Progress Toward Topical Therapy of AMD

A. INTRODUCTION

VEGF-triggered fluid leakage can be prevented by a drug applied topically in eye drop form

- The availability of a topically applied inhibitor of vascular permeability would represent a therapeutic advance with potential widespread application (diabetic macular edema, CNV, retinal vein occlusion)
- The ability to provide effective topical therapies for intraocular neovascularization and retinal edema could revolutionize the current care of many diseases that lead to these conditions.

1. Existing Therapies
   - 1982: Argon laser photocoagulation
   - 2000: Photodynamic therapy with vertorporin (photothombosis)
   - 2004: Macugen (anti-VEGF)
   - 2006: Lucentis (anti-VEGF, current gold standard)

2. Problems with Existing Therapies
   - Thermal laser: Vision loss with subfoveal lesions, high recurrence
   - PDT: Unable to improve acuity, decline of acuity with time, recurrence
   - anti-VEGF: frequent intravitreal injections, tachyphylaxis

B. TOPICAL THERAPIES: PROS AND CONS

1. Advantages of topical therapy
   - Decreased risk of complication (endophthalmitis)
   - Decreased cost (surgeon fee)
   - Increased convenience (avoid office visits)

2. Disadvantages of topical therapy
   - Decreased drug bioavailability at the retina (lacrimal washout)
   - Decreased compliance (compared to office visit)
   - More frequent administration (compared to depot injections)
   - Increased latency before therapeutic effect seen (compared to intravitreal inj)

3. Potential changes in AMD treatment paradigm

- Prophylactic therapy: at-risk populations
- Contingency therapy: start therapy first, then get retinal consult
- Optometric Co-management: few intravitreal injections first, then topical maintenance tx

C. THE PIPELINE

Almost without exception, every ophthalmic drug either currently available or under development for the treatment of AMD began life as a cancer therapy.

Neovascular AMD: beneficiary of research into antiangiogenic cancer therapies over the past 25 years.

Geographic atrophy: key feature is apotosis of RPE. Research into regulators of apotosis have yielded clues to how to help promote cell survival, and lead to the development of drugs that may slow the progression of GA.

1. adPEDF.11
   - Genetic therapy, intravitreal injection
   - DNA for pigment epithelial derived factor delivered using adenoviral vector
   - Phase 1 clinical trials – no serious adverse events. Single intravitreal injection provides several months of antiangiogenic activity

2. Bevasiranib
   - siRNA, intravitreal injection
   - downregulates the production of certain proteins by degradation of specific mRNA. Synthetic, double-stranded RNA with nucleic acid sequences homologous to the targeted single-stranded mRNA within the cell is introduced into the cell, the targeted mRNA can be destroyed
   - siRNAs targeting the mRNA specific to the genes that encode for the production of VEGF protein
   - Phase 2 trial: CARE study – marginal improvement in vision and lesion size over natural history based on TAP study data.
   - Treatment does not effect VEGF already in the eye at the time of treatment, it only prevents production of new VEGF. Therefore it needs to be used in conjunction with an anti-VEGF drug
   - Phase 3 trial: COBALT – administer bevasiranib every 8 or 12 weeks following 3 monthly injections of Lucentis

3. AGN211745
   - siRNA, intravitreal injection
   - targets mRNA for VEGFR-1 (transmembrane endothelial VEGF tyrosine kinase receptors)

- Phase 1 study found single intravitreal injection to be safe and well-tolerated
- Phase 2 study is currently enrolling

4. Zybrestat
   - Vascular disrupting agent, topical
   - No clinical trials
   - 2 animal studies with topical delivery (rabbits, primates)
   - one human IV administered study for myopic macular degeneration

5. Sirolimus
   - Multiple mechanisms of action, subconj or intravitreal injection, oral
   - Alters cell growth and metabolism. Transplant rejection coronary stents
   - downregulates Hypoxia-inducible Factor 1-altha (HIF-1a). Decreases VEGF production
   - Phase 1 trial: Ongoing. subconj or intravitreal injection
   - Phase 2 trial : Enrolling. Oral administration

6. ATG003
   - nAChR antagonist (mecamylamine), topical
   - cholinergic angiogenesis: stimulation of nAChR in the vasculature stimulates angiogenesis
   - mecamylamine: Noncompetitive nicotinic acetylcholine receptor antagonist. Used to treat high blood pressure (INVERSINE)
   - Phase 1 trial: good ocular tolerability and lack of serious adverse events
   - Phase 2 trial: Ongoing

7. Avastin and Lucentis
   - Lucentis is a humanized anti-VEGF antibody fragment that inhibits VEGF activity by competitively binding with VEGF
   - Lucentis (ranibizumab) is derived from Avastin (bevacizumab), a full-length humanized monoclonal antibody against VEGF.

8. Macugen
   - Pegaptanib is an aptamer, an oligonucleotide (short strands of RNA) that assumes a specific three-dimensional shape to facilitate high- affinity binding to specific target molecules.
   - Pegaptanib is a selective vascular endothelial growth factor (VEGF) antagonist that binds to extracellular VEGF-165, which is thought to be the primary isoform in ocular neovascularization. Pegaptanib binds to VEGF165, thereby inhibiting VEGF165 binding to its VEGF receptors.

- In humans, there are at least five subtypes or isoforms of VEGF. Pegaptanib has no effect on other variants of VEGF (ie VEGF-121)

9. VEGF Trap
    - receptor decoy, intravitreal injection
    - targets VEGF with higher affinity than any other currently available anti-VEGF agents
    - Unlike other currently available anti-VEGF drugs that only target VEGF-A, VEGF Trap targets all members of the VEGF family (A, B, C, D, PlGF-1, PlGF-2)
    - Phase 1 study: CLEAR-IT-1. No adverse events. At 6 weeks VA stable or improved in 95% of the patients, CNV shrinkage, OCT thickness decrease.
    - Phase 2 study: CLEAR-IT-2: Five different tx regimens (monthly and quarterly). No statistically significant difference noted. Completion in 2010.
    - Phase 3 study: Large head-to-head, non-inferiority trial with Lucentis

10. Vatalanib
    - Tyrosine kinase, oral
    - multi-VEGF receptor inhibitor that binds to the intracellular kinase domain of all three VEGF receptors (VEGFR-1, 2 ,3)
    - Phase 1-2 trial: combo-therapy with either PDT or Lucentis currently under way. No results publically reported.

11. Pazopanib
    - Tyrosine kinase, topical
    - Phase 2 trial: began enrolment in March 2007

12. TG101095
    - Tyrosine kinase, topical
    - Specifically targets VEGFR-2 (transmembrane endothelial VEGF tyrosine kinase receptors)
    - Animal studies only

13. TG100801
    - Tyrosine kinase, topical
    - Phase 1 trial completed: safe and well-tolerated BID x 14 days
    - Phase 2a: underway

14. AL-39324

- Tyrosine kinase, intravitreal injection
- Animal studies only

15. AG013958
    - Tyrosine kinase, subtenon injection
    - Animal studies only

16. JSM6427
    - Selective αvβ1 integrin antagonist, intravitreal injection
    - Integrins are cell surface receptors that mediate survival signals from the extracellular matrix.
    - Certain subpopulations of integrins show increased expression on vascular endothelial cells participating in retinal neovascularization, and of these, only αvβ1 has been shown to also be upregulated in vascular cells in an animal model of CNV.
    - Phase 1 trial: Ongoing

D. COMBRETASTATIN A4 PHOSPHATE (ZYBRESTAT, OXIGENE)

1. Mechanism of action

a. Vascular Disrupting Agent (VDA)

- OXiGENE believes that ZYBRESTAT is poised to become the first therapeutic product in a novel class of drug candidates called vascular disrupting agents (VDAs).

- target neovasculature associated with tumors or other diseases (macular degeneration) by disrupting the physical structure of the existing but pathologically abnormal vessels

- Vascular targeting strategies can be divided into two different approaches:
    - antiangiogenic approach
    - vascular disrupting approach

- Vascular disrupting agents (VDAs) target endothelial cells of the already established neovascular tissue leaving other blood vessels relatively unscathed.

- Selective CNV shutdown suggests a structural difference in endothelium of neovascular vessels compared to that of normal vessels.
    - high rate of endothelial cell proliferation,

    - the absence of pericytes,
    - abnormalities in the basement membrane
    - increased vascular permeability.
    - Absence of smooth muscle and pericyte coats.
    - highly dependent on tubulin cytoskeleton for their motility, invasion, attachment, alignment and proliferation

- Most VDA act by disruption of the cytoskeleton and cell-to-cell junctions

- Two types of VDA:
    - small molecule
        - tubulin-binding agents (ZYBRESTAT)
        - flavonoids
    - ligand directed VDAs

- Tubulin-binding agents
    - Disruption of the endothelial cytoskeleton: acts on endothelial tubulin, causing depolymerisation of microtubules that results in conformational changes and loss of blood flow
    - Loss of this cell-cell contact: disrupts the VE-cadherin/b-catenin complex that binds cells together. This increases vascular permeability and decreases blood flow

2. Clinical Status

a. Animal Studies

- Primate ocular penetration study: Reported positive results with two topical formulations of ZYBRESTAT (fosbretabulin).
    - When applied topically to the surface of the eye the drug is absorbed and result in concentrations of drug in the retina and choroid that are within the expected therapeutic range.

- These results confirm results seen in earlier preclinical studies conducted in rabbits.

b. Human Studies

- Intravenous Combretastatin A4 Phosphate in Patients With Subfoveal Choroidal Neovascular Membranes (CNV) in Pathologic Myopia

- 22 subjects with CNV secondary to pathologic myopia at 20 sites in North America, Tiwan, and Russia

- Subjects divided into 3 different IV dosages of Zybrestat
- Each subject received 2 IV infusions 1 week apart
- Results:
    - all subjects in each of the 3 dosing groups maintained (i.e. a decrease of <3 or more lines) VA at 3 months follow-up
    - Decreased size and leakage of CNV
    - Some systemic effects, but none serious (headache (39.1%), hypoaesthesia (26.1%), nausea (21.7%), tachycardia (13%)

c. Future Plans

- The Company currently anticipates that it will file an IND for the topical ZYBRESTAT ophthalmology program by year-end (2008)
- Has opted to undertake further preclinical studies to better understand the drug's therapeutic index and determine an optimal dosing regimen

E. ATG003 (MECAMYLAMINE, COMENTIS)

1. Mechanism of action

a. Nicotine is an agent of angiogenesis

- Nicotine acts via nicotinic acetylcholine receptors (nAChR) that mediate fast synaptic transmission.
- 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
    - acetylcholine is the endogenous agonist of nAChRs and is synthesized and stored in ECs and blood cells, suggesting that acetylcholine may act as an autocrine factor in the cardiovascular system
    - non-neuronal nAChRs are involved in the regulation of vital cell functions, such as mitosis, differentiation, organization of the cytoskeleton, cell-cell contact, locomotion, and migration
    - Thus, acetylcholine may function as a local "hormone" that is able to modulate cell functions that require adaptation to new conditions

- Nicotinic acetylcholine receptors (nAChR)
    - best known for their role in neurotransmission,
    - recently been demonstrated on vascular endothelial cells.
    - Acetylcholine is their endogenous ligand,
    - also stimulated by nicotine.
    - By stimulating nAChR, nicotine promotes tumor angiogenesis as well as atherosclerotic plaque neovascularization.

- nicotine has a potent angiogenic effect
    - nicotine increases endothelial cell proliferation, reduces apoptosis and increases capillary network formation in vitro
    - nicotine enhances the angiogenic response to inflammation, ischemia, atherosclerosis and neoplasia
    - nicotine is associated with increased blood flow and tissue growth
    - there is an endogenous cholinergic pathway for angiogenesis. This cholinergic pathway may play a role in pathological as well as therapeutic angiogenesis

- the proangiogenic effects of nicotine are mediated by non-neuronal nAChR and might involve the elaboration of nitric oxide, prostacyclin and VEGF
    - Antagonists of the nAChR abolished the proangiogenic effect of nicotine
    - synthesis of nitric oxide was required for the angiogenic effect of nicotine
    - Nicotine increased expression and activity of eNOS in vitro.
    - Nicotine releases prostacyclin from human vascular endothelial cells. Several lines of evidence indicate that prostacyclin is involved in angiogenesis, and might contribute to the angiogenic effects of VEGF
    - We also found that nicotine increased serum levels of VEGF.

b. Relation to VEGF

- two distinct but interdependent pathways for angiogenesis
- the nAChR and VEGF receptor appear to mediate distinct but interdependent pathways of angiogenesis.
- nAChRs are involved in the native angiogenic response, and that this pathway is distinct from those triggered by VEGF or FGF.
- Nicotine induces morphological changes in endothelial cells identical to those induced by VEGF. Specifically, both agents cause endothelial cells to align themselves into whorls on a two-dimensional matrix
- Neutralization of VEGF resulted in a significant but not complete inhibition of nAChR-mediated network formation.
- Neutralizing antibodies against bFGF had no significant effect on nAChR-mediated network formation

c. Tobacco smoke

- 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.

d. Mecamylamine

- nonselective nAChR antagonist
- completely and reversibly inhibited endothelial network formation
- INVERSINE (Mecamylamine HCl) is a potent, oral antihypertension agent

2. Clinical Status

a. Animal study (Kiuchi K, et al 2008)

- nAChR was identified in retinal and choroidal microvascular endothelial cells,
- the ability of endothelial cells to form tubules when grown in culture supplemented with VEGF was suppressed by mecamylamine.
- Supplementation of the drinking water of mice with nicotine increased the size of CNV lesions in a mouse model of CNV
- Nicotine enhancement of CNV was blocked by subcutaneous administration of mecamylamine (50 mg/kg/d) by an osmotic pump.
- In the absence of nicotine, CNV formation was suppressed by the infusion of 50 mg/kg/d mecamylamine or by topical application 0.1 or 1% mecamylamine to the cornea.
- ATG003 significantly inhibits laser-induced CNV in a mouse model of AMD. Topical delivery of ATG003 leads to high levels of the active drug in the retina and choroid with little reaching the systemic circulation.

b. Phase 1

- successfully completed a Phase I trial in January 2008
- promising pre-clinical efficacy studies. Good ocular penetration and little systemic absorption
- the first human study of an eye drop antiangiogenic therapy for AMD

c. Phase 2

Safety and Efficacy of ATG003 in Patients With Wet AMD

- This study has been completed.
- This is a Phase II randomized, double-masked study comparing the safety and efficacy of ATG003 (mecamylamine HCl) 1.0% and 0.3% ophthalmic solutions to placebo in patients with neovascular AMD
- Primary Outcome Measures: Visual Acuity (ETDRS)

- Secondary Outcome Measures: OCT, FA
- Estimated Enrollment: 330
- Study Start Date: March 2007
- Study Completion Date: September 2008

Safety and Efficacy of ATG003 in Patients With AMD Receiving Anti-VEGF

- This study is currently recruiting participants
- PURPOSE: Double-masked, randomized, placebo-controlled study of the safety and preliminary efficacy of ATG003 (topical mecamylamine) in patients receiving maintenance injections of either ranibizumab or bevacizumab.
- Primary Outcome Measures: To evaluate the safety of ATG003 [Time Frame: Day 1 - Week 50]
- Secondary Outcome Measures: To evaluate the efficacy of ATG003 [Time Frame: Day 1 - Week 50]
- Estimated Enrollment: 60
- Study Start Date: February 2008
- Estimated Primary Completion Date: February 2009
- TRIAL ARMS
    - Placebo Comparator Drug: Placebo eyedrops, BID, 48 weeks
    - Experimental Drug: ATG003 (mecamylamine). 1% Ophthalmic solution, eyedrop BID, 48 weeks

F. PAZOPANIB (GW786034, GSK)

1. Mechanism of action

a. Multitargeted tyrosine kinase inhibitor (Expert Opin Investig Drugs. 2008 Feb;17(2):253-61.)

- second-generation multitargeted tyrosine kinase inhibitor
- Pazopanib is an investigational, oral angiogenesis inhibitor used to treat renal cell carcinoma. Pazopanib is currently in Phase III development for the treatment of advanced or metastatic RCC
- effective against:
    - VEGF receptor-1, -2, and -3,
    - Platelet-derived growth factor receptor-alpha, and beta (PDGFR)
    - c-kit

- Pazopanib is an oral, investigational angiogenesis inhibitor targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor

receptor (PDGFR), and c-kit, key proteins responsible for tumor growth and survival

- vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), angiopoietins, etc., act by binding to tyrosine kinase receptors on endothelial and other stromal cells

- Members of the VEGF family (VEGF-A, VEGF-B, VEGF-C, and VEGF-D) bind to the corresponding receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3). Mol Cancer Ther2007;6(7). July 2007
    - VEGFR2 is the primary tyrosine kinase receptor mediating downstream events such as vascular permeability, endothelial cell proliferation, invasion, migration, and survival
    - Other receptors, such as PDGF receptors, are expressed on multiple cell types, including pericytes and smooth muscle cells, and regulate pericyte differentiation and vascular survival
    - Stem cell factor receptor (Kit) is expressed on primitive hematopoietic cells, melanocytes, and germ cells and has been implicated in the pathogenesis of several human malignancies

2. Clinical Status

a. Animal

- Preclinical evaluation has revealed excellent antiangiogenic and antitumor activity
- Preclinical studies show that pazopanib is a potent inhibitor of all three VEGF receptors

b. Phase 1

- Concluded with good safety and tolerability with 38 healthy volunteers

c. Phase 2

A Study to Evaluate the Pharmacodynamics, Safety, and Pharmacokinetics of Pazopanib Drops in Adult Subjects With Neovascular AMD

- This study is currently recruiting participants.
- PURPOSE: This is a 28 day study to evaluate the pharmacodynamic effect of pazopanib eye drops on the central retinal thickness of AMD patients
- Phase 2 clinical trial
- Primary Outcome Measures: central retinal thickness measured by OCT [Time Frame: at each weekly visit for 4 weeks]
- Secondary Outcome Measures: Retinal morphology, neovascular size, and lesion size and characteristics, Change in visual acuity [Time Frame: at each weekly visit for 4 weeks]

- Estimated Enrollment: 60
- Study Start Date: December 2007
- Estimated Study Completion Date: September 2008

Pazopanib Eye Drops in Subjects With Neovascular Age-Related Macular Degeneration

- This study is currently recruiting participants
- This is a two month study to allow continued treatment with pazopanib eye drops. Study may be extended to 5 months.
- Phase 2
- Drug: Pazopanib (5 mg/mL, TID) for 28 days, Pazopanib (2 mg/mL, TID) for 28 days, Pazopanib (5 mg/mL, QD) for 28 days
- Primary Outcome Measures: Safety and tolerability by ophthalmic examinations, vital signs, clinical laboratory tests performed monthly and AE reporting
- Secondary Outcome Measures: Change in visual acuity, central retinal thickness retinal (measured monthly by OCT), neovascular size lesion size and characteristics (measured fundus photography)
- Estimated Enrollment: 99
- Study Start Date: June 2008
- Estimated Study Completion Date: May 2009

G. TG100801/ TG101095 (TargeGen)

1. Mechanism of action

- Recent studies have shown that VEGF-induced vascular leakage is mediated by cytoplasmic protein kinase members of the Src proto-oncogene family.
    - Inhibitors of Src kinase activity prevent VEGF-induced vascular permeability, block angiogenesis, and reduce edema and functional loss.
    - Investigators working with mice and rabbits found that VEGFR/Src kinase antagonists may be applied topically in eye drop form, accumulate at high levels in the retina, retain biological activity, and strongly inhibit VEGF-mediated vascular leakage.
    - While Src kinase activity appears critical for VEGF-induced permeability, it appears not to affect other physiologically important effects of VEGF. Thus, inhibiting Src kinase may be potentially safer than other anti-VEGF therapies

- a small molecule, topically applied, multi-target kinase inhibitor
    - multitargeted kinase inhibitors have the potential to take us beyond VEGF.
    - The inhibition of multiple targets simultaneously tends to result in a robust therapeutic effect

- TG100801 is actually a prodrug. The active form is TG100572.
    - The prodrug allows even better penetration and greater VEGF inhibition than the actual drug itself
- It's in the class of tyrosine kinase inhibitors, working on kinases that are involved in the vascular endothelial growth factor (VEGF)-signaling pathway.
    - It inhibits downstream VEGF activation of endothelial cells and blocks the effect of VEGF on the receptors

- Topical administration results in very high levels at the choroid.
    - appears to enter the eye via a trans-scleral entry route
    - Kinase inhibitors may not be suitable for systemic administration, particularly from the safety perspective.

TG101095 was designed to inhibit both VEGFR and JAK2

- JAK2: a key signaling kinase downstream of erythropoietin (EPO)
- EPO linked to the pathogenesis of diabetic retinopathy (DR)

2. Clinical Status

a. Preclinical / Animal

- Inhibits VEGF and CNV growth multiple animal models
    - VEGF induced vascular permeability model
    - Ryan laser-induced CNV model
    - similar efficacy as pegaptanib sodium, bevacizumab, VEGF Trap, and other drugs that have been tested in these models

- Twice daily application of 1% TG101095 has been shown to reduce CNV in the murine laser-induced model

- Scheppke et al.
    - established a role for Src and Yes kinases in VEGF-mediated retinal vascular permeability
    - showed that topical application of a VEGF receptor Src–Yes kinase inhibitor can essentially eliminate retinal edema in animals

- Doukas et al.

- showed that a topical multitargeted kinase inhibitor of VEGF, PDGF, and FGF pathways can reduce choroidal neovascularization and retinal edema in animals
- Neither TG100801 nor TG100572 were detectable in plasma following topical delivery of TG100801, and adverse safety signals (such as weight loss) were not observed even with prolonged dosing schedules.

b. Phase 1

- phase I trial completed in February 2007, TG100801 was well tolerated by 42 healthy volunteers when administered topically twice daily for 14 consecutive days

c. Phase 2

Open-Label, Pilot Study of TG100801 in Patients With Choroidal Neovascularization Due to AMD

- This study is ongoing, but not recruiting participants.
- PURPOSE: evaluate the ability of topical administration of TG100801 to reduce the amount of fluid in the retina in patients with AMD following 30 days of treatment
- Primary Outcome Measures: Change from baseline in central retinal/lesion thickness as measured by OCT
- Secondary Outcome Measures: Mean/median change in visual acuity from baseline.
- Intervention: Eye drop at each of 2 doses, twice a day, 30 days
- Estimated Enrollment: 40
- Study Start Date: July 2007

H. OT551 (Othera)

1. Mechanism of action

a. Down-regulate overexpression of nuclear factor kappa B (NF-kB)

b. NF-kB

- Transcription factor
  - Turns genes on and off
  - Involved in regulation of approximately 2000 genes

- Genes regulated fall into 4 broad functional categories:
    - immunoregulatory and inflammatory genes
    - anti-apoptotic genes
    - genes that positively regulate cell proliferation
    - genes that encode negative regulators of NF-kB

- Immunoregulatory and inflammatory effects
    - Needed for proper immune system function
    - NF-kB activates innate and adaptive immune responses
    - Most inflammatory agents mediate their effects through the activation of NF-kB
    - Antiinflammatory agents (including ASA) suppress NF-kB
    - NF-kB ties together inflammation and cancer

- anti-apoptotic effects
    - NF-kB is also an inhibitor of programmed cell death
    - NF-kB activates the several genes that are known to block the induction of apoptosis by TNF-a and other pro-apoptotic agents
    - NF-kB is a part of the cells' autodefense mechanism
    - may mediate desensitization, chemoresistance, and radioresistance
    - NF-kB can attenuate the apoptotic response to anticancer drugs and ionizing radiation
    - crucial role of NF-kB in cell survival

- Cell proliferation
    - NF-kB is constitutively active in most tumor cell lines
    - Several carcinogens activate NF-kB
    - Numerous NF-kB-regulated cytokines are growth factors for tumor cells.
    - NF-kB activation can mediate cellular invasion and angiogenesis
    - NF-kB activation can mediate metastasis
    - Suppression of NF-kB in tumor cells inhibits proliferation, causes cell cycle arrest, and leads to apoptosis

c. Effects of NF-kB inhibition

- antioxidative
- antiangiogenic
- antiinflammatory

2. Clinical Status

a. Preclinical / Animal

- OT-551 may protect retina from oxidative damage

- blocks angiogenesis
- OT-551 protected retina from light-induced damage in rats
- Reaches retina 15 min after instillation

b. Phase 1

???

c. Phase 2

Two ongoing Phase 2 trials

1. Conducted by NEI
- small number (10) of subjects with bilateral GA

2. Conducted by Othera (OMEGA study)

The OMEGA Study: Use of Eye Drops to Treat Geographic Atrophy Associated With Age-Related Macular Degeneration (Dry AMD)

- This study is ongoing, but not recruiting participants
- PURPOSE: compare the ability of two doses of OT-551 ophthalmic solution and drug-free solution to safely and effectively treat geographic atrophy associated with age-related macular degeneration.
- Primary Outcome Measures: Change in the area of GA [Time Frame: 2 years]
- Secondary Outcome Measures: include change in vision function, conversion from dry to wet AMD
- Estimated Enrollment: 198
- Study Start Date: June 2007
- Estimated Primary Completion Date: February 2010
- Experimental Drug: OT-551 0.3% ophthalmic solution, 2 drops 4 times daily
- Experimental Drug: OT-551 0.45% ophthalmic solution, 2 drops 4 times daily

d. Future Plans

- adjunctive therapy with Lucentis for wet AMD