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- Screening for drugs that prevent and cause hearing loss
- Delivery of anti-angiogenic therapies for retinal disease
- Treatment strategies for age-related optic nerve disease



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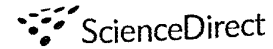
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Delivery of anti-angiogenic molecular therapies for retinal disease

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Angiogenic diseases of the retina are the leading cause of blindness in the developed world. The development of anti-angiogenic molecular therapies has transformed the prognosis of these conditions, especially age-related macular degeneration. With these new treatments comes the new challenge of delivering an effective dosage to the retina, over a prolonged period of time and in a safe and cost-effective manner. A range of new anti-angiogenics are on the horizon, offering new and varied modes of drug delivery. In addition, a range of new sustained-release drug delivery technologies are being developed.

Retinopathy of prematurity (ROP), diabetic retinopathy (DR) and age-related macular degeneration (AMD) are three different conditions that broadly affect three different age groups. In the developed world, ROP, DR and AMD are the largest causes of blindness in infants, adults of working age and the elderly, respectively [1–3]. One feature they all have in common is the pathological proliferation of new blood vessels (neovascularization). In DR and ROP, these blood vessels originate from the retina, bleed into the vitreous and, subsequently, cause fibrosis, tractional retinal detachment and visual loss. In AMD, these blood vessels normally originate from the choroid and invade the overlying retina. Subsequent bleeding and exudation can lead to scarring and permanent loss of central vision. The neovascularization in all three conditions is driven by an angiogenic cascade, the trigger of which is believed to be relative hypoxia and oxidative stress. Vascular endothelial growth factor (VEGF-A) is a key component of this cascade but is by no means the only mediator of angiogenesis. In addition to promoting neovascularization, angiogenic factors also promote increased vascular permeability. This can lead to sight-threatening oedema in the most sensitive part of the retina, the macula. This is a complication seen in both DR and AMD, as well as in retinal vein occlusions (RVOs). Molecular treatments aimed at halting or reversing angiogenesis (anti-angiogenics) can be used to treat both neovascularization and macular oedema.

Research into the field of ocular angiogenesis has increased rapidly, with a variety of treatments coming to clinical trial. From 2001 to 2004, 25 clinical trials involving retinal anti-angiogenic molecular therapies were registered on the ClinicalTrials.gov registry (<http://clinicaltrials.gov>). During the following four-year period (2005–2008), 273 clinical trials were registered, representing a more than tenfold increase (Figure 1).

The resultant new therapies targeting the VEGF-A molecule have produced a paradigm shift in the management of neovascular AMD. They have not only improved the prognosis dramatically, to a degree not seen before, but also altered patient expectations, clinical workload and the clinical costing of disease management. In addition to patient benefit, the success of the first back-of-the-eye pharmacotherapies has also triggered a massive increase in capital investment and interest from larger pharmaceutical companies. Whereas the turn of the millennium saw only a handful of biotech start-ups – such as the developer of the first anti-VEGF for ocular use, Eyetech – today there at least 30 or 40 small biotechs fuelling drug development for blinding retinal disease.

With the design of the new battery of drugs comes the question of how to deliver them to the target tissue. Delivering drugs to the retina is problematic, often resorting to invasive means such as repeated intraocular injections [4]. Newer and potentially safer methods are needed. This need has never been greater, owing to the rapid rise in new molecular entities becoming available for retinal disease.

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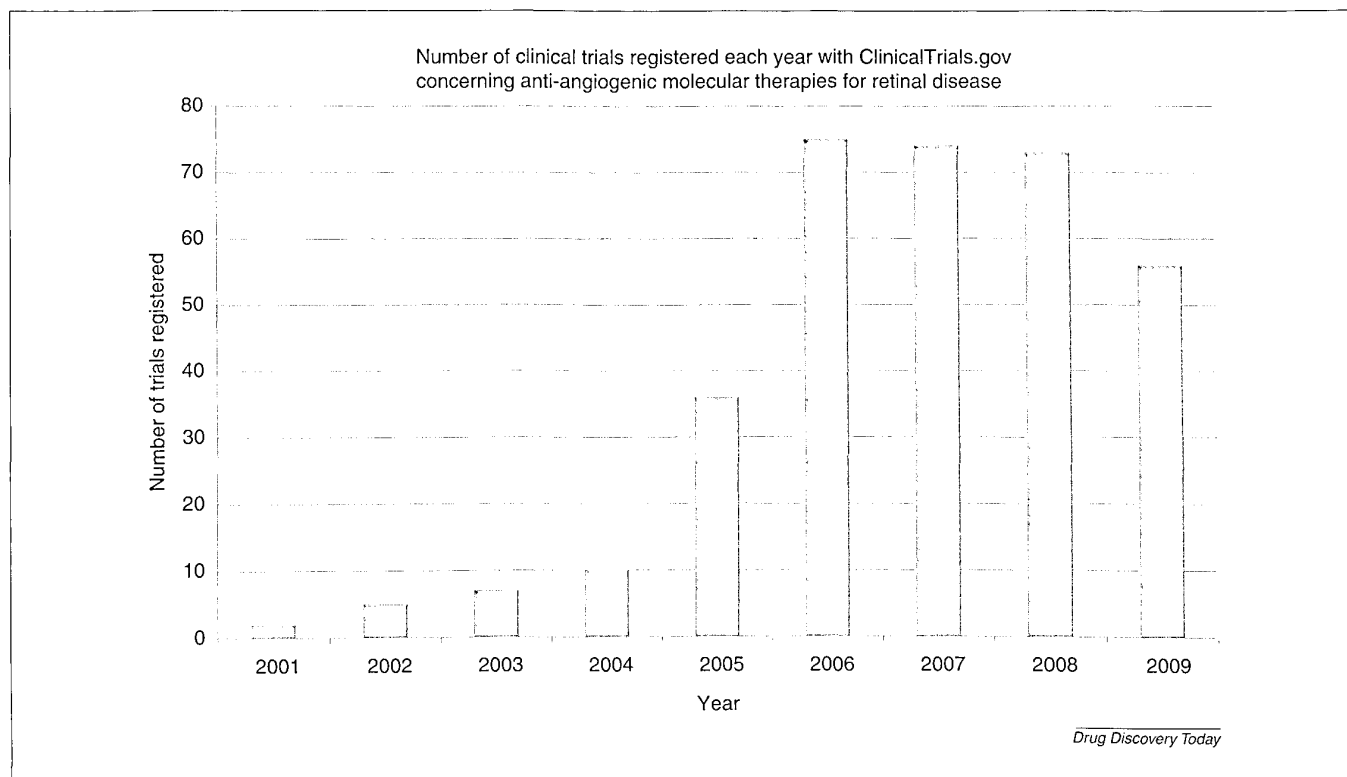


FIGURE 1

Graph displaying the number of clinical trials registered with the ClinicalTrials.gov registry (<http://clinicaltrials.gov>) each year between 2001 and 2009. Each entry concerns the application of an anti-angiogenic molecular therapy in the treatment of either neovascular AMD, DR, RVO or ROP.

Scope

This paper is divided into two parts. The first part will briefly highlight current and potential molecular therapies for the treatment of conditions such as AMD, DR, RVO and ROP. Only therapies currently undergoing development in phase I–IV human clinical trials will be covered. A detailed discussion of individual treatments is beyond the scope of the paper. The second part will be the main focus of the review. Molecular therapies are only useful if they can reach the target tissue; therefore, we will discuss current and potential methods for the delivery of anti-angiogenic molecular therapies in the treatment of retinal disease.

Current and potential anti-angiogenic molecular therapies

So far, only two anti-angiogenic drugs have received Food and Drug Administration (FDA) and European Medicines Agency approval for the treatment of neovascular AMD. To date, no molecular therapies have received FDA approval for the treatment of diabetic macular oedema (DMO), proliferative diabetic retinopathy (PDR) or ROP. Ozurdex (dexamethasone) has received FDA approval for the treatment of RVO-associated macular oedema. Although it is not formally considered to be an anti-angiogenic agent, it does have some intrinsic anti-angiogenic activity [5]. The main reason for including it, however, is that it is the first FDA-approved biodegradable sustained-release device for the treatment of angiogenic retinal disease. Numerous compounds are undergoing phase I–III clinical trials (Table 1), and in the meantime, many compounds are often used off-label. Here, we briefly discuss compounds that have

received FDA approval and highlight certain compounds in common off-label use or in the very latest stages of development.

FDA-approved therapies

Pegaptanib (Macugen; Eyetech/Pfizer, Inc.) was the first FDA-approved anti-angiogenic treatment for neovascular AMD [6]. It is a 28-base PEGylated aptamer, which when folded correctly has a three-dimensional conformational shape that potently (dissociation constant ~ 50 pM) and specifically binds to the major heparin-binding isoforms of VEGF-A, blocking their action [7]. The aptamer's nucleotides have been modified to make it more resistant to degradation by endogenous endonucleases and exonucleases. The addition of polyethylene glycol (PEG) moieties, or PEGylation, increases the molecular weight and increases the half-life in the vitreous (Macugen Information Sheet, http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021756s006,s0071bl.pdf). Both of these modifications increase the biological half-life of the drug [8].

Pegaptanib was designed to be delivered by intravitreal injection every six weeks for the treatment of neovascular AMD, although its use for this condition has been largely superseded by ranibizumab [6]. Pegaptanib is perceived to have a more robust effect in DMO, however, and is in phase III clinical testing in Europe.

Ranibizumab (Lucentis; Genentech/Novartis/Roche, Inc.) was the second FDA-approved anti-angiogenic treatment for neovascular AMD. Unlike pegaptanib (which is RNA based), ranibizumab is a humanized Fab fragment of a mouse monoclonal antibody with high affinity for all isoforms of VEGF-A (unlike pegaptanib, which only binds VEGF165 and VEGF189).

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TABLE 1

Anti-angiogenic molecular therapies that are currently under clinical development^a.

Disease	Phase	Mode of action	Name
nAMD	FDA✓	VEGF inhibitor	Ranibizumab, pegaptanib
	P III	VEGF inhibitor	Bevacizumab, VEGF trap
	P II	Tyrosine kinase inhibitor	AL-39324, pazopanib, TG100801, vatalanib
		mTOR inhibitor	Everolimus, sirolimus
		nAChR inhibitor	Mecamylamine
	P I	RTP801 inhibitor	PF-4523655
		Corticosteroid	Fluocinolone, triamcinolone
		NSAID	Brofenac
		VEGF inhibitor (viral delivery)	AAV2-sFLT01
		PEDF inhibitor (viral delivery)	AdGVPEDF.11D
		PDGF inhibitor	E10030
		α5β1 integrin receptor inhibitor	JSM6427, volociximab
		Complement inhibitor	ARC1905, POT-4
		C-raf kinase inhibitor	iCo-007
		S1P inhibitor	iSONEP
TORC1/TORC2 inhibitor	Palomid 529		
TNFα inhibitor	Adalimumab, infliximab		
Anti VEGF receptor vaccine	VEGF R1 & R2		
PDR	P III	VEGF inhibitor	Bevacizumab, ranibizumab
		PKCβ inhibitor	Ruboxistaurin
	P II	Somatostatin analogue	Octreotide
DMO	P III	Corticosteroid	Triamcinolone
		PKCβ inhibitor	Doxycycline
		Somatostatin analogue	
	P II	VEGF inhibitor	Ranibizumab, pegaptanib, bevacizumab
		mTOR inhibitor	Fluocinolone, triamcinolone, dexamethasone
		nAChR inhibitor	Ruboxistaurin
		RTP801 inhibitor	Octreotide
		TNFα inhibitor	VEGF trap
		NSAID	Sirolimus
		NSAID	Mecamylamine
P I	TNFα inhibitor	PF-4523655	
NSAID	Infliximab		
VEGF inhibitor	Nepafenac		
RVO	FDA✓	Corticosteroid	Dexamethasone
		VEGF inhibitor	Bevacizumab, ranibizumab, VEGF Trap
	P III	Corticosteroid	Triamcinolone
	P II	VEGF inhibitor	Pegaptanib
		Corticosteroid	Fluocinolone
P I	Plasma kallikrein inhibitor	Ecallantide	
ROP	P II	VEGF inhibitor	Bevacizumab

^aTherapies are grouped according to the latest phase of clinical development (FDA approval, phase I-III clinical trial) and their mode of action. Information is courtesy of the ClinicalTrials.gov registry (<http://clinicaltrials.gov>) and was updated on 1 February 2010. To the best of the authors' knowledge, all the therapies described are still under development; however, development of certain drugs might have been cancelled without public knowledge.

Abbreviations: DMO, diabetic macular oedema; FDA✓, Food and Drug Administration approved; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; nAChR, nicotinic acetylcholine receptor; nAMD, neovascular age-related macular degeneration; NSAID, non-steroidal anti-inflammatory drug; PDGF, platelet-derived growth factor; PDR, proliferative diabetic retinopathy; PEDF, pigment epithelium-derived factor; PKCβ, protein kinase C beta; P III, phase III; ROP, retinopathy of prematurity; RVO, retinal vein occlusion; S1P, sphingosine-1-phosphate; TNFα, tumour necrosis factor alpha; VEGF, vascular endothelial growth factor.

Ranibizumab was designed to be delivered by intravitreal injection every four weeks [9,10], although current practice is to administer three doses at four-week intervals, then to administer according to clinical need [11]. Importantly, it was the first treatment for neovascular AMD that resulted in a statistically significant improvement in visual acuity in all lesion subtypes [9,10]. Although no head-to-head trial was performed

against pegaptanib, better perceived clinical outcomes with ranibizumab make blockage of all VEGF-A isoforms the current strategy of choice for AMD. Ranibizumab is also in clinical testing for PDR, DMO and RVOs. Results seem promising in the short term; however, in the long term, it needs to show benefit over and above that of laser therapy. Although laser therapy is potentially destructive, side-effects of long-term

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