The dream of treating AMD with an eye drop is now a reality.

Numerous drugs in eye drop form are currently undergoing clinical trials and will, hopefully, soon be available to you to prescribe for your patients with AMD.

We will review the AMD drug pipeline, giving you a peek at some of the drugs under development for AMD. Then, we will focus on 5 eye drops that either are or will soon be in clinical trials for AMD.
Topical Nepafenac Inhibits Ocular Neovascularization

Yasuichi Takahashi,1 Yusufali Salibi,1 Yuukiko Satoh,3 Kojiro Miyak5,1 Akio Araki,1
Satoshi Yamamoto,1 Yuji Kobayashi,1 Tatsuyoshi Sato,1,3 Mitchell R. Stiel,1
David P. Bresnick,2 and Reyer A. Campochiaro1

Prodrug:
• Not metabolized by the body until they reach their target tissue
• Another pharmacologic characteristic that helps make a drug a good candidate for topical delivery
• Converts to amfenac in the eye

First report in the literature of a topical eye drop effectively inhibiting retinal and chroidal neovascularization

COX mediated up-regulation of VEGF in ischemia-induced neovascularization

Excellent penetration to retina after topical administration – “UNIQUE” among topical NSAIDS

Not effective in AMD-associated CNV, so we will not be talking about Nevanac today
Not approved for treatment of diabetic retinopathy

Approved only for the treatment of pain and inflammation associated with cataract surgery

Off-label use

Alcon received a warning letter from the FDA in 2006 in part because sales literature mentioned its excellent ability to inhibit prostaglandin synthesis in the posterior segment of the eye and this was viewed by the FDA as an attempt to broaden the indications for the drug.
What we are talking about here is nothing short of revolutionary

- much as the first laser treatment back in the 1980s changed everything about the management of AMD
- these drugs will change everything about the management of AMD once again

The impetus for this talk came from an article in the Aug 2008 NEJM.

It reviewed 2 papers on animal studies that demonstrated the safety and effectiveness of 2 drugs applied topically in eye drop form in controlling retinal edema and neovascularization.

The article commented on the potential widespread application (diabetic macular edema, CNV, retinal vein occlusion) of these findings.
Existing AMD Therapies

- 1982: Laser Photocoagulation
  - Vision loss with subfoveal lesions
  - High recurrence rate
- 2000: Photodynamic Therapy
  - Unable to improve vision
  - Decline of acuity with time
  - High recurrence rate
- 2004: Macugen (anti-VEGF)
  - Frequent intravitreal injections
- 2006: Lucentis (anti-VEGF, Current Gold Standard)
  - Frequent intravitreal injections
  - Tachyphylaxis

Before looking ahead, let us take a quick look behind to see how we got to where we are today.
Topical Therapy of AMD

- **Advantages**
  - Decreased risk of complication
  - Decreased cost
  - Increased convenience

- **Disadvantages**
  - Decreased drug bioavailability at the retina (lacrimal washout)
  - Increased risk of systemic side effects
  - Decreased compliance

==== PRO ====

DECREASED RISK OF COMPLICATIONS
- If systemic absorption is avoided
- enophthalmitis

DECREASED COST
- Fewer office visit, avoid surgeon’s fee

INCREASED CONVENIENCE
- Ability of patient’s to self-administer treatment

=== CON ====

BIOAVAILABILITY
- Traditionally major hurdle to topical therapy
- Use of small molecules and prodrugs

SYSTEMIC TOXICITY
- Multi-targeted drugs more effective, but carry higher toxicity risk
- Higher absorption through conj and naso-lacrimal mucosa that intravitreal delivery

COMPLIANCE
- Traditionally poor with chronic disease with few symptoms (glaucoma)
New AMD Treatment Paradigms

- **Prophylactic therapy of at-risk populations**
  - Many topical drugs have demonstrated benefit in inhibiting onset as well as regression of existing CNV

- **Contingency therapy**
  - Start therapy, then get retinal consult

- **Optometric Co-management**
  - Topical therapy opens the door to the optometric management of neovascular AMD
  - Replacing invasive tests (FA) with noninvasive tests (OCT)

Why is topical therapy such a big deal?
The Angiogenesis Revolution

Almost every ophthalmic drug either currently available or under development for the treatment of AMD began life as a cancer therapy.

Three potential targets for therapeutic intervention

![Diagram showing the effects of inhibiting angiogenic proteins](image)
FDA-Mandated Clinical Trials

- **PHASE I**
  - Initial studies to determine the actions of drugs in humans
  - Determine side effects associated with increasing doses
  - Gain early evidence of effectiveness
  - May include healthy participants

- **PHASE II**
  - Controlled studies
  - Evaluate effectiveness in patients with the disease under study
  - Determine the common short-term side effects and risks.

- **PHASE III**
  - Expanded controlled and uncontrolled trials
  - Evaluate the overall benefit-risk relationship of the drug

- **PHASE IV**
  - Post-marketing studies
  - Collect additional information about the drug's risks, benefits, and optimal use.
Wet AMD pipeline: not an exhaustive list. Only most promising candidates

- **adPEDF.11**: Gene therapy, intravitreal injection, Phase 1
- **Bevasiranib**: siRNA, intravitreal injection, Phase 3
- **AGN211745**: siRNA, intravitreal injection, Phase 2
- **Zybrestat**: vascular disrupting agent, TOPICAL, animal studies
- **Sirolimus**: Multi-mechanism, Subconj or intravitreal injection or oral, Phase 2
- **ATG003**: nAChR antagonist, TOPICAL, Phase 2
- **Avastin and Lucentis**: anti-VEGF, intravitreal injection, available
- **Macugen**: inti-VEGF, intravitreal injection, available
- **VEGF Trap**: VEGF receptor decoy, intravitreal injection, Phase 3
- **Vatalanib**: Tyrosine kinase inhibitor, oral, Phase 2
- **Pazopanib**: Tyrosine kinase inhibitor, TOPICAL, Phase 2
- **TG101095 / TG100801**: Tyrosine kinase inhibitor, TOPICAL, Phase 2
- **AL-39324**: Tyrosine kinase inhibitor, intravitreal injection, animal studies
- **AG013958**: Tyrosine kinase inhibitor, subtenon injection, animal studies
- **JSM6427**: integrin antagonist, intravitreal injection, Phase 1
Combretastatin A4 Phosphate

- Trade name: Zybrestat (fosbretabulin)
- Company: Oxigene
- Mechanism of action: Vascular disrupting agent (VDA)
  - Dual action: tubulin depolymerizing agent, cell junction disruption
  - Upsets the physical structure of the existing blood vessels
  - Selective CNV shutdown suggests a structural difference of neovascular vessels compared to that of normal vessels

Could be the first ever VDA on the market

Thyroid cancer therapy
- Currently in Phase 2/3 study for anaplastic thyroid cancer (ATC).
- Currently there are no approved treatments for ATC
- Newly diagnosed patients have a median life expectancy of about three months.

Synthetic prodrug
- Combretastatin A4 Phosphate converted to Combretastatin inside endothelial cell

Originally derived from the root bark of the South African Bushwillow tree (*Combretum caffrum*)
Vascular Disrupting Agents

Dual action
- VE-cadherin
  - disrupts the VE-cadherin/b-catenin complex interfering with cell-cell contact
  - Loss of cell-cell contact increases vascular permeability leading to increased interstitial pressure and additional loss of blood flow.
- Tubulin depolymerization
  - act at the colchicines-binding site of the b-subunit of endothelial tubulin
  - Disruption of the endothelial cytoskeleton
  - results in shape changes. Normally flat, the endothelial cells become more spherical, and this decreases the size of the blood vessel lumen, causing decreased blood flow and thrombosis

It appears that the cytoskeleton of newly formed cells is sensitive to CA-4-P, whereas the cytoskeleton of mature cells is not.
This appears to underlie the preferential sensitivity of endothelial cells in tumor vessels
Combretastatin A4 Phosphate

- **Animal Studies**
  - Good ocular penetration after topical application
  - Prevents development of new CNV and causes partial regression of established CNV in mice

- **Human Study**
  - 22 subjects with CNV due to pathologic myopia
  - Intravenous Combretastatin A4 Phosphate
  - All subjects maintained VA after 3 months follow-up
  - Decreased size and leakage of CNV

- **Future Plans**
  - Initiate clinical trials of topical agent next year

Combo therapy with angiogenic inhibitor being investigated
Mecamylamine

- Code Name: ATG003
- Company: Comentis
- Mechanism of action: Nicotinic acetylcholine receptor (nAChR) antagonist
  - Non-neuronal nAChR present on endothelial cells
    - Involved in the regulation of vital cell functions, such as mitosis, differentiation, cell-cell contact, locomotion, and migration
  - By stimulating nAChR, nicotine promotes angiogenesis

INVERSINE (Mecamylamine HCl) is a potent, oral antihypertension agent

Some non-neuronal cells also express nAChR
- bronchial epithelial cells, endothelial cells, smooth muscle cells, and skin keratinocytes

Nicotine is an exogenous agonist of the nAChR
- ACh is the endogenous agonist of nAChRs
- ACh is synthesized and stored in ECs and blood cells
- Ach may act as an autocrine factor in the cardiovascular system

Non-neuronal nAChRs are involved in the regulation of vital cell functions,
- mitosis, differentiation, organization of the cytoskeleton, cell-cell contact, locomotion, and migration

Ach may function as a local "hormone" that is able to modulate cell functions that require adaptation to new conditions
Nicotine and Angiogenesis

- Endogenous cholinergic angiogenesis pathway
  - Nicotine induces morphological changes in endothelial cells identical to those induced by VEGF
    - Increases endothelial cell proliferation, reduces apoptosis and increases capillary network formation
  - Antagonists of nAChR abolish the proangiogenic effect of nicotine
- nAChR and VEGF: Two distinct but interdependent angiogenesis pathways
  - Neutralization of VEGF resulted in a significant but not complete inhibition of nAChR-mediated network formation

- nicotine has a potent angiogenic effect

two distinct but interdependent pathways for angiogenesis

nAChRs are involved in the native angiogenic response, and that this pathway is distinct from those triggered by VEGF or FGF
tobacco smoke is a complex mixture of over 4,000 chemical constituents

The net effect of cigarette smoke on endothelial function might be quite different from that of nicotine alone.
Mecamylamine

- Animal studies
  - Topical delivery of ATG003 significantly inhibits laser-induced CNV in a mouse model of AMD
- Phase 1
  - successfully completed in January 2008
- Phase 2
  - Completed 330 subject safety and efficacy study
  - Ongoing 60 subject study in patients receiving maintenance injections of either ranibizumab or bevacizumab

Phase 1: the first human study of an eye drop antiangiogenic therapy for AMD
- Data not published

Phase 2a study
- 330 subjects
- Dose ranging: 0.3% and 1% topical solutions
- Primary outcome: Visual acuity
- Secondary outcome: OCT, FA
- Completion: Sept 2008

Phase 2b study
- 60 subjects
- Safety of 1% topical mecamylamine BID for 48 weeks in pts receiving maintenance injections of lucentis or avastin
- Primary outcome: safety measures
- Secondary outcomes: efficacy measures
- Expected completion: Feb 2009
Moving inside the cell… Tyrosine kinase inhibitors
Pazopanib

- Code Name: GW786034
- Company: Galaxo Smith Klein
- Mechanism of action: Multitargeted tyrosine kinase inhibitor
  - VEGF receptor activation triggers the tyrosine kinase cascade leading to changes in cellular behavior
  - Inhibitors of tyrosine kinase prevent VEGF-induced vascular permeability and block angiogenesis
  - Multitargeted: Inhibits kinases that interact with multiple receptors (VEGFR, PDGFR, C-kit)

Currently in Phase 3 trials of oral formulation used to treat renal cell carcinoma

Second generation drug: Targets multiple receptor kinases
- VEGF receptor -1, -2, -3
- PDGR –alpha, -beta (Platelet-derived growth factor receptor)
- C-kit (stem cell factor receptor – implicated in tumor pathogenesis)

Targeting multiple molecules in the signaling pathway would be expected to increase efficacy, but also carries with it the risk of increased toxicity if systemic absorption occurs
- In cancer trials, systemic administration resulted in Grade 3 toxicities in 5/35 patients. Reactions include HTN, SOB, and reduced WBC count. One Grade 4 reaction occurred (pulmonary embolus)
Receptor tyrosine kinase (RTK)
- high affinity cell surface receptors for many polypeptide growth factors, cytokines and hormones.
- key regulators of normal cellular processes
- critical role in the development and progression of many types of cancer

Kinase enzymes perform phosphorylation
- Transfers phosphate groups from ATP to specific target molecules (substrates)
- enzymes that specifically phosphorylate tyrosine amino acids are termed tyrosine kinases.

VEGF RTK
- When VEGF binds to its receptor, it triggers the intracellular portion of the receptor to bind with an adjacent kinase molecule.
- Dimerization leads to a rapid activation of the kinase
- The activated receptor then becomes autophosphorylated on multiple specific intracellular tyrosine residues.
- Phosphorylation of tyrosine residues within the activated VEGF receptor creates binding sites for intracellular messenger proteins, including Src. The phosphorylation and activation of intracellular messenger proteins on receptor activation leads to the initiation of signal transduction pathways within the cell.
Illustration of intracellular signal transduction pathway for RTK
Pazopanib

- Animal studies
  - Potent inhibitor of all three VEGF receptors
  - Excellent antiangiogenic activity
- Phase 1
  - Good safety and tolerability in 38 healthy volunteers
- Phase 2
  - Ongoing 99-subject dose-ranging study of safety and effectiveness of pazopanib eye drops in wet AMD
  - Ongoing 60-subject study of efficacy of pazopanib eye drops in patients with wet AMD

Phase 2a study
- 99 subjects
- Dose-ranging: 5mg/ml TID, 5mg/ml QD, 2mg/ml TID topical solution
- Primary outcome: safety and tolerability
- Secondary outcomes: efficacy (visual acuity, OCT)
- Expected completion: May 2009

Phase 2b study
- 60 subjects
- Efficacy after 28 days of use
- Primary outcome: central retinal thickness (OCT)
- Secondary outcomes: visual acuity, FA
- Expected completion: Sept 2008
TG100801 / TG101095

- Company: TargeGen
- Mechanism of action: Multitargeted tyrosine kinase inhibitors
  - Prodrug: TG100801, Active drug: TG100572
    - Inhibits Src and Yes kinases of VEGF pathway
  - TG101095 inhibits kinases of VEGFR and JAK2
    - Shuts down VEGF, PDGF, and FGF pathways
    - Inhibition of multiple targets simultaneously tends to result in a more robust therapeutic effect

Tyrosine kinase inhibitor developed specifically for use in the eye

First generation drug (TG100801) currently in Phase 2 clinical trials

Second generation drug (TG101095) in animal studies
VEGF is not the only protein involved in CNV

- PDGF: blockade of both VEGF and PDGF superior to VEGF alone in animal studies
- FGF: Does not stimulate CNV, but does contribute to CNV growth when there is tissue disruption from the disease itself or attempts at treatment
- Therefore, combined blockade of all 3 may be more effective against CNV and macular edema than just one
- Blockage of more than one may also increase risk of toxicity if systemic absorption occurs

Dual VEGF receptor / Src kinase inhibition would provide a double hit against VEGF-induced edema

- The Src-family kinases c-Src and Yes mediate the vascular permeability actions of VEGF
Animal studies (TG100801/TG101095)
- Inhibits VEGF and CNV growth with similar efficacy as Avastin, VEGF Trap, other drugs
- Not detectable systemically after topical application

Phase 1
- Well tolerated by 42 healthy volunteers

Phase 2
- Ongoing 40 subject dose-ranging study of efficacy of TG100801 eye drops in patients with wet AMD

Animal studies
- Only drug to have animal study findings published in peer reviewed literature
- the first published report of a topically-applied kinase inhibitor that achieves therapeutic efficacy in the choroid and retina.
- Second published report topical eye drop with demonstrated efficacy in inhibiting CNV (first was Nevanac – NSAID from Alcon – published in 2003)

No systemic toxicity noted
- Not detectable in systemic circulation or contralateral eye after topical administration
- Assets for limiting systemic exposure:
  - No oral bioavailability. Drugs are not absorbed from GI tract
  - Rapidly cleared after IV admin

Enter posterior segment by transcleral route
- extends from sclera to choroid to retina
- delivery to the retina is the greatest challenge for topically delivered compounds that follow this path
- substantial levels detectable in the choroid and retina 30 min after administration
OT551

- Company: Othera
- Mechanism of action: Down-regulate nuclear factor kappa B (NF-κB)
  - Transcription factor. Turns genes on and off.
  - Involved in regulation of about 2000 genes that fall into 4 broad categories:
    - Immunoregulatory and inflammatory genes
    - Anti-apoptotic genes
    - Genes that positively regulate cell proliferation
    - Genes that encode negative regulators of NF-κB

Only drug being studied for dry AMD that we will be discussing today
NF-κB = dimer composed of RelA and P50 subunits

In the cytoplasm, NF-κB is inactive when bound to IκB

An extracellular signal will trigger the release of IκB. The now active NF-κB can enter the nucleus to initiate the transcription of genes that will cause the cell to respond to the signal
Effects of NF-κB inhibition are reported to be:

- Anti-oxidative
- Antiangiogenic
- Anti-inflammatory
OT551

- Animal studies
  - Protects retina from oxidative & light-induced damage
  - Blocks angiogenesis - adjunctive therapy in wet AMD

- Phase 1 - No data publicly available

- Phase 2
  - NEI study: 10 subjects with bilateral GA
  - OMEGA study
    - Ongoing 198 subject dose-ranging study of safety and efficacy of OT551 eye drops in GA
    - Primary outcome: Change in area of GA
    - Intervention: 2gtt QID x 2yrs

The initial phase 2 study was undertaken by the NEI.

It is thought that bilateral GA may be a more severe phenotype of the disease that may have a graver prognosis, therefore a second larger phase 2 study was undertaken by the company.

OMEGA Phase 2 study
- 198 subjects
- Dose-ranging: 0.3% or 0.45% OT551 2gtt QID x 2yrs
- Primary outcome: Change in area of GA
- Secondary outcome: visual acuity, conversion to wet AMD
- Expected completion date: Feb 2010

Future plans:
- Adjunctive therapy with Lucentis for wet AMD
Thank You!