. G., Akiyama, H., Tooyama, I. & McGeer, E. G. (1993). Microglia in degenerative neurological disease. *GLIA*, Vol.7, No.1, 84-92

Meyer, C. H., Michels, S., Rodrigues, E. B., Hager, A., Mennel, S., Schmidt, J. C., Helb, H. M. & Farah, M. E. (2010). Incidence of rhegmatogenous retinal detachments after intravitreal antivascular endothelial factor injections. *Acta Ophthalmologica*, Vol.89, No.1, 70-75

Meyer, C. H., Rodrigues, E. B., Michels, S., Mennel, S., Schmidt, J. C., Helb, H. M., Hager, A., Martinazzo, M. & Farah, M. E. (2010). Incidence of damage to the crystalline lens during intravitreal injections. *Journal of Ocular Pharmacology and Therapeutics*, Vol.26, No.5, 491-495

Millauer, B., Wizigmann-Voos, S., Schnurch, H., Martinez, R., Moller, N. P. H., Risau, W. & Ullrich, A. (1993). High affinity VEGF binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis. *Cell*, Vol.72, No.6, 835-846

Min, K.-J., Pyo, H.-K., Yang, M.-S., Ji, K.-A., Jou, I. & Joe, E.-H. (2004). Gangliosides activate microglia via protein kinase C and NADPH oxidase. *GLIA*, Vol.48, No.3, 197-206

Mohle, R., Green, D., Moore, M. A. S., Nachman, R. L. & Rafii, S. (1997). Constitutive production and thrombin-induced release of vascular endothelial growth factor by human megakaryocytes and platelets. *Proc Natl Acad Sci U S A*, Vol.94, No.2, 663-668

Molina, R. P., Ye, H. Q., Brady, J., Zhang, J., Zimmerman, H., Kaleko, M. & Luo, T. (2004). A synthetic rev-independent bovine immunodeficiency virus-based packaging construct. *Human Gene Therapy*, Vol.15, No.9, 865-877

Nakanishi, H. (2003). Microglial functions and proteases. *Mol Neurobiol*, Vol.27, No.2, 163-176

Niethammer, A. G., Xiang, R., Becker, J. C., Wodrich, H., Pertl, U., Karsten, G., Eliceir, B. P. & Reisfeld, R. A. (2002). A DNA vaccine against VEGF receptor 2 prevents effective angiogenesis and inhibits tumor growth. *Nature Medicine*, Vol.8, No.12, 1369-1375

Olsen, T. W. (2007). Drug delivery to the suprachoroidal space shows promise. *Retina Today*, Vol.March, 36-39

Olsen, T. W., Feng, X., Wabner, K., Conston, S. R., Sierra, D. H., Folden, D. V., Smith, M. E. & Cameron, J. D. (2006). Cannulation of the suprachoroidal space: A novel drug delivery methodology to the posterior segment. *Am J Ophthalmol*, Vol.142, No.5, 777-787

Olsen, T. W., Feng, X., Wabner, K., Csaky, K., Pambuccian, S. & Cameron, J. D. (2011). Pharmacokinetics of pars plana intravitreal injections versus microcannula suprachoroidal injections of bevacizumab in a porcine model. *Invest Ophthalmol Vis Sci*, Vol.52, No.7, 4749-4756

On Demand Therapeutics Inc The ODTx solution, Available from:
<http://www.ondemandtx.com/the-odtx-solution.aspx>

Oner, A., Karakucuk, S., Mirza, E. & Erkilic, K. (2005a). Electrooculography after photodynamic therapy. *Documenta Ophthalmologica*, Vol.111, No.2, 83-86

Oner, A., Karakucuk, S., Mirza, E. & Erkilic, K. (2005b). The changes of pattern electroretinography at the early stage of photodynamic therapy. *Documenta Ophthalmologica*, Vol.111, No.2, 107-112

Oosterink, B. J., Harkany, T. & Luiten, P. G. M. (2003). Post-lesion administration of 5-HT1A receptor agonist 8-OH-DPAT protects cholinergic nucleus basalis neurons against NMDA excitotoxicity. *NeuroReport*, Vol.14, No.1, 57-60

Ophthotech Corporation E10030 - Anti-PDGF Aptamer, Available from: <http://www.ophthotech.com/products/e10030/>

Orr, C. F., Rowe, D. B. & Halliday, G. M. (2002). An inflammatory review of Parkinson's disease. *Prog Neurobiol*, Vol.68, No.5, 325-340

Ozdemir, H., Karacorlu, S. A. & Karacorlu, M. (2006). Early optical coherence tomography changes after photodynamic therapy in patients with age-related macular degeneration. *Am J Ophthalmol*, Vol.141, No.3, 574-576

Pan, J., Jin, P., Yan, J. & Kabelitz, D. (2008). Anti-angiogenic active immunotherapy: A new approach to cancer treatment. *Cancer Immunology, Immunotherapy*, Vol.57, No.8, 1105-1114

Patel, J. J., Mendes, M. A., Bounthavong, M., Christopher, M. L., Boggie, D. & Morreale, A. P. (2010). Cost-utility analysis of bevacizumab versus ranibizumab in neovascular age-related macular degeneration using a Markov model. *J Eval Clin Pract*, doi: 10.1111/j.1365-2753.2010.01546.x.

Pawate, S., Shen, Q., Fan, F. & Bhat, N. R. (2004). Redox regulation of glial inflammatory response to lipopolysaccharide and interferongamma. *J Neurosci Res*, Vol.77, No.4, 540-551

Pechan, P., Rubin, H., Lukason, M., Ardinger, J., DuFresne, E., Hauswirth, W. W., Wadsworth, S. C. & Scaria, A. (2009). Novel anti-VEGF chimeric molecules delivered by AAV vectors for inhibition of retinal neovascularization. *Gene Therapy*, Vol.16, No.1, 10-16

Piera, M. J., Beaughard, M., Michelin, M. T. & Massingham, R. (1995). Effects of the 5-hydroxytryptamine1A receptor agonists, 8-OH-DPAT, buspirone and flesinoxan, upon brain damage induced by transient global cerebral ischaemia in gerbils. *Arch Int Pharmacodyn Ther*, Vol.329, No.3, 347-359

Pilli, S., Kotsolis, A., Spaide, R. F., Slakter, J., Freund, K. B., Sorenson, J., Klancnik, J. & Cooney, M. (2008). Endophthalmitis associated with intravitreal anti-vascular endothelial growth factor therapy injections in an office setting. *Am J Ophthalmol*, Vol.145, No.5, 879-882

QLT Ophthalmics Visudyne® Available from: <http://www.visudyne.com/>

Ramos, A. J., Rubio, M. D., Defagot, C., Hischberg, L., Villar, M. J. & Brusco, A. (2004). The 5HT1A receptor agonist, 8-OH-DPAT, protects neurons and reduces astroglial reaction after ischemic damage caused by cortical devascularization. *Brain Res*, Vol.1030, No.2, 201-220

RetinaToday (2010). Laser-activated, on-Demand drug delivery technology tested in vivo, Available from: <http://bmctoday.net/retinatoday/2010/06/article.asp?f=laser-activated-on-demand-drug-delivery-technology-tested-in-vivo>

Rhoades, K. L., Patel, Y., Collier, R. J. & Romano, C. (2009). AL-8309, A Serotonin 5-HT1A Agonist, Protects RPE Cells From Oxidative Damage. *ARVO Meeting Abstracts*, Vol.50, No.5, 677

Risau, W. (1997). Mechanisms of angiogenesis. *Nature*, Vol.386, No.6626, 671-674

Rizzo, S., Augustin, A. J., Tetz, M., Genovesi-Ebert, F. & Di Bartolo, E. (2010). Suprachoroidal drug delivery for the treatment of advanced, exudative age-related macular degeneration. *ARVO Meeting Abstracts*, Vol.51, No.5, 1256

Roque, R. S., Imperial, C. J. & Caldwell, R. B. (1996). Microglial cells invade the outer retina as photoreceptors degenerate in Royal College of Surgeons rats. *Invest Ophthalmol Vis Sci*, Vol.37, No.1, 196-203

Rosenberg, A. S. (2006). Effects of protein aggregates: An Immunologic perspective. *AAPS Journal*, Vol.8, No.3, E501-E507

Saati, S., Lo, R., Li, P. Y., Meng, E., Varma, R. & Humayun, M. S. (2010). Mini drug pump for ophthalmic use. *Curr Eye Res*, Vol.35, No.3, 192-201

Saruhashi, Y., Matsusue, Y. & Hukuda, S. (2002). Effects of serotonin 1A agonist on acute spinal cord injury. *Spinal Cord*, Vol.40, No.10, 519-523

Schaal, S., Kaplan, H. J. & Tezel, T. H. (2008). Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? *Ophthalmology*, Vol.115, No.12, 2199-2205

Scharioth, G. B., Raak, P. & Pavlidis, M. (2011). Suprachoroidal bevacizumab delivery for neovascular AMD treatment, Retinal Physician.

Schnitzer, J. E. & Oh, P. (1994). Albondin-mediated capillary permeability to albumin. Differential role of receptors in endothelial transcytosis and endocytosis of native and modified albumins. *Journal of Biological Chemistry*, Vol.269, No.8, 6072-6082

Sieving, P. A., Caruso, R. C., Tao, W., Coleman, H. R., Thompson, D. J., Fullmer, K. R. & Bush, R. A. (2006). Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. *Proc Natl Acad Sci U S A*, Vol.103, No.10, 3896-3901

Sima, J., Zhang, S. X., Shao, C., Fant, J. & Ma, J. X. (2004). The effect of angiostatin on vascular leakage and VEGF expression in rat retina. *FEBS Letters*, Vol.564, No.1-2, 19-23

Simone Fishburn, C. (2008). The pharmacology of PEGylation: Balancing PD with PK to generate novel therapeutics. *Journal of Pharmaceutical Sciences*, Vol.97, No.10, 4167-4183

SurModics Inc News Release: SurModics enters ophthalmic lisence and development agreement with Roche and Genentech includes development and commercialization of a sustained drug delivery formulation of Lucentis and potential other Genentech compounds, Available from:
<http://phx.corporate-ir.net/phoenix.zhtml?c=80353&p=irol-newsArticle&ID=1339001&highlight=genentech>

Talcott, K. E., Ratnam, K., Sundquist, S. M., Lucero, A. S., Lujan, B. J., Tao, W., Porco, T. C., Roorda, A. & Duncan, J. L. (2011). Longitudinal study of cone photoreceptors during retinal degeneration and in response to ciliary neurotrophic factor treatment. *Invest Ophthalmol Vis Sci*, Vol.52, No.5, 2219-2226

Tezel, T. H., Bodek, E., Sonmez, K., Kaliappan, S., Kaplan, H. J., Hu, Z. & Garen, A. (2007). Targeting tissue factor for immunotherapy of choroidal neovascularization by intravitreal delivery of factor VII-Fc chimeric antibody. *Ocular Immunology and Inflammation*, Vol.15, No.1, 3-10

Thanos, S. (1992). Sick photoreceptors attract activated microglia from the ganglion cell layer: a model to study the inflammatory cascades in rats with inherited retinal dystrophy. *Brain Res*, Vol.588, No.1, 21-28

Torup, L., Moller, A., Sager, T. N. & Diemer, N. H. (2000). Neuroprotective effect of 8-OH-DPAT in global cerebral ischemia assessed by stereological cell counting. *Eur J Pharmacol*, Vol.395, No.2, 137-141

Tzekov, R., Lin, T., Zhang, K. M., Jackson, B., Oyejide, A., Orilla, W., Kulkarni, A. D., Kuppermann, B. D., Wheeler, L. & Burke, J. (2006). Ocular changes after photodynamic therapy. *Invest Ophthalmol Vis Sci*, Vol.47, No.1, 377-385

Vitiello, A., Marchesini, D., Furze, J., Sherman, L. A. & Chesnut, R. W. (1991). Analysis of the HLA-restricted influenza-specific cytotoxic T lymphocyte response in transgenic mice carrying a chimeric human-mouse class I major histocompatibility complex. *Journal of Experimental Medicine*, Vol.173, No.4, 1007-1015

Wada, M., Ogata, N., Otsuji, T. & Uyama, M. (1999). Expression of vascular endothelial growth factor and its receptor (KDR/flk-1) mRNA in experimental choroidal neovascularization. *Curr Eye Res*, Vol.18, No.3, 203-213

Wada, S., Tsunoda, T., Baba, T., Primus, F. J., Kuwano, H., Shibuya, M. & Tahara, H. (2005). Rationale for antiangiogenic cancer therapy with vaccination using epitope peptides derived from human vascular endothelial growth factor receptor 2. *Cancer Research*, Vol.65, No.11, 4939-4946

Wang, B., Chen, Y. B., Ayalon, O., Bender, J. & Garen, A. (1999). Human single-chain Fv immunoconjugates targeted to a melanoma-associated chondroitin sulfate proteoglycan mediate specific lysis of human melanoma cells by natural killer cells and complement. *Proc Natl Acad Sci U S A*, Vol.96, No.4, 1627-1632

Wang, Y., Martin, E., Hoang, H., Rector, R., Morgan, S., Romano, C. & Collier, R. (2009). Inhibition of complement deposition by AL-8309A, a 5-HT1a agonist, in the rat photic-induced retinopathy model. *ARVO Meeting Abstracts*, 685

Whitton, P. S. (2007). Inflammation as a causative factor in the aetiology of Parkinson's disease. *Br J Pharmacol*, Vol.150, No.8, 963-976

Yafai, Y., Yang, X. M., Niemeyer, M., Nishiwaki, A., Lange, J., Wiedemann, P., King, A. G., Yasukawa, T. & Eichler, W. (2011). Anti-angiogenic effects of the receptor tyrosine kinase inhibitor, pazopanib, on choroidal neovascularization in rats. *European Journal of Pharmacology*, Vol.666, No.1-3, 12-18

Yanez-Munoz, R. J., Balaggan, K. S., MacNeil, A., Howe, S. J., Schmidt, M., Smith, A. J., Buch, P., MacLaren, R. E., Anderson, P. N., Barker, S. E., Duran, Y., Bartholomae, C., Von Kalle, C., Heckenlively, J. R., Kinnon, C., Ali, R. R. & Thrasher, A. J. (2006). Effective gene therapy with nonintegrating lentiviral vectors. *Nature Medicine*, Vol.12, No.3, 348-353

Zeiss, C. J. & Johnson, E. A. (2004). Proliferation of Microglia, but not Photoreceptors, in the Outer Nuclear Layer of the rd-1 Mouse. *Invest Ophthalmol Vis Sci*, Vol.45, No.3, 971-976

Zhang, C., Shen, J. K., Lam, T. T., Zeng, H. Y., Chiang, S. K., Yang, F. & Tso, M. O. (2005). Activation of microglia and chemokines in light-induced retinal degeneration. *Mol Vis*, Vol.11, 887-895

Zhang, K., Hopkins, J. J., Heier, J. S., Birch, D. G., Halperin, L. S., Albini, T. A., Brown, D. M., Jaffe, G. J., Taoj, W. & Williams, G. A. (2011). Ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for treatment of geographic atrophy in age-related macular degeneration. *Proc Natl Acad Sci U S A*, Vol.108, No.15, 6241-6245

Zhang, M., Mo, X., Fang, Y., Guo, W., Wu, J., Zhang, S. & Huang, Q. (2009). Rescue of photoreceptors by BDNF gene transfer using in vivo electroporation in the RCS rat of retinitis pigmentosa. *Curr Eye Res*, Vol.34, No.9, 791-799
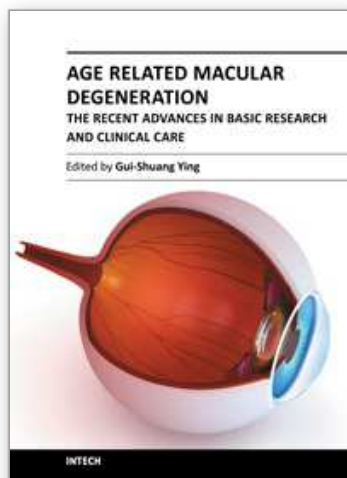
Age Related Macular Degeneration - The Recent Advances in Basic Research and Clinical Care

Edited by Dr. Gui-Shuang Ying

Age-related Macular Degeneration (AMD) is the leading cause of vision loss and blindness in the developed countries. In the past decade, great progress has been made in understanding the pathobiology and genetics of this blinding disease, as well as in finding new therapies for its treatment. These include the discovery of several genes that are associated with the risk of AMD, new anti-VEGF treatments for wet AMD and new imaging techniques to diagnose and monitor the AMD. All chapters in this book were contributed by outstanding research scientists and clinicians in the area of AMD. I hope this timely book will provide the basic scientists and clinicians with an opportunity to learn about the recent advances in the field of AMD.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

INTECH
open science | open minds