Therapeutic stratagems for vascular degenerative disorders of the posterior eye

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In this review we discuss insights into therapeutic stratagems that can selectively target the choroid, retinal cells and vitreoretinal space for the treatment of vision-threatening vascular degenerative disorders of the posterior eye. Despite the relative success of these novel drugs, new problems related to its delivery remain. Systems carrying drugs to the target site, such as nanoparticles, liposomes, vectosomes, spanlastics, micelles, dendrimers and implants are also discussed. Further, we also consider drug penetration enhancement approaches along with cutting-edge strategies for regaining vision during vision-threatening vascular degenerative disorders of the eye. Finally, challenges, such as ocular or even systemic complications associated with use of prolonged therapies and future prospects, such as combination of approaches with multidisciplinary integration to optimize delivery to the posterior eye are also addressed.

Vascular degenerative disorders of the posterior eye, such as age-related macular degeneration (ARMD), diabetic retinopathy (DR) and diabetic macular edema (DME) are responsible for causing visual impairment and blindness worldwide [1–5]. Retina is vulnerable to changes owing to aging, including alterations in retinal pigment epithelium (RPE) cellular morphology, thickening of Bruch's membrane and internal limiting membrane, and accumulation of extracellular glycoproteins and lipids deposits (drusen) beneath the retina and in the macula. These drusen eventually can increase in number and size to coalesce throughout the macula, a condition called as non-exudative or dry ARMD [3]. Exudative or wet ARMD is marked by the growth of aberrant leaky blood vessels under the retina and choroid along with epithelial proliferation and inflammation. If left untreated, these lesions progress to form an organized fibrous scar which results in irreversible loss of vision [3]. In normal health state, the retinal blood microvessels have tight junctions that protect them from leaking. However, an over-accumulation of glucose (as in case of diabetes mellitus) damages the tight junctions and the vessels become leaky enabling fluid or blood to seep into the retina, thus resulting in the swelling of the retina (non-proliferative DR). If left untreated, proliferative DR characterized by abnormal growth of new vessels in the retina (retinal neovascularization) develops, followed by retinal detachment and blindness [4]. Furthermore, increased vascular permeability of the blood–retinal barrier contributes to leakage of fluid and plasma constituents, such as lipoproteins, and thickening of the retina. This pathological state is called DME and is another cause of visual impairment in diabetic patients [5]. The pathogenesis of vascular degeneration is mystifying and consequently our therapeutic arsenal remains limited. The use of topical, systemic, transscleral, and intravitreal administration of pharmacological agents for treating these conditions has been the subject of myriad laboratory and clinical trial investigations [2]. Until recently, there was limited evidence from large clinical trials that pharmacotherapy demonstrated a useful biological effect or comparable clinical outcome compared with surgical approaches for the treatment of posterior ailments [1,2]. However, within the past decade this paradigm has shifted, and advances in understanding of molecular events and signaling pathways presaging vascular degenerative disorders of the eye (Fig. 1) have been paralleled by the burgeoning

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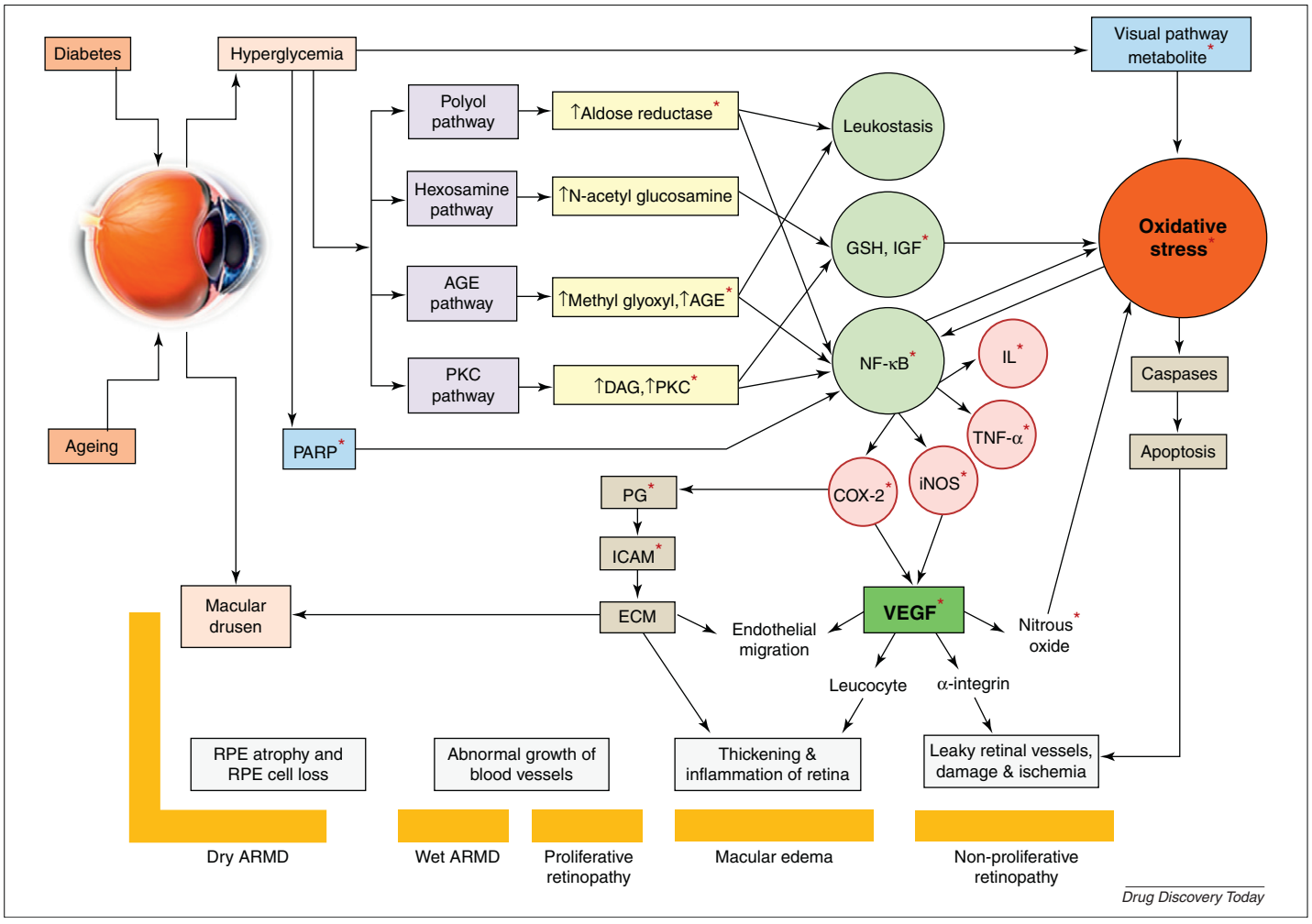

FIGURE 1

Signaling pathways and molecular events presaging vascular degenerative disorders of the eye. *Abbreviations*: ARMD: age-related macular degeneration; AGE: advanced glycosylation end products; DAG: diacylglycerol; ECM: extracellular matrix; ICAM: intercellular adhesion molecule; IGF: insulin growth factor; GSH: growth stimulating hormone; IL: interleukin; PARP: poly (ADP-ribose) polymerase; RPE: retinal pigment epithelium; TNF: tumor necrosis factor; NF κB: nuclear factor kappa B; iNOS: inducible nitric oxide synthase; PKC: protein kinase C; VEGF: vascular endothelial growth factor.

development of novel therapies (Table 1), targeted delivery modalities (Table 2) and devices (Table 3). In this article we consider how the experimental therapeutic targets might enable the development of novel drugs that can selectively target the choroid, RPE and vitreoretinal space. We also discuss the therapeutic strategies including delivery systems, devices and implants which are currently under development or are in pivotal stages of clinical trials. Furthermore, this review also considers drug penetration enhancement approaches along with cutting-edge strategies for regaining vision during vision-threatening vascular degenerative disorders of the eye.

Therapeutic targets and drugs

The process of vascular degeneration is multifactorial, involving events within the vascular lumen, intrinsic to the vessel wall and within the macula, choroid or retinal parenchyma. Because ocular vascular degeneration is the result of microvascular damage and ischemia, all treatment concepts ideally should aim to improve vascular integrity and/or ocular oxygenation in the long term [3–5]. All extracellular and intracellular signals converge on proinflammatory transcription factors to regulate various aspects of vascular function. Therapies that have been found to inhibit the increase in ocular vascular permeability include vascular endothelial growth factor (VEGF) inhibitors, nuclear factor kappa B (NF-κB) inhibitors, inducible nitric oxide synthase (iNOS) inhibitors, cyclooxygenase (COX)-2 inhibitors, advanced glycosylation end products (AGE) inhibitors, peroxisome proliferator-activated receptors (PPARs) inhibitors, tumor necrosis factor alpha (TNF-α) inhibitors and protein kinase inhibitors. Experimental studies have also demonstrated the role of antioxidants, visual cycle inhibitors, complement pathway inhibitors, photodynamic therapy and gene therapy in management of progression of vascular degenerative disorders of the posterior eye. Table 1 summarizes the therapeutic targets and pharmacotherapies in preclinical and clinical studies.

VEGF inhibitors

VEGF has been one of the major proinflammatory molecules associated with vascular leakage, inflammation and proliferation, thus contributing to the progression of retinopathy and wet ARMD [3]. Monoclonal antibodies, such as bevacizumab (Avastin) and ranibizumab (Lucentis) and aptamers, such as pegaptanib (Macugen)

TABLE 1

Therapeutic targets and drugs for vascular degenerative disorders of the posterior eye Novel drugs for posterior ocular ailments, their development stage and probable mechanism of action

Targets	Drug candidate	Description/mechanism	Development stage	Company [Refs]
Drugs for vascular degenerative disorders				
VEGF inhibitors	Bevacizumab	Avastin; full-length recombinant human anti-VEGF antibody	Phase II completed (DME)	Genentech [6, ClinicalTrials.gov: http://clinicaltrials.gov/]
	Ranibizumab	Lucentis; fragment of recombinant human (Ig)G1 monoclonal anti-VEGF antibody	Approved (ARMD)	Genentech [ClinicalTrials.gov: http://clinicaltrials.gov/]
	Pegaptanib sodium	Macugen; RNA aptamer directed against VEGF-165	Approved (DME, DR)	Eyetech Pharmaceuticals/ Pfizer [ClinicalTrials.gov: http://clinicaltrials.gov/, 7]
	Aflibercept	Eylea; VEGF trap is recombinant soluble VEGF receptor protein	Phase I completed (ARMD)	Regeneron Pharmaceuticals [ClinicalTrials.gov: http://clinicaltrials.gov/, 8]
NF-κB inhibitors	Benfotiamine	Activates transketolase	Preclinical	[9]
NOS inhibitors	Aminoguanidine	Selective iNOS inhibitor	Preclinical	[10]
COX-2 inhibitors	Meloxicam	Selective COX-2 inhibitor, downregulates COX-2 gene expression.	Preclinical	[11]
	Nepafenac	Nevanac; metabolized to amfenac, which is a potent COX-1 and COX-2 inhibitor	Phase III (DME)	Alcon [ClinicalTrials.gov: http://clinicaltrials.gov/, 12]
Antioxidants	α-Tocopherol	Phase II enzyme inducer with a chain-breaking antioxidant property	Preclinical	[15]
	Nicanartine	Antioxidant and lipid-lowering compound	Preclinical	[15]
	Lutein	Protect against peroxidation of fatty acids	Phase II (ARMD)	[ClinicalTrials.gov: http://clinicaltrials.gov/, 15]
	Zeaxanthin	Protect against peroxidation of fatty acids	Phase II (ARMD)	[ClinicalTrials.gov: http://clinicaltrials.gov/, 15]
NADPH oxidase inhibitors	Apocynin	Reduces reactive oxygen species by inhibiting NADPH oxidase.	Preclinical	[16]
AGE inhibitors	PEDF	Acts on (PI3K)/Akt to inhibit AGEs, increased expression of tight junction	Research	[18]
PARP inhibitors	PJ34	Cell-permeable inhibitor of PARP	Preclinical	[19]
GH receptor antagonists	Octreotide	Inhibits growth hormone, inhibits angiogenesis	Clinical (DR)	[20]
	Pegvisomant	Inhibits functional growth hormone receptor dimerization.	Preclinical	[5]
TNF-α inhibitor	Eternacept	TNF-α receptor/Fc construct	Preclinical	[21]
PKC inhibitors	Ruboxistaurin mesilate	Macrocyclic bisindolylmaleimide; oral inhibitor of PKC-β	Approved (DME)	Eli Lilly and Company [22]
	PKC-412	Midostaurin; oral multi-targeted PKC inhibitor including FLT3 inhibition	Preclinical	[23]
Visual cycle inhibitors	Fenretinide	Binds to excess Vit A and decreases toxin production.	Phase II completed (CNV) Phase III (ARMD)	ReVision Therapeutics Inc. [24]
Anti-angiogenic steroids	Anecortave acetate	Angiostatic agent.	Approved (ARMD)	Alcon Research [ClinicalTrials.gov: http://clinicaltrials.gov/, 25]
Complement system	Compstatin	Peptide inhibitor of complement C3 activation, suppress drusen formation.	Preclinical	[26]
	POT-4	Complement C3 inhibitor.	Phase I completed (ARMD)	Potentia Pharmaceuticals [ClinicalTrials.gov: http://clinicaltrials.gov/, 26]
Photosensitizers	Verteporfin	Visudyne; light-activated benzoporphyrin derivative used for PDT to remove abnormal vessels.	Approved (ARMD)	QLT Inc. [27]

TABLE 1 (*Continued*)

Targets	Drug candidate	Description/mechanism	Development stage	Company [Refs]
	Rostaporfin	Photrex; a light-activated cytotoxic drug used for PDT	Phase III (ARMD)	Miravant Pharmaceuticals [ClinicalTrials.gov: http://clinicaltrials.gov/, 28]
RNA interference	Bevasiranib sodium	siRNA that shuts down the genes that produce VEGF	Phase I completed (ARMD) Phase II completed (DME)	Opko Health, Inc. [ClinicalTrials.gov: http://clinicaltrials.gov/]
Gene therapy	Anti-CD105 MAb + mitomycin C-dextran	Inhibits human umbilical vein endothelial cells	Preclinical	[29]
	$\alpha v\beta 3$ integrin + mitomycin C-dextran	Anti cell adhesion molecules	Preclinical	[29]
Miscellaneous drugs	Ovine hyaluronidase	Vitrase; effective in clearing vitreous hemorrhage	Approved (DR)	ISTA Pharmaceuticals [30]
	Minocycline	Inhibits activation of retinal microglia and prevents early caspase-3 activity	Preclinical	[31]
	Pycnogenol	Extract from bark of pine tree with antioxidant properties	Preclinical	[32]
	Pazopanib	Multi-targeted receptor tyrosine kinase inhibitor of VEGF	Phase I completed (ARMD)	GlaxoSmithKline [ClinicalTrials.gov: http://clinicaltrials.gov/, 33]
	Strontium-90-β radiation	Emit beta particles that contain radioactive energy.	Phase IV (ARMD)	NeoVista Inc. [ClinicalTrials.gov: http://clinicaltrials.gov/, 34]

Abbreviation: FLT: fms-like tyrosine kinase.

directed against VEGF have demonstrated beneficial effects in patients with ocular vascular diseases [6,7, ClinicalTrials.gov: http://clinicaltrials.gov/]. Ranibizumab and pegaptanib have already been approved for the treatment of ARMD and DME, whereas bevacizumab for DME is in Phase III trial stage [6,7, ClinicalTrials.gov: http://clinicaltrials.gov/]. However, frequent injections (every 4–6 weeks) for an extended period, which might exaggerate infectious endophthalmitis, pose major drawbacks of currently available anti-VEGF compounds. Recently, aflibercept (Eylea^{TM}), a recombinant soluble VEGF receptor protein, has been approved for the treatment of wet-ARMD [8]. Its large size prolongs its presence in the subretinal milieu, thus requiring less frequent administration. More importantly, recent findings suggested development of retinal ischemia following VEGF inhibiting. Thus, the long-term advantage of anti-VEGF therapy without improving the oxygenation of retina is questionable and at the moment anti-VEGF remains an experimental treatment for DME.

NF-κB and proinflammatory protein inhibitors

NF-κB is a widely expressed transcription factor that is an important regulator of many genes involved in inflammatory and immune responses, proliferation and apoptosis and its role in the pathogenesis of vascular degeneration is clearly evident [4]. Proinflammatory proteins and cellular signaling molecules including iNOS, COX-2, PPAR and aldose reductase can contribute to cell damage in the retina, at least in part through activation of NF-κB. Benfotiamine, a novel NF-κB inhibitor, has shown to inhibit oxidative stress-induced NF-κB activation by activating transketolase in retinas of diabetic animals. Furthermore, the author reported that the expression of cytokines, proinflammatory proteins, iNOS and COX-2, was also blocked significantly [9]. Results of the recent studies conducted by Zhang *et al*., demonstrated vital role of iNOS in retinal neovascularization (NV) [10]. The authors reported that administration of aminoguanidine, a relatively selective inhibitor of iNOS, significantly suppressed oxygen-induced retinal NV in mice [10]. Thus, aminoguanidine appears to be a novel and effective therapeutic for retinal NV.

In view of the fact that COX-2 is responsible for the increase in prostaglandin (PG) levels in retina of diabetic rats, COX inhibitors have been evaluated for the treatment of ocular vascular disorders [11]. Topically administered nepafenac was found to inhibit choroid neovascularization (CNV), possibly through suppression of VEGF. Furthermore, nepafenac has been found to inhibit diabetes-induced retinal microvascular disease and underlying abnormalities of retinal metabolism and physiology [12]. The beneficial effect of nepafenac is owing to its excellent corneal penetration and inhibition of PG production and leukocyte adhesion in retinal vessels. Because of the advantages of the topical route, this is a potential topic for investigation.

NF-κB has been found to upregulate aldose reductase gene expression [13]. Thus, inhibition of aldose reductase resulted in inhibition of development of retinopathy. The effects are mediated through reduced expression of COX-2 and leukostasis. Although, results of clinical studies of aldose reductase inhibitors demonstrated reduction in nonperfused capillaries, vascular leakage, and microaneurysm counts, no significant effect on the progression of DR was reported [14].

As the ocular vascular disease progresses, the microvasculature of the retina is damaged and the oxidative stress in the retina causes fragile, new blood vessels to proliferate along the retina. Oxidative stress has also been implicated in upregulation of VEGF expression [15]. Thus, management of oxidative stress is an important strategy in preventing vascular degeneration. This supposition is further facilitated by the finding that antioxidants through NF-κB and iNOS inhibition were found to prevent development of inflammation in retinas of diabetic animals.

TABLE 2

Drug delivery systems for vascular degenerative disorders of the posterior eye, their description and development stage

Delivery system	Drug candidate	Description/polymer	Target disease	Company [Refs]
Micro-particulate systems	PKC412	PLGA-glucose	CNV	[36]
	Pegaptanib	Polyimide	Approved (ARMD)	Eyetech Inc. [ClinicalTrials.gov: http://clinicaltrials.gov/]
	AS-ODN	PLGA	CNV	[37]
	Nanosized anti-TGFβ2 AS-ODN	PLGA	CNV	[38]
Nano-particulatesystems	Rhodamine	PLA	Posterior segment uptake studies	[39]
	Plasmid DNA	PEG/POD nanoparticles containing expression cassette for glial cell line–derived neurotrophic factor	Light-induced photoreceptor apoptosis	[45]
	-	Silver nanoparticles	Retinal edema	[17]
	-	Gold nanoparticles	RNV	[65]
Emulsified systems	Dexamethasone palmitate	Cortiject; (NOVA63035) Cationic emulsion of oil/phospholipid	Phase I DME	[ClinicalTrials.gov: http://clinicaltrials.gov/, 41]
Vesicular systems (liposomes)	Bevacizumab	Phospholipid/cholesterol (nanoliposome)	ARMD, DR	[42]
	Coumarin-6	L-α-Distearoyl PC (submicron-sized liposomes)	Posterior segment uptake studies	[43]
	Edaravone	L-α-Distearoyl PC (submicron-sized liposomes)	Retinal disorders	[44]
	AS-ODNs	Phosphatidylethanolamine (anionic pH-sensitive liposome)	CNV	[45]
	Plasmid DNA encoding luciferase gene	N-[1-(2,3-dioleyloxy)propyl]–N,N,N-trimethylammonium chloride/ cholesterol (cationic liposome)	Gene transfer	[45]
	Plasmid DNA containing the LacZ reporter gene	Liposomes with envelope of inactivated hemagglutinating virus of Japan	CNV	[45]
	Phosphorothioate ODNs	Liposomes with envelope of inactivated hemagglutinating virus of Japan	CNV	[46]
	Therapeutic DNA	PEG-DSPE (cationic liposomes complexed with therapeutic DNA to form Lipoplex)	Retinal diseases	[46]
	Verteporfin	Visudyne; heat-sensitive artificial phospholipids for PDT	Approved (ARMD)	Novartis Pharmaceuticals [27]
	Rostaporfin	Photrex; heat-sensitive artificial phospholipids for PDT	Phase III (ARMD, CNV)	Miravant Medical Technologies [ClinicalTrials.gov: http://clinicaltrials.gov/]
Vectosomes	ODNs	VP22, a structural protein of herpes simplex virus which can be destabilized by the illumination of a laser light	Retinal delivery	[48]
Spanlastics	6-Carboxyfluorescein	Span 60/Tween 80	Posterior segment uptake studies	[49]
Miceller system	Dendritic phthalocyanine	Polyion complex Dendritic system	Preclinical	[50]
	Voclosporin	Vitamin E/D-α-tocopheryl PEG 1000 succinate stabilized with octoxynol-40	Retinal diseases	[a]
Gelifying systems	Triamcinolone acetonide	Verisome (IBI-20089); biodegradable benzyl benzoate	Clinical (DR, ARMD)	Icon Bioscience, Inc. [51]
Dendritic systems	ODN-1	Lipid-lysine (cationic dendrimer)	CNV	[53]

Abbreviation: RNV: retinal neovascularization, TGF: transforming growth factor.

[a] Velagaleti, P. *et al.* A clear, mixed nanomicellar formulation of voclosporin (LX214), achieves therapeutic levels in ocular posterior segment after single and multiple topical dosing in rabbits. In *Proceedings of ARVO 2010 Annual Meeting*, Fort Lauderdale, FL, USA, 2–6 May 2010; E-Abstract 5323.

TABLE 3

Therapeutic devices for vascular degenerative disorders of the posterior eye, their description and development stage

Device	Drug candidate	Description/ polymer	Development stage	Company/reference
Non-biodegradable devices				
Iluvein	Fluocinolone acetonide	Polyimide/PVA	Phase III (DME); Phase II (ARMD)	Alimera Sciences [ClinicalTrials.gov: http://clinicaltrials.gov/, 54]
Medidur	Fluocinolone acetonide	Polyimide/PVA	Phase II (ARMD)	Alimera Sciences [ClinicalTrials.gov: http://clinicaltrials.gov/]
I-vationTA	Triamcinolone acetonide	PMMA/EVA	Phase I (macular edema)	SurModics [ClinicalTrials.gov: http://clinicaltrials.gov/, 55]
Thermally responsive gel	Anti-VEGF	NIPAM	Preclinical	[54]
Implant	Betamethasone	PVA/EVA	Preclinical	[54]
Biodegradable devices				
Ozurdex	Dexamethasone	PLGA	Approved (macular edema); Phase III (ARMD)	Allergan [ClinicalTrials.gov: http://clinicaltrials.gov/]
Novadur	Brimonidine	PLGA	Phase II (retinal disease)	Allergan [ClinicalTrials.gov: http://clinicaltrials.gov/]
LX212	Voclosporin	Tyrosine-derived	Preclinical	Isotechnika [ClinicalTrials.gov: http://clinicaltrials.gov/]
Drug penetration enhancement devices				
Microneedles	Fluorescein	Drug-coated solid needle	Research	[56,57]
Iontophoresis	Triamcinolone acetonide	Macroesis	Preclinical	[59]
	Ranibizumab	Macroesis	Preclinical	[59]
	Citrate buffer	EyeGate II	Phase I completed	Eyegate Pharmaceuticals Inc. [ClinicalTrials.gov: http://clinicaltrials.gov/]
	Pegaptanib	OcuPhor	Approved	IOMED, Inc. [ClinicalTrials.gov: http://clinicaltrials.gov/]
Visual prosthetic devices				
CentraSight	–	Implantable miniature telescope	Approved (ARMD)	VisionCare Ophthalmic Technologies, Inc., [61]
Lipshitz macular implant	–	Miniature mirrors	Clinical (ARMD)	OptoLight Vision Technologies [ClinicalTrials.gov: http://clinicaltrials.gov/]
Retinal implant	–	Electrode/eyeglass	Research	[62]
Miscellaneous devices				
Encapsulated cell technology	Rh CNTF	Genetically modified ARPE-19 cell line	Phase I (retinal pigmentation); Phase III (ARMD)	Neurotech Pharmaceuticals [ClinicalTrials.gov: http://clinicaltrials.gov/, 63]
	VEGF antagonist	Genetically modified ARPE-19 cell line	Phase I (ARMD)	Neurotech Pharmaceuticals [ClinicalTrials.gov: http://clinicaltrials.gov/]
Photonic crystals	–	Doped p-type silicon	Research	[64]

Abbreviations: EVA – ethylvinyl acetate; NIPAM – poly(N-isopropylacrylamide); PEG – polyethylene glycol; PVA – polyvinyl alcohol; RNV – retinal neovascularization.

Antioxidants might act at different levels; they might inhibit the formation of reactive oxygen species (ROS) or scavenge free radicals, or increase the antioxidants defense enzyme capabilities [15]. Nicanartine, an antioxidant with lipid lowering properties, can partially inhibit pericyte loss in diabetic rats. However, it is of limited benefit in DR [15]. Trolox, a water soluble analog of vitamin E with potent antioxidant properties, is shown to partially prevent the loss of pericytes in diabetic rats [15]. However, no additional follow-up studies have been reported by either the same group or other investigators. Partial reductions in the development of retinal acellular capillaries and pericyte ghosts are seen in diabetic rats given the combination of vitamins C and E [15]. Calcium dobesilate, a compound with potent antioxidant capacity against hydroxyl radical, is shown to reduce the progression of DR [15]. Recently, inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase with apocynin has been shown to prevent retinal degeneration and choroid NV. Additional testing on the use of NADPH oxidase inhibitors to treat NV, wet ARMD and DR could be focused area in the near future [16].

Increased formation of advanced glycosylation end products (AGE) has been proposed as another possible mechanism leading to vascular degeneration. Binding of AGEs to receptor for advanced glycation end products (RAGE) stimulates leukostasis and activation of NF-κB. Interruption of AGE–RAGE interaction

might inhibit the degeneration of retinal capillaries. A recent study on cultured porcine retinal endothelial cells demonstrated that both silver nanoparticles (Ag-NPs) [17] and pigment epithelium-derived factor (PEDF) [18] inhibited AGE-modified bovine serum albumin-induced permeability through Src kinase and phosphatidylinositol 3-kinase (PI3K)/Akt pathway, respectively. Finally, these compounds could possibly act as potent antipermeability molecules and offers potential targets to inhibit posterior ailments [17,18]. PARP-1 is another transcription factor expressed in inflammatory and immune responses. A potent PARP inhibitor, PJ-34, was found to subdue the diabetes-induced death of retinal microvascular cells and capillary degeneration following a 9-month therapy. Evidence suggests that these beneficiary effects of PJ-34 are mediated through inhibition of NF-κB expression [19]. However, there are no controlled trials supporting these anecdotal observations.

Growth factor and cytokine inhibitors

Various growth factors and cytokines, including insulin growth factor (IGF-1) and TNF-α contribute to vascular permeability and retinal angiogenesis. Treatment with octreotide (inhibitor of growth hormone and IGF-1) had shown positive effects on cystoid macular edema, however, no efficacy in the retinopathy was observed [20]. By contrast, pegvisomant, the mutated human growth hormone molecule that blocks the IGF-1 receptor had a favorable effect on microvascular complications [5]. However, extensive trials are necessary to elucidate its role in diabetic retinopathy. In another study, pharmacokinetic and safety of intravitreal eternacept, a soluble TNF-α receptor/Fc construct, was evaluated. Intravitreally delivered etanercept is safe and results in high concentrations in the retina and choroid over a long period of time [21].

Protein kinase C (PKC) inhibitors

Substantial preclinical and clinical data imply that the β-isoform of PKC may have an important role in the development of diabetic microvascular complications in the eyes. The effect of VEGF on retinal vascular permeability seems to be mediated predominantly through β-isoform of PKC. Ruboxistaurin mesilate, an orally administered specific inhibitor of PKC-β 1 and β 2 prevents microvascular complications, blocks neovascularization and is also effective against DME [22]. Further randomized clinical trials are underway to determine its role in the prevention of loss of vision in patients with diabetes. Another compound, PKC-412, is a selective inhibitor of the conventional isoforms of PKC. Orally administered PKC-412 successfully prevents choroid NV in the mouse through the inhibition of multiple PKCs. Studies also showed that inhibition of p38 mitogen-activated protein kinase (MAPK) resulted in inhibition of death of endothelial cells and pericytes, leading to inhibition of degeneration of retinal capillaries [23]. This finding is important, because capillary degeneration is believed to have a major role in the development of retinal NV.

Visual cycle inhibitors

Visual pathway metabolites have shown to be toxic to the retina. Accumulation of these metabolites results in inflammation, increased oxidative damage and destabilization of cell membranes, and often precedes damage and death of photoreceptors and RPE cells. Inhibitor of visual cycle metabolites has been hypothesized to decrease the rate of accumulation of toxic metabolites [24]. Fenretinide, a synthetic retinoid, strongly binds to excess vitamin A, thus decreasing the amount of retinol in the visual cycle and inhibiting the production of toxic metabolites in RPE cells [24]. Trials are underway to determine the efficacy of fenretinide in preventing exudative ARMD [ClinicalTrials.gov: http://clinicaltrials.gov/].

Antiangiogenic steroids

Antiangiogenic therapy would not only stop the progress of CNV but also enable freedom from recurrences. Steroids' broad-spectrum suppression of inflammation often translates into antiangiogenic activity. However, it is possible that neovascular pathways employed by the highly vascular choroid demand more comprehensive strategies compared with that of the retina. A parallel neuroprotective approach might prove highly valuable. Anecortave acetate, an angiostatic steroid, has antiangiogenic activity independent of glucocorticoid action. It rapidly deacetylates and achieves ocular penetration even upon topical application. Its antiangiogenic activity was demonstrated in several neovascular models and is reported to be related to upregulation of plasminogen activator inhibitor expression in the retinas of rats [25].

Complement pathway inhibitors

In the normal eye, the complement system is continuously activated at low levels and enables protection against pathogens without damage to self-tissue and vision loss. Complement proteins are often triggered in inflammatory diseases and there are multiple reports indicating their role in the development of ARMD, DR and autoimmune uveitis. Hypothesis stating that complement inhibition is a relevant therapeutic target in the treatment of various ocular diseases is supported by recent evidence derived from both animal models and patient studies [ClinicalTrials.gov: http://clinicaltrials.gov/; 26]. Compstatin and its derivative, POT-4, are the first molecules of their kind to prevent overactivation of the complement pathway [26]. In animal studies, complement inhibitors have been shown to prevent the inflammatory response that accompanies both the wet and dry forms of macular degeneration. At present, a clinical trial using complement inhibitor is underway and it is possible that, in the near future, complement inhibitor might be used as therapeutic agent in eye clinics [ClinicalTrials.gov: http://clinicaltrials.gov/].

Photosensitizers: photodynamic therapy

Photodynamic therapy (PDT) is a two-phase treatment modality that employs: (i) local or systemic delivery of a photosensitizer, followed by (ii) light irradiation at a specific wavelength appropriate for absorption by the sensitizer. The excited sensitizer results in a cascade of chemical reactions that allows for the selective damage of tissue. Targeting of photosensitizer might be accomplished using liposomes, polymeric micelles or emulsions; however, selectivity is obtained through use of monoclonal antibodies, antibody fragments, or peptides. Furthermore, lipophilic photosensitizers might be taken up selectively by proliferating tissues, such as choroid NV because proliferating tissues have greater low density lipoprotein (LDL) receptor expression. Photosensitizing agents, such as verteporfin [27] and rostaporfin [28] have

expanded the possible therapeutic uses of PDT to ophthalmic applications.

RNAi and gene therapy

RNA interference (RNAi) is a phenomenon in which small interfering RNA (siRNA) interacts with RNA-induced silencing complex (RISC) to promote degradation of the complementary mRNA. Bevasiranib sodium is a first-in-class siRNA designed to turn off or silence the gene that produces VEGF [5]. Subretinal and intravitreal delivery of siRNA dose-dependently inhibited the growth and vascular permeability of laser-induced CNV. It also showed a safe profile and clinical efficacy in the results obtained from the clinical trial for the treatment of wet ARMD and DME [ClinicalTrials.gov: http://clinicaltrials.gov/]. Although this class of medication has no effect on VEGF already produced, it might have a key role as an adjunctive agent with currently available anti-VEGF agents to provide longer-acting blockade of the VEGF pathway.

Exploiting the presence of CD105 (endoglin) in CNV membranes, immunoconjugates of mitomycin C-dextran and anti-CD105 MAb were found to inhibit the proliferation of human umbilical vein endothelial cells [29]. Likewise, a MAb to αvβ3 integrin coupled to mitomycin C-dextran was shown to inhibit laser-induced CNV in rats. Subretinal administration of adenoviral construct expressing the tissue inhibitor of metalloproteinases-3 (TIMP-3) gene was shown to inhibit the progress of laser-induced CNV in rats [29].

Miscellaneous drugs

A recent study proposed that intravitreal administration of purified ovine hyaluronidase (Vitrase®) accelerates the clearance of vitreous hemorrhage from proliferative DR [30]. Another drug, minocycline, inhibits the activation of retinal microglia and prevents early caspase-3 activity and neuronal apoptosis in the retina of diabetic rats [31]. Pycnogenol has shown to improve symptoms of decreased visual acuity from DR in small randomized controlled study on 46 patients [32]. A novel drug, pazopanib, causes regression of neovascularization and was found to be safe in a 28-day safety study [33]. Another novel therapeutic intervention which might reduce the dosing frequency of anti-VEGF is the brachytherapy using strontium-90-β radiation directly over the CNV lesion [34].

Drug delivery systems

Among the diverse approaches that have been taken to develop more efficient treatments to combat vision-threatening diseases, the development of ocular drug delivery systems is noteworthy. The ocular delivery system intends to achieve: (i) new and convenient route of administration for drugs to reach locations that are otherwise difficult to access, (ii) controlled release of the active agent so as to maintain prolonged therapeutic concentration, and (iii) site-specific or even disease-specific targeting. The recent ocular drug delivery systems designed to deliver drugs to the posterior segment of the eye are summarized in Table 2.

Particulate systems

Particulate systems, such as microparticles (1–1000 μm) and nanoparticles (1–1000 nm) have been widely investigated as a topically suspended or local injectable system for treating various ocular ailments. Advantages of particulate system include sustained release of the drug, reduced frequency of administration, ability to overcome ocular barriers, and ability to prevent drug efflux. Furthermore, these systems can also overcome stability issues of drug molecules. Various preclinical studies have established the efficacy of particulate system in delivering drugs and genes to the posterior ocular tissue [1,2]. However, there are conflicting reports regarding suitability of particles size of carrier for posterior delivery. Studies inferred that 200-nm particles are better for retinal delivery compared to 20 nm particles, however, few studies demonstrated internalization of nano-size particles in posterior ocular tissues [1,2]. Besides, selection of polymer, surface charge and surface modification of particles also has a vital role in ocular disposition. Cardillo *et al*. investigate the therapeutic response of a single intravitreal injection of 1 mg triamcinolone acetonide in a polylactic co-glycolic acid (PLGA) microsphere system (RETAAC) in comparison with a single intravitreal injection of 4 mg triamcinolone acetonide for the treatment of DME. RETAAC-treated eyes showed marked decrease of retinal thickness and improved visual acuity [35]. In addition, the RETAAC injections were well tolerated. Finally, the author suggested that RETAAC is a promising approach for the intraocular delivery of drugs [35]. Likewise, Saishin *et al*. successfully used PKC412-loaded microspheres for the treatment of CNV in porcine model [36]. In another study entrapment of antisense oligodeoxynucleotide (AS-ODN) within PLGA microspheres reduces the effective dose of ODN, improves its stability, and decreases toxicity associated with ODN. The limitation associated with this system is that microspheres failed to increase the intracellular penetration of the AS-ODN [37]. To overcome this limitation, Gomes dos Santos *et al*., suggested a 'trojan' delivery system consisting of PLGA microspheres encapsulating nanosized anti-TGFβ2 phosphorothioate AS-ODN complex [38]. This, Trojan, delivery system significantly prolonged the bleb survival (from 28 to 42 days) following trabeculectomy. It was proposed that the intracellular traverse of nanosized AS-ODN complex was responsible for the effect obtained [38]. Another study by Bourges *et al*. depicted that an intravitreal injection of polylactic acid (PLA) nanoparticles resulted in trans-retinal movement, with a preferential localization in the RPE for 4 months [39]. Both these studies highlighted the importance of polymeric nanoparticles to deliver drug and/or gene to the retina and more especially to the RPE cells.

Novel nanoparticles composed of lipids, called solid lipid nanoparticles (SLN) have also been proposed to reach the back of the eye [40]. SLNs are reportedly easier to make and are well tolerated by eyes. In a recent study, the transfection capacity of SLNs in the human RPE established cell line [ARPE-19 (human retinal pigment epithelia cells-19)] was evaluated to elucidate the potential application of this vector in the treatment of retinal diseases [40]. The clathrin-mediated endocytosis of SLN was observed, however, the low division rate of the cell line hampers the entrance of DNA into the nucleus [40]. Additional research will be needed to prove SLNs as clinically useful vectors for posterior ocular delivery.

Emulsified systems

Emulsified systems, such as microemulsions and nanoemulsions, are an attractive alternative to topical ocular drug delivery, because

they can be easily prepared, sterilized, are stable and have ability to dissolve drugs. These systems present added advantages including possibility of prolonged drug release, enhanced corneal permeability and improved drug uptake. There are many microemulsion formulations intended for anterior eye disorders, however, its use for back-of-eye disorders has also been demonstrated [1,2]. Nova63035 (Cortiject®, Novagali Pharma SA) is a dexamethasone lipid emulsion currently under Phase I trials for DME [41]. Nova63035 contains prodrug dexamethasone palmitate, which is activated at the retinal level to efficiently treat DME without steroid-induced side effects. In addition, a single intravitreal injection of emulsion provides sustained release of drug over 6–9 months [41]. Nevertheless, these promising results need to be confirmed with further and larger studies.

Vesicular systems

Lipid vesicles, known as liposomes, are biodegradable and biocompatible systems composed of one or more concentric phospholipid bilayers separated by aqueous compartments. Liposomes have been widely investigated for the treatment of vascular degenerative disorders of the posterior eye [1,2]. Intravitreal administration of liposomes can improve the intravitreal half-life of encapsulated drug owing to sustained drug release and slow vitreous clearance. In a study, Abrishami *et al*. developed nano-sized liposomes of VEGF inhibitor bevacizumab [42]. Researchers attempted to reduce the clearance of nano-sized liposomes by incorporation of cholesterol. The nano-sized liposomes were able to deliver bevacizumab in a controlled manner for more than 6 weeks. The pharmacokinetic data revealed that in comparison to free drug, concentration of liposomal formulation was five-fold higher at 42 days [42].

Another application of liposomes is that they can be used in form of topical eyedrops to deliver therapeutic drug concentrations to the posterior parts of the eye. In a recent study, Hironaka *et al*. demonstrated localization of submicron-sized liposomes (ssLips) composed of L-α-distearoyl phosphatidylcholine in retina after topical administration [43]. It was suggested that the ssLip was delivered to the retina through the non-corneal pathway. The same group using NMDA-induced retinal disease model demonstrated better retinal protection ability of edaravone-loaded ssLip compared with that of free edaravone [44]. The results suggested that ssLip is a promising carrier for edaravone in treating oxidative stress-induced retinal diseases [44].

Liposomal encapsulation offer a viable pharmaceutical alternative for the delivery of plasmids and ODNs to posterior segment of the eye, which otherwise is challenging owing to side effects associated with viral vectors and poor cellular entry of non-viral vectors. Liposomes are phagocytosed by RPE cells thus enabling efficient intracellular delivery of plasmids and ODNs to retinal layers and the RPE cells [45]. The efficacy of liposomes for delivery of ODN has been demonstrated in a work by Bochot *et al*. [46]. The authors reported that intravitreal administration of liposome-encapsulated ODN resulted in significantly higher concentration of ODN into the vitreous and the retina-choroid than the solution and in reduced distribution of ODN to non-target tissues. The authors concluded that intravitreal liposome is a promising approach to deliver intact ODN to the eye in a controlled manner for the treatment of retinal diseases [46].

Liposomes have also been used in combination with a photosensitizer for photodynamic therapy. Photodynamic therapy is a treatment modality that relies on a photosensitizer agent delivered locally or systemically to the selective target tissue and is activated by light. Photodynamic therapy incorporates the use of second-generation (PhotoTargeted) liposomes (PhotoTarget™, RetinaPharma Technologies, FL, USA). The PhotoTargeted liposomes are large (~200 μm), unilamellar vesicles composed of dipalmitoylphosatidylcholine and methyl polyethylene glycol 2000, proportioned to result in a phase transition at 41 °C [47]. Liposomal verteporfin (Visudyne®, Novartis Pharmaceuticals, USA) is a clinically available photodynamic therapy for wet ARMD, whereas liposomal rostaporfin (Photrex®, Miravant Medical Technologies, USA) is currently in Phase III clinical trial for CNV and ARMD [27,28,47].

Another interesting study illustrated the use of photosensitive vectosomes for delivery of ODNs to posterior tissues of the eye [48]. Vectosomes are vesicles made up of VP22, a structural protein of herpes simplex virus. ODNs can be bound to the C-terminal amino acids of the purified VP22 protein, forming spherical particles of 0.3–1 μm in diameter [48]. Vectosomes have been observed in retinal layers, specifically in the cytoplasm of RPE cells 24-hour post-intravitreal injection. Following illumination, vectosomes destabilize and release ODN [48]. Another vesicular innovation entails the use of novel surfactant-based elastic vesicular nanocarriers, spanlastics, for posterior delivery of topically applied drug(s) [49]. The 6-carboxyfluorescein labeled vesicles composed of span 60 and Tween 80 were observed intact in vitreous and intraocular tissues, 2 hour post-topical application. The results suggested that spanlastics can be a breakthrough for effective delivery of agents to posterior eye [49]. Nonetheless, before clinical acceptance of vesicular systems for ocular delivery, limitations associated with their preparation (poor stability, limited drug loading, sterilization problem) and use (intraocular clouding, retinal abnormalities and transient impaired vitreous) need to be overcome.

Miceller systems

Self-assembled micelles, widely assessed as nanocarriers for drug and gene delivery, offer innovative opportunities for drug delivery to posterior eye segment. For instance, micelles can potentially be smaller, stable and can act as a reservoir for photosensitizers intended for PDT. Recently, a polyion complex miceller system that incorporates a dendritic phthalocyanine photosensitizer [50] was tested in experimental CNV rats for its efficacy. Evidence suggested that micelles selectively accumulate to the CNV lesions and resulted in a remarkably efficacious CNV occlusion with minimal unfavorable phototoxicity [50].

In another study, mixed nanomicelles made up of vitamin E TPGS (D-alpha-tocopheryl polyethylene glycol 1000 succinate) and octoxynol-40 (octyl phenol ethoxylate) was evaluated as carrier for delivery of voclosporin (LX214) to posterior segment of rabbit eye (see footnote of Table 2). Pharmacokinetic data revealed significantly higher drug concentrations in retina and choroid after topical administration of nanomicellar formulation. Authors surmised that the nanomicelles traverse conjunctival, scleral pathway and reaches choroid. In choroid micelles reach the Bruch's membrane, fuse with it, and release its therapeutic cargo into the cell (see footnote of Table 2). Thus, it can be accepted that the use of miceller systems for vascular degenerative

disorders of the posterior eye is an attractive area, offering a great possibility to overcome the inherent difficulties associated with ocular drug delivery.

Gelifying systems

Another strategy to obtain an ocular prolonged drug delivery system is to use various gelifying polymers. These formulations can be delivered in a liquid form, as an eye drop or intravitreal injection. After administration the polymer undergoes a phase change to form a semi-solid or solid matrix that releases the encapsulated drug over a prolonged period. The phase change can be stimulated by the change in the ion concentration, temperature, or pH. For posterior ocular application, the biodegradable gel forming solution, such as IBI-20089 (Verisome™, Icon Bioscience, Inc. USA) are already under clinical investigation [51]. The results of the clinical trial in patients with cystoid macular edema confirm the expected safety and efficacy characteristics of the product, along with the controlled-release attributes of the technology [ClinicalTrials.gov: http://clinicaltrials.gov/]. Further, parabulbar and subconjunctival gelifying injections or use of FDA approved fibrin sealant containing the drug for ARMD, DME and DR are attractive alternatives, but their final therapeutic value requires additional investigation.

Chemically modified systems

Peptide for ocular delivery (POD) is a novel and unique peptide that can be conjugated with ocular drugs to improve their delivery to posterior regions of the eye. Upon ocular delivery, POD selectively retained in neural retina and in the RPE, photoreceptor, and ganglion cells [52]. POD with a protein transduction property can compact and deliver plasmid DNA and had shown transgene expression in >50% of human embryonic retinoblasts [52]. It also functions as a bacteriostatic, a useful property for a carrier of molecules to post-mitotic neural ocular tissues.

Dendritic systems

Dendrimers are three-dimensional, hyperbranched, monodisperse molecules having defined molecular weights and host–guest entrapment properties. Dendrimers made up of cationic amines, such as poly-L-lysine, polyamidoamine, and polyethylenimine have proved themselves to be suitable in delivering plasmid DNA, gene or short hairpin RNA (shRNA) to RPE and retinal ganglion cells [53]. Marano *et al*. have designed synthetic lipid–lysine dendrimers in an attempt to improve the delivery of ODN-1, anti-VEGF agent, into the nuclei of retinal cells [53]. The authors have experimentally proved that dendrimer and/or ODN-1 complex significantly suppressed VEGF expression [53]. Furthermore, fluorescein angiography demonstrated that dendrimer and/or ODN-1 complex persisted in the retinal tissue for up to 2 months and reduced the severity of laser-mediated CNV [53]. Ophthalmological examinations and immunohistochemistry indicated that the complexes were well tolerated *in vivo*. It could be surmised that dendrimers might be used as biocompatible carriers for posterior ocular gene therapy.

Therapeutic devices

Implants

Advances in technology and surgical techniques have led to the development of ocular implants (Table 3), which can overcome many of the limitations of other therapeutic approaches. Devices present several advantages that outweigh the inconvenience of implantation. The advantages include: (i) bypassing the blood–retinal barrier associated with systemic therapy, (ii) delivery of drug directly to target site, (iii) prolonged drug delivery, (iv) fewer side effects compared with systemic dosages and intravitreal injections [54,55]. The structures of polymeric devices for sustained release are classified as non-biodegradable, such as Iluvien® (Alimera Sciences, GA, USA), I-vation™ (SurModic, MN, USA) and thermally-responsive gel implant and biodegradable such as Ozurdex® (Allergan, CA, USA) and LX212 (Isotechnika, Inc.) [54,55]. The drug encapsulated in the implant, polymer used for its preparation and the developmental stage of the implant is described in Table 3. Biodegradable implants do not require removal, they increase the half-life of the drug, can be fashioned into many shapes and enable flexibility in dose and treatment from short duration (weeks) to longer duration (months to a year). Non-biodegradable implants have the advantage of controlled and prolonged release of a drug and the disadvantage of replacement and/or removal when the drug has depleted.

Drug penetration enhancement devices

Microneedles

Microneedles are drug-coated solid or hollow needles that provide a minimally invasive method to inject particles into the suprachoroidal space for delivery to the back of the eye [56]. Following administration, coated molecules dissolve rapidly, and subsequently, microneedles are removed from the tissue. Jiang *et al*. evaluated the use of this technology to deliver small model drug and micro- and nanoparticles using whole rabbit, pig and human cadaver eyes [57]. The study showed that an individual needle was able to deliver up to 35 μL of a fluid into the sclera, forming an intrascleral drug depot [57]. Results showed that needle lengths of 800–1000 μm and applied pressures of 250–300 kPa provided most unswerving delivery. Posterior segment access technology (iCath™ PSAT, iScience Interventional, USA) is another interventional ophthalmology procedure that facilitates the delivery of sterile injectables to the back of the eye. The technology involves small pars plana incision to expose the suprachoroidal or subretinal space, insertion of special microcatheter (iTrack™) to the specific target area and delivery of any sterile ophthalmic solution. The specialized microcatheter also enables traceability through illuminated tip [58].

Iontophoresis

Iontophoresis is a non-invasive technique in which a small electric current is applied to enhance ionized drug penetration into tissue [59]. Successful iontophoretic delivery of anti-NOSII ODNs in patients with DR; and triamcinolone, anecortave and anti-VEGF in the treatment of ARMD has been demonstrated. OcuPhor/pegaptanib is an example of a commercially available iontophoretic unit [59].

Ultrasound

Ultrasound is a physical approach in which sonoporation effect is created with the help of microbubbles to potentiate pore formation in cell or polymeric membranes [60]. *In vitro* and *in vivo* experiments had shown that ultrasound induce drug release from

biodegradable in addition to non-biodegradable matrix [60]. Enhanced drug delivery across the sclera is anticipated with the use of polymeric microbubbles as carriers and ultrasound as the stimulus, enabling more successful treatment strategies for macular diseases [60].

Visual prosthetic devices

Implantable miniature telescope

Recently, an implantable miniature telescope (IMT, CentraSight®) that fits directly into the eye has received US FDA approval for the treatment of ARMD [61]. The IMT is surgically implanted into the back of the eye in the lens capsule and acts to expand an incoming image onto the peripheral parts of the retina that are typically unaffected by ARMD. Multicenter clinical data involving 217 patients at 1 year revealed that 90.1% of implanted patients achieved a 2-line or greater gain in visual acuity and 75% improved their level of vision [61].

Retinal implants

Optical nerves could be stimulated using a mild electrical charge, applied using a self-contained, surgically implanted device. Based on this concept the artificial retinal implants an electrode array atop the degenerated retina to stimulate the undamaged nerve ganglia lying underneath [62]. Image information is wirelessly transmitted to it from a video camera mounted on a pair of eyeglasses, which capture the image. The artificial retina fabricated on silicon wafers using polymer-based micro-fabrication techniques has been implanted to patients with blinding disorders such as wet ARMD or retinitis pigmentosa [62].

Miscellaneous devices

Encapsulated cell technology

Encapsulated cell technology (ECT) is a cell-based device that can be used to deliver therapeutic agents, even large-molecular-weight compounds, to the eye [63]. ECT developed by Neurotech Pharmaceuticals, Inc. (Lincoln, RI, USA) contains human RPE cells [ARPE-19, genetically modified to secrete recombinant human ciliary neurotropic factor (CNTF)] packaged in a hollow tube of semipermeable membrane [63]. The semi-permeable membrane enables the outward diffusion of CNTF and the inward diffusion of nutrients necessary to support the cell survival while preventing immune-cell entry. The device is surgically implanted in the vitreous through a tiny scleral incision anchored through a titanium loop at one end of the device. The Phase I clinical trial results were successful for retinal pigmentation and the device was well tolerated for 6 months post-implantation [ClinicalTrials.gov: http://clinicaltrials.gov/]. Phase II study for patients with dry ARMD are ongoing. Furthermore, Phase I trials for ECT releasing a VEGF antagonist for treatment of wet ARMD are ongoing [ClinicalTrials.gov: http://clinicaltrials.gov/].

Photonic crystals

Photonic crystals are devices for treating intraocular diseases wherein porous film impregnated with a drug are sized and configured to permit its intraocular injection as a particle [64]. A rugate structure was electrochemically etched into a highly doped p-type silicon substrate to create a porous silicon film that was ultrasonically fractured into particles. The porous silicon photonic crystals showed good biocompatibility, no toxicity (for >4 months) and might be used as controlled drug delivery system to treat chronic vitreoretinal diseases [64].

Concluding remarks

A broad range of strategies for treatment of vascular degenerative disorders of the posterior eye is currently being investigated. As new pharmacotherapies continue to be developed for posterior segment disorders, novel technologies for sustained intraocular delivery of drugs will be required, with preference for non-invasive methods. Ophthalmology is currently rife with many exciting technologies for improving drug delivery for potential clinical application in cases of ocular vascular degenerative diseases, such as ARMD, DR and DME. For vision-threatening disorders, devices and implants such as those discussed above presents an exciting new avenue to help patients when drugs have not markedly improved vision. Motivated by this success, the field is poised to produce more advanced therapeutics that can track pathophysiology and trigger drug delivery at target site to prevent vascular degeneration. Much of this progress has been stimulated by recent technological advances at a variety of temporal and spatial levels, including monoclonal antibodies, RNAi and gene therapies. The initial results with these technologies are exhilarating, but considerable development and controlled clinical trials will be required before these treatments earn a place in our standard of clinical care. Apparently, no single technology and/or device will be sufficient to meet the range of needs, and a combination of approaches with multidisciplinary integration is required to optimize delivery to the eye.

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