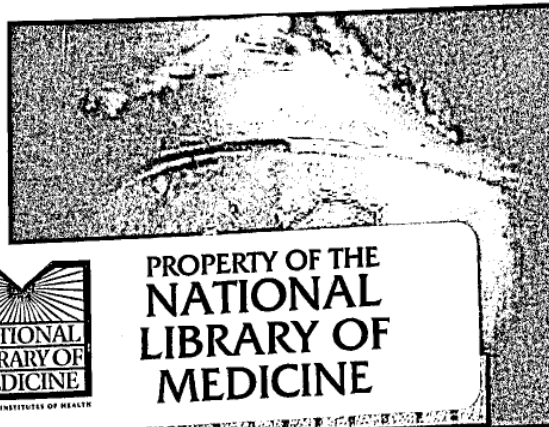
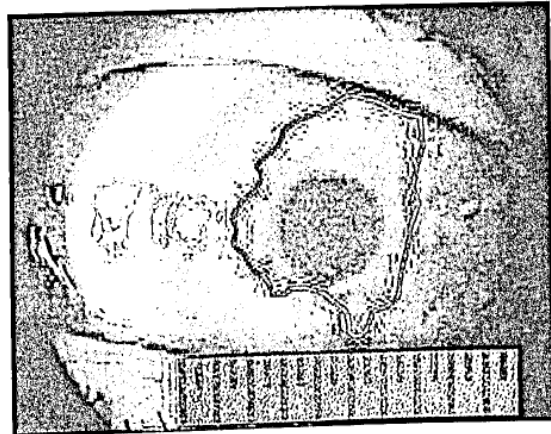
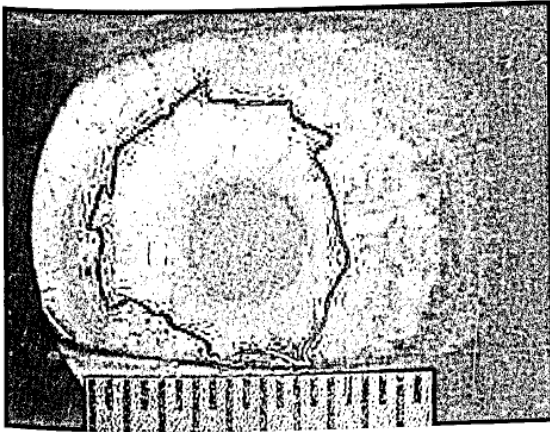


Ophthalmologica. Journal
v. 223, no. 6 (2009)
General Collection
W1 OP337
2009-12-01 11:06:01

Ophthalmologica



PROPERTY OF THE
NATIONAL
LIBRARY OF
MEDICINE

S. Karger
Medical and Information Science
Basel · Freiburg · Fribourg
London · New York ·
Bangalore · Bangkok · Shanghai ·
Singapore · Sydney



This material was copied
at the NLM and may be
Subject US Copyright Laws

Samsung v. Regeneron
IPR2023-00442
U.S. Pat. 10,130,681
Exhibit 2363

ISSN Print Edition: 0030-3755
ISSN Online Edition: 1423-0267

Journal Homepage: www.karger.com/oph

Publication Data: 'Ophthalmologica' is published 6 times a year. Volume 223 with 6 issues appears in 2009.

Copyright: © 2009 S. Karger AG, Basel (Switzerland). All rights reserved. No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher or, in the case of photocopying, direct payment of a specified fee to the Copyright Clearance Center.

Disclaimer: The statements, opinions and data contained in this publication are solely those of the individual authors and contributors and not of the publisher and the editor(s). The appearance of advertisements in the journal is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality or safety. The publisher and the editor(s) disclaim responsibility for any injury to persons or property resulting from any ideas, methods, instructions or products referred to in the content or advertisements.

Subscription Rates: Subscriptions run for a full calendar year. Prices are given per year.

Personal subscription:

Print or Online	Print+Online combined
CHF 787.50	CHF 832.50
EUR 562.50	EUR 594.50
USD 750.00	USD 793.00
postage and handling (added to print and print+online)	
CHF 37.80 Europe, CHF 56.70 Overseas	
EUR 27.-	
USD 53.70	

Institutional subscription:

Print or Online	Print+Online combined
CHF 1575.-	CHF 1733.-
EUR 1125.-	EUR 1238.-
USD 1500.00	USD 1650.00
postage and handling (added to print and print+online)	
CHF 47.40 Europe, CHF 70.80 Overseas	
EUR 33.60	
USD 67.20	

Airmail surcharge: CHF 48.- / USD 45.60

Discount subscription prices:

- Association for Research and Vision in Ophthalmology (ARVO)
- Dutch Ophthalmological Society
- EVER
- Schweizerische Ophthalmologische Gesellschaft
- and other related societies

Back Volumes and Single Issues: Information on availability and prices of single print issues and print or electronic back volumes can be obtained from Customer Service at service@karger.ch.

Bibliographic Indices: This journal is regularly listed in bibliographic services, including *Current Contents** and PubMed/MEDLINE.

Photocopying: This journal has been registered with the Copyright Clearance Center (CCC), as indicated by the code appearing on the first page of each article. For readers in the US, this code signals consent for copying of articles for personal or internal use, or for the personal or internal use of specific clients, provided that the stated fee is paid per copy directly to Copyright Clearance Center Inc.

222 Rosewood Drive
Danvers, MA 01923 (USA)

A copy of the first page of the article must accompany payment. Consent does not extend to copying for general distribution, for promotion, for creating new works, or for resale. In these cases, specific written permission must be obtained from the copyright owner, S. Karger AG, P.O. Box CH-4009 Basel (Switzerland).

Subscription Orders:

Orders can be placed at agencies, bookstores, directly with the Publisher

S. Karger AG
Medical and Scientific Publishers
P.O. Box
CH-4009 Basel
Switzerland
(for courier services only:
Allschwilerstrasse 10
CH-4055 Basel)
Tel. +41 61 306 11 11
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

or further Karger offices
or representatives:

France:
Librairie Medi-Sciences Sarl
36, bd de Latour-Maubourg
75007 Paris
France
Tél. +33 (0) 1 45 51 42 58
Fax +33 (0) 1 45 56 07 80
E-Mail librairie@medi-sciences.fr
www.medi-sciences.fr

Germany:
S. Karger GmbH
Postfach
79095 Freiburg
Deutschland
(Hausadresse: Lörracher Strasse 16A
79115 Freiburg)
Tel. +49 761 45 20 70
Fax +49 761 45 20 714
E-Mail information@karger.de
www.karger.de

India, Bangladesh, Sri Lanka:
Panther Publishers Private Ltd.
33, First Main
Koramangala First Block
Bangalore 560 034
India
Tel. +91 80 25505 836
Tel. +91 80 25505 837
Fax +91 80 25505 981
E-Mail panther_publishers@vsnl.com
www.pantherpublishers.com

Japan:
Karger Japan, Inc.
Yushima 5 Bld. 3F
4-2-3, Yushima, Bunkyo-ku
Tokyo 113-0034
Japan
Tel. +81 3 3815 1800
Fax +81 3 3815 1802
E-Mail publisher@karger.jp

China, Taiwan and Malaysia:
Karger China
Suite 409, Apollo Building
1440 Central Yan An Road
Shanghai 200040
China
Tel. +86-21-6133 1861
Fax +86-21-6133 1862
E-Mail karger.ray@gmail.com

South America and Central America:
Cranbury International LLC
7 Clarendon Ave., Suite 2
Montpelier, VT 05602
USA
Tel. +1 802 223 6565
Fax +1 802 223 6824
E-Mail eatkin@cranburyinternational.com
www.cranburyinternational.com

United Kingdom, Ireland:
S. Karger AG
c/o London Liaison Office
4 Rickett Street
London SW6 1RU
United Kingdom
Tel. +44 (0) 20 7386 0500
Fax +44 (0) 20 7610 3337
E-Mail uk@karger.ch

USA:
S. Karger Publishers, Inc.
26 West Avon Road
P.O. Box 529
Unionville, CT 06085
USA
Toll free: +1 800 828 5479
Tel. +1 860 675-7834
Fax +1 860 675-7302
E-Mail karger@snet.net

Change of Address:

Both old and new address should be sent to the subscription source.

KARGER

© 2009 S. Karger AG, Basel

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

The Journal Home Page is available at:
www.karger.com/oph

This material was copied
at the NLM and may be
Subject US Copyright Laws

Emerging Pharmacologic Therapies for Wet Age-Related Macular Degeneration

Zhang Ni^{a–c} Peng Hui^{a–c}

^aDepartment of Ophthalmology, First Affiliated Hospital of Chongqing Medical University, ^bChongqing Key Laboratory of Ophthalmology, ^cChongqing Eye Institute, Chongqing, PR China

Key Words

Age-related macular degeneration · Vascular epithelial growth factor · Choroidal neovascularization · Antiangiogenesis · Anti-inflammatory · Target therapy

Abstract

As researchers and clinicians are beginning to understand that wet age-related macular degeneration (AMD) is more than simply a vascular disease that includes angiogenic, vascular and inflammatory components, they are exploring new agents with different mechanisms of action addressing multiple targets in this complex pathophysiology. Some of them are already available in human trials or even approved vascular epithelial growth factor (VEGF) blockers such as Macugen, Lucentis, Avastin, VEGF Trap-Eye and Cand5; VEGF receptor blockers such as TG100801, vatalanib, pazopanib, Sirna-027 and a vaccine approach; inflammation inhibitors and immunosuppressants such as Retaane, Kenalog, ARC1905, POT-4, OT-551. The last group is mixed, containing agents such as Zybrestat, AdPEGF, Sirolimus, JSM6427, ATG003, E10030. This article reviews these currently emerging agents and briefly discusses the next step for the treatment of wet AMD.

Copyright © 2009 S. Karger AG, Basel

Introduction

One of the most common and poorly treated back-of-the-eye diseases is age-related macular degeneration (AMD). It is the leading cause of blindness in the developed countries for people over 50 years [1]. The most severe form, wet AMD, accounts for 10% of cases, but 90% of the severe vision loss is associated with all AMD [2]. It is complicated by choroidal neovascularization (CNV), during which the choroidal new vessels invade the sub-retinal space through Bruch's membrane to form fibrovascular proliferative tissue containing vascular endothelial cells, fibroblasts, retinal pigment epithelial cells, and various inflammatory cells [3]. Retinal neurons are irreversibly damaged by lipid leakage and bleeding from the immature new vessels in the CNV tissue. Although molecular and cellular mechanisms are not fully elucidated, various efficacious target therapies are emerging and successful in human trials.

Against VEGF

Out of a panel of recently discovered and promising therapeutic targets, the most efficacious CNV treatment has relied on the vascular endothelial growth factor (VEGF). It is a subfamily of growth factors including members of VEGF-A, VEGF-B, VEGF-C, VEGF-D,

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2009 S. Karger AG, Basel
0030-3755/09/2236-0401\$26.00/0

Accessible online at:
www.karger.com/oph

Peng Hui
Department of Ophthalmology
First Affiliated Hospital of Chongqing Medical University
Chongqing 400016 (PR China)
Tel. +86 23 8901 3056, E-Mail pengh9@yahoo.com.cn

VEGF-E and placenta growth factor [4]. They are important signalling proteins involved in vasculogenesis, angiogenesis and vascular permeability. VEGF-A is the most important member which is up-regulated by hypoxia. It has been shown to stimulate endothelial cell mitogenesis and cell migration. It is also a vasodilator that increases microvascular permeability. There are multiple isoforms of VEGF-A including VEGF-A₁₂₁, VEGF-A₁₄₅, VEGF-A₁₄₈, VEGF-A₁₆₂, VEGF-A₁₆₅, VEGF-A₁₈₃, VEGF-A₁₈₉ and VEGF-A₂₀₆ (classified by amino acid number) [5], of which VEGF-A₁₂₁ and VEGF-A₁₆₅ are the most abundantly expressed isoforms in the retina [6].

Macugen (Pegaptanib Sodium 0.3 mg; Eyetech/Pfizer)

Pegaptanib [7] is a 28-base ribonucleic acid aptamer, covalently linked to two branched 20-kDa polyethylene glycol moieties to increase residency time within the eye following intravitreal injection (IVT). It selectively binds to the VEGF-A₁₆₅, which is the most potent and prevalent isoform expressed during pathologic neovascularization [8]. Macugen was approved by the Food and Drug Administration (FDA) in December 2004 for the treatment of wet AMD [9], becoming the first pharmacological agent approved for ocular angiogenesis.

Its efficacy and safety were confirmed by a pivotal phase III trial VISION [7], in which 1,208 patients with all CNV subtypes secondary to AMD received Macugen IVT or sham injections every 6 weeks for 48 weeks. The results demonstrated that 70% of Macugen-treated patients lost fewer than 15 letters compared with 55% of sham-treated patients at 12 months ($p < 0.001$). Among the adverse events that occurred, endophthalmitis (1.3%), traumatic injury to the lens (0.7%), and retinal detachment (0.6%) were the most serious that have been reported and required vigilance.

Lucentis (Ranibizumab 0.5 mg; Genentech/Novartis Ophthalmics)

Ranibizumab is a 48-kDa humanized monoclonal antibody fragment that neutralizes and inhibits all known forms of VEGF-A, including their protein degradation products [10]. It was approved by FDA in June 2006 for the treatment of wet AMD [11].

In a pivotal clinical trial, MARINA [10], 716 patients with minimal classic or occult CNV secondary to AMD were treated with a 0.3- or 0.5-mg dose of Lucentis IVT or sham injections monthly. The results demonstrated that 94.5 and 94.6% of Lucentis-treated patients lost fewer than 15 letters (0.3 and 0.5 mg, respectively), compared with 62% of sham-treated patients after 12 months. What

is more, the Lucentis-treated patients gained an average of 6.5 and 7.2 letters of visual acuity (VA), whereas the sham-treated patients lost an average of 10.4 letters ($p < 0.001$ for each comparison).

The results of another pivotal clinical trial, ANCHOR [12], were very similar; 423 patients with predominantly classic CNV secondary to AMD were treated with a 0.3- or 0.5-mg dose of Lucentis IVT monthly and sham photodynamic therapy (PDT) or sham injection and PDT every 3 months. 94.3 and 96.4% of Lucentis-treated patients lost fewer than 15 letters compared with 64.3% of PDT-treated patients. Mean VA increased by 8.5 letters and 11.3 letters in the Lucentis-treated patients compared with a decrease of 9.5 letters in the PDT-treated patients ($p < 0.001$ for each comparison).

These two trials, as well as the other key trials, PIER [13], FOCUS [14] and SAILOR [15], suggested that the treatment of Lucentis IVT is well tolerated and efficacious. More recently, the study HORIZON [16] supported the long-term safety of Lucentis. It is a phase III extension study allowing patients completing the trials MARINA, ANCHOR and FOCUS to continue to receive Lucentis less frequent 'as needed', but patients on average had a 5.3-letter decline in VA with 3–4 injections over the entire year, suggesting that monthly dosing may be better in some patients.

Avastin (Bevacizumab, 1.25 mg; Genentech/Novartis Ophthalmics)

Avastin [17] is a 149-kDa humanized full-length monoclonal antibody which is approximately 3 times larger than Lucentis and is capable of inhibiting all isoforms of VEGF-A. It was FDA approved in February 2004 for the treatment of metastatic colon cancer, but was not yet originally approved for ocular disease [18]. In spite of this, as there were several uncontrolled studies [19, 20] on wet AMD showing that Avastin IVT may be efficacious and safe, also at much lower cost than Lucentis, it is used as off-label drug to treat patients with wet AMD and macular edema.

Recently, the result of a small study [21] comparing Lucentis and Avastin monotherapy in 46 patients for the treatment of wet AMD has shown that Lucentis has a slight advantage over Avastin. But due to the small number of patients and the retrospective nature of this analysis, conclusions should be made with caution.

What is desperately needed is a larger head-to-head comparison of the efficacy and adverse consequences between Avastin and Lucentis or Macugen. A randomized phase II trial, MAAM [22], comparing Avastin and Ma-

cugen IVT in 60 patients with wet AMD is under way and will soon be finished. Another ongoing clinical trial is CATT [23]. It is a phase III trial comparing Avastin and Lucentis IVT in 1,209 patient with wet AMD. If the trials demonstrate equivalence between these two drugs this would allow more affordable and widespread use of anti-VEGF therapy.

VEGF Trap-Eye (Regeneron)

VEGF Trap-Eye [24] is a 110-kDa recombinant protein with the binding portions of VEGF receptors (VEGFR) VEGFR-1 and VEGFR-2 fused to the Fc region of human IgG that binds all forms of VEGF-A, placenta growth factor and VEGF-B with a very high affinity (about 140 times that of Lucentis).

In a phase I trial (CLEAR) AMD-1 was administered intravenously for the treatment of CNV. The investigators found a dose-dependent decrease in the central retinal thickness, as well as a dose-dependent increase in systemic blood pressure with a maximum tolerated dose of 1 mg/kg. Since then, systemic VEGF Trap-Eye was halted, only IVT is being evaluated for ocular disease [25].

Recently, the result of CLEAR IT-2 [26] was released. In this phase II trial, patients were initially treated with either fixed monthly or quarterly doses for 12 weeks and then continued to receive treatment for another 40 weeks on a PRN (as needed) dosing schedule. It demonstrated up to 9 mean letters gained in VA and up to 161 μm reduction in central retinal thickness at 52 weeks ($p < 0.0001$). The patients received on average only two additional injections over 40 weeks after a 12-week fixed dosing period. It was generally well tolerated, and there were no drug-related serious adverse events.

After these positive initial results, it is reasonable to take VEGF Trap-Eye into phase III clinical trials VIEW1 [27] and VIEW2 [28], which are ongoing to compare with Lucentis in 2,400 patients with wet AMD in the US, Europe, Asia, Japan, Australia and South America. These global clinical programs will provide additional data to further evaluate the efficacy and safety of VEGF Trap-Eye.

Cand5 (Bevasiranib; OPKO Health)

Cand5 [29] is a small interfering mRNA working by shutting down the mRNA specific to the genes that encode for the production of VEGF-A; it therefore inhibits CNV, but has no effect on residual VEGF in the eye.

In a phase I dose-escalation study [30] in 15 patients with wet AMD, Cand5 was found to be safe and well tolerated at doses up to 3.0 mg over a 6-week period, and the

investigators concluded that Cand5 did not escape the eye to the systemic circulation.

During a phase II randomized study of trial CARE [29], 129 patients with classic or active minimally classic AMD, including those patients who had failed previous treatments, received multiple Cand5 IVT of 3 doses over 6 months. The results showed that the average time to rescue (need for another injection) in patients given the lowest dose (0.2 mg) was 153 days [31]. Patients who received higher doses (1.5 and 3 mg) had an average time to rescue that was much longer.

Due to its different mechanisms of action, compared to the other anti-VEGF agents, researchers considered that combining Cand5 with a VEGF-binding agent might offer a better response. Therefore, a phase III clinical trial, CARBON [32], is under way that will compare the efficacy of Cand5 administered every 8 weeks or 12 weeks after an initial pretreatment with 3 injections of Lucentis versus Lucentis monotherapy every 4 weeks in patients with wet AMD.

Against VEGFR and PDGFR

VEGFR mediate the biological functions of the VEGF family. They consist of three protein-tyrosine kinases (VEGFR-1, VEGFR-2, and VEGFR-3) and two non-protein kinase coreceptors (neuropilin-1 and neuropilin-2) [33]. VEGFR-2 appears to mediate almost all of the known cellular responses to VEGF; the role of VEGFR-1 has been characterized as a decoy receptor evolved to trap free VEGF-A, that prevents continuous VEGFR-2 activation [34]. Platelet-derived growth factor is a growth factor which has been demonstrated to stimulate angiogenesis and pericyte recruitment [35]. Loss of pericytes in retinal vessels is thought to be associated with abnormalities and instability of vasculature, including the formation of microaneurysms and vascular permeability, and it was also thought to be associated with regression of maturing neovascularization [36, 37]. Therefore, inhibition of VEGFR and platelet-derived growth factor receptor (PDGFR) seems to be another approach to prevent CNV.

TG100801 (TareGen)

TG100801 is a potent tyrosine kinase inhibitor and a prodrug administration of TG100572, which binds VEGFR and PDGFR and inhibits their activity [38]. Data have suggested that the delivery of the agent occurs by local penetration through the sclera rather than by system-

ic absorption, as neither compound was detectable in the plasma [38]. For reasons of noninvasiveness, it is used as an eye drop.

A phase I trial [39], using low and high doses applied topically twice daily for 14 days in 42 healthy volunteers, was completed and showed good tolerance. A phase II randomized study [40] is ongoing to evaluate the efficacy and safety of dosing with two dose levels of TG100801. It will be good news if these eye drops work, as this route of administration would be more suited for prophylaxis in AMD patients who are at risk of progressing to CNV.

Vatalanib (PTK787; Novartis)

Vatalanib [41] is another potent tyrosine kinase inhibitor with good oral bioavailability and activity against the VEGFR family, PDGFR β and c-Kit receptor kinases. Pre-clinical studies [41] suggest that vatalanib induces dose-dependent inhibition of VEGF-induced angiogenesis. A phase I/II trial, ADVANCE [42], to evaluate the safety and efficacy of oral vatalanib combined with PDT with verteporfin in 50 patients has been completed, but the data have not yet been published in a peer-reviewed journal.

Pazopanib (GW786034; GlaxoSmithKline)

Pazopanib [43] is a second-generation multitargeted tyrosine kinase inhibitor against all VEGFR, PDGFR α , PDGFR β , and c-kit. A phase I clinical trial using pazopanib as eye drops in 38 healthy volunteers has successfully demonstrated its safety and tolerability. Subsequently, a phase II trial [44] to evaluate its pharmacodynamics, pharmacokinetics and safety is currently recruiting patients.

Sirna-027/AGN211745 (Allergan)

Sirna-027 [45] is a chemically stabilized small interfering mRNA (siRNA) designed to silence the gene for VEGFR-1 so that it is unable to translate the message to increase vascular production.

The investigators estimated that Sirna-027 has a long-lasting effect on VA after a single-dose IVT. A phase I study [46] evaluated a single Sirna-027 IVT ranging from 100 to 1,600 mg in 26 patients with wet AMD. Three months after the single injection, 24 patients (92%) showed VA stabilization, with 4 patients (15%) experiencing clinically significant improvement in VA.

At present, investigators are in a phase II randomized study [47] that evaluates the safety and efficacy of Sirna-027 IVT in comparison with Lucentis in 135 patients with wet AMD.

Anti-VEGFR Vaccine Therapy

This is an immunologic approach to combat CNV. A recent report demonstrated CD8+ cytotoxic T lymphocyte (CTL)-mediated regression of physiologic and pathologic retinal new vessels [48], thus a hypothesis of a possible immunologic therapy for CNV by inducing CTL responses targeting a specific molecule highly expressed in CNV-associated endothelial cells was raised. It was approved by a study [49] using an animal model which first showed that CNV can be reduced by inducing cellular immunity specific for VEGFR-2.

More recently, a phase I study [50] of anti-VEGFR vaccine therapy has been recruiting participants. The patients will be vaccinated once a week for 12 weeks. On each vaccination day, VEGFR-1 peptide (1 mg) and VEGFR-2 peptide (1 mg) mixed with Montanide ISA 51 will be administered by subcutaneous injection. This study will evaluate the safety and tolerability as well as the immunological and clinical response of the vaccine therapy to treatment of wet AMD and neovascular maculopathy.

Against Inflammatory and Immune-Mediated Events

Studies strongly suggested that the process of drusen formation includes inflammatory and immune-mediated events, especially in the progression from dry to wet AMD.

A previous study [51] suggested that drusen include remnants of the retinal pigment epithelium, dendritic cell processes, and a variety of immune-associated molecules including immunoglobulins, class II antigens, and a host of complement components, activators, and regulators. The observations led the investigators to conclude that AMD, like other age-related diseases, could involve a major inflammatory component. Another report [52] has documented macrophages as the predominant type of leukocytes involved in CNV. An earlier study [53] demonstrated that lymphocytes, fibroblasts, and myofibroblasts may also play a role. Therefore, by inhibiting immune and inflammatory responses, therapeutic benefit may be achieved in both dry and wet AMD.

Retaane 15 mg (Anecortave Acetate Suspension, 15 mg; Alcon)

Retaane [54, 55] is an analog of cortisol acetate that inhibits multiple steps within the angiogenic cascade, both upstream and downstream of angiogenic growth

factor ligand-receptor interaction. It is administered with a special blunt-tipped cannula used to deliver a periocular posterior juxtасcleral depot onto the outer surface of the sclera once every 6 months. In September 2007, Alcon received an approvable letter from FDA for Retaane in the treatment of wet AMD; however, the FDA will require an additional clinical trial before it grants final approval [56].

A 6-month study [57] involving 136 patients evaluated Retaane (15 or 30 mg) versus placebo following initial treatment with PDT. The Retaane-treated patients maintained better VA than placebo-treated patients. In a 2-year phase III trial comparing Retaane with PDT in 530 patients with predominantly classic subfoveal CNV secondary to AMD, the proportion of patients losing less than 3 lines of vision in the Retaane and PDT groups were 45 and 49%, respectively ($p = 0.43$, not statistically different). The study demonstrated the safety and efficacy for the treatment of wet AMD with either the drug or the posterior juxtасcleral depot administration procedure.

Kenalog (Triamcinolone Acetonide, 40 mg/ml; Schering-Plough)

Kenalog is known as a corticosteroid hormone that has a multitude of anti-inflammatory effects and also seems to have direct antiangiogenic properties. It has been used as an off-label drug for the treatment of wet AMD over the last several years.

Results at 1 year following a single IVT in a prospective randomized trial [58] did not support the use of Kenalog IVT as a monotherapy for wet AMD. Subsequently, to reduce subretinal edema and the burst of VEGF produced immediately after PDT [59], use of Kenalog IVT with PDT has become common practice with approved efficacy.

POT-4 (Potentia Pharmaceuticals)

POT-4 [60] is a peptide capable of binding to human complement factor C3 (C3). As C3 is a central component of all known complement activation pathways, its inhibition effectively shuts down all downstream complement activation that could otherwise lead to local inflammation, tissue damage and up-regulation of angiogenic factors such as VEGF.

A phase I single escalating dose study [61] has just released its first results, which indicate that POT-4 IVT is safe, and the data accumulated so far support the continued investigation of POT-4 for the treatment of both dry and wet AMD with a larger randomized phase II trial to further define its efficacy profile.

ARC1905 (Ophthotech Corp.)

ARC1905 [60] is an anti-C5 aptamer, which prevents the formation of key terminal fragments (C5a and C5b-9) by inhibiting human complement factor C5 (C5). C5a fragment is an important inflammatory activator inducing vascular permeability, recruitment and activation of phagocytes. C5b-9 is involved in the formation of membrane attack complex (C5b-9), which initiates cell lysis [60]. Thus by inhibiting these C5-mediated inflammatory, ARC1905 might be beneficial in wet AMD.

A phase I study [62] to evaluate the safety, tolerability, and pharmacokinetic profile of multiple doses of ARC1905 IVT in combination with multiple doses of Lucentis is currently in progress.

OT-551 (Othera)

OT-551 [63], an antiangiogenic drug in eye drop form, operates within the cell to down-regulate nuclear factor kappa B, which is an important transcription factor complex playing a fundamental role in the regulation of acute inflammation through activating the cytokine cascade and production of other pro-inflammatory mediators [64].

A phase I trial [63] demonstrated that when the compound is added to Lucentis or Avastin treatment, there is a synergistic effect in patients with wet AMD. At present, two phase II studies [65, 66] for dry AMD are under way.

Others

Zybrestat (Combretastatin A4 Phosphate/CA4P; OXiGENE)

The antimitotic agent CA4P [67] is a water-soluble prodrug of combretastatin A4 that was originally isolated from the tree *Combretum caffrum*. Histological and immunohistochemical analysis indicated that CA4P causes changes in shape, cytotoxicity and apoptosis of proliferating endothelial cells, but not of quiescent cells; it permits the development of normal retinal vasculature while inhibiting aberrant neovascularization [68, 69].

A phase I/II trial [70] in 15 patients with wet AMD using intravenous CA4P administration once a week for 4 weeks with a 6-month follow-up demonstrated that CA4P had been well tolerated up to doses of 36 mg/m² and the side effects observed were increased blood pressure below clinical significance. Positive results were also reported in a phase II study [71] in patients with CNV associated with myopic macular degeneration.

Table 1. Summary

Classification	Agent	Phase ¹	Property	Target	Route
Against VEGF	Macugen (pegaptanib)	IV	ribonucleic acid aptamer (50 kDa)	VEGF-A165 isoform	IVT
	Lucentis (ranibizumab)	IV	monoclonal antibody fragment (48 kDa)	all VEGF-A isoforms	IVT
	Avastin (bevacizumab)	III	monoclonal antibody (149 kDa)	all VEGF-A isoforms	IVT
	VEGF Trap-Eye	III	decoy receptor (110 kDa)	all VEGF-A isoforms and VEGF-B, PIGF	IVT
	Cand5 (bevasiranib)	III	small interfering mRNA	VEGF-A mRNA	IVT
Against VEGFR and PDGFR	TG100801	II	tyrosine kinase inhibitor	VEGFR, PDGFR	eye drop
	vatalanib (PTK787)	I/II	tyrosine kinase inhibitor	VEGFR, PDGFR β , c-kit	oral
	pazopanib (GW786034)	II	tyrosine kinase inhibitor	all VEGFR, PDGFR α , PDGFR β , c-kit	eye drop
	Sirna-027 (AGN211745)	II	small interfering mRNA	VEGFR-1	IVT
	vaccine therapy	I	inducing CTL responses	VEGFR-1, VEGFR-2	IH
Against inflammatory and immune events	Retaane (anecortave acetate)	III	steroid	inhibits proteolytic cascade	PJD
	Kenalog (triamcinolone acetonide)	III	steroid	inhibits proteolytic cascade	IVT
	ARC1905	I	anti-C5 aptamer	complement factor C5	IVT
	POT-4	I	C3 inhibitor	complement factor C3	IVT
	OT-551	II	free radical scavenger	nuclear factor kappa B	oral
Others	Zybrestat (CA4P)	II	analogue of colchicine	vascular disruption	oral
	AdPEDF	I	adenoviral PEDF	PEDF	IVT
	JSM6427	I	integrin $\alpha 5\beta 1$ -antagonist	integrin $\alpha 5\beta 1$	IVT
	ATG003	II	mecamylamine (nACh receptor)	nicotinic acetylcholine (nACh)	eye drop
	Sirolimus (rapamycin)	II	macrolide	mTOR/Akt	ISC IVT
	E10030	I	three compounds (an aptamer + ARC1905 + volociximab)	PDGF-B, integrin $\alpha 5\beta 1$, C5	oral

PIGF = Placenta growth factor; mTOR = mammalian target of rapamycin; ISC = subconjunctival injection; IH = hypodermic injection; PJD = periocular posterior juxtasceral depot.

¹ Phase of FDA-mandated clinical trials.

Believing that it is feasible to deliver CAP4 topically, OXiGENE Co. is currently advancing the development of a topical formulation of CA4P for ophthalmological diseases.

AdPEDF (GenVec)

Pigment epithelium-derived factor (PEDF) is one of the most potent antiangiogenic proteins found in humans, which were shown to inhibit VEGF-induced proliferation, migration of microvascular endothelial cells, reduce VEGF-induced hypermeability and cause vessel regression in established neovascularization [72, 73]. AdPEDF uses GenVec's proprietary adenovector, a DNA carrier, to deliver the PEDF gene, resulting in the local production of AdPEDF in the treated eye. It is currently under development for the treatment of wet AMD.

A phase I escalating-dose clinical trial [74] in 28 patients with advanced wet AMD was completed. Three to six months after a single injection, it suggested that 50–94% of patients had a stabilization or improvement in lesion size from baseline, suggesting that antiangiogenesis may last for several months after a single IVT. Another phase I study [75] in 22 patients with less severe wet AMD was similar; there were no dose-limiting toxicities or drug-related severe adverse events reported. Further studies investigating the efficacy of AdPEDF in patients with wet AMD are under way.

JSM6427 (Jerini Ophthalmic)

JSM6427 [76] is a potent, highly specific integrin $\alpha 5\beta 1$ -antagonist that is absorbed, broken down and eliminated from the body when it is given as a single dosage strength

by injection into the eye. Integrin $\alpha 5\beta 1$ is the most important fibronectin receptor and has been shown to play a critical role during angiogenesis [77]. Blockade of $\alpha 5\beta 1$ can lead to suppression of tube formation stimulated by VEGF and apoptosis of proliferation but not quiescent endothelial cells [77]. It has been demonstrated to inhibit angiogenesis both stimulated by VEGF and independent of VEGF [77].

A phase I study [78] is underway. Investigators are planning to use an anti-VEGF agent in combination with this integrin antagonist agent to simultaneously inhibit multiple pathways involved in the pathophysiology of wet AMD.

ATG003 (Athenagen)

ATG003 [79], a proprietary ophthalmic formulation of mecamlamine, is an antagonist of the nicotinic acetylcholine receptor pathway that mediates angiogenesis and also down-regulates VEGF. It is the first noninvasive eye drop therapy for AMD that has entered the clinic [80].

A phase II clinical trial [81] comparing the safety and efficacy of ATG003 1.0 and 3.0% ophthalmic solutions with placebo in 330 patients has recently been completed, but no data was released for the moment. Another phase II study [82] of ATG003 1.0% ophthalmic solution in patients receiving maintenance injections of either Lucentis or Avastin is in progress.

Sirolimus (Rapamycin; MacuSight's)

Sirolimus [83], originally known as Rapamycin, is a macrolide fungicide with potent antimicrobial and immunosuppressive properties, which possesses significant antitumor and antiangiogenic features. The antiangiogenic properties are associated with a decrease in VEGF production and a reduction in the response of vascular endothelial cells to stimulation by VEGF.

It has been shown to reduce significantly the extent of neovascularization in an animal study [84], and a phase I prospective trial [85] of 30 patients with wet AMD demonstrated that it was safe and well tolerated in all doses tested with two different routes of administration (subconjunctival injection and IVT). Based on these positive results, the phase II trial EMERALD [86] will start soon, which will evaluate its efficacy and safety in combination with Lucentis.

E10030 (Ophthotech)

E10030 [87] is the first of three compounds that Ophthotech is developing to treat AMD. It is an aptamer directed against PDGF-B; additional molecular entities in-

Table 2. Phases of FDA-mandated clinical trials [88]

Phase I trials	Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients
Phase II trials	Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks
Phase III trials	Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide and adequate basis for physician labeling
Phase IV trials	Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use

clude ARC1905 and volociximab (M200, an antiangiogenesis monoclonal antibody targeting $\alpha 5\beta 1$ integrin).

A phase I study [16] using E10030 in combination with the anti-VEGF agent Lucentis has just been completed; it showed that AV improved by 21–27 letters from baseline at 8 weeks, and 43, 54, 62% of patients had gained 3 lines at 4 weeks, 8 weeks, and 12 weeks, respectively. As the findings are very promising, further trials are currently being developed.

Conclusion and Outlook

In addition to these agents (tables 1, 2), there were many agents halted in human trials for the treatment of wet AMD, for example, due to not providing the anticipated results such as AG-013958 (an anti-VEGFR-2) [41], prinomastat (a matrix metalloprotease inhibitor) [89] and all interferon α -2a agents [90]; due to the inability of patients to tolerate agents such as thalidomide (an antiangiogenic compound) [91], and even due to competitors of other new products that improve vision in wet AMD such as squalamine (an antibiotic aminosterol with antiangiogenic properties) [92]. Certainly, there are also many promising therapies for wet AMD under clinical

investigation, such as Endostatin [93] (an experimental drug derived from type XVIII collagen), RetinoStat [94] (a gene-based product that is designed to halt CNV). Whether they were halted or under development, they have pharmacological means for treating wet AMD.

With these increasingly successful studies and emerging agents, numerous pharmacological therapies are available for wet AMD, which give us lots of confidence to combat this disease. These agents act in different ways such as anti-VEGF, anti-VEGFR, anti-PDGFR, anti-inflammatory and immunosuppression; therefore, the obvious next phase in the evolution of treatment strategies

for wet AMD, similar to treatment regimens in oncology, is to determine viable combination therapies, which is based on the concept that drugs with different mechanisms of action may have additive or synergistic effects and may therefore improve efficacy, also may reduce the number of treatments needed and decrease total risk or side effects. Retina specialists have already begun to explore novel modalities of combination therapies for wet AMD [32, 44, 62, 63, 82, 86, 95], and some of those in small-scale studies have already shown positive results [63, 95], but further research is warranted.

References

- Klein R, Wang Q, Klein BE, Moss SE, Meuer SM: The relationship of age-related maculopathy, cataract, and glaucoma to visual acuity. *Invest Ophthalmol Vis Sci* 1995;36:182–191.
- Harvey PT: Common eye diseases of elderly people: identifying and treating causes of vision loss. *Gerontology* 2003;49:1–11.
- Grossniklaus HE, Martinez JA, Brown VB, Lambert HM, Sternberg P, Capone A, et al: Immunohistochemical and histochemical properties of surgically excised subretinal neovascular membranes in age-related macular degeneration. *Am J Ophthalmol* 1992;114:464–472.
- Ferrara N: Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev* 2004;25:581–611.
- Holmes DI, Zachary L: The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. *Genome Biol* 2005;6:209.
- Rakic JM, Lambert V, Devy L, Luttun A, Carmeliet P, Claes C, et al: Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. *Invest Ophthalmol Vis Sci* 2003;44:3186–3193.
- Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR: Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;351:2805–2816.
- Eyetech Study Group: Preclinical and phase 1A clinical evaluation of an anti-VEGF pegylated aptamer (EYE001) for the treatment of exudative age-related macular degeneration. *Retina* 2002;22:143–152.
- FDA, FDA Approves New Drug Treatment for Age-Related Macular Degeneration. <http://www.fda.gov/bbs/topics/news/2004/new01146.html> (accessed December 20, 2004).
- Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al: Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–1431.
- FDA, FDA Approves New Biologic Treatment for Wet Age-Related Macular Degeneration. <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01405.html> (accessed June 30, 2006).
- Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432–1444.
- Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, Shams N: Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol* 2008;145:239–248.
- Antoszyk AN, Tuomi L, Chung CY, Singh A, and FOCUS Study Group: Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration (FOCUS): year 2 results. *Am J Ophthalmol* 2008;145:862–874.
- Roberts D: SAILOR Study Results Favorable: Los Angeles: Bascom Palmer Eye Institute's Angiogenesis Meeting, 2008. <http://www.mdssupport.org/library/sailor.html> (accessed February 23, 2008).
- Singh RP: Highlights of the 26th Annual Meeting of the American Society of Retinal Specialists. <http://www.medscape.com/view/article/582820> (accessed November 6, 2008).
- Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS: Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005;112:1035–1047.
- FDA, FDA Approves First Angiogenesis Inhibitor to Treat Colorectal Cancer. <http://www.fda.gov/bbs/topics/NEWS/2004/NEW01027.html> (accessed February 26, 2004).
- Bashshur ZF, Bazarbaachi A, Schakal A, Hassad ZA, El Haibi CP, Nouredin BN: Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2006;142:1–9.
- Ehrlich R, Weinberger D: Outcome of bevacizumab (Avastin) injection in patients with age-related macular degeneration and low visual acuity. *Retina* 2008;28:1302–1307.
- Wolf A, Kook D, Strauss R, Kampik A, Haritoglou C: How to treat recurrences after Avastin treatment for neovascular AMD: stick to Avastin or switch to Lucentis? *Br J Ophthalmol* 2008;92:1297–1298.
- MAAM Study: Avastin and Macugen versus Avastin versus Macugen. <http://www.clinicaltrials.gov/ct2/show/NCT00531336?order=1> (accessed September 15, 2007).
- Comparison of Age-Related Macular Degeneration Treatment Trials: Lucentis-Avastin Trial. <http://clinicaltrials.gov/ct2/show/NCT00593450?order=1> (accessed January 3, 2008).
- Wulff C, Wilson H, Wiegand SJ, Rudge JS, Fraser HM: Prevention of thecal angiogenesis, antral follicular growth, and ovulation in the primate by treatment with vascular endothelial growth factor Trap R1R2. *Endocrinology* 2002;143:2797–2807.
- Nguyen QD, Shah SM, Hafiz G, Quinlan E, Sung J, Chu K, Cedarbaum JM, Campochiaro PA: A phase I trial of an IV-administered vascular endothelial growth factor trap for treatment in patients with choroidal neovascularization due to age-related macular degeneration. *Ophthalmology* 2006;113:1521–1522.

- 26 Bayer Health Care and Regeneron Announce VEGF Trap-Eye Achieved Durable Improvement in Vision over 52 Weeks in a Phase 2. <http://www.medicalnewstoday.com/articles/119267.php> (accessed August 26, 2008).
- 27 Double-Masked Study of Efficacy and Safety of IVT VEGF Trap-Eye in Subjects with Wet AMD (VIEW 1). <http://www.clinicaltrials.gov/ct2/show/NCT00509795?order=1> (accessed July 31, 2007).
- 28 Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (AMD) (VIEW 2). <http://clinicaltrials.gov/ct2/show/NCT00637377?order=1> (accessed March 12, 2008).
- 29 Acuity Pharmaceuticals Reports Positive Initial Phase II Results for Bevasiranib (Cand5) in Wet AMD. <http://www.medicalnewstoday.com/articles/44387.php> (accessed June 2, 2006).
- 30 Michels S, Schmidt-Erfurth U, Rosenfeld PJ: Promising new treatments for neovascular age-related macular degeneration. *Expert Opin Investig Drugs* 2006;15:779–793.
- 31 OPKO's siRNA Drug for AMD Shows Promise. Accessed January 2008 at: <http://www.retinalphysician.com/article.aspx?article=101325>
- 32 Safety and Efficacy Study Evaluating the Combination of Bevasiranib and Lucentis Therapy in Wet AMD (CARBON). <http://www.clinicaltrials.gov/ct2/show/NCT00499590?order=1> (accessed July 10, 2007).
- 33 Ferrara N, Gerber HP, LeCouter J: The biology of VEGF and its receptors. *Nat Med* 2003;9:669–676.
- 34 Zeng H, Dvorak HF, Muchopadhyay D: Vascular permeability factor (VPF)/vascular endothelial growth factor (VEGFR-1) modulates mitogenic activity of VEGFR-2 in endothelial cells. *J Biol Chem* 2000;159:993–10008.
- 35 Hellström M, Gerhardt H, Kalén K, Li X, Eriksson U, Wolburg H, et al: Lack of pericytes leads to endothelial hyperplasia and abnormal vascular morphogenesis. *J Cell Biol* 2001;153:543–553.
- 36 Benjamin LE, Hemo I, Keshet E: A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF. *Development* 1998;125:1591–1598.
- 37 Jo N, Maihos C, Ju M: Inhibition of platelet-derived growth factor B signalling enhances the efficacy of anti-vascular endothelial growth factor therapy in multiple models of ocular neovascularization. *Am J Pathol* 2006;168:2036–2053.
- 38 Doukas J, Mahesh S, Umeda N, Kachi S, Akiyama H, Yokoi K, et al: Topical administration of multi-targeted kinase inhibitor suppresses choroidal neovascularization and retinal edema. *J Cell Physiol* 2008;216:29–37.
- 39 Roberts D: Antiangiogenic drugs are stopping neovascularization in wet macular degeneration. <http://www.mdsupport.org/library/anti-angio.html> (accessed January 2008).
- 40 Open-Label, Pilot Study of TG100801 in Patients with Choroidal Neovascularization due to AMD. <http://www.clinicaltrials.gov/ct2/show/NCT00509548?order=1> (accessed July 27, 2007).
- 41 Kaiser PK: Antivascular endothelial growth factor agents and their development: therapeutic implications in ocular diseases. *Am J Ophthalmol* 2006;142:660–668.
- 42 Safety and Efficacy of Oral PTK787 in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (AMD) (ADVANCE). <http://www.clinicaltrials.gov/ct2/show/NCT00138632?order=1> (accessed August 29, 2005).
- 43 Sonpavde G, Hutson TE, Sternberg CN: Pazopanib, a potent orally administered small-molecule multitargeted tyrosine kinase inhibitor for renal cell carcinoma. *Expert Opin Investig Drugs* 2008;17:253–261.
- 44 A Study to Evaluate the Pharmacodynamics, Safety, and Pharmacokinetics of Pazopanib Drops in Adult Subjects with Neovascular AMD. <http://www.clinicaltrials.gov/ct2/show/NCT00612456?order=1> (accessed January 29, 2008).
- 45 Shen J, Sarmul R, Silva RL, Akiyama H, Liu H, Saishin Y, et al: Suppression of ocular neovascularization with siRNA targeting VEGF receptor 1. *Gene Ther* 2006;13:225–234.
- 46 Sirna Therapeutics Reports Final Results from Phase I Study on Its RNAi-Based Therapeutic for Age-Related Macular Degeneration. <http://www.medicalnewstoday.com/articles/49334.php> (accessed August 11, 2006).
- 47 A Study Using Intravitreal Injections of a Small Interfering RNA in Patients with Age-Related Macular Degeneration. <http://www.clinicaltrials.gov/ct/show/NCT00395057?order=1> (accessed October 31, 2006).
- 48 Wigginton JM, Gruys E, Geiselhart L, Subleski J, Komschlies KL, Park JW, Wiltrout TA, Nagashima K, Back TC, Wiltrout RH: IFN-gamma and Fas/FasL are required for the antitumor and antiangiogenic effects of IL-12/pulse IL-2 therapy. *J Clin Invest* 2001;108:51–62.
- 49 Mochimaru H, Nagai N, Hasegawa G, Kudo-Saito C, Yaguchi T, Usui Y, et al: Suppression of choroidal neovascularization by dendritic cell vaccination targeting VEGFR2. *Invest Ophthalmol Vis Sci* 2007;48:4795–4801.
- 50 Anti-VEGFR Vaccine Therapy in Treating Patients with Neovascular Maculopathy. <http://www.clinicaltrials.gov/ct2/show/NCT00791570?order=1> (accessed October 31, 2008).
- 51 Bok D: Evidence for an inflammatory process in age-related macular degeneration gains new support. *Proc Natl Acad Sci USA* 2005;102:7053–7054.
- 52 Grossniklaus HE, Ling JX, Wallace TM, Dithmar S, Lawson DH, Cohen C, et al: Macrophage and retinal pigment epithelium expression of angiogenic cytokines in choroidal neovascularization. *Mol Vis* 2002;8:119–126.
- 53 Van der Schaft TL, Mooy CM, Bruijn WC, Jong PT: Early stages of age-related macular degeneration: an immunofluorescence and electron microscopic study. *Br J Ophthalmol* 1993;81:38–47.
- 54 Yang R, McCollm JR, Bingaman DP, Penn JS: The effect of anecortave acetate on VEGF message and protein levels in hypoxic Muller cells and in rat OIR. *Invest Ophthalmol Vis Sci* 2005;46:E-abstr 4177.
- 55 Liu C, Gu X, Wang W, Bingaman DO, Bingaman H: Local delivery of anecortave acetate inhibits the expression of retinal IGF-1/IGF-1 receptor in the rat OIR model. *Invest Ophthalmol Vis Sci* 2005;46:E-abstr 4135.
- 56 Clinical Policy Bulletin: Anecortave acetate (Retaane). http://www.aetna.com/cpb/medical/data/700_799/0706.html (accessed November 2007).
- 57 Slakter JS, Bochow T, D'Amico DJ, Marks B, Jerdan J, Sullivan EK, et al: Anecortave acetate (15 milligrams) versus photodynamic therapy for treatment of subfoveal neovascularization in age-related macular degeneration. *Ophthalmology* 2006;113:3–13.
- 58 Gillies MC, Simpson JM, Luo W, Penfold P, Hunyor AB, Chua W, et al: A randomized clinical trial of a single dose of intravitreal triamcinolone acetonide for neovascular age-related macular degeneration: one-year results. *Arch Ophthalmol* 2003;121:667–673.
- 59 Uckermann O, Kutzera F, Wolf A, Pannicke T, Reichenbach A, Wiedemann P, et al: The glucocorticoid triamcinolone acetonide inhibits osmotic swelling of retinal glial cells via stimulation of endogenous adenosine signaling. *J Pharmacol Exp Ther* 2005;315:1036–1045.
- 60 Nozaki M, Raisler BJ, Sakuri E, Baffi JZ, Ambati BK, Ambati J: Drusen complement components C3. *Proc Natl Acad Sci USA* 2006;103:2328–2333.
- 61 AMD Patients Treated with POT-4 Demonstrate No Adverse Toxic Effects during Phase I Clinical Trial. <http://www.medicalnewstoday.com/articles/128837.php> (accessed November 11, 2008).
- 62 ARC1905 (ANTI-C5 APTAMER) Given either in Combination Therapy with Lucentis® 0.5 mg/Eye in Subjects with Neovascular Age-Related Macular Degeneration. <http://www.clinicaltrials.gov/ct2/show/NCT00709527?order=1> (accessed July 1, 2008).

- 63 Treating Wet Form of AMD – Othera Eye Drop Data Shows Synergistic Effect with Lucentis and Avastin. <http://www.medicalnewstoday.com/articles/63892.php> (accessed February 26, 2007).
- 64 Christman JW, Lancaster LH, Blackwell TS: Nuclear factor kappa B: a pivotal role in the systemic inflammatory response syndrome and new target for therapy. *Intensive Care Med* 1998;24:1131–1138.
- 65 OT-551 Antioxidant Eye Drops to Treat Geographic Atrophy in Age-Related Macular Degeneration. <http://www.clinicaltrials.gov/ct2/show/NCT00306488?order=1> (accessed March 22, 2006).
- 66 The OMEGA Study: Use of Eye Drops to Treat Geographic Atrophy Associated with Age-Related Macular Degeneration (Dry AMD). <http://www.clinicaltrials.gov/ct2/show/NCT00485394?order=1> (accessed June 11, 2007).
- 67 Pettit GR, Singh SB, Hamel E, Lin CM, Alerts DS, Garcia Kendall D: Isolation and structure of the strong cell growth and tubulin inhibitor combretastatin A-4. *Experientia* 1989;45:209–211.
- 68 Tozer GM, Prise VE, Wilson J: Mechanisms associated with tumor vascular shut-down induced by combretastatin A-4 phosphate: intravital microscopy and measurement of vascular permeability. *Cancer Res* 2001;61:6413–6422.
- 69 Griggs DJ, Skepper JN, Smith GA, Brindle KM, Metcalfe JC, Hesketh R: Inhibition of proliferative retinopathy by the anti-vascular agent combretastatin-A4. *Am J Pathol* 2002;160:1097–1103.
- 70 OXiGENE-Newsrelease. OXiGENE Announces Interim Results of Wet Age-Related Macular Degeneration Trial of Combretastatin A4 Prodrug. <http://www.oxigene.com/press/pressreleases.asp> (accessed May 18, 2004).
- 71 OXiGENE-Newsrelease. OXiGENE Announces Positive Results from its Phase II CA4P Clinical Trial in Myopic Macular Degeneration (MMD-213). <http://www.oxigene.com/press/pressreleases.asp> (accessed February 15, 2007).
- 72 Duh EJ, Yang HS, Suzuma I, Miyagi M, Youngman E, Mori K, et al: Pigment epithelium-derived factor suppresses ischemia-induced retinal neovascularization and VEGF-induced migration and growth. *Invest Ophthalmol Vis Sci* 2002;43:821–829.
- 73 Mori K, Gehlbach P, Ando A, McVey D, Wei L, Campochiaro PA: Regression of ocular neovascularization in response to increased expression of pigment epithelium-derived factor. *Invest Ophthalmol Vis Sci* 2002;43:2428–2434.
- 74 Campochiaro PA, Nguyen QD, Shah SM, Klein ML, Holz E, Frank RN, et al: Adenoviral vector-delivered pigment epithelium-derived factor for neovascular age-related macular degeneration: results of a phase I clinical trial. *Hum Gene Ther* 2006;17:167–176.
- 75 Rasmussen H, Chu KW, Campochiaro P, Gehlbach PL, Haller JA, Handa JT, et al: An open-label, phase I, single administration, dose-escalation study of ADGVPEDF.11D (ADPEDF) in neovascular age-related macular degeneration (AMD). *Hum Gene Ther* 2001;12:2029–2032.
- 76 Maier AK, Kociok N, Zahn G, Vossmeier D, Stragies R, Muether PS, Jousen AM: Modulation of hypoxia-induced neovascularization by JSM6427, an integrin $\alpha 5 \beta 1$ inhibiting molecule. *Curr Eye Res* 2007;32:801–812.
- 77 Ramakrishnan B, Bhaskar V, Law DA, Wong MH, DuBridge RB, Breinberg D, et al: Pre-clinical evaluation of an anti- $\alpha 5 \beta 1$ integrin antibody as a novel anti-angiogenic agent. *J Exp Ther Oncol* 2006;5:273–286.
- 78 A Phase 1 Safety Study of Single and Repeated Doses of JSM6427 (Intravitreal Injection) to Treat AMD. <http://clinicaltrials.gov/ct2/show/NCT00536016?order=1> (accessed September 25, 2007).
- 79 Athenagen's Eye Drop Therapy for AMD Is Safe and Well Tolerated in Phase I Study. <http://www.charterls.com/news-013107.html> (accessed January 31, 2007).
- 80 Athenagen's Eye Drop Therapy for AMD is Safe and Well Tolerated in Phase I Study. <http://www.charterls.com/news-013107.html> (accessed January 31, 2007).
- 81 Safety and Efficacy of ATG003 in Patients with Wet Age-Related Macular Degeneration (AMD). <http://www.clinicaltrials.gov/ct2/show/NCT00414206?order=1> (accessed December 19, 2006).
- 82 Safety and Efficacy of ATG003 in Patients with AMD Receiving Anti-VEGF. <http://www.clinicaltrials.gov/ct2/show/NCT00607750?order=1> (accessed January 23, 2008).
- 83 Guba M, Breitenbuch PV, Geissler E, Koehl G, Steinbauer M, Jauch K: Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002;8:128–135.
- 84 Dejneka NS, Kuroki AM, Fosnot J, Tang W, Tolentino MJ, Bennett J: Systemic rapamycin inhibits retinal and choroidal neovascularization in mice. *Mol Vis* 2004;10:964–972.
- 85 MacuSight™ Announces Positive Preliminary Results from Phase 1 Study of Sirolimus in Wet Age-Related Macular Degeneration. <http://www.medicalnewstoday.com/articles/98491.php> (accessed February 26, 2008).
- 86 Phase 2 Study of an Ocular Sirolimus (Rapamycin) Formulation in Combination with Lucentis® in Patients with Age-Related Macular Degeneration (EMERALD). <http://www.clinicaltrials.gov/ct2/show/NCT00766337?order=1> (accessed October 1, 2008).
- 87 Roberts D: New Anti-PDGF Aptamer Now in Trials. <http://www.mdsupport.org/library/E10030.html> (accessed February 15, 2008).
- 88 Glossary of Clinical Trials Terms. <http://clinicaltrials.gov/ct2/info/glossary> (accessed March 18, 2008).
- 89 Garcia C, Bartsch DU, Rivero ME, Hagedorn M, McDermott CD, Bergeron-Lynn G, et al: Efficacy of Prinomastat (AG3340), a matrix metalloprotease inhibitor, in treatment of retinal neovascularization. *Curr Eye Res* 2002;24:33–38.
- 90 Pharmacological Therapy for Macular Degeneration Study Group: Interferon alfa-2a is ineffective for patients with choroidal neovascularization secondary to age-related macular degeneration: results of a prospective randomized placebo-controlled clinical trial. *Arch Ophthalmol* 1997;115:865–872.
- 91 Maguire MG, Fine SL, Maguire AM, D'Amato RJ, Singerman LJ: Results of the age-related macular degeneration and thalidomide study (AMDATS). *Invest Ophthalmol Vis Sci* 2001;42:1233–1255.
- 92 Genaera Press Room: Genaera Corporation Terminates Evizon Clinical Program and Restructures. http://www.genaera.com/press_room.php?page=133 (accessed January 3, 2007).
- 93 Endostatin Inhibiting Neovascularization to Aid Age-Related Macular Degeneration Treatment. <http://www.medinewsdirect.com/?p=362> (accessed December 11, 2007).
- 94 Age-Related Macular Degeneration – Pre-clinical Efficacy Data with Retinostat(R). <http://www.medicalnewstoday.com/articles/23896.php> (accessed May 5, 2005).
- 95 Augustin AJ, Puls S, Offermann I: Triple therapy for choroidal neovascularization due to age-related macular degeneration: verteporfin PDT, bevacizumab, and dexamethasone. *Retina* 2007;27:133–140.