

IBC's 4th International Conference on

Ocular Anti-angiogenesis

*Translating Preclinical Indications to
Successful Clinical Development*



April 16-17, 2007 • Royal Sonesta • Cambridge MA

*Distinguished Chairpersons
and Speaker Faculty:*

Bela Anand-Apte, Ph.D.,
Cole Eye Institute
Paul Ashton, Ph.D.,
pSivida
David Bingaman, Ph.D.,
Alcon Research Ltd.
Perry Calias, Ph.D.,
EyeGate Pharmaceuticals, Inc.
Lucian Del Priore, M.D., Ph.D.,
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Pascal Deschatelets, Ph.D.,
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Vanderbilt Eye Institute
Paul Schmidt, Ph.D.,
PR Pharmaceuticals, Inc.
Susan Schneider, Ph.D.,
Genentech Inc.
Edward Schnipper, Ph.D.,
Cellgate, Inc.
David Sherris, Ph.D.,
Paloma Pharmaceuticals, Inc.
Richard Soll, Ph.D.,
TargeGen, Inc.
Signe Varner, Ph.D.,
SurModics
Keith W. Ward, Ph.D.,
Bausch & Lomb
David Weber, Ph.D.,
MacuSight, Inc.
Lisa Wei, Ph.D.,
GenVec, Inc.
Andrea Weir, Ph.D.,
Charles River Laboratories
Margaret Wills, MS,
Charles River Laboratories

Keynote Addresses from Industry Experts:

Examining the Role of Cyclooxygenase in Retinal Angiogenesis

John Penn, Ph.D.

Vice-Chair and Professor, Ophthalmology, Vanderbilt Eye Institute

**Innovations in Ocular Anti-angiogenic Therapeutic Approaches:
Opportunities and Challenges**

Ira M. Herman, Ph.D.

*Professor, Cellular and Molecular Physiology and Professor, Ophthalmology
Tufts University School of Medicine*

**Role of Bruch's Membrane Aging in RPE Behavior: What Have We
Learned from Transplantation Studies?**

Lucian Del Priore, M.D., Ph.D.

*Associate Professor, Ophthalmology, College of Physicians and Surgeons,
Columbia University*

**A Novel Anti-angiogenic Function for TIMP-3: Implications for Ocular
Angiogenesis**

Bela Anand-Apte, Ph.D. M.B.B.S

Director, Ophthalmic Research, Cole Eye Institute

**Rapid Choroidal Neovascularization Induced in Mice by Human VEGF
and it's Inhibition by Adenovirus Delivered shRNA**

Rajendra Kumar-Singh, Ph.D.

Associate Professor, Ophthalmology, Tufts University School of Medicine

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Ocular Anti-angiogenesis

Dear Colleague:

Over last four years ocular drug development has undergone a remarkable renaissance relative to angiogenesis modalities and anti-angiogenic treatment options for back of the eye neovascular pathologies. VEGF, a known angiogenesis inducer, has been clearly shown as a key player in these diseases, namely age-related macular degeneration and diabetic retinopathy. For this reason, drugs have anti-VEGF components have proliferated including antibodies, oligonucleotides, small molecule drugs, peptides and protein fragments. Although VEGF has been shown to play a role in angiogenesis, it is a pleiotropic cytokine having a number activities, including but not limited to vascular permeability and survival. Whether anti-VEGF treatments predominantly work as an anti-angiogenic agent or functions through one or multiple activities remains an active area of research. However, one aspect is clear in that monotherapy anti-VEGF drugs will not be sufficient to fight back of the eye diseases. Drugs with broader anti-angiogenic activity, ability to regress existing vessels and even have effects on reducing damage caused by retinal detachment are without a doubt the next generation drug highly sought after by pharma companies. Furthermore, means to keep these drugs in the eye for longer periods of times are needed to get away from monthly needle sticks to the eye. In this forum, you will learn how to develop drugs for back of the eye diseases through discussions of predictive preclinical animal models including means for slow drug release, regulatory/toxicology pathways to allow one to enter the clinic and case examples of clinical development of ocular drugs. On behalf of IBC Life Sciences, Sherris Pharma Partners and the Foundation for Fighting Blindness, we invite you to come, listen and learn how to better develop innovative drugs for back of the eye diseases.

David Sherris, Ph.D., Co-Chair,
Sherris Pharma Partners

Tim Schoen, Ph.D., Co-Chair,
Foundation for Fighting Blindness

Deb Fowler Clare
IBC Life Sciences

Call for Poster Submissions

The organizers of Ocular Anti-angiogenesis recognize the significant educational value in the poster presentations, and encourage any researcher to submit an abstract and share your experiences at this event!

Any registered conference attendee may sign up to present a poster. The deadline to submit your abstract is March 23, 2007, for the abstract to be included in the conference handbook. All abstracts must be submitted online at www.IBCLifeSciences.com/ocular. All abstracts are subject to review and approval by the organizers. Full payment of the conference registration and poster fee must be received by March 23, 2007 for the abstract to be included in the conference handbook and assigned a poster-board. Please see registration page for details on poster fees. Poster abstracts and registrations received after the deadline of March 23, 2007 will be subject to availability of on-site poster-boards and will not be included in the conference handbook. The size of the poster board is 4'h x 8'w.

Please note: Poster presentations may not be used as exhibit displays or for marketing purposes. Only one poster abstract will be accepted per registered attendee/author. No more than two poster presentations will be accepted per company/organization.

About the Conference Co-Organizer

David Sherris, Ph.D. (dsherris@sherrispharma.com), Chief Executive Officer of Sherris Pharma Partners (www.sherrispharma.com), has an over 21-year history in the biopharmaceutical and diagnostics world. Sherris Pharma Partners is a consulting group, based in Jamaica Plain, MA, specializing in identifying and facilitating corporate alliances, M&As, in/out-licensing, R&D project management, strategy and planning for biopharmaceutical and diagnostic companies, academic institutions and venture capital groups for oncology, inflammation, infection and that of ocular diseases. Sherris Pharma Partners works with biotech CEO's, CSO's, CFO's and executive managers; venture capitalists; academic scientists; entrepreneurs; investment bankers and biotech visionaries. Sherris Pharma Partners prides itself as a consulting firm with an additional specialty focus in angiogenesis and vascular targeting.

Venue & Travel Information

Venue:

Royal Sonesta Hotel Boston

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Registration Information

SUBSTITUTIONS & CANCELLATIONS: Should you be unable to attend for any reason, please inform IBC in writing 10 business days prior to the start date of the conference and a credit voucher for the full amount will be issued which must be used within one year of issuance. If you prefer, a full refund less a \$395 non-refundable deposit will be issued. No refunds or credits will be given for cancellation received on or after 10 business days from the start of the program.

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8:30 *Chair Introductions***Keynote Speaker****8:45 Innovations in Ocular Anti-angiogenic Therapeutic Approaches: Opportunities and Challenges**

Work is focused on revealing the molecular/cellular mechanisms regulating microvascular morphogenesis during human development and disease. In our efforts aimed at identifying molecular components controlling fundamental processes governing physiologic angiogenesis, we hope to reveal cell-specific targets and innovative strategies capable of abrogating pathologic angiogenesis and vascular proliferative disorders responsible for visually-blinding disorders associated with our globally-aging population. Focus will be on recent advances in understanding molecular and cellular signaling pathways controlling ocular angiogenesis and will offer insights into innovative strategies focused on development of anti-angiogenic therapeutic approaches capable of abrogating unwanted ocular neo-vascularization observed during diabetes and age-related macular degeneration.

Ira M. Herman, Ph.D., *Professor, Cellular and Molecular Physiology and Professor, Ophthalmology, Tufts University School of Medicine*

Animal Models**9:30 Conflict/Complexities Resolution During Ophthalmic Anti-angiogenic Lead Optimization**

Many potential ocular anti-angiogenic approaches have their genesis in oncology, with applications for ophthalmic use being an "add-on" rather than the primary purpose of original lead optimization effort. While efficient, this approach can lead to disconnects and misdirection early in the life of subsequent ophthalmic effort. Here, an exemplar ophthalmic anti-angiogenic lead optimization program based on an oncology target, and its successes/failures, will be discussed. Specific discussion points will include degree of concordance between cell based assays in oncology versus ophthalmology, relative importance of measures of cell viability, and ongoing challenge of successful drug delivery for posterior ophthalmic space.

Keith W. Ward, Ph.D., *Vice President, Global Preclinical Development, Bausch & Lomb*

10:00 *Networking Break***10:15 Preliminary Animal Testing for a Test Article's Potential Efficacy in Treating Adult Macular Degeneration**

Due to lack of macula, laboratory animals outside of the monkey are only useful to test early stages of AMD. Dutch Belted rabbits are the system of choice, as opposed to non-pigmented New Zealand White rabbits. From a safety point, rabbits are very responsive to intraocular insult. If reaction to intravitreal test article (TA) is not seen in rabbits, it won't be seen in monkeys or humans. From an efficacy point, if an effect of TA on angiogenesis is observed in rabbits, it might be seen in monkey/human. Thus study design involves laser to injure both retinas once near the fovea centralis followed by intravitreal administered TA. Follow up consists of fluorescein angiography (FA) pre/post-laser, and complete ophthalmic examinations, emphasis on indirect examination/measurement of flare. Eye histology is employed at 1, 2, 4, 7 and 10 days, emphasis on early time points. "n" of 6/variable is ideal, both eyes injured, a total of about 21 study rabbits. Endpoints, length of vessels/confluence in FA, flare from OEs, inflammatory parameters from histopath exam. If efficacy, safety trend is observed, then follow in monkeys.

Vince Mendenhall, DVM, Ph.D., *Principal Scientist, Preclinical Surgery, Charles River Laboratories*

10:45 Use of the Non-human Primate as a Model to Assess Anti-angiogenic Efficacy for Treatment of AMD

Species used for efficacy assessment of anti-angiogenic agents are monkey, rabbit and rodent. The primate model is advantageous in having similar anatomy and physiology and in providing a direct transition into human toxicity testing. It is the animal of choice for biotech-derived drugs. Laser-induced model of CNV is used to assess anti-angiogenic efficacy in cyno monkeys. This model can be used in rodents, but extrapolation to potential human effects is much greater than with primate model. CNV is induced by laser treatment via a 510 nm diode laser, with lesions placed in a 9-spot grid in perimacular region. Test article can be added at same time as laser treatment, prior to laser treatment or after CNV has developed. Common routes are intravitreal and

subtenon injections. CNV is assessed weekly via fluorescein angiography beginning approximately 14 days after laser treatment and continuing to 28-42 days post-laser. Fluorescein leakage is graded and compared to previous time points to assess changes in leakage. The eyes are assessed on a weekly basis for changes in anterior segment and fundus. Retinal function can be assessed via electroretinography providing preliminary safety data.

Margaret C. Wills, MS, *Senior Research Scientist, Charles River Laboratories*

Regulatory Perspectives**11:15 Considerations for the Nonclinical Development of Ophthalmic Drug Products**

Development of products for treatment of ocular neovascularization and other ocular indications is an active area of drug development. Similar to therapeutics for other indications, those intended for treatment of ocular conditions undergo safety evaluation in nonclinical studies conducted in animals or other appropriate test systems prior to initiation of clinical trials. Data from those studies, in combination with a clinical protocol, chemistry and manufacturing data, and other appropriate information are submitted to the FDA for regulatory review prior to initiating clinical trials. This presentation will provide a regulatory perspective on types of nonclinical safety studies appropriate for ocular therapeutics.

Andrea B. Weir, Ph.D., *Senior Scientific Advisor, Charles River Laboratories*

11:45 *Lunch on your own***Keynote Speaker****1:15 Role of Bruch's Membrane Aging in RPE Behavior: What Have We Learned from Transplantation Studies?**

AMD is the leading cause of blindness in the western world. Patients with AMD lose vision via two distinct mechanisms: nonexudative AMD, with atrophy of the outer retina, RPE and choriocapillaris; and exudative AMD, with neovascular ingrowth from outer blood supply (choriocapillaris) into Bruch's membrane, into subretinal space, and sometimes into neurosensory retina itself. Over the last 2 years, significant advances in management of exudative AMD with the introduction of anti-VEGF drugs; however, many patients with exudative AMD continue to lose vision and there are no effective treatments for advanced exudative AMD. Initial attempts at macular reconstruction using cellular transplantation have not been effective in reversing vision loss for several reasons, including presence of age-related disease within elderly human Bruch's membrane. Herein we discuss current status of surgical attempts to reconstruct damaged subretinal anatomy in advanced AMD, with an emphasis on effects of age-related changes within human Bruch's membrane on initial attachment and subsequent proliferation of transplanted cells. We will discuss status of efforts to repair Bruch's membrane and consider implications of our results for role of Bruch's membrane aging in controlling RPE behavior.

Lucian Del Priore, M.D., Ph.D., *Associate Professor, Ophthalmology, College of Physicians and Surgeons, Columbia University*

Drug Delivery**2:00 Medidur: An Adaptable Simple Injectable System for Long Term Drug Delivery to the Vitreous/Retinal**

It is difficult to deliver drugs to the back of the eye. Although effective agents are being developed for ocular angiogenesis, clinical use is mitigated by requirement for repeated intraocular injection. There have been significant advances in back of the eye drug delivery. There are a series of FDA approved devices that deliver drugs to the vitreous/retina in excess of 6 months. The first FDA approved device, VitrasertR, is implanted into the vitreous through a 5 mm incision maintaining effective ocular intravitreal levels of gancyclovir for 8 months. The second, Retisert™, was approved for chronic uveitis, significantly smaller (inserted through a 3 mm incision), providing a steady release of fluocinolone acetonide for 30 months. The next injectable long term drug release advance was designed to retain extremely long duration of the Retisert/Vitrasert systems but small enough to be injected via a 25 gauge needle. These systems are intended for an office visit. The first of these Medidur™, began Phase III clinical trials in diabetic macular edema in late 2005. New in development, OptiCon, is based on nano-structured BioSilicon™ with potential of precise drug release control, bio-erodible, using fabrication based on the electronics industry.

Paul Ashton, Ph.D., *Director, Strategy, pSivida*

2:30 I-vation™ Sustained Release Drug Delivery System

The I-vation™ Sustained Release Drug Delivery System offers controlled delivery of therapeutics to back of the eye in a platform balancing minimally invasive implantation, sustained release, and retrievability. Its unique coiled geometry allows implantation through a 25 gauge transscleral needle stick, maximizing the surface area available for drug delivery. The platform comprises a metallic backbone coated with a polymer/drug matrix. This configuration offers wide formulation versatility, leveraging an array of SurModics' polymer coating technologies. I-vation TA is the first product based upon this platform capable of delivering the triamcinolone acetonide into the vitreous for up to 2 years. A prospective, randomized, double-masked, multi-center, three-year study is currently being conducted to evaluate thirty patients with DME following I-vation TA intravitreal implantation. Patients were randomized to either a slow-release or fast-release formulation and stratified by baseline visual acuity and presence or absence of prior laser treatment. Six month follow-up data on thirty implanted eyes of thirty subjects revealed no safety issues. No reportable SAEs were noted at any of the four study sites. Investigators reported the product was easily implanted and easily exchanged. Clinical outcomes including best corrected visual acuity by ETDRS, intraocular pressure, and retinal thickness by OCT indicated controlled, sustained drug delivery.

Signe Varner, Ph.D., Director, Ophthalmology R & D, SurModics

3:00 Biodegradable Microparticle Formulation Advances Optimizing Drug Delivery for Treating Ocular Angiogenesis

Intravitreal injections of biodegradable microparticles have been tested in laboratories for ocular sustained release of therapeutic molecules. Because the dose volume is limited, it becomes important to maximize drug content and minimize "burst". Also patient comfort and compliance are greatly enhanced if dosing is done infrequently. Encapsulating PEGylated bioactive molecules in PLGA microspheres results in high drug content, low burst, and excellent stability of the active. Release kinetics are controlled by PLGA degradation rather than PEG hydrodynamic radius, so sustained release from weeks to months is achieved depending on polymer selected. PEG size and attachment to active molecule can be engineered not to reduce bioactivity, for example, microspheres encapsulating a PEGylated aptamer provide efficacious rabbit intraocular pegaptanib levels several months after intravitreal injection.

Paul G. Schmidt, Ph.D., Chief Scientific Officer, PR Pharmaceuticals, Inc.

3:30 Networking Break & Opening of the Exhibit/Poster Viewing

4:15 Ocular Drug Delivery: An Alternative to a Poke-in-the Eye

Current delivery modalities for ocular indications suffer from ineffective dosing, frequent administrations, collateral toxicities, sight threatening infections, and/or retinal damage. EyeGate Delivery System represents a non-invasive, well tolerated alternative for ocular indications. Utilizing a unique annular design, iontophoretic delivery of a wide range of therapeutics has been achieved without ocular side effects. Initial studies with corticosteroids and agents for treatment of glaucoma demonstrated safe delivery of therapeutically relevant quantities to anterior segments of the eye. More recently, we have demonstrated iontophoretic deliver of oligonucleotides to retina, enabling the use of biotherapeutics for the treatment of neovascular diseases.

Perry Calias, Ph.D., Vice President Research and Development, EyeGate Pharmaceuticals, Inc.

Keynote Speaker

4:45 Rapid CNV in Mice by Human VEGF and it's Inhibition by Adenovirus Delivered shRNA

Adenovirus-delivered human VEGF to the murine retina rapidly generates choroidal neovascularization (CNV), allowing use of this model for the screening of anti-VEGF therapies that may be useful in the treatment of age related macular degeneration (AMD). We have developed adenovirus vectors expressing short hairpin RNAs (shRNAs) targeting human VEGF that prevent formation of CNV in this mouse model of AMD. Given that adenovirus vectors have shown to be safe in human ocular gene therapy trials coupled with the observation that such vectors persist in human ocular tissues, approach described may be a safe, long lasting method to prevent CNV in AMD patients.

Rajendra Kumar-Singh, Ph.D., Associate Professor, Ophthalmology, Tufts University School of Medicine

5:30 Networking Break & Exhibit/Poster Viewing

6:30 End of Day One

Clinical and Preclinical Stage Therapeutics

Tuesday, April 17, 2007

8:15 Chair Introductions

Keynote Speaker

8:30 Examining the Role of Cyclooxygenase in Retinal Angiogenesis

The cyclooxygenase enzymes (COX-1 and -2) are responsible for catalyzing production of biologically active prostanoids from membrane-derived arachadonic acid. Cancer literature provides evidence of a role for COX and its prostanoid metabolites in tumor-related angiogenesis including confirmation that NSAIDs targeting COX affectively inhibit tumor growth by reducing tumor angiogenesis. At least two mechanisms have been proposed for inhibition of angiogenesis by NSAID: 1) inhibition of COX reduces growth factor production in hypoxia-responsive cells; and 2) inhibition of COX negatively influences the response of vascular endothelial cells to angiogenic factors. Recent findings in our lab support the notion that both mechanisms play roles in retinal angiogenesis. Employing relevant models, including retinal Müller cells and vascular endothelial cells in primary culture, and animal models of oxygen-induced retinal angiogenesis, we will examine the validity of targeting COX-derived prostanoids to inhibit retinal angiogenesis. The prospect of employing one agent to target prostanoid-mediated events both upstream and downstream of growth factor receptor activation holds exceptional promise for therapeutic intervention.

John Penn, Ph.D., Vice-Chair and Professor, Ophthalmology, Vanderbilt Eye Institute

Preclinical Stage Therapeutics

9:15 Palomids as Inhibitors of Retinal Diseases of Neovascularization

Palomids are broad spectrum small molecule drug inhibitors of angiogenesis and activated cells involved in downstream effects of diseases of ocular neovascularization. Data will be presented to outline their mechanism of action, sustained long-term delivery and work on animal models of diabetic retinopathy and macular degeneration.

David Sherris, Ph.D., President and Chief Executive Officer, Paloma Pharmaceuticals, Inc.

9:45 Technology Workshop

For more information on presenting a technology workshop at this meeting, please contact Kristen Schott at 508-614-1239 or kschott@ibcusa.com.

10:15 Networking Break & Exhibit/Poster Viewing

10:45 AL-39324 - A Novel Receptor Tyrosine Kinase Inhibitor

AL-39324 is Alcon's lead RTKi for the treatment of visually devastating retinal diseases, such as exudative age-related macular degeneration (wet AMD) and diabetic macular edema (DME). The preclinical data in support of this novel agent will be reviewed.

David P. Bingaman, DVM, Ph.D., Dipl. ACVO, Associate Director, Retina Discovery Unit, Alcon Research Ltd.

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11:15 Polyamine Analogs: Novel Mechanism for Treating AMD

Polyamines are low molecular weight positively charged molecules found in all mammalian cells, essential for growth. Interference with the polyamine pathway blocks cell proliferation. Therefore agents such as CGC 11047 that interfere with polyamine action are potentially useful as treatments for diseases in which there is excessive proliferation, as exemplified by the abnormal neovascularization in AMD. The effect of CGC 11047 has been demonstrated in three mouse models of neovascularization, laser induced injury model, hyperoxia model and in animals over expressing VEGF. In all these models CGC 11047 was administered a single subconjunctival injection. Results showed both suppression and regression of the neovascular lesions. A toxicology program in both rabbits and dogs revealed no abnormal findings. A Phase I clinical program is underway, preliminary results will be presented.

Edward F. Schnipper M.D., *President and Chief Executive Officer, Cellgate, Inc.*

11:45 Complement Inhibition, Therapeutic Approach to AMD

Pioneering work published 6 years ago demonstrated that activated complement components were present in drusen of age-related macular degeneration (ARMD) patients. However, it was not until genetic studies published in 2005, specifically linking complement factor H polymorphisms to drusen formation and ARMD, that the theory suggesting an important role for complement activation in the pathogenesis of ARMD gained prominence. Since then, numerous other genetic studies confirmed this correlation, expanding to include other complement components e.g. complement component C2 and complement factor B. Few researchers would dispute that excessive complement activation is an important factor in initiation/progression of ARMD, and the first few complement inhibitors for this indication are already in drug companies' pipelines. One such drug candidate is Potentia Pharmaceuticals' POT-4, a peptide inhibitor of complement component C3, able to interfere with all three major pathways of complement activation. We will summarize the potential of complement inhibitors as a new class of ARMD therapeutic intervention aimed at both dry and wet form of the disease and introduce Potentia's strategy to bring to market a pharmaceutical option to treat millions of patients afflicted with dry ARMD.

Pascal Deschatelets, Ph.D., *Potentia Pharmaceuticals, Inc.*

12:15 Networking Lunch & Exhibit/Poster Viewing

Clinical Stage Therapeutics

1:45 Topically Efficacious Kinase Inhibitors for Treatment of AMD, Diabetic Macular Edema and Proliferative Diabetic Retinopathy

Age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), and diabetic macular edema (DME) are characterized by neovascularization, vascular leakage and inflammation. To date, a topically applied therapy for these chronically-driven indications remains elusive. In this presentation we describe TG100801, the first topically applied multi-targeted VEGFR/Src kinase inhibitor to advance into the clinic, and other blended kinase inhibitors as topical treatments. Agents such as TG100801 exhibit efficacy in vivo after topical application in models of angiogenesis and permeability, and have the potential to address the underlying inflammation associated with these blinding diseases.

Richard M. Soll, Ph.D., *Vice President of Research & Development, TargeGen, Inc.*

2:15 Profile of a Novel Topical Small Molecule Anti-angiogenic Therapy for AMD

ATG003 (mecamylamine ophthalmic solution) is a novel topical (eye drop) anti-angiogenic drug candidate in clinical development for AMD where standard-of-care has to be given intraocular. ATG003 inhibits angiogenesis mediated by nicotinic acetylcholine receptors found on endothelial cells (EC-NAChR). Inhibiting this pathway also inhibits the synthesis and cellular responses mediated by growth factors such as VEGF and bFGF. Cigarette smoking is the major independent risk factor in the pathogenesis of neovascular AMD as well as the transition from dry AMD to neovascular AMD. ATG003 significantly inhibits laser-induced CNV and enhanced vascular permeability in a mouse AMD model. ATG003 is currently completing Phase I studies with Phase II studies expected to commence in Q1, 2007. ATG003 has the potential to be used in the clinical management of angiogenesis dependent ocular diseases such as neovascular AMD either in conjunction with Lucentis® or for treatment of earlier disease. In addition, this agent may also be useful for the prevention of transition to neovascular AMD from dry AMD.

(Ken) M. Kengatharan, Ph.D., *Vice President, Pre-clinical Research, Athenagen Inc.*

2:45 Sirolimus for the Treatment of Serious Ocular Diseases: Leveraging Broad Mechanisms of Action

Sirolimus (rapamycin) is a potent, broad-acting small molecule with physicochemical characteristics making it a promising candidate for minimally-invasive, local ocular delivery. Sirolimus inhibits the activity of all forms of VEGF, other pro-angiogenic factors, and has also been shown to inhibit proliferation, inflammation and fibrosis, processes which are pertinent to many ocular diseases. Sirolimus has already demonstrated promising results in several animal models of choroidal neovascularization and retinal angiogenesis, and has recently been found to exert a direct inhibitory effect on VEGF-induced microvascular hyperpermeability. Because of its broad mechanisms of action, sirolimus may provide a unique opportunity to mimic combination therapy using a single compound. MacuSight has developed a proprietary formulation for sustained, minimally-invasive, local delivery of sirolimus to the eye. Two Phase I clinical trials are currently in progress in patients with wet AMD and diabetic macular edema.

David A. Weber, Ph.D., *President & Chief Executive Officer, MacuSight, Inc.*

3:15 Networking Break & Exhibit/Poster Viewing

3:45 Gene Delivery of PEDF for Subfoveal CNV due to AMD

Purpose: Safety/feasibility evaluation of single intravitreal injection of AdPEDF in patients with AMD. **Methods:** Open, label, multi-center, dose-escalating study of AdPEDF (1 x 10⁶ – 1 x 10^{9.5} particle units and 1 x 10^{8.5} and 1 x 10^{9.5} pu) in patients with subfoveal CNV and best corrected vision of 20/200 or worse and in patients with best corrected vision of 20/40 to 20/320 in the study eye, respectively. **Results:** AdPEDF was found to be safe and generally well-tolerated at all dose levels in the initial portion of the phase I study (n=28). There were no SAEs related to AdPEDF and no DLTs. Signs of mild, transient intraocular inflammation occurred in 25% of patients, without severe inflammation. Some patients experienced increased IOP controlled by topical medication. There were no cases of endophthalmitis. Enrollment in study second portion (n=22) has completed and continues to affirm that a single AdPEDF administration into a patient population with better visual acuity is safe and generally well tolerated. Secondary outcomes include changes in visual acuity, changes in angiographic parameters and OCT measurements. **Conclusions:** Intravitreal delivery with adenovectors appears safe and feasible and secondary outcomes will be presented. Additionally, research continues, to investigate potential improvements to the frequency schedule of intraocular administrations.

Lisa L. Wei, Ph.D., *Director, Preclinical Sciences, GenVec, Inc.*

4:15 Ranibizumab (LUCENTIS™) for AMD

Neovascular age-related macular degeneration (AMD) is the leading cause of blindness in the elderly population in the western world. Vascular endothelial growth factor (VEGF-A), discovered and cloned by Ferrara at Genentech, plays a key role in the pathogenesis of neovascular (wet) AMD. LUCENTIS™ (ranibizumab injection), now approved for the treatment of patients with wet AMD, targets VEGF-A. The purpose of this lecture is to review the basic physiology of VEGF and provide an update on ranibizumab clinical trials.

Susan Schneider, M.D., *Assistant Medical Director, Ophthalmic Medicine, BioTherapeutics Unit, Genentech, Inc.*

Keynote Speaker

4:45 A Novel Anti-angiogenic Function for TIMP-3: Implications for Ocular Angiogenesis

CNV is the major cause of severe vision loss in patients with AMD. The neovascularization originates from the choriocapillaris and grows through Bruch's membrane, in the RPE space. Sorsby's Fundus Dystrophy (SFD), a rare, dominantly inherited, early onset AMD is of considerable interest as it is the only genetic disorder in which choroidal neovascularization occurs in the majority of affected patients. Mutations in the Tissue Inhibitor of Metalloproteinases-3 (TIMP-3) gene cause SFD. TIMP-3, an inhibitor of matrix metalloproteinases (MMPs) is deposited by RPE cells into Bruch's membrane where it is a component of the extracellular matrix (ECM). We have demonstrated that TIMP-3 is a potent inhibitor of angiogenesis and functions independent of its MMP inhibition in this respect. We have also shown that expression of SFD mutant TIMP-3 in RPE cells reduces MMP inhibition and promotes angiogenesis. Since CNV is a prominent feature of SFD, we have examined the possible molecular mechanisms by which wild type and mutant TIMP-3 regulate neovascularization.

Bela Anand-Apte, Ph.D., M.B.B.S., *Director, Ophthalmic Research, Cole Eye Institute*

5:30 Conference Closing Remarks

5:45 Conference Ends

Ocular Anti-angiogenesis

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