Purpose: Fas ligand (FasL) has been shown to inhibit neovascularization by inducing apoptosis in Fas+ endothelial cells. However, using a knock-in mouse in which the FasL cleavage sites were mutated to prevent cleavage of mFasL (ΔCS mice) we previously demonstrated that mFasL alone neither inhibits CNV nor prevents vascular leakage in a mouse model of laser-induced CNV. Unexpectedly, we observed that sFasL is also required for inhibition of vascular leakage. The current studies elucidate the mechanism by which the two forms of FasL work together to inhibit vascular leakage in a mouse model of laser-induced CNV.

Methods: Laser CNV was induced in WT mice (B6.FasL+/+) that express low mFasL and low sFasL, and B6.FasL ΔCS/+ mice which are heterozygous for the knock-in mutation and thus express more mFasL and less sFasL, as compared to WT mice. Vascular leakage was assessed by fluorescein angiography and CNV lesion size by optical coherence tomography. Vessel maturation was assessed in choroidal whole mounts perfused with FITC dextran and stained for collagen IV, CD31 (endothelial cells), and NG2 (pericytes). Quantitative PCR was performed for pro- and antiangiogenic factors. Choroidal explant matrigel cultures were used to examine sprouting and maturation of choroidal vessels.

Results: Reduced vascular leakage was observed at all time points in B6.FasL ΔCS/+ mice as compared to WT mice. Confocal analysis revealed well perfused and highly organized vessels in CNV lesions of B6.FasL ΔCS/+ mice and staining with CD31 and NG2 revealed increased co-localization of endothelial cells and pericytes. The mature vascular phenotype in B6.FasL ΔCS/+ mice correlated with increased mRNA expression of PDGFβ, PDGFrβ, and TGFβ1, factors that promote vessel stabilization via recruitment and differentiation of pericytes. In addition, a reduced VEGF/PEDF ratio was observed in in B6.FasL ΔCS/+ mice as compared to WT mice. Choroidal explants from B6.FasL ΔCS/+ mice also showed accelerated outgrowth of vessels with a highly reticular phenotype and increased co-localization of CD31 with NG2.

Conclusions: The optimal ratio of mFasL and sFasL (high mFasL/low sFasL) promotes vessel maturation and prevents vascular leakage via accelerated recruitment and differentiation of pericytes and reduced VEGF/PEDF ratio. These data support vascular normalization as a novel approach to preventing vascular leakage in AMD.

Commercial Relationships: Adarsha Koirala, None; Ann Marshak Rothstein, None; Bruce R. Ksander, None; Meredith S. Gregory-Ksander, None

Support: NIH Grant EY22433
Results: When administered after laser-induced injury (day 0), VGX-300 significantly reduced CNV leakage and lesion formation to a comparable extent as Eylea® in a dose-responsive manner. In a regression model in which treatments 7 days after CNV lesions were established, VGX-300 and combination of VGX-300 and Eylea® inhibited lesion development and vascular leakage more effectively than Eylea® alone. In these cases, 90% of lesions graded as 2B on experimental day 7 had reduced in size to Grade 0 on day 14. Overall, all treatments were more effective at inhibiting CNV when administered on day 0 compared to day 7.

Conclusions: Inhibition of VEGF-C and D by VGX-300 inhibited laser-induced CNV and vascular leakage to a comparable extent as Eylea®. Combination of VGX-300 and Eylea® demonstrated superior inhibition of CNV lesion development and vascular leakage compared to either agent alone. A more complete blockade of VEGF pathways can be more effective in reducing wet AMD lesion development and leakage and may be an effective way to target resistance to anti-VEGF-A monotherapy. Treatment with VGX-300 alone or in combination with other anti-VEGF-A agents may be an effective approach for clinically resistant cases of wet AMD.

Commercial Relationships: Kameran Lashkari, None; Jie Ma, None; Yu Sun, None; Gianna C. Teague, None; Megan E. Baldwin, Circadian Technologies Ltd, Opthea Pty Ltd, South Yarra, Victoria, Australia (F)

Program Number: 4803
Presentation Time: 4:30 PM–4:45 PM
IL-18 immunotherapy for neovascular AMD; Tolerability and efficacy in non-human primates
Matthew Campbell1, Peter S. Adamson1, Francisco J. Lopez2, Edit Kurail3, Peter Humphries3, Sarah Doyle4, 1Genetics, Trinity College Dublin, Dublin, Ireland; 2Ophthalmology Discovery Performance Unit, GlaxoSmithKline, King of Prussia, PA; 3Statistics Consulting Group., GlaxoSmithKline, King of Prussia, PA; 4Ophthalmology Discovery Performance Unit, GlaxoSmithKline, Stevenage, United Kingdom; 5Clinical Medicine, Trinity College Dublin, Dublin, Ireland.

Purpose: Age-related macular degeneration (AMD) is the most common form of central retinal blindness in the developed world. Inflammation is known to play a key role in the pathogenesis of AMD. The activation of the NLRP3-inflammasome, has come to the fore in recent years as being involved, in some capacity, in the development of both “dry” and neovascular (“wet”) forms of the disease. We have shown that IL-18 can regulate choroidal neovascularization (CNV) formation in mice. We observed that exogenous administration of mature recombinant IL-18 has no effect on experimental day 7 had reduced in size to Grade 0 on day 14. Overall, all treatments were more effective at inhibiting CNV when administered on day 0 compared to day 7.

Conclusions: Inhibition of VEGF-C and D by VGX-300 inhibited laser-induced CNV and vascular leakage to a comparable extent as Eylea®. Combination of VGX-300 and Eylea® demonstrated superior inhibition of CNV lesion development and vascular leakage compared to either agent alone. A more complete blockade of VEGF pathways can be more effective in reducing wet AMD lesion development and leakage and may be an effective way to target resistance to anti-VEGF-A monotherapy. Treatment with VGX-300 alone or in combination with other anti-VEGF-A agents may be an effective approach for clinically resistant cases of wet AMD.

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Program Number: 4803
Presentation Time: 4:30 PM–4:45 PM
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Matthew Campbell1, Peter S. Adamson1, Francisco J. Lopez2, Edit Kurail3, Peter Humphries3, Sarah Doyle4, 1Genetics, Trinity College Dublin, Dublin, Ireland; 2Ophthalmology Discovery Performance Unit, GlaxoSmithKline, King of Prussia, PA; 3Statistics Consulting Group., GlaxoSmithKline, King of Prussia, PA; 4Ophthalmology Discovery Performance Unit, GlaxoSmithKline, Stevenage, United Kingdom; 5Clinical Medicine, Trinity College Dublin, Dublin, Ireland.

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Conclusions: Inhibition of VEGF-C and D by VGX-300 inhibited laser-induced CNV and vascular leakage to a comparable extent as Eylea®. Combination of VGX-300 and Eylea® demonstrated superior inhibition of CNV lesion development and vascular leakage compared to either agent alone. A more complete blockade of VEGF pathways can be more effective in reducing wet AMD lesion development and leakage and may be an effective way to target resistance to anti-VEGF-A monotherapy. Treatment with VGX-300 alone or in combination with other anti-VEGF-A agents may be an effective approach for clinically resistant cases of wet AMD.

Commercial Relationships: Kameran Lashkari, None; Jie Ma, None; Yu Sun, None; Gianna C. Teague, None; Megan E. Baldwin, Circadian Technologies Ltd, Opthea Pty Ltd, South Yarra, Victoria, Australia (F)

Program Number: 4803
Presentation Time: 4:30 PM–4:45 PM
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Matthew Campbell1, Peter S. Adamson1, Francisco J. Lopez2, Edit Kurail3, Peter Humphries3, Sarah Doyle4, 1Genetics, Trinity College Dublin, Dublin, Ireland; 2Ophthalmology Discovery Performance Unit, GlaxoSmithKline, King of Prussia, PA; 3Statistics Consulting Group., GlaxoSmithKline, King of Prussia, PA; 4Ophthalmology Discovery Performance Unit, GlaxoSmithKline, Stevenage, United Kingdom; 5Clinical Medicine, Trinity College Dublin, Dublin, Ireland.

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Commercial Relationships: Kameran Lashkari, None; Jie Ma, None; Yu Sun, None; Gianna C. Teague, None; Megan E. Baldwin, Circadian Technologies Ltd, Opthea Pty Ltd, South Yarra, Victoria, Australia (F)
Results: No IL-18-related ophthalmoscopic findings were apparent even at a dose of 10,000 ng per eye. In addition, we show that IL-18 has efficacy in preventing laser induced CNV development in the non-human primate eye, paving the way for its potential use in human subjects. Recombinant human IL-18 has already entered clinical trial as a systemic agent in a range of cancer indications.

Conclusions: We now show that IL-18 is safe and has efficacy in preventing laser induced CNV in the non-human primate eye. Human IL-18 is bioactive in monkeys yet does not cause RPE or retinal cell death and could now represent a novel immuno-therapeutic based adjunctive strategy for the treatment of neovascular AMD in human subjects.

Commercial Relationships: Matthew Campbell, GSK (F), TCD (P); Peter S. Adamson, GSK (E); Francisco J. Lopez, GSK (E); Edit Kurali, GSK (E); Peter Humphries, TCD (P); Sarah Doyle, GSK (F), TCD (P)

Support: GlaxoSmithKline, Enterprise Ireland, BrightFocus Foundation, Science Foundation Ireland

Program Number: 4804
Presentation Time: 4:45 PM–5:00 PM
A Phase 1 Safety Study of an Orally Available Tyrosine Kinase Inhibitor X-82 in Previously Treated Wet AMD Patients
Philip J. Rosenfeld1, Jason S. Slakter2, David S. Boyer3, David M. Brown,4 Nauman A. Chaudhry1, Michael J. Elman5, Sunil S. Patel6, Denis O’Shaughnessy7
1Bascom Palmer Eye Institute, Univ of Miami Miller Sch of Med, Miami, FL; 2Digital Angiographic Reading Center, New York, NY; 3Retina-Vitreous Associates Medical Group, Beverly Hills, CA, CA; 4Retina Consultants of Houston, Houston, TX; 5Emory Retina Associates, Atlanta, GA; 6Retina Research Institute of Texas, Abilene, TX; 7Xcovery Vision Inc, West Palm Beach, FL

Purpose: A phase 1 dose-escalation study to investigate the safety of systemic administration of X-82, an orally active tyrosine kinase inhibitor with activity against all PDGF and all VEGF subtypes.

Methods: Thirty five previously treated subjects with wet AMD were enrolled and received X-82 for up to 6 months at the following doses: 50 mg qod (3 subjects), 50 mg qd (8 subjects), 100 mg qod (4 subjects), 100 mg qd (10 subjects), 200 mg qd (7 subjects) and 200 mg qd (3 subjects). Subjects were seen every 4 weeks and underwent ETDRS VA measurement and SD-OCT assessment to determine the need for ranibizumab rescue therapy at each visit. SD-OCT images were read by DARC, which acted as the independent reading center (IRC).

Results: Twenty-seven of the 35 randomized subjects completed the full 24-week treatment period and 2 subjects are still ongoing. The remaining 6 subjects either withdrew consent or discontinued the study before reaching the 24-week study period. The majority of all patients maintained or improved their baseline visual acuity scores and 24 of the 27 subjects (89%), who completed the 24 week treatment period, did not require any rescue therapy with ranibizumab during the treatment period. Eight subjects (1 who received 100 mg, 5 who received 200 mg and 2 who received 300 mg) experienced significant reductions in fluid on SD-OCT within the first weeks of starting X-82, and these observations were confirmed by the Independent Reading Center (DARC, NY). Three subjects experienced transaminase elevations within the first month of starting therapy, and these parameters returned to normal when X-82 was discontinued. There was no dose relationship in these three cases (1 occurred at 50 mg, 1 at 100 mg and 1 at 200 mg) and none was associated with any other laboratory abnormality or clinical symptoms. One patient on the 300 mg dose discontinued treatment due to grade 2 diarrhea.

Conclusions: The stability of vision without the need for rescue therapy strongly suggests a therapeutic effect for this oral anti-VEGF/PDGF, and the significant reductions in fluid on SD-OCT provide objective support for its activity in previously and frequently treated wet AMD patients. X-82 may offer an alternative way of delivering anti-VEGF and anti-PDGF therapy to patients with wet AMD. Further randomized controlled studies are warranted.

Commercial Relationships: Philip J. Rosenfeld, Xcovery Vision Inc. (C); Jason S. Slakter, Xcovery Vision (F), Xcovery Vision Inc. (C); David S. Boyer, Xcovery Vision Inc. (F); David M. Brown, Xcovery Vision Inc. (F); Nauman A. Chaudhry, Xcovery Vision Inc. (F); Michael J. Elman, Xcovery Vision Inc. (F); Sunil S. Patel, Xcovery Vision Inc. (F); Denis O’Shaughnessy, Xcovery Vision Inc. (E)

Clinical Trial: NCT01674569

Program Number: 4805
Presentation Time: 5:00 PM–5:15 PM
Final Results from a Phase 2 Study of Squalamine Lactate Ophthalmic Solution 0.2% (OHIR-102) in the Treatment of Neovascular Age-related Macular Degeneration (AMD)
Jason S. Slakter1, Thomas A. Ciulla2, Michael J. Elman3, Lawrence J. Singerman4, Glenn Stoller1, Peter K. Kaiser5, Idrach B. Taraporewala1, Sam Backenroth3,1, Vitreous Retina Macula Consultants of New York, New York, NY; 2Cole Eye Institute, Cleveland, OH; 3Ohr Pharmaceutical, New York, NY; 4Elman Retina, Baltimore, MD; 5OCLI, Rockville Center, NY; 6Midwest Eye Institute, Indianapollis, IN; 7Retina Associates of Cleveland, Cleveland, OH

Purpose: To determine if topical OHIR-102 administered BID in combination with Ranibizumab (RBZ) PRN can safely improve visual outcomes and reduce treatment frequency of RBZ compared to RBZ monotherapy in patients with treatment naïve neovascular AMD.

Methods: Phase 2, prospective, randomized, double-masked, placebo-controlled, multicenter study in treatment naïve patients with CNV due to AMD measuring ≥ 12 disc areas, OCT central subfield ≥ 300 microns with subretinal fluid or cystoid macular edema, any lesion composition, and BCVA of 20/40 to 20/320. Diabetics without diabetic retinopathy were included. All patients received RBZ at baseline and randomized 1:1 to topical OHIR-102 BID (combination group) or placebo vehicle solution BID (monotherapy group).

Patients were followed monthly for 9 months. Retreatment with RBZ was performed if OCT demonstrated cystoid macular edema, intraretinal/subretinal fluid, or RPE elevation.

Results: A total of 142 patients were enrolled. In an interim analysis of the first 62 patients to complete the study, mean baseline BCVA was 59.8 letters (~20/63 Snellen). Mean total lesion size on FA was 8.5 mm² with 53.2% having some classic CNV component. At the 9 month endpoint, the mean change in BCVA in the OHIR-102 combination group (n=29) was +10.4 letters vs +6.3 letters in the RBZ PRN monotherapy group (n=33). At least 3 line vision gain was seen in 48.3% in the combination group vs 21.2% in the monotherapy group. Subretinal hyper-reflective material (SHRM) was noted at baseline in 87% of these 62 patients. At month 9, there was a 75% reduction and 59% had total resolution of SHRM in the combination group vs 56% reduction and 44% had total resolution in the monotherapy group. Visual gains correlated with anatomic improvements in the OHIR-102 combination group. There was no difference in frequency of RBZ retreatment between the groups. No safety issues were identified. Final Phase 2 data will be presented.

Conclusions: In the interim analysis, OHIR-102 BID used with RBZ PRN demonstrated marked improvements over RBZ monotherapy in mean gain in visual acuity and percentage of patients gaining ≥
Commercial Relationships: Jason S. Slakter, Genentech (F), Ohr Pharmaceutical (C), Ohr Pharmaceutical (I), Ohr Pharmaceutical (S), Regeneron (F), Regeneron (R); Thomas A. Ciulla, Ohr Pharmaceutical (C), Ohr Pharmaceutical (F), Ohr Pharmaceutical (I); Michael J. Elman, Ohr Pharmaceutical (C), Ohr Pharmaceutical (F), Ohr Pharmaceutical (I); Lawrence J. Singerman, Genentech (F), Novartic (F), Ohr Pharmaceutical (C), Ohr Pharmaceutical (F), Ohr Pharmaceutical (I), Ophthotech (C), Ophthotech (F), Ophthotech (I); Glenn Stoller, Ohr Pharmaceutical (C), Ohr Pharmaceutical (I), Ohr Pharmaceutical (S); Peter K. Kaiser, Bayer (C), Genentech (C), Ohr Pharmaceutical (C), Ohr Pharmaceutical (I), Ohr Pharmaceutical (S), Ophthotech (C), Ophthotech (I), Regeneron (C); Irach B. Taraporewala, Ohr Pharmaceutical (E), Ohr Pharmaceutical (I); Sam Backenroth, Ohr Pharmaceutical (E), Ohr Pharmaceutical (I)

Clinical Trial: NCT01678963

Program Number: 4806
Presentation Time: 5:15 PM–5:30 PM
Phase I/II Prospective Randomized Sham-controlled Study of Low Dose Proton Beam Irradiation combined with Intravitreal anti-VEGF Therapy for Exudative Age-related Macular Degeneration: One-year Results

Senad Osmanovic1, Elad Moisseiev1, Kavita Mishra2, Inder Daftari2, Ala Moshiri1, Lawrence S. Morse1, Mohammad Ashrafzadeh3, Susanna S. Park1.

1Ophthalmology, University of California Davis, Sacramento, CA; 2Radiation Oncology, University of California San Francisco, San Francisco, CA; 3Ophthalmology, Northern California VA, Mather, CA.

Purpose: Intravitreal antiVEGF is the treatment of choice for exudative age-related macular degeneration (eAMD), but the therapy is transient and requires retreatment. Since a synergism between antiVEGF therapy and radiation has been observed in oncology and possibly in eAMD, this phase I/II prospective, randomized, double-blinded sham-controlled study was initiated to explore the safety and efficacy of proton beam irradiation (PBI) combined with antiVEGF therapy in eAMD.

Methods: Thirty eyes (30 subjects) with newly-diagnosed eAMD were randomized 1:1:1 to 24Gy: 16Gy: sham PBI, delivered in two fractions, 24 hours apart. Subjects were seen monthly and treated with intravitreal ranibizumab (0.5mg) or bevacizumab (1.25mg) monthly for the first 3 months and prn thereafter for new macular fluid on optical coherence tomography (OCT) or macular hemorrhage on examination. Main outcome measures were incidence of radiation retinopathy and severe vision loss (> 15 letter loss), mean number of antiVEGF therapies, and change in BCVA. Changes in macular morphology on OCT and the neovascular lesion on angiography were also assessed.

Results: The groups were evenly distributed in terms of demographics, BCVA, and lesion size at baseline. Interim analysis of the first 19 subjects who completed the one-year follow-up included the following: 24Gy (n=7); 16Gy (n=6); sham (n=6). An improvement in mean BCVA was noted in all three groups compared to baseline (p<0.02) with no significant differences between groups. The mean number of additional antiVEGF treatments after month 3 was 2 ±1.1 (24Gy Group) vs 5 ±1.6 (sham Group) (p=0.005). There was a trend toward complete dryness on OCT at month 3 in the 24Gy Group compared to the sham Group (p=0.16). Imaging analysis indicated a trend towards reduction in central macular thickness and size of pigment epithelial detachments with combination treatments (both 16Gy and 24Gy). There was no case of severe visual loss or radiation retinopathy.

Conclusions: Interim one-year analysis revealed no safety concerns with combination therapy and a possible synergistic effect utilizing 24Gy PBI, resulting in a decreased treatment burden. The complete one-year follow-up data will be presented to determine whether these initial findings may also be applicable the 16Gy group.

Commercial Relationships: Senad Osmanovic, None; Elad Moisseiev, None; Kavita Mishra, None; Inder Daftari, None; Ala Moshiri, None; Lawrence S. Morse, None; Mohammad Ashrafzadeh, None; Susanna S. Park, None

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Clinical Trial: NCT01213082